Original article

# Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma

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**Background:** Selective transarterial chemoembolization (TACE) and portal vein embolization (PVE) could improve the rate of hypertrophy of the future liver remnant (FLR) in patients with chronic liver disease. This study evaluated the feasibility and efficacy of this combined procedure.

**Methods:** Between November 1998 and October 2004, 36 patients with cirrhosis and hepatocellular carcinoma underwent right hepatectomy after PVE. Additional TACE preceded PVE by 3–4 weeks in 18 patients (TACE + PVE group) and the remaining 18 patients had PVE alone (PVE group).

**Results:** PVE was well tolerated in all patients. The mean increase in percentage FLR volume was significantly higher in the TACE + PVE group than in the PVE group (mean(s.d.) 12(5) *versus* 8(4) per cent; $P = 0{\cdot}022$). The rate of hypertrophy was more than 10 per cent in 12 patients in the TACE + PVE group and in five who had PVE alone ($P = 0{\cdot}044$). Duration of surgery, blood loss, incidence of liver failure and mortality (two patients in each group) were similar in the two groups. None of the 17 patients with an increase in FLR volume of more than 10 per cent died, whereas there were four deaths among 19 patients with a smaller increase. The incidence of complete tumour necrosis was significantly higher in the TACE + PVE group (15 of 18 *versus* one of 18; $P < 0{\cdot}001$), with a higher 5-year disease-free survival rate (37 *versus* 19 per cent; $P = 0{\cdot}041$).

**Conclusion:** Sequential TACE and PVE before operation increases the rate of hypertrophy of the FLR and leads to a high rate of complete tumour necrosis associated with longer recurrence-free survival.

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## Introduction

Preoperative portal vein embolization (PVE) before scheduled liver resection has been proposed to induce contralateral compensatory hypertrophy of the future liver remnant (FLR), thus preventing postoperative liver failure, especially for major liver resection requiring the removal of a large quantity of functional liver parenchyma[1–13]. It was reported previously that hypertrophy of the FLR significantly decreased the rate of postoperative complications in patients with chronic liver disease[14]. Although hypertrophy of the FLR occurs reproducibly after PVE in patients with a normal liver, the degree of hypertrophy is variable in those with chronic liver disease[14–21]. This is the main limitation to the use of PVE before major hepatectomy in patients with chronic liver disease[14–21].

It has been suggested that preoperative sequential selective transcatheter arterial chemoembolization (TACE) and PVE could increase the rate of hypertrophy, mainly by decreasing the arterial flow in the embolized liver, suppression of arterioportal shunts and increasing parenchymal damage in the embolized liver[20,22]. In addition, it has been shown that TACE combined with PVE has a strong anticancer effect in patients with hepatocellular carcinoma (HCC)[20,22–25]. A theoretical drawback of this strategy is the risk of liver parenchymal necrosis induced by double occlusion of blood supply[23,24]. An interval of several days to weeks between the two procedures has been suggested to reduce this risk[20,22]. However, the feasibility and impact of this combined strategy, and the appropriate interval between embolizations, on hypertrophy of the

FLR and postoperative outcome are unknown in the setting of cirrhosis.

The aim of this study was to investigate the tolerance and efficacy of preoperative sequential TACE and PVE before right hepatectomy in patients with cirrhosis and HCC, and to compare perioperative outcome with that of a matched group of patients undergoing PVE alone.

## Patients and methods

The outcome of 18 patients with chronic liver disease and HCC who underwent right hepatectomy (removal of Couinaud segments V–VIII) after TACE followed by PVE between November 1998 and October 2004 was compared with that of 18 consecutive patients who underwent PVE alone before right hepatectomy. Eleven of these patients were included in previous prospective study on PVE[14]. In patients with HCC requiring right hepatectomy, biopsy of the non-tumorous liver was performed routinely to assess the presence or absence of chronic liver disease. The status of the non-tumorous liver parenchyma was defined according to the classification of Knodell *et al.*[26]. Patients with a fibrosis score of F3 (extensive fibrosis) or F4 (cirrhosis), in the absence of impaired preoperative liver function (Child–Pugh grade A), were suitable for PVE before right hepatectomy. Only patients who had a fibrosis score of F3 (14 patients) or F4 (22 patients) were included in the study.

