Percutaneous radiofrequency-assisted liver partition versus portal vein embolization before hepatectomy for perihilar cholangiocarcinoma

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Background: Percutaneous radiofrequency-assisted liver partition with portal vein embolization in staged liver resection (PRALPPS) represents an alternative to portal vein embolization (PVE) followed by major liver resection in patients with perihilar cholangiocarcinoma.

Methods: This was an observational case–control study. Both procedures were applied in patients with a future liver remnant (FLR) volume of less than 40 per cent. The main end points of the study were short-term morbidity and mortality for the two procedures. The study also compared the efficacy of the preresection phases estimated by kinetic growth rate (KGR), time interval and degree of hypertrophy of the FLR.

Results: The first phase (preresection) was completed in 11 and 18 patients, and the second phase (resection) in nine and 14 patients, in the PRALPPS and PVE groups respectively. Major morbidity after the first stage did not differ between the groups. There were no differences in blood loss, severe morbidity or liver failure rate after the second stage, with no deaths. The mean KGR of the FLR after the preresection phase for PRALPPS was 3.8 (0.6–9.8) per cent/day, and that after PVE was 1.8 (0.6–7) per cent/day\(^{(*)} \left( P = 0.037 \right)\). The mean time interval for FLR hypertrophy in the PRALPPS and PVE groups was 15 (6–29) and 20 (8–35) days respectively\(^{(**)} \left( P = 0.039 \right)\).

Conclusion: Short-term outcomes were similar for PRALPPS and PVE in terms of safety. Remnant hypertrophy was achieved more rapidly by PRALPPS.

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Introduction

Cholangiocarcinoma remains the most common malignant tumour of the biliary tract and the second most common primary liver malignancy\(^1,2\). Most patients present with advanced-stage tumours, so that only 10–40 per cent are considered resectable\(^3,4\). Major hepatic resection designed to achieve negative resection margins is the mainstay of attempted curative treatment for perihilar cholangiocarcinoma (PHCC)\(^3,5\), but carries a risk of posthepatectomy liver failure, particularly in patients with compromised liver function or where the volume of remaining liver is inadequate. Portal vein occlusion has been advocated as a method to induce future liver remnant (FLR) hypertrophy. Although generally safe, growth of the FLR volume can be slow and may be inadequate in patients with cholangiocarcinoma\(^5,6\).

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been proposed\(^7\) as an effective method to induce marked and rapid hypertrophy of the FLR, with 95–100 per cent completion rates for the resectional second stage. Short- and long-term results of ALPPS remain variable. Unsatisfactory immediate outcomes of ALPPS in surgery of cholangiocarcinoma, with a mortality rate approaching 50 per cent in patients with PHCC, suggest that patients with biliary cancer should not be treated by ALPPS\(^8,9\).
Modifications to the technique have been designed to minimize the operating injury in the first stage, increasing the numbers of patients likely to benefit from a later resection and reducing subsequent postoperative morbidity. There is, however, no evidence of benefit for any modification in reducing the morbidity of cholangiocarcinoma.

The present study compared the short-term outcomes of percutaneous radiofrequency-assisted liver partition with portal vein embolization in staged liver resection (PRALPPS) with those of conventional portal vein embolization (PVE) followed by major liver resection in patients with PHCC.

Methods

Consecutive patients who underwent PVE or PRALPPS for PHCC were enrolled chronologically in a specific database between October 2013 and March 2018. All patients had percutaneous biliary drainage as a preliminary procedure, designed to achieve a total serum bilirubin level of less than $50\,\mu\text{mol/l}$. PVE plus hepatectomy was performed at the beginning of the series, being gradually replaced by PRALPPS. The indication for PRALPPS and PVE was the same. Both procedures were applied in patients with a FLR volume of less than 40 per cent.

PRALPPS and PVE were both considered to be contraindicated in patients with jaundice (total bilirubin level above $50\,\mu\text{mol/l}$), an international normalized ratio (INR) greater than 2, or unresolved surgical complications following biliary drainage procedures. Patients with allergy to iodinated contrast media were also excluded. Patients with Bismuth–Corlett type II–IV tumours and those with UICC TNM-8T1–3 N0–1 M0 tumours were included, whereas those with stage IIIB or IV were excluded.

The maximum total bilirubin concentration, duration of jaundice and presence of acute cholangitis were considered as factors influencing liver hypertrophy. CT volumetry was used to estimate the FLR volume, which was calculated as a percentage of the total liver volume using the Vauthey formula.

