MSL Liem
CL Liu 廖子良
WK Tso 曹偉權
CM Lo 盧寵茂
ST Fan 范上達
J Wong 黃健靈

Portal vein embolisation prior to extended right-sided hepatic resection

右肝葉擴大切除手術前進行的門靜脈栓塞術

Objectives. To determine whether preoperative portal vein embolisation improves the operative outcome of patients undergoing extended right-sided hepatic resection for hepatobiliary malignancy.

Design. Prospective non-randomised study.

Setting. University teaching hospital, Hong Kong.

Patients. Ninety-two patients underwent extended right-sided hepatic resection for hepatobiliary malignancy during a 45-month period (January 2000 to September 2003). Among them, 15 (16%) underwent portal vein embolisation via a percutaneous ipsilateral approach (n=9) or through the ileocolic vein with a mini-laparotomy (n=6). The remaining 77 (84%) patients underwent hepatic resection without portal vein embolisation.

Main outcome measures. Operative morbidity and mortality.

Results. Patients undergoing portal vein embolisation were older (69 years vs 55 years; P=0.009), and had significantly worse preoperative renal function (creatinine, 96 μmol/L vs 86 μmol/L; P=0.039) and liver function (bilirubin, 23 μmol/L vs 12 μmol/L; P<0.001). Portal vein embolisation resulted in an increase in the future liver remnant of 9% (interquartile range, 7-13%) of the estimated standard liver volume. The operating time for patients receiving portal vein embolisation was significantly longer (medium, 660 min vs 420 min; P<0.001) with more complicated surgery performed in terms of concomitant caudate lobectomy and hepaticojejunostomy. There was no hospital mortality in patients who underwent portal vein embolisation whereas five without the treatment died (P=0.587). The operative morbidity of patients who underwent portal vein embolisation and those who did not was 20% and 30%, respectively (P=0.543).

Conclusions. In older patients who have worse preoperative liver and renal functions, portal vein embolisation enhances the possibility to perform extended right-sided hepatic resection for hepatobiliary malignancies with potentially lower operative mortality and morbidity.

目的：評估術前門靜脈栓塞術能否改善肝膽惡性腫瘤患者進行右肝葉擴大切除手術的效果。

設計：非隨機性前瞻研究。

安排：大學教學醫院，香港。

患者：92名肝膽惡性腫瘤患者於45個月內（2000年1月至2003年9月）接受右肝葉擴大切除手術，其中15人(16%)接受術前門靜脈栓塞術(簡稱PVE組)：其中9位透過經皮經肝途徑，6位則以經回結腸靜脈法以微型剖腹術完成。餘下77位（84%）病人術前沒有進行門靜脈栓塞術（簡稱非PVE組）。

主要結果測量：手術發病率及死亡率。

結果：PVE組年紀較非PVE組大（69歲比55歲；P=0.009），腎功能（肌

Key words:
Carcinoma, hepatocellular;
Cholangiocarcinoma;
Embolization, therapeutic;
Hepatectomy;
Portal vein

關鍵詞：
癌症，肝細胞；
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門靜脈

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The Dutch Cancer Society, Queen Wilhelmina Fund, Amsterdam, The Netherlands
MSL Liem, MD, PhD
University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong: Centre for the Study of Liver Disease, Department of Surgery
CL Liu, FRCS (Edin), FACS
CM Lo, FRCS (Edin), FACS
ST Fan, FRCS (Glasg & Edin), FACS
J Wong, FRCS (Edin), FACS
Department of Radiology
WK Tso, MB, BS, FRCR

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Correspondence to: Dr CL Liu (e-mail: clliu@hkucc.hku.hk)

酸酐，96 μmol/L 比 86 μmol/L；P=0.039）和肝功能（膽紅素，23 μmol/L 比 12 μmol/L；P<0.001）亦明顯較差。門靜脈栓塞術使術後的殘留肝臟較估計的標準肝重增大 9%（四分位數間距，7-13%）。此外，PVE 組的手術時間明顯較非 PVE 組長（中位數，660 分鐘比 420 分鐘；P<0.001），手術亦更複雜，包括附帶的尾狀肺葉切除術和肝管空腸吻合術。PVE 組沒有病人在住院期內死亡，而非 PVE 組則有 5 位（P=0.587）。手術發病率方面，PVE 組為 20%，非 PVE 組則為 30%（P=0.543）。

