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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Sequential Transcatheter Arterial Chemoembolization and Portal Vein Embolization versus Portal Vein Embolization Only before Major Hepatectomy for Patients with Hepatocellular Carcinoma

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ABSTRACT

Purpose. To evaluate the safety and efficacy of sequential transcatheter arterial chemoembolization (TACE) and portal vein embolization (PVE) prior to surgery in hepatocellular carcinoma (HCC) patients and to compare the clinical outcome of the combined procedure with that of a matched group of patients undergoing PVE alone.

Patients and Methods. From 1997 to 2008, 135 patients with HCC underwent sequential TACE and PVE ($n = 71$) or PVE alone ($n = 64$) before right hepatectomy. PVE was performed mean 1.2 months after TACE. In both groups, computed tomography (CT) and liver volumetry were performed before and 2 weeks after PVE to assess degree of left lobe hypertrophy.

Results. Baseline patient and tumor characteristics were similar in the two groups. After PVE, the chronological changes of liver enzymes were similar in the two groups. The mean increase in percentage future liver remnant (FLR) volume was higher in the TACE + PVE group (7.3%) than in the PVE-only group (5.8%) ($P = 0.035$). After surgery, incidence of hepatic failure was higher in the PVE-only group (12%) than in the TACE + PVE (4%) group ($P = 0.185$). Overall ($P = 0.028$) and recurrence-free ($P = 0.001$) survival rates were significantly higher in the TACE + PVE group than in the PVE-only group.

Conclusion. Sequential TACE and PVE before surgery is a safe and effective method to increase the rate of hypertrophy of the FLR and leads to longer overall and recurrence-free survival in patients with HCC.

Major hepatic resections are increasingly performed for large hepatocellular carcinoma (HCC) to achieve complete resection and provide the possibility of cure, given that liver transplantation or ablative therapy is not indicated for these tumors.[1–3] However, major hepatic resection is frequently contraindicated in many HCC patients because of the increased risk of postoperative hepatic failure.[2,3] Portal vein embolization (PVE), which induces atrophy of the embolized lobe with compensatory hypertrophy of the nonembolized future liver remnant (FLR), has been increasingly used to reduce the risk of postoperative hepatic failure in patients undergoing major hepatic resection.[4–7]

The degree of FLR hypertrophy after PVE is predictable in patients with healthy livers; however, it varies in patients with chronic liver disease.[8–15] In addition, it is possible that, after PVE, there can be a compensatory increase in the hepatic arterial flow to the embolized segments, thus resulting in insufficient nonembolized liver hypertrophy or rapid tumor growth.[16] These may be the major limitations of using PVE before major hepatic resection in HCC patients with underlying chronic liver disease.

Despite the theoretical drawback of increased risk of liver damage caused by double occlusion of blood supply, sequential transcatheter arterial chemoembolization (TACE) and PVE before major hepatic resection has recently shown promising results for increasing the rate of hypertrophy in HCC patients with chronic liver disease, as

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it decreases arterial flow and thus increases parenchymal damage in the embolized liver and suppresses arterioportal shunts.[14,17] In addition, TACE combined with PVE may have a strong anticancer effect by obstructing tumor-feeding vessels and suppressing intrahepatic spread by portal vein invasion from HCC and arterioportal shunts in HCC patients.[1,18,19]

However, previous studies reporting clinical outcomes of combined TACE and PVE before major hepatic resection have been limited by their small numbers of patients ($n < 20$).[3,17] The objectives of our study are: (1) to evaluate the safety and efficacy of this combined procedure before surgery in 71 patients with HCC, and (2) to compare the clinical outcome with that of a matched group of patients undergoing PVE only (64 patients).

PATIENTS AND METHODS

Patient Population

All patients provided written, informed consent for the procedure, and our institutional review board approved the retrospective review of the patients' medical and imaging records. From May 1997 to November 2008, a total of 135 patients with HCC underwent right PVE, which was indicated in patients undergoing right hepatectomy for HCC and with only a small future liver remnant (FLR) of less than 40% of total liver volume.[4,20] Among these 135 patients, 71 underwent sequential TACE and right PVE, while the remaining 64 patients underwent right PVE only before right hepatectomy. There was no established institutional consensus on the antitumor and FLR hypertrophy effects of precedent TACE before PVE and liver resection, thus TACE before PVE was decided by surgeon preference. All patients were considered to be candidates for right hepatectomy; all patients were classified as Child–Pugh class A and had no vascular invasion or extrahepatic metastases, and no portal hypertension. All patients also met criteria for PVE or TACE; all patients had no portal vein (PV) invasion, total bilirubin level less than 2 mg/dl, and international normalized ratio less than 1.5.