The degree of hypertrophy (DH) of the FLR was calculated according to the previously published formula: $\left( sF1R2 - sF1R1 \right) / sF1R1$, where $sF1R1/2$ is the standardized FLR before the first and second stages. The kinetic growth rate (KGR) was calculated by the formula: $\text{KGR} (\% / \text{day}) = \text{DH} (\%) \div \text{time between stage 1 and imaging before stage 2}$. The time interval for FLR hypertrophy was measured in days between the first stage and imaging before the second stage, commencing no earlier than 7 days after the first stage. The decision to proceed with the second stage was contingent upon achievement of a second stage only if the FLR volume was greater than 40 per cent. The timing of CT was based on ultrasound examinations that provided estimates of the degree of FLR hypertrophy. If FLR did not increase to the necessary volume, the next CT scan was performed 7–11 days later.

If FLR hypertrophy did not reach the target volume of more than 40 per cent, a procedure with reduced liver parenchyma resection was considered. Hepatic failure after liver resection was classified according to International Study Group of Liver Surgery (ISGLS) criteria. Hepatic function was assessed using the criteria recommended by ISGLS (INR and neurological symptoms). Morbidity was evaluated according to the Clavien–Dindo classification, including 90-day mortality.

Surgical technique

The first stage of PRALPPS included percutaneous embolization of the right portal vein under ultrasonographic control and radiofrequency ablation (RFA) of liver parenchyma along the right side of the middle hepatic vein in the plane of future liver transection (main portal fissure) (Fig. 1). When extended right hepatectomy was considered appropriate, percutaneous embolization of the right portal vein was combined with RFA applied along the umbilical plane, including ablation of branches to segment 1, Water-cooled radiofrequency ablation (RFA) probe sequentially sets along the right side of the middle hepatic vein (3–4 probe insertions); 2, area of necrotic tissue after RFA application (yellow); 3, middle hepatic vein; 4, thrombus in right portal vein and its tributaries after portal vein embolization.
Percutaneous radiofrequency-assisted liver partition for perihilar cholangiocarcinoma

Table 1 Demographic and perioperative data

|                      | PRALPPS (n = 11) | PVE (n = 18) | P‡ |
|----------------------|------------------|--------------|----|
| Age (years)*         | 58 (42–73)      | 59 (35–79)   | 0.842 |
| Sex ratio (F : M)    | 5 : 6           | 7 : 11       | 0.728§ |
| ASA grade*           | III (III–IV)    | III (II–IV)  | 0.740 |
| Total bilirubin before drainage (μmol/l)* | 217 (106–313) | 249 (119–493) | 0.877 |
| Cholangitis before procedure | 9              | 14            | 0.794§ |
| Duration of jaundice (weeks)* | 4 (0–8)      | 6 (0–16)     | 0.188 |
| Chemotherapy before procedure | 1              | 2             | 0.320§ |
| Bismuth–Corlette type† | 9              | 10            | 0.078§ |
| Ilia                 | 9               |              |    |
| IV                   | 0               | 4            |    |
| Volume of FLR (%)*   | Initial 32 (20–41) | 33 (24–43)   | 0.521 |
|                      | After stage 1 45 (35–58) | 44 (30–63) | 0.550 |
| Volume of sFLR (%)*  | Initial 38 (18–88) | 39 (21–65)   | 0.387 |
|                      | After stage 1 52 (30–116) | 50 (26–92) | 0.808 |
| Degree of hypertrophy (%)* | 46 (17–117) | 32 (0–100) | 0.146 |
| Time interval for hypertrophy (days)* | 15 (6–29) | 20 (8–35) | 0.039 |
| Kinetic growth rate (%/day)* | 3.8 (0.6–9.8) | 1.8 (0–6.7) | 0.037 |

*Values are mean (range). †In patients who had a second-stage procedure. PRALPPS, percutaneous radiofrequency-assisted liver partition with portal vein embolization in staged liver resection; PVE, portal vein embolization; (s)FLR, (standardized) future liver remnant. ‡Mann–Whitney U test, except §Fisher’s exact test.

IV. RFA was applied along the left side of the right hepatic vein before extended left hepatectomy. A water-cooled 17-G RFA probe (Cool-tip™; Medtronic, Minneapolis, Minnesota, USA) was used with 3–4-min activation cycles under general anaesthesia. Liver partition was performed by RFA alone under ultrasonographic guidance without surgical division. Thermal ablation involved around 50 per cent of the future transection plane, retaining a minimum distance of 2 cm from the hilar plate to avoid bile duct and inflow vascular damage (Fig. 1).

Blood flow after percutaneous PVE, as a separate procedure or as a part of the first stage in PRALPPS, was reduced by coils placed in the right/left portal vein and/or its sectional branches. Embolization of veins supplying the anterior and posterior right sections for right hepatectomy, or of the left portal vein and right anterior sectional branch for extended left hepatectomy, used a mixture of gelatin sponge and radio-opaque oil solution. For extended right hepatectomy, veins of anterior and posterior right sections and portal vein branches to segment IV (P4) were embolized by the same technique.