結論：門靜脈栓塞術能提高肝膽惡性腫瘤患者進行右肝葉擴大切除手術的可能性，並減低術前腎肝功能較差的年老病人的手術發病率和死亡率。

Introduction

Hepatic resection is the treatment of choice for both primary and metastatic tumours of the liver.[1,2] The safety of surgery has dramatically improved with better perioperative and intra-operative care in recent decades. However, major hepatic resection still carries a substantial risk of mortality and morbidity. Moreover, there may also be room for improvement in terms of survival for these patients after major resection.[3] Preoperative portal vein embolisation (PVE) has been advocated to improve the safety of major hepatic resection by increasing the volume of the future liver remnant (FLR).[4-6] Although it is unclear whether PVE affects survival in patients with hepatocellular carcinoma (HCC),[7] it may contribute to higher safety margins after major hepatic resection and result in better postoperative outcome, particularly in cirrhotic patients.[4,8] We report the use of preoperative PVE in patients who underwent extended right-sided hepatic resection, and investigate whether PVE can improve the operative outcome.

Methods

A prospective study was performed on all patients who underwent extended right-sided hepatic resection for hepatobiliary malignancy between January 2000 and September 2003 at the Department of Surgery, Queen Mary Hospital, Hong Kong. Extended right-sided hepatic resection was defined as right-sided hepatic resection with more than four Couinaud's segments, including right hepatectomy with extension to segment 4, right hepatectomy with caudate lobectomy, and right trisectionectomy. Preoperative PVE was performed on patients when hepatectomy comprised more than 70% of the functional hepatic parenchyma without biliary obstruction, or more than 60% with a history of biliary obstruction. Patients who underwent extended right-sided hepatic resection during the same study period but without prior PVE constituted the control group.

The percentage of functional hepatic parenchyma was estimated by volumetry with computed tomography (CT). Following administration of intravenous contrast medium, consecutive transverse scans using a slice thickness of 3 to 5 mm were used to trace the tumour and the left, caudate, and right lobe areas of the liver. If a trisectionectomy was planned, segment 4 area was also traced. The volume of each lobe and the FLR was calculated by adding the areas of the consecutive slices. In patients with obstructive jaundice, biliary obstruction was relieved by either percutaneous transhepatic biliary drainage or endoscopic drainage. After the serum total bilirubin level had dropped to less than 50 μmol/L, PVE was performed percutaneously by an interventional radiologist using an ipsilateral approach,[9] or by a mini-laparotomy via the transileocolic vein approach.[6] A 5.5 French triple lumen balloon catheter (Clinical Supply, Nagoya, Japan) was used for both approaches. A single surgeon who was responsible for all open PVE with the transileocolic vein approach was present during all percutaneous PVEs. The portal anatomy was studied under direct portal venography with real-time fluoroscopy to confirm a normal portal blood supply to the FLR. Portal vein embolisation was then performed using a mixture of fibrin glue (Beriplast; Aventis Behring GmbH, Marburg, Germany) and lipiodol (Lipiodol ultra-fluide; Laboratoire Guerbet, Aulnay-sous-Bois, France). Injection of the mixture was stopped when the whole right portal venous system was obstructed. The balloon was kept inflated for 3 minutes to prevent accidental embolisation of the main or left portal venous system. The success of PVE was then evaluated with fluoroscopy. Patients were discharged when they were able to walk independently, usually on the second day after the procedure. A repeated CT was performed 4 to 6 weeks after PVE and surgery performed the following week.

Future liver remnant was reassessed by CT volumetry and the hypertrophy ratio determined by dividing the post-PVE volume by the pre-PVE volume. In addition, the standard total liver volume (STLV) was estimated using the formula devised by Urata et al,[10] and the percentage increase of the FLR as a

Table 1. Preoperative clinical and laboratory data of patients who underwent extended right-sided hepatic resection with preoperative portal vein embolisation (PVE group) and those without (non-PVE group)*

Clinical parameter	PVE group	Non-PVE group	P value
No. of patients	15	77	-
Sex (male:female)	11:4	52:25	0.768
Age (years)	69 (51-75)	55 (47-64)	0.009
Body weight (kg)	63.8 (58.3-71.2)	56.7 (50.0-69.0)	0.549
Serum albumin (g/L)	37 (36-41)	39 (36-42)	0.534
Serum total bilirubin (μmol/L)	23 (17-33)	12 (9-17)	<0.001
Serum creatinine (μmol/L)	96 (85-112)	86 (74-95)	0.039
Alanine aminotransferase (U/L)	54 (46-107)	44 (26-72)	0.048
Haemoglobin (g/L)	129 (110-143)	128 (116-138)	0.857
Prothrombin time (sec)	12.5 (12.0-13.0)	12.6 (11.8-13.1)	0.900
Indocyanine green retention at 15 min (%)	12.1 (10.2-17.2)	10.9 (6.7-14.3)	0.279
Child-Pugh's grading[15]			<0.001
A	8 (53%)	74 (96%)	
B	7 (47%)	3 (4%)	