### Selective transarterial chemoembolization

Transarterial chemoembolization was performed before PVE. Conventional mesenteric arteriography was performed to check the hepatic arterial anatomy and to outline the portal circulation in the venous-phase films. After the assessment, the tip of the catheter was placed selectively in the right hepatic artery. A mixture of 10–15 ml iodinized oil (Lipiodol Ultrafluid®; Guerbet Laboratories, Paris, France) and 40–60 mg doxorubicin was injected under fluoroscopic control, followed by embolization with gelatin-sponge particles (Gelfoam; Upjohn Laboratories, Kalamazoo, Michigan, USA)[27].

### Volumetric assessment

All patients underwent volumetric helical computed tomographic estimation of liver volume before PVE and before surgery[14]. The interval between preoperative volumetry and surgery was 6–8 days. Measurements were performed for the whole liver as well as for the right and left parts, using the middle hepatic vein, identified by intravenous bolus injection of contrast, and the gallbladder as landmarks. The FLR volume was defined as the volume of the left liver (segments I–IV). The estimated percentage FLR volume was calculated as (left liver volume × 100)/total liver volume.

### Right portal vein embolization

PVE was carried out at least 3 weeks after TACE (mean interval 3·6 weeks). Right PVE was performed using the contralateral transhepatic approach as described in detail previously[14]. In brief, the left portal branch was punctured under light general anaesthesia and ultrasonographic guidance. Following venous portography, the right anterior and posterior portal branches were embolized with a mixture of cyanoacrylate (Histoacryl®; B. Braun, Melsungen, Germany) and iodinized oil (Lipiodol Ultrafluid®).

### Follow-up after portal vein embolization

Liver function tests including prothrombin time and serum levels of total bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were performed before PVE, daily until discharge thereafter, and before surgery. Volumetric assessment was performed before PVE and before surgery. The increase in percentage FLR volume after PVE was calculated as the percentage FLR volume measured after PVE subtracted from the value measured before PVE. The response was classified as good if the increase in percentage FLR volume was greater than 10 per cent, mild if 5–10 per cent and poor if less than 5 per cent.

### Right hepatectomy

Right hepatectomy was performed 4–8 weeks after PVE. All patients underwent liver resection by one of two senior liver surgeons, using a standardized technique for right hepatectomy[14]. Parenchymal transection was performed by either the clamp-crush technique or with an ultrasound aspiration dissector (Dissectron™; Satelec Medical, Merignac, France), with intermittent clamping of the hepatic pedicle[28]. Patients were routinely transferred to the intensive care unit and returned to the wards at the discretion of the intensive care consultant.

After right hepatectomy, the resected specimens were examined pathologically, paying attention to the extent of necrosis of HCC. Tumour necrosis was defined as complete if no viable cells were observed in any nodule.

### Definition of postoperative complications

Liver failure was defined by a prothrombin time of less than 50 per cent (of normal) and serum bilirubin level greater than 50 μmol/l on postoperative day 5[29]. Postoperative pulmonary complications included all clinically symptomatic pleural effusions, atelectasis and infections. Other complications included intra-abdominal haemorrhage requiring reoperation, biliary fistula, significant ascites (abdominal drain output more than 500 ml/day on or after postoperative day 5) and renal insufficiency (serum creatinine level greater than 150 μmol/l).

### Statistical analysis

Data are expressed as mean(s.d.). Statistical analysis was performed using Medcalc® version 7.3 (Frank Schoonjans, Broekstraat, Belgium). Comparison of liver function tests was performed using Student's *t* test. Qualitative variables were compared with Fisher's exact test. Survival rates were calculated using the Kaplan–Meier method, and groups were compared with the log rank test. $P < 0{\cdot}050$ was considered significant.