The second stage included regional lymphadenectomy, extrahepatic bile duct resection, right, extended right or extended left hepatectomy, and biliary reconstruction with Roux-en-Y hepaticojejunostomy.
The kinetic growth rate (KGR) is represented by the increase in the size of the standardized future liver remnant (sFLR) before stage 1 (central scale) and before stage 2 in a portal vein embolization (PVE) and b percutaneous radiofrequency-assisted liver partition with portal vein embolization in staged liver resection (PRALPPS) groups. The dashed lines reflect the mean KGR value for PVE and PRALPPS: 1·8 versus 3·8 per cent/day respectively (\( P = 0·037 \), Mann–Whitney \( U \) test).

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent for the treatment was obtained from all individual participants included in the study.

Outcomes
The main endpoints of the study were comparisons of morbidity and mortality following PRALPPS and conventional PVE. Complications were recorded using the Clavien–Dindo classification\textsuperscript{18}. Secondary endpoints were first stage efficacy using time interval and degree of FLR hypertrophy.

Statistical analysis
Continuous data are presented as mean (range) values and compared with the Mann–Whitney \( U \) test. The \( \chi^2 \) test or two-tailed Fisher’s exact test was used to compare categorical variables. \( P < 0·050 \) was considered statistically significant. The software package SPSS\textsuperscript{®} version 23.0 (IBM, Armonk, New York, USA) was used.

Results
Between October 2013 and March 2018, 84 patients with PHCC were treated with curative intent. All of these patients underwent liver and bile duct resection. Because of the extent of the proposed resection, 23 patients had the complete two-stage procedure of PVE or PRALPPS followed by liver resection; the second stage was not performed in six patients.

First stages in the PRALPPS and PVE groups were undertaken in 11 and 18 patients respectively. Patient demographics, tumour details, laboratory data before surgery, and outcomes from the first stage are shown in Table 1. The groups were comparable in terms of age, sex and ASA grade, as well as for factors thought to influence liver hypertrophy (maximum total bilirubin level before
Fig. 3 Acute surgical infectious complications in patients with and without posthepatectomy liver failure for the whole cohort

| No. of patients | Posthepatectomy liver failure | No liver failure |
|----------------|-----------------------------|-----------------|
| Acute cholangitis | 20                           | 0               |
| Infected fluid collection | 18                           | 2               |
| No acute surgical infection | 0                            | 10              |

$P < 0.001$ (posthepatectomy liver failure versus no liver failure, Fisher’s exact test).

drainage, duration of jaundice, acute cholangitis and neoadjuvant chemotherapy).

PRALPPS and PVE were completed by liver resection as a second stage in nine and 14 patients respectively. In one patient, the first stage of PRALPPS led to an insufficient volume (35 per cent) of FLR despite a high DH (75 per cent) and long time after the first stage (23 days), so major liver resection was considered inadvisable. This patient underwent a parenchyma-sparing resection (segments I, IVb and V) involving separate hepaticojejunostomies with five bile duct orifices, resulting in an R0 resection. In two patients in the PRALPPS group and three undergoing PVE, the subsequent resectional phase was not performed because of peritoneal carcinomatosis. One patient in the PVE group did not have the second stage because of relapse of cholangitis with tumour progression during the time required for treatment of cholangitis.

Morbidity according to the stage of surgery is presented in Table 2. After the first stage of PRALPPS, an uneventful course and complications (grade II–IIIa) were registered in five and six patients respectively. After PVE, 16 patients had no complication, one patient had a grade II and one had a grade IIIa complication. The first stage of PRALPPS was complicated by abscesses (grade IIIa) in the ablated liver parenchyma in three patients, successfully dealt with by percutaneous drainage. Major complications (grade IIIa,b) after the resectional phase of PRALPPS included anastomotic bile leakage and hepaticojejunal anastomositis that required percutaneous placement of additional drains. There were no deaths within 90 days of resection.

No differences were found in blood loss, rate of R0 resection, severe morbidity or rate of liver failure. Residual tumour (R1/2 resection) was found in three patients in the PVE group and in one patient in the PRALPPS group. Three of these patients (all in the PVE cohort) had a type IV tumour.

A significant difference in favour of the PRALPPS group was found in the mean KGR of FLR after the first stage of PRALPPS and PVE (3.8 versus 1.8 per cent/day; $P = 0.037$) (Fig. 2). The time interval for FLR hypertrophy after the first stage of PRALPPS was significantly shorter than that after PVE (mean 15 versus 20 days respectively; $P = 0.039$). For the entire series there were no significant differences in FLR and sFLR, DH or KGR between patients who developed or did not develop posthepatectomy liver failure. After liver resection, acute cholangitis (2 patients) and infected fluid collection (3) occurred in the five patients with ISGLS grade B posthepatectomy liver failure. These complications were significantly more frequent than in patients without liver failure, where only a single patient developed an infected fluid collection after the resection ($P < 0.001$) (Fig. 3).