Transcatheter Arterial Chemoembolization

Superior mesenteric and common hepatic arteriographies were initially performed to assess patient anatomy, tumor burden, vascularity, and portal vein patency. After selective catheterization of the right hepatic artery using a microcatheter, cisplatin was then infused for 15 min into the hepatic artery. The infused dose of cisplatin was 2 mg/kg body weight. Thereafter, an emulsion of iodized oil (Lipiodol; Laboratoire Guerbet, Cedex, France) and cisplatin was infused into the selected segmental feeding artery (anterior segmental branch, posterior segmental branch, or both anterior and posterior segmental branches), followed by embolization with 1-mm-diameter absorbable gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, MI) until arterial flow stasis was achieved.

Portal Vein Embolization and Follow-Up Liver Function Tests

In 71 patients who had received TACE, PVE was performed 1 week to 2.8 months (mean 1.2 ± 0.7 months) after TACE, following recovery of liver function. The detailed technique for PVE was similar to that noted in previous reports.[7,21,22] Under fluoroscopic guidance, the right PV was embolized using only gelatine sponges ($n = 69$), the liquid embolic material Embol-78 ($n = 25$), a gelatin sponge with an Amplatzer vascular plug (AGA Medical, Golden Valley, MN) ($n = 21$) or a gelatin sponge with coils ($n = 20$), depending on availability of embolic material and operator preference.[22]

CT Volumetry

CT and liver volumetry were performed before and 2 weeks after PVE to assess degree of hypertrophy. Multidetector dynamic CT scans were performed, and volumetric data were obtained from the portal phase image.

Volumetric evaluation was performed in consensus by two radiologists using a CT analysis system. The outer margin of the liver was drawn, excluding large vessels such as the portal vein at the porta hepatis and the inferior vena cava as well as hepatic fissures. These manual delineation methods were performed slice by slice from the hepatic dome to the inferior tip. Using a summation-of-area method, the volume (V) was then calculated using the following equation: $V = T \times A$, where T is the slice thickness (0.5 cm interval) and A is the enclosed area (cm^2). Volume was measured three times for each patient, and the average value was obtained to resolve any discrepancies that might occur. The gallbladder and middle hepatic vein were used as markers to define the border of the right and left lobes of the liver. The caudate lobe was calculated as a part of the left lobe, because its portal vein was not embolized. In each hepatic volumetry, the hepatic tumor volume was excluded from the hepatic volume to prevent overestimating the hepatic volume because of any tumor growth. The total estimated liver volume (TELV) and FLR were obtained from the CT volumetry. The FLR volume was considered to represent the left hepatic lobe and caudate.

Right Hepatectomy and Follow-Up

To minimize ischemia–reperfusion injury, a gabexate mesilate solution was continuously infused beginning 12 h before surgery and until 3–4 days after surgery.[23,24] Right hepatectomy was performed by one of two experienced hepatic surgeons. The liver parenchyma was transected using a Cavitron ultrasonic aspirator under hemihepatic inflow occlusion. Any significant postoperative complications, particularly hepatic failure, were evaluated. Hepatic failure was defined by prothrombin time of less than 50% (of normal) and serum bilirubin level greater than 3 mg/dl (51.3 μmol/l) on postoperative day 5.[25]

Data Analysis

The TACE + PVE group and PVE-only group before major hepatectomy were compared in terms of baseline characteristics and tumors, changes in liver enzymes after PVE, changes in degree of liver hypertrophy (percentage FLR to TELV) after PVE, rates of surgery after PVE, rates of postoperative liver failure, rates of postoperative mortality, patient survival period after PVE, and recurrence-free patient survival period after PVE.

Statistical Analysis

Student's *t*-test (parametric test) or Mann–Whitney *U* test (nonparametric test) was used to compare pairs of independent continuous variables, and Fisher's exact test was used to compare categorical variables. Overall survival and recurrence-free survival were calculated using the Kaplan–Meier method and compared using the log-rank test. All statistical analyses were performed using the SPSS package (version 14.0, SPSS), and a two-sided *P* value of <0.05 was considered statistically significant.

TABLE 1 Baseline patient and tumor characteristics

Demographics	TACE + PVE group	PVE-only group	*P*-value
Patients	71	64	
Age, mean ± SD, years	56.0 ± 9.4	58.2 ± 9.2	0.175
Sex			0.805
Male	60	56	
Female	11	8	
Etiology			0.216
HBV	2	0	
HBV LC	55	52	
HCV LC	9	3	
Alcoholic LC	3	5	
Cryptogenic LC	2	4	
ECOG score