Original article

Preoperative portal vein embolization improves prognosis after right hepatectomy for hepatocellular carcinoma in patients with impaired hepatic function

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Background: Percutaneous transhepatic portal vein embolization (PTPE) increases the safety of subsequent major hepatectomy. The aim of this study was to determine the effect of PTPE on long-term prognosis after hepatectomy in patients with hepatocellular carcinoma (HCC).

Methods: Seventy-one patients with HCC underwent right hepatectomy between 1984 and 1998. Preoperative PTPE was performed in 33 patients (group 1) and was not used in 38 patients (group 2). Outcome after operation was compared between the groups. The patients were further divided according to the median tumour diameter (cut-off 6 cm) and indocyanine green retention rate at 15 min ($ICGR_{15}$) (cut-off 13 per cent).

Results: The cumulative survival rate was significantly higher in group 1 than in group 2 in patients with an $ICGR_{15}$ of at least 13 per cent. Tumour-free survival rates were similar in both groups. Of patients with tumour recurrence after right hepatectomy, those in group 1 were more frequently subjected to further treatment.

Conclusion: Preoperative PTPE improves the prognosis after right hepatectomy for HCC in patients with impaired hepatic function, although it does not prevent tumour recurrence.

Paper accepted 4 January 2000 British Journal of Surgery 2000, **87**, 879–882

Introduction

A variety of therapeutic techniques has recently become available for the treatment of hepatocellular carcinoma (HCC)[1]. Percutaneous transhepatic portal vein embolization (PTPE) was developed to increase the safety of subsequent hepatectomy, to prevent transportal metastasis, and to increase the anticancer effect of transcatheter arterial embolization[2]. PTPE has been shown to produce atrophy of the embolized liver and compensatory hypertrophy of the non-embolized liver, even in patients with impaired hepatic function[3–5]. This increases the safety of subsequent hepatectomy[6,7]. PTPE has also been proposed as a treatment for irresectable HCC[8]. The purpose of this study was to investigate the effects of preoperative PTPE on the long-term prognosis and tumour recurrence rates after hepatectomy for HCC.

Patients and methods

The outcome was studied retrospectively in 71 patients with HCC who underwent right hepatectomy with or without preoperative PTPE between 1984 and 1998. There were 66 men and five women, with a median age of 58 years. The median tumour diameter was 6·0 cm. The median indocyanine green retention rate at 15 min ($ICGR_{15}$) was 13 per cent. Tumour extension, hepatic function and hepatitis viral infection were used to determine the necessity and desirability of right hepatectomy. Written informed consent was obtained from each patient.

Group 1 consisted of 33 patients who underwent PTPE before right hepatectomy. Group 2 comprised 38 patients who underwent hepatectomy without PTPE. In the early period of the study an attempt was made to allocate all candidates for right hepatectomy at random to the two groups. However, since the late 1980s, in the light of previous results[2,9], the indication for right hepatectomy with preoperative PTPE was extended to patients with relatively impaired hepatic function.

PTPE was performed according to previously reported methods[2]. After portography, a 5·5-Fr double-lumen balloon catheter (Herstellung und Vertrieb Medizinischer Produkte, Hamburg, Germany) was introduced under fluoroscopic control into the right portal vein through a

catheter introducer (Cook Group, Bloomington, Indiana, USA). A mixture of fibrin glue (Beriplast P; Hoechst, Tokyo, Japan) and iodized oil (Lipiodol; Kodama Pharmaceutical, Tokyo, Japan) was then injected through the catheter. All patients tolerated PTPE without major complications, although transient increases in serum transaminase concentration and white blood cell count were noted.

Following PTPE the median value of the proportional volume of the right lobe was reduced from 63 to 51 per cent by 2 weeks. Right hepatectomy was performed after a median interval of 21 days. During operation, ligation of the right portal vein preceded mobilization of the right liver.

The main tumour was significantly larger in patients in group 2 (*Table 1*). The $ICGR_{15}$, alanine aminotransferase (ALAT) concentration and histological stage of fibrosis indicated significantly more advanced disease in group 1. To minimize the influence of these differences in patient background, the patients were divided into subgroups according to tumour diameter (cut-off 6·0 cm) and $ICGR_{15}$ (cut-off 13 per cent).

The results were expressed as medians with tenth and 90th centiles. Differences in the background factors between the two groups were analysed with the Mann–Whitney *U* test or Fisher's exact test. Cumulative survival rates and tumour-free survival curves were calculated using the Kaplan–Meier method. To confirm the importance of PTPE on the prognosis, Cox stepwise multiregression analysis was performed using clinical factors such as patient age, tumour size, portal venous tumour thrombus, intrahepatic metastasis, $ICGR_{15}$, ALAT concentration and preoperative PTPE. Differences in survival rates were evaluated with the log rank test. $P < 0{\cdot}05$ (two-tailed) was considered significant.