* Values are expressed as median (interquartile range), unless otherwise stated

Table 2. Pathologies of patients with preoperative portal vein embolisation (PVE group) and those without (non-PVE group)

Pathology	PVE group, n=15	Non-PVE group, n=77
Hepatocellular carcinoma	4 (27%)	50 (65%)
Hilar cholangiocarcinoma	10 (67%)	1 (1%)
Intrahepatic cholangiocarcinoma	0	8 (10%)
Combined hepatocholangiocarcinoma	1 (7%)	1 (1%)
Liver metastasis	0	13 (17%)
Others*	0	4 (5%)

* Other pathologies included metastatic neuroendocrine tumour (n=2), rhadomyosarcoma (n=1), and sarcoma (n=1)

result of PVE relative to the STLV was determined. Hepatic resection was performed using a standard technique[11,12] and an ultrasonic dissector was used for parenchymal transection.[13,14] All patients received the same perioperative care by the same team of surgeons and were treated in the intensive care unit during the early postoperative period. All intra-operative complications and postoperative morbidities were recorded prospectively. Hospital mortality was defined as death during the same period of hospitalisation for the hepatic resection.

Clinical data of all patients were recorded prospectively in a computerised database by a single research assistant. Continuous data were expressed as medians with their interquartile range. Proportions were given as number and percentages. Differences between two groups were assessed with either the Mann-Whitney *U* test for continuous data or the Chi squared test or Fisher's exact test where appropriate for proportions. All reported P values are two-tailed. A P value of less than 0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (Windows version 11.0; SPSS Inc, Chicago [IL], US).

Results

Between January 2000 and September 2003, 274 (23.6%) of 1162 patients with hepatobiliary malignancy underwent hepatectomy. Ninety-two patients received extended right-sided hepatic resection, of whom 15 (16.3%) received preoperative PVE (PVE group). The remaining 77 patients underwent resection without prior PVE (non-PVE group). One patient who had HCC, and in whom preoperative PVE was performed, was excluded from the present analysis. Hepatic resection was not performed because of inadequate hypertrophy of the remnant liver, thought to be related to underlying liver cirrhosis. The clinical parameters of both groups of patients are listed in Table 1. The median age of the patients in the PVE group was 69 years, significantly higher than that of the non-PVE group (55 years, P=0.009). They also had significantly worse preoperative renal (median serum creatinine, 96 μmol/L vs 86 μmol/L; P=0.039), and liver functions in terms of higher serum alanine aminotransferase and total bilirubin levels. In addition, there were significantly more Child-Pugh's grade[15] B patients in the PVE group than in the non-PVE group (P<0.001) [Table 1]. These 10 patients were considered suitable for major hepatic resection because indocyanine green retention at 15 minutes was smaller than 16%.[1] The pathologies of both groups of patients are listed in Table 2.

Table 3. Clinical details of 15 patients who underwent portal vein embolisation (PVE)*

Clinical details	Value
Types of procedure (No. of patients)	
Open (through ileocolic vein)	6 (40%)
Percutaneous ipsilateral approach	9 (60%)
Time interval between PVE and hepatic resection (days)	37 (32-61)
Future liver remnant before PVE (mL)	411 (360-494)
Future liver remnant after PVE (mL)	540 (456-588)
Hypertrophy ratio	1.26 (1.21-1.36)
Standard total liver volume (STLV) [mL]	1172 (1110-1258)
Increase in future liver remnant after PVE/STLV (%)	9 (7-13)

* Values are expressed as median (interquartile range), unless otherwise stated

Table 4. Extent of hepatic resection in patients with preoperative portal vein embolisation (PVE group) and those without (non-PVE group)*

Hepatic resection	PVE group, n=15	Non-PVE group, n=77
Right hepatectomy+caudate lobectomy	4 (27%)	5 (7%)
Right hepatectomy with extension to segment 4	3 (20%)	33 (43%)
Right hepatectomy with extension to segment 4+ caudate lobectomy	0	6 (8%)
Right trisectionectomy	2 (13%)	22 (27%)
Right trisectionectomy+ caudate lobectomy	6 (40%)	11 (14%)
Concomitant hepaticojejunostomy	11 (73%)	8 (10%)

* The nomenclature of types of hepatic resection was based on the Brisbane 2000 terminology of liver anatomy and resections[12]

Table 5. Intra-operative and postoperative data of patients with preoperative portal vein embolisation (PVE group) and those without (non-PVE group)*