## Results

The two groups were comparable with respect to age, sex, tumour size, histological and functional liver status, and liver volume (*Table 1*).

### Liver function after portal vein embolization

Right PVE was feasible in all patients and they were discharged after 2–7 days with no complications. Results of liver function tests after PVE and before surgery in patients who had TACE plus PVE and those who had PVE alone are shown in *Fig. 1*. After PVE, minimum prothrombin time (*Fig. 1d*) and peak serum total bilirubin (*Fig. 1c*) were similar in the two groups, but peak levels of AST and ALT were significantly higher in the TACE + PVE group ($P = 0{\cdot}026$ and $P = 0{\cdot}031$ respectively) (*Fig. 1a,b*). Before surgery, liver function test results were comparable to those before PVE in both groups.

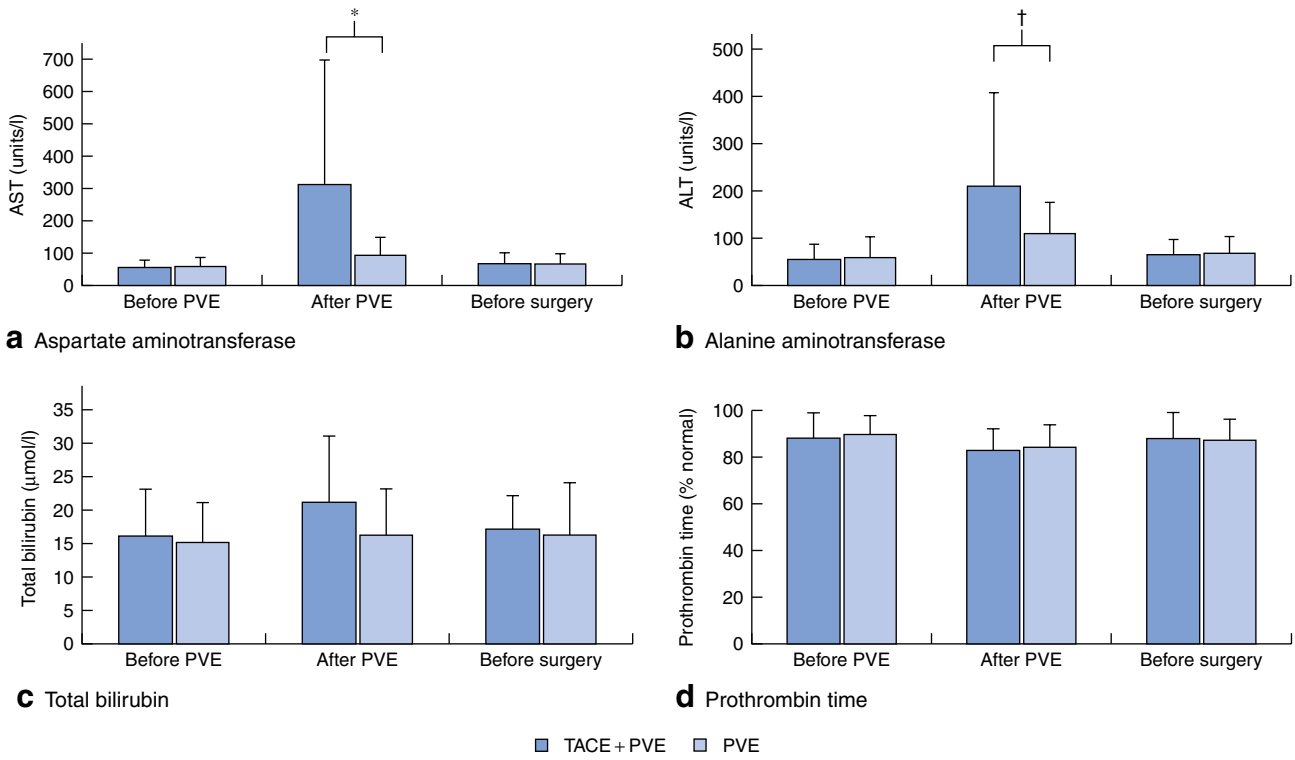


**Fig. 1** Results of liver function tests before portal vein embolization (PVE), after PVE and before surgery in patients who had transarterial chemoembolization (TACE) plus PVE or PVE alone. Values are mean(s.d.). Peak values of **a** aspartate aminotransferase (AST), **b** alanine aminotransferase (ALT) and **c** total bilirubin, and **d** minimum value of prothrombin time were assessed before PVE, within 5 days after PVE and within 5 days before surgery. *$P = 0{\cdot}026$, †$P = 0{\cdot}031$ (Student's *t* test)

**Table 1** Patient characteristics

| | TACE + PVE ($n = 18$) | PVE ($n = 18$) | $P$ |
|---|---|---|---|
| Men | 14 | 13 | 1·000‡ |
| Age (years)* | 64(7) | 63(9) | 0·738§ |
| Hepatocellular carcinoma | 18 | 18 | 1·000‡ |
| Aetiology of chronic liver disease | 14 | 13 | 1·000‡ |
| Hepatitis B virus | 4 | 6 | |
| Hepatitis C virus | 11 | 8 | |
| Fibrosis score 4 | 11 | 11 | 1·000‡ |
| Tumour diameter (cm)* | 7(3) | 7(2) | 0·662§ |
| Total bilirubin (μmol/l)* | 16(7) | 15(6) | 0·671§ |