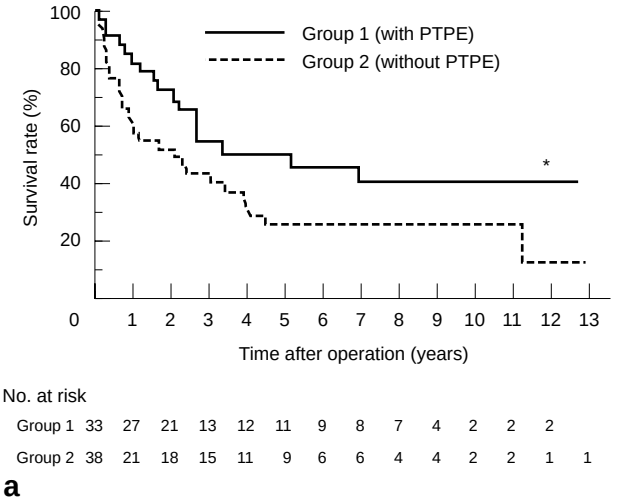
Table 1 Details of patients who underwent right hepatectomy with (group 1) or without (group 2) preoperative percutaneous transhepatic portal vein embolization

	Group 1 ($n = 33$)	Group 2 ($n = 38$)	*P*
Median age (years)	58 (44–68)	58 (38–68)	0·95*
Sex ratio (M : F)	32 : 1	34 : 4	0·36†
Tumour factors			
Diameter of main tumour (cm)	5 (2–10)	10 (2–17)	0·003*
Portal tumour thrombus	11	21	0·094†
Intrahepatic metastasis	13	19	0·34†
Hepatic functional factors			
$ICGR_{15}$ (%)	17 (8–25)	10 (4–24)	0·001*
ALAT (units/l)	85 (39–154)	58 (31–107)	0·015*
Volume of right lobe (%)	63 (47–77)	59 (31–69)	0·077*
Histological grade of hepatitis (0–4)	2 (0–3)	2 (0–3)	0·47*
Histological stage of fibrosis (0–4)	2 (0–3)	2 (1–4)	0·039*
Status of hepatitis virus			
HBsAg+	10 of 33	14 of 37	0·62†
HCVAb+	11 of 21	15 of 29	1·0†

Values in parentheses are tenth and 90th percentiles. $ICGR_{15}$, indocyanine green retention rate at 15 min; ALAT, alanine aminotransferase; HBsAg, hepatitis B surface antigen, HCVAb, hepatitis C virus antibody. *Mann–Whitney *U* test; †Fisher's exact test

Results

The postoperative mortality rate within 30 days was one (3 per cent) of 33 in group 1 and two (5 per cent) of 38 in group 2. The cumulative survival rate was higher in group 1 than in



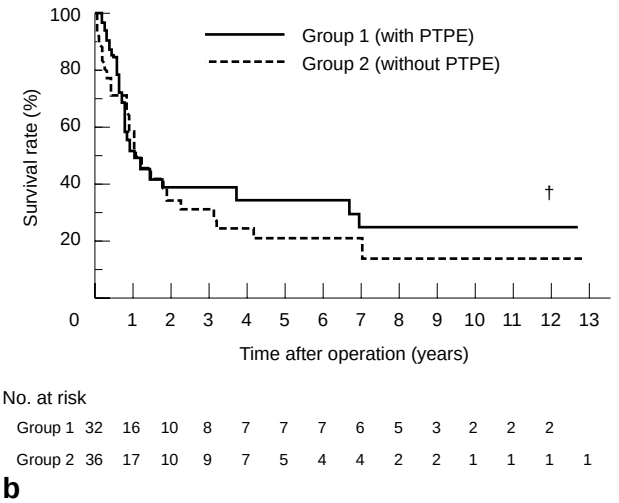


Fig. 1 **a** Cumulative survival rate.
b Tumour-free survival rate after right hepatectomy with (group 1) or without (group 2) preoperative percutaneous transhepatic portal vein embolization (PTPE). Patients who died within 30 days of operation were excluded from tumour-free survival calculations. *$P = 0{\cdot}059$, †$P = 0{\cdot}60$ (log rank test)

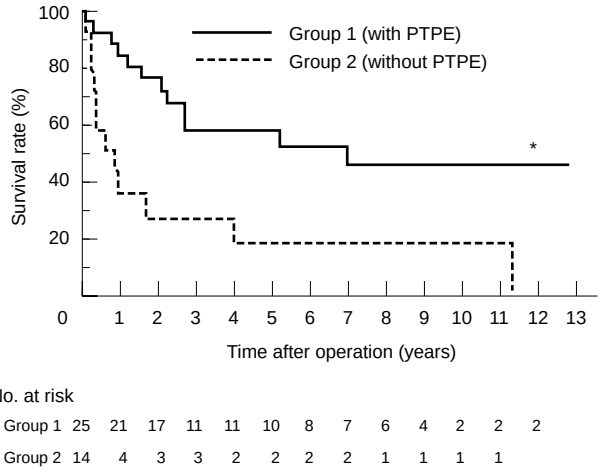


Fig. 2 Cumulative survival rate after right hepatectomy with (group 1) or without (group 2) preoperative percutaneous transhepatic portal vein embolization (PTPE) in patients with an indocyanine green retention rate at 15 min of at least 13 per cent. *$P = 0{\cdot}0024$ (log rank test)