Discussion

This study highlights the early outcomes of the modified version of ALPPS (PRALPPS) in patients with PHCC.

The main features were no deaths and no differences in major morbidity, including the rate and severity of posthepatectomy liver failure, between PRALPPS and PVE groups after each phase of the two approaches. The KGR and time interval for FLR hypertrophy were better in the PRALPPS than in the PVE group.

Early reports generated from the International ALPPS Registry indicated poor results in patients with PHCC, with major complications in 60 per cent (2014) and 64 per cent (2015). Rates of posthepatectomy liver failure and 90-day mortality were 57 and 36 per cent respectively in patients with PHCC.

In a recent multicentre study of high-risk patients with PHCC, the 90-day mortality rate reached 48 per cent. This was considered inferior to standard extended resections, leading the authors to recommend that ALPPS should not be performed for PHCC. Among several reasons for poor outcomes, the small initial volume of FLR has been considered important, suggesting the need for revised strategies for the first stage of ALPPS, including reduced surgical trauma.
These modifications, however, remain largely confined to case reports or small series. Boggi and colleagues described successful laparoscopic ALPPS with portal vein ligation and microwave ablation in a patient with PHCC, and several case series have described patients with intrahepatic cholangiocarcinoma using modified ALPPS techniques with reduced trauma in the first stage.

The core feature of modified ALPPS in the present series was a percutaneous approach for the first stage. A similar approach using percutaneous PVE and microwave ablation has been described, but percutaneous RFA with PVE as an original technique has been demonstrated only in an experimental study in pigs (PRALPPS). According to new consensus terminology proposed by Linecker et al., this technique could be named as radiofrequency PVE-partial-ALPPS.

The problem of achieving significant liver hypertrophy in jaundiced patients was highlighted by Higuchi and Yamamoto, who performed a meta-analysis in which the mean FLR volume increase after PVE in 836 patients with PHCC was found to be only 33.6 per cent.

In patients with cholangitis and complications after the first stage of the procedure, functional liver capacity is compromised even further, and an FLR volume of around 40 per cent may be insufficient, especially if major complications develop after the resectional stage. As a result, the threshold for the FLR is 50 per cent in some centres.

In the present study, the rate of major complications after the first stage was lower than that seen in other recent studies of cholangiocarcinoma. Major morbidity was seen in only three of 11 patients, compared with 13 of 29 patients with PHCC who underwent conventional ALPPS in one series. There were no significant differences in major morbidity between either of the modalities chosen after the first stage. Only grade IIIa complications (abscesses) were identified after the first stage of PRALPPS; these were treated successfully by percutaneous intervention.

Major morbidity after the resection phase of PRALPPS occurred in six of nine patients, similar to 19 of 29 after conventional ALPPS in the case series of Olthof and co-workers. Most of these severe complications were not life-threatening, and were classified as grade IIIa in the present series. Major complication rates after resection were also similar in the PRALPPS and PVE groups in the present study. High rates of serious complications lead to death. This was reported as 8.8 per cent for patients with biliary cancer undergoing PVE in a high-volume experienced centre. In the present series, there were no procedure-related deaths.

A combination of sFLR, DH and KGR was used to estimate FLR hypertrophy after PVE. Despite a tendency to more pronounced hypertrophy after PRALPPS, there was no significant difference in DH between the PRALPPS (46 per cent) and PVE (32 per cent) groups.

Shindoh and colleagues found that KGR was a more useful factor for the prediction of postoperative hepatic insufficiency than sFLR volume or DH. In the present series, mean KGR after PRALPPS was significantly greater than that after PVE (3.8 versus 1.8 per cent/day respectively).

Some studies have indicated that the interval between PVE and CT before liver resection should be 30 days or more. One advantage of ALPPS is the substantial reduction of the interval between the stages; this may be important in terms of the tumour progression risk, especially when FLR hypertrophy is slow. In the present series, the time interval between the stages was significantly shorter in the PRALPPS group, although this did not impact on short-term oncological results (R0 resection rates). Failure to progress to planned hepatectomy after PVE affected 22 per cent of patients with PHCC in one series, due mainly to distant metastasis or local progression. In the present series, five of the 29 patients did not reach the second stage due to tumour progression.

This study has limitations. The patient groups are small and analysis relies on retrospective data collection. The limited number of patients reflects restricted ability to accumulate patients with PHCC in a single centre over a short time interval when other elements of care remain unchanged. In the context of PHCC, a multicentre approach seems essential to determine whether there is a role for PRALPPS. Although the degree of hypertrophy appears to be slightly less than that often achieved after conventional ALPPS, the fact that PRALPPS is a potentially reversible procedure that can be safely interrupted after the first stage may offset this.

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