Intra-operative and postoperative data	PVE group, n=15	Non-PVE group, n=77	P value
Intra-operative blood loss (L)	1.43 (1.09-1.80)	1.40 (0.65-2.00)	0.866
Intra-operative blood transfusion (L)	0	0 (0-0.3)	0.344
No. of patients without blood transfusion	12 (80%)	53 (69%)	0.539
Operating time (min)	660 (495-720)	420 (360-555)	<0.001
Indocyanine green retention at 15 min on postoperative day 7 (%)	21.8 (12.0-39.3)	23.9 (11.7-31.2)	0.693
Postoperative stay in intensive care unit (days)	3 (2-4)	1 (1-3)	0.019
Postoperative hospital stay (days)	14 (11-21)	10 (7-14)	0.005
Operative morbidity	3 (20%)	23 (30%)	0.543
Hospital mortality	0	5 (6.5%)	0.587

* Values are expressed as median (interquartile range), unless otherwise stated

Nine patients received preoperative PVE via a percutaneous transhepatic ipsilateral approach. The remaining six underwent diagnostic laparoscopy, laparoscopic ultrasonography, and mini-laparotomy with a short lower right paramedian incision. Portal vein embolisation was performed with the open method through cannulation of the ileocolic vein. No complications related to PVE occurred, except for one patient who developed segmental cholangitis after the procedure, resulting in a procedure-related morbidity rate of 6.7%. The complication was probably related to inadvertent puncture and injection of contrast to a segmental bile duct obstructed by hilar cholangiocarcinoma during percutaneous PVE. The attack of cholangitis subsided after a few days following treatment with a broad-spectrum antibiotic.

Among the 15 patients in the PVE group, preoperative PVE achieved a median hypertrophy ratio of 1.26 (range, 1.21-1.36) of the FLR. The percentage increase in FLR relative to the STLV was 9% (range, 7-13%) [Table 3].

The extent of hepatic resection in both groups of patients is listed in Table 4.[12] Ten (67%) patients in the PVE group and 22 (29%) patients in the non-PVE group underwent caudate lobectomy (P=0.005). In addition, 11 (73%) patients in the PVE group underwent concomitant hepaticojejunostomy: this was significantly more than that in the non-PVE group (10%, P<0.001). The operating time of the patients in the PVE group was significantly longer, but the intra-operative blood loss was comparable (Table 5).

Sixty-five (70.7%) patients, including 12 patients in the PVE group and 53 patients in the non-PVE group, did not require blood transfusion. The median postoperative intensive care unit and hospital stay of the patients in the PVE group was 3 days and 14 days, respectively, and was significantly longer than that of the non-PVE group (1 day, P=0.019; 10 days, P=0.005, respectively). The operative morbidity rate was 20% in the PVE group, and 30% in the non-PVE group (P=0.543). There was no hospital mortality in the PVE group, whereas five (6.5%) patients in the non-PVE group died after hepatic resection (P=0.587). The causes of hospital mortality were liver failure (n=3), chest infection (n=1), and intra-abdominal sepsis (n=1).

Discussion

Preoperative PVE has been advocated for patients who require major hepatic resection. However, previous studies[16,17] have focused on the technical aspects such as volume increase, liver function after PVE, and PVE-related complications. Few report on its benefits in terms of better operative outcomes compared with a control group. Azoulay et al[18] and Shimamura et al[19] reported comparable complication rates in HCC patients who received PVE compared with a control group. Hemming et al[4] reviewed 52 patients, of whom 39 had preoperative PVE, and found a lower incidence of liver failure in the PVE group. In a prospective non-randomised trial, Farges et al[8] found significantly fewer complications in patients with cirrhosis who underwent PVE and right hepatectomy compared with those who did not undergo PVE. The present study evaluated the influence of PVE on the early postoperative outcome for patients who underwent extended right-sided hepatic resection. There was no hospital mortality in the PVE group, and the hospital morbidity rate was numerically lower but not statistically different from that of the non-PVE group, despite the fact that the former belonged to an older age-group, had significantly worse preoperative liver and renal functions, and underwent more complicated surgery.

There are two major techniques to access the portal vein for embolisation: direct cannulation of the ileocolic vein and the percutaneous transhepatic approach. The former requires a laparotomy under general anaesthesia in which the ileocolic vein is cannulated.[6] Tumour extent and liver status can be assessed during the laparotomy with or without prior laparoscopy. Although the open approach for PVE may have the disadvantage of requiring a general anaesthesia and a theoretically higher risk of postoperative complications, we elected to use an open approach for PVE via the ileocolic vein in patients with bulky liver tumours including those with HCC. By avoiding percutaneous puncture of the liver, the risk of inadvertently puncturing the tumour leading to tumour rupture or tumour seeding, and spread of tumour cells through the portal or systemic circulations could be avoided. In addition, a diagnostic laparoscopy and laparoscopic ultrasonography performed during the same anaesthesia may provide accurate staging of the disease and prevent unnecessary PVE and laparotomy in patients with unresectable disease.[20] In patients with less bulky tumours, and in whom direct puncture of the portal venous system was considered feasible on preoperative CT scan, we adopted the percutaneous ipsilateral approach.[9] It has the advantages of direct access to the portal branches and a minimal risk of portal vein thrombosis and inadvertent vascular injury to the FLR. We did not use a contralateral percutaneous approach in any of the patients in the present series, as this technique may lead to vascular injury of the FLR, and bleeding will not be controlled by PVE of the contralateral side as opposed to the ipsilateral approach.

There has been a wide range of preference in the use of embolic materials for preoperative PVE, including cyanoacrylate and ethiodised oil, Gelfoam (Upjohn, Kalamazoo[MI], US) and thrombin, fibrin glue, metallic coils, polyvinyl alcohol, and absolute alcohol. Cyanoacrylate has been recommended as the best substance for PVE as it leads to fast and reliable hypertrophy of the FLR.[21] However, it may cause a severe inflammatory reaction with peribiliary fibrosis and casting of the portal vein, leading to increased operative difficulty. Nagino et al[22] advocated the use of fibrin glue for PVE. Although the recanalisation rate may be higher, fibrin glue appeared to be safe and effective without the complication of extensive inflammatory fibrosis. Following the experience of Nagoya,[23] fibrin glue was used for PVE in all patients in the present study. The extent of hypertrophy of FLR of our patients fell within a range comparable with that reported by others.[8,16] In addition, none of the patients in the PVE group developed liver failure or had hospital mortality, suggesting that the rate of hypertrophy achieved as a result of PVE was sufficient for the patients to undergo extended hepatic resection. It has been suggested that PVE may result in a more difficult resection.[4] It is possible that the use of fibrin glue as embolic material in this series meant that we experienced no increased

difficulty in both hilar dissection or parenchymal transection in patients who had preoperative PVE compared with those without the procedure.

An interesting finding was the satisfactory increase in the size of FLR after preoperative PVE, although the median age of PVE group was 69 years. This suggests that PVE is effective in inducing hypertrophy of FLR in elderly patients. Since elderly patients may have reduced functional reserves of the cardiovascular system, respiratory system, or kidney that may result in increased risks of morbidity and mortality after major hepatic resection, preoperative PVE may be particularly useful by providing adequate liver reserve compared with the younger patients.

Although PVE appears to be a safe and effective procedure with no mortality or major morbidity reported in the literature, complications including recanalisation of the portal vein,[24] haemobilia,[25] and small bowel obstruction[17] have been encountered. In the limited experience of this study, only one patient developed a procedure-related complication of segmental cholangitis. There is a theoretical risk of promoting tumour growth by PVE especially in patients with colorectal liver metastases.[26,27] Nonetheless, subsequent studies[28,29] have shown an equivalent survival between standard resection patients and patients who undergo preoperative PVE. There is no evidence to suggest that PVE can induce tumour growth in patients with HCC and other hepatobiliary malignancies including cholangiocarcinoma, and we experienced no accelerated tumour growth after PVE in this study. Regrettably this study could not identify the group of patients who would benefit most from PVE. The evidence that supports the use of preoperative PVE can only be derived from prospective comparison series and inference from PVE series with previously reported studies that describe the results of hepatic resection without PVE. Future prospective randomised studies should be conducted to verify the benefits and efficacy of preoperative PVE in patients with hepatobiliary malignancy and to better identify patients who will benefit from the procedure. Other limitations of the present study included the presence of heterogeneous hepatobiliary malignancies and a relatively small number of patients in the study group. Nevertheless, this study represented the initial local experience of the procedure. With improved understanding of the technique and indications for the procedure, the number of patients undergoing preoperative PVE for various indications has increased in recent years. In future, prospective evaluation of a specific group of patients including patients with HCC will be performed.

Conclusions

Preoperative PVE increases the possibility to perform extended right-sided hepatic resection for hepatobiliary malignancy in older patients with worse renal and hepatic functions, without increasing operative blood loss, morbidity, or mortality. Portal vein embolisation is a useful technique to extend the limits of hepatic resection. Future studies, possibly randomised controlled trials, should further define its precise indication.

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