Table 2 Factors that affected postoperative cumulative survival

	Regression coefficient	Standard error	Risk ratio	P*
All patients ($n = 71$)				
Tumour size	0·058	0·029	1·060	0·044
Portal tumour thrombus	0·460	0·145	1·585	0·002
Intrahepatic metastasis	0·564	0·164	1·758	0·001
Patients with $ICGR_{15} \geqq 13$ per cent ($n = 39$)				
Preoperative PTPE	−1·062	0·483	0·346	0·028
Tumour size	0·161	0·048	1·174	0·001

$ICGR_{15}$, indocyanine green retention rate at 15 min; PTPE, percutaneous transhepatic portal vein embolization. *Cox multiregression test using stepwise method

Table 3 Tumour recurrence and treatment after right hepatectomy

	Group 1 ($n = 22$)	Group 2 ($n = 26$)
Location		
Liver	21	20
Other	8	12
Treatment for recurrence		
Resection	8*	3*
TAE or HAI	34*	18*
PEIT or MCT	2*	6*

Values in parentheses denote the total frequency of the treatments. TAE, transcatheter arterial embolization; HAI, hepatic arterial infusion chemotherapy; PEIT, percutaneous ethanol injection therapy; MCT, microwave coagulation therapy. *Total frequency of the treatment

group 2 (*Fig. 1a*). The tumour-free survival rate, excluding patients who died within 30 days of operation, was similar in the two groups (*Fig. 1b*). The cumulative survival rate in patients in whom the $ICGR_{15}$ was at least 13 per cent was significantly higher in group 1 than in group 2 (*Fig. 2*). There were no significant differences in the tumour-free survival rate between groups 1 and 2 in any of the subgroups. Using a stepwise multiregression analysis, tumour size, portal venous tumour thrombus and intrahepatic metastasis were identified as significant prognostic factors in all patients. However, in patients in whom the $ICGR_{15}$ was at least 13 per cent, preoperative PTPE and tumour size were the significant factors (*Table 2*).

During follow-up (mean 1286 (range 13–4750) days), recurrent tumour was detected in the remnant liver or extrahepatic organs in 22 of the 33 patients in group 1 and in 26 of the 38 in group 2 (*Table 3*). Of patients with tumour recurrence, those in group 1 were more frequently subjected to further treatment than those in group 2 ($P = 0{\cdot}022$, Mann–Whitney U test).

Discussion

Decisions regarding the therapeutic strategy for patients with HCC are controversial, because of the frequent coincidence of liver cirrhosis and associated infection with hepatitis viruses[10]. These factors limit the surgical options and may be responsible for multicentric tumour occurrence[11]. Over the past 15 years, the authors have attempted to define better the therapeutic strategies for patients with HCC[12]. Decisions regarding the therapeutic approach should be made after careful evaluation of tumour extension, hepatic function and status of hepatitis virus infection.

The tumour-free survival rate in the 2 years after operation, which appears to reflect the incidence of metastatic recurrence rather than multicentric recurrence, was similar in both groups. This suggests that preoperative PTPE does not prevent metastasis through the portal vein. HCC tends to invade into the portal vein at a relatively early stage. It is therefore important to prevent dissemination of cancer cells via the portal circulation during operative manipulation[13]. In the present patients, ligation of the right portal vein preceded mobilization of the right liver. Since PTPE did not improve the tumour-free survival rate, taking particular care during the operative procedure to prevent tumour dissemination may suffice to prevent iatrogenic spread of disease.

PTPE did improve the survival rate in patients with an $ICGR_{15}$ of at least 13 per cent. The survival rate after tumour recurrence was better in patients with sufficient residual hepatic function to tolerate further treatment, including second hepatic resection[12,14]. More of the

patients who underwent preoperative PTPE were able to tolerate treatment for recurrent tumour, despite worse hepatic function before the original operation. Therefore preoperative PTPE may preserve hepatic function and allow treatment of tumour recurrence.

Although further prospective investigation of a large number of patients is needed, preoperative PTPE might be considered in patients with poor hepatic function who require right hepatectomy.

Acknowledgements

This work was supported by a grant for scientific research from the Ministry of Education, Science and Culture of Japan, and by a grant-in-aid from the Osaka City University Medical Research Foundation Fund.

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