| Prothrombin time (% normal)* | 88(12) | 89(13) | 0·612§ |
| Aspartate aminotransferase (units/l)* | 54(22) | 54(30) | 0·523§ |
| Alkaline phosphatase (units/l)* | 133(52) | 121(64) | 0·331§ |
| GGT (units/l)* | 161(86) | 170(192) | 0·415§ |
| Liver volume (ml)* | 1782(567) | 1612(401) | 0·488§ |
| FLR (ml)* | 521(172) | 474(169) | 0·446§ |
| %FLR volume (range)† | 30(6) (21–43) | 29(5) (23–40) | 0·606§ |

*Values are mean(s.d.); †values are mean(s.d.) (range). TACE, transarterial chemoembolization; PVE, portal vein embolization; GGT, γ-glutamyltransferase; FLR, future remnant liver volume corresponding to the left liver volume (Couinaud segments I–IV); %FLR volume, estimated percentage remnant liver volume = (left liver volume ×100)/total liver volume. ‡Fisher's exact test; §Student's *t* test.

## Volumetry after portal vein embolization

The mean interval between PVE and right hepatectomy was similar in the TACE + PVE and PVE groups (5·3 and 5·7 weeks respectively; range 4–8 weeks). The mean interval between volumetry before and after PVE was also similar (4·8 *versus* 5·2 weeks; range 4–8 weeks). Before PVE, the FLR was similar in the two groups, but after PVE it was significantly higher in the TACE + PVE group ($P = 0·013$) (*Fig. 2*). In the TACE + PVE group, the mean increase in percentage FLR was significantly higher than that in the PVE group (12(5) *versus* 8(4) per cent; $P = 0·022$). Overall, the increase in percentage FLR volume was greater than 10 per cent in 17 patients, 5–10 per cent in 15 patients and less than 5 per cent in four patients. Twelve of the 18 patients in the TACE + PVE group had an increase of more than 10 per cent compared with five of 18 in the PVE group ($P = 0·044$). Among the 22 patients with F4 fibrosis, only six had an increase of more than 10 per cent and all were in the TACE + PVE group.

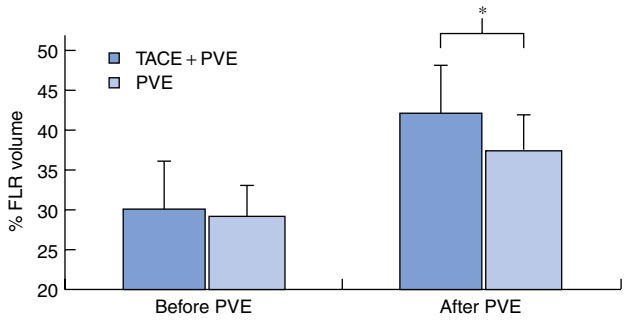


**Fig. 2** Change in percentage future liver remnant (FLR) volume in the transarterial chemoembolization (TACE) plus portal vein embolization (PVE) and PVE alone groups. Values are mean(s.d.). *$P = 0·013$ (Student's *t* test)

## Intraoperative and postoperative course after right hepatectomy

No specific intraoperative difficulties were encountered after TACE and PVE. The duration of surgery, number of patients who required blood transfusion and the amount of blood transfused were comparable in the two groups (*Table 2*), and the incidence of postoperative liver failure and postoperative mortality were similar. Seven patients in the TACE + PVE group had 13 complications, and ten patients in the PVE group had 18 complications. Mean hospital and intensive care unit stays were similar. Results of postoperative liver function tests were almost identical.

There was a clear relationship between the increase in percentage FLR volume and postoperative risk. The overall morbidity rate was 18 per cent (three of 17), 67 per cent (ten of 15) and 100 per cent (four of four) in groups with a good, mild and poor response, respectively. Of those with F3 fibrosis, only one patient with a good or mild response experienced a complication (8 per cent, one of 12), whereas both patients with a poor response had complications. In patients with F4 fibrosis, the morbidity rate was 33 per cent (two of six), 71 per cent (ten of 14) and 100 per cent (two of two) in good, mild and poor response groups, respectively.

The overall mortality rate among good, mild and poor responders was 0 per cent (0 of 17), 13 per cent (two of 15) and 50 per cent (two of four). None of the patients with F3 fibrosis died, whereas mortality rates in those with F4 fibrosis were 0 per cent (none of six), 14 per cent (two of 14) and 100 per cent (two of two) in good, mild and poor response groups.

Examination of the resected specimens showed that complete necrosis of the tumour induced by TACE combined with PVE occurred in 15 of 18 patients, compared with one of 18 patients following PVE alone ($P < 0·001$).

**Table 2** Perioperative results and postoperative complications in patients undergoing right hepatectomy

| | TACE + PVE ($n = 18$) | PVE ($n = 18$) | $P$ |
|---|---|---|---|
| Perioperative data | | | |
| Duration of surgery (min)* | 296(45) | 310(72) | 0·562¶ |
| Blood transfusion | 2 | 3 | 1·000# |
| Units of blood transfused* | 2·0(1·0) | 3·3(0·6) | 0·148¶ |
| Postoperative complications | | | |
| No. with complications | 7 | 10 | 0·731# |
| Liver failure† | 2 | 3 | 1·000# |
| Intra-abdominal bleeding | 1 | 1 | 1·000# |
| Pulmonary | 2 | 3 | 1·000# |
| Biliary fistula | 0 | 0 | 1·000# |
| Significant ascites‡ | 7 | 9 | 0·738# |
| Renal failure§ | 0 | 1 | 1·000# |
| Portal thrombosis | 1 | 1 | 1·000# |
| In-hospital death | 2 | 2 | 1·000# |
| Stay in intensive care (days)* | 6(3) | 7(3) | 0·334¶ |
| In-hospital stay (days)* | 16(6) | 15(7) | 0·265¶ |

*Values are mean(s.d.). †Prothrombin time less than 50 per cent and serum bilirubin level above 50 μmol/l on postoperative day 5. ‡Abdominal drain output greater than 500 ml/day on or after postoperative day 5. §Serum creatinine level greater than 150 μmol/l. TACE, transarterial chemoembolization; PVE, portal vein embolization. ¶Student's *t* test; #Fisher's exact test.

## Overall and recurrence-free survival rates

Overall survival rates in the TACE + PVE group were 83, 54 and 43 per cent at 1, 3 and 5 years respectively, and were not significantly different from rates of 72, 31 and 31 per cent in the PVE group ($P = 0·275$). However, 1-, 3- and 5-year recurrence-free survival rates were higher in the TACE + PVE group than in the PVE group (93, 37 and 37 *versus* 63, 19 and 19 per cent; $P = 0·041$) (*Fig. 3*).

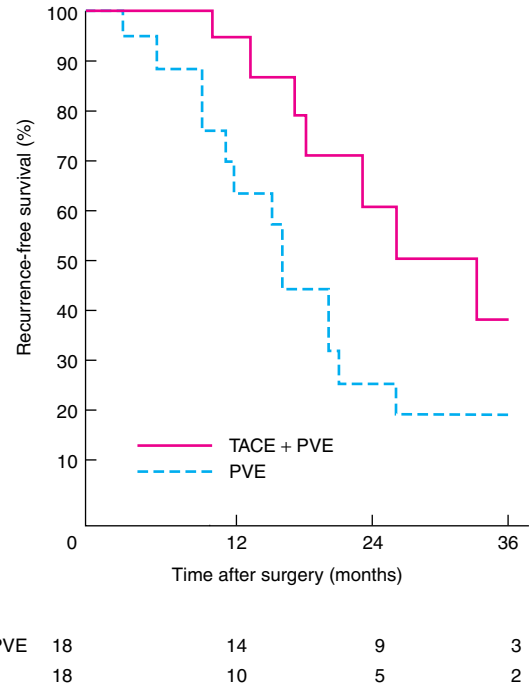


**Fig. 3** Recurrence-free survival after right hepatectomy in patients with cirrhosis and hepatocellular carcinoma who underwent transarterial chemoembolization (TACE) plus portal vein embolization (PVE) or PVE alone. $P = 0·041$ (log rank test)

## Discussion

Despite improvements in preoperative assessment and intraoperative techniques in liver resection over the past 10 years, major liver resection in diseased liver is still considered a risky procedure[13,29–33]. Preoperative PVE in patients with chronic liver disease has broadened the indications for and safety of major hepatectomy[14–21], although the degree of liver hypertrophy induced by PVE is variable and an insufficient hypertrophy is associated with postoperative death after major hepatectomy[14–21]. Certain Japanese groups have suggested that additional TACE before PVE might improve the rate of hypertrophy of the FLR in patients with chronic liver disease[20,22–24] and, on the basis of these reports, the authors have started to use sequential TACE and PVE before right hepatectomy in patients with cirrhosis and HCC.

After PVE, changes in liver function are generally minor and transient in both normal and chronic liver disease[4,10,14,16,18,21]. In the present study, although none of the patients had complications, a greater increase in aminotransferase levels was noted in patients who underwent PVE after TACE[20,22]. This might be attributed to the presence of parenchymal damage induced by TACE in embolized liver. However, the mean peak aminotransferase level in this study was less than half that of values reported previously[20,22]. The lower level in this series might be explained by the longer interval between TACE and PVE, which was a minimum of 3 weeks, compared with only 7 days in a study by Aoki *et al.*[22]. A shorter interval between TACE and PVE results in more damage to embolized liver, and therefore carries a greater risk, especially in patients with cirrhosis. In the present study cyanoacrylate was used for PVE, whereas Yamakado *et al.*[20,24,25] used absolute ethanol as embolic material for PVE after TACE, which has a stronger coagulation effect with a better hypertrophy rate. However, ethanol causes more parenchymal necrosis. Considering the balance of risk and benefit, the authors believe that there should be a minimum interval of 3 weeks between embolizations and that use of appropriate embolic material such as

cyanoacrylate or microparticles for PVE is mandatory in the setting of cirrhosis.

The present study confirmed that the increased damage in embolized liver induced by the combined approach also affects the tumour tissue[20,22–25]. Sequential TACE and PVE achieved complete tumour necrosis in more than 80 per cent of patients, compared with only 5 per cent after PVE alone. TACE alone induces complete tumour necrosis in around 50 per cent of patients[34–41]. There are several reasons for the high rate of necrosis in the present study. First, arterioportal shunts frequently observed in HCC are embolized by double occlusion[23,24]. Second, although most HCCs are hypervascular with predominantly arterial flow, TACE probably induces a compensatory increase in portal flow to these tumours. Additional occlusion of portal flow by PVE leads to profound tumour necrosis[23,24]. These results provide a rationale for use of TACE before PVE in patients with HCC. As the combined treatment is associated with a high rate of complete tumour necrosis, this itself could be considered as an appropriate treatment for patients in whom surgery is contraindicated because the degree of hypertrophy is poor[25].

The rate of early recurrence, which is generally correlated with incomplete tumour excision or multiple tumour cell dissemination within or beyond the liver during surgical manipulation[42,43], is lower after anatomical than non-anatomical resection[44]. Right hepatectomy represents a perfect model of anatomical resection and was used in all patients in this study. The survival curves demonstrated the beneficial effect of TACE combined with PVE, especially during the first postoperative year, suggesting a positive effect against early recurrence. As the rate of tumour necrosis was higher with the combined treatment, there was probably less tumour cell dissemination during surgery. Late recurrence, which has a different pathogenesis, probably related to unarrested carcinogenesis in the cirrhotic parenchyma and development of multifocal tumours[45,46], was not affected by these preoperative radiological procedures.

Sequential TACE and PVE was more efficient than PVE alone in increasing the FLR volume in patients with chronic liver disease. Possible reasons for the enhancement of hypertrophy with the combined approach are that TACE may diminish a compensatory increase in arterial flow in embolized liver induced by PVE[47,48], it may suppress arterioportal shunts frequently observed in cirrhotic liver[20,22], and it may induce severe damage in the embolized liver, which may stimulate hypertrophy in the FLR[49,50]. Such damage to the embolized liver could induce atrophy resulting in increased FLR volume[20,22]. The 42 per cent FLR volume after sequential TACE and PVE was lower than the 51 per cent reported by the Tokyo group[22], probably because the present study included a higher proportion of patients with F4 fibrosis (22 of 36 *versus* 12 per cent in Aoki's series).

In this study, postoperative risks were clearly related to the increase in percentage FLR volume; all postoperative deaths and severe complications affected patients with F4 fibrosis and an increase in percentage FLR volume less than 10 per cent. Twelve of 14 patients with F3 fibrosis had a hypertrophy rate greater than 5 per cent; none died and only one had major complications. Based on these observations, the authors propose that a minimum increase of 5 per cent of the FLR in patients with F3 fibrosis and a minimum increase of 10 per cent in those with F4 fibrosis is essential if right hepatectomy is to be performed with no risk of death and acceptable morbidity in patients with cirrhosis. Applying these criteria to the present study, 12 of 14 patients with F3 and six of 22 with F4 fibrosis would have undergone resection with no deaths and minimal morbidity (three of 18). Thus, preoperative assessment of the increase in FLR volume appears to be an accurate predictor of postoperative risk and could be used to select patients with cirrhosis who would benefit from major hepatectomy for HCC.

This study has confirmed that a small preoperative increase in FLR volume after PVE predicts a poor outcome after major hepatectomy in patients with cirrhosis. Sequential TACE and PVE effectively increases the FLR, and application of this strategy should broaden the indication for major resection of cirrhotic liver. The combined procedure also induces a high rate of complete tumour necrosis which is associated with an improvement in recurrence-free survival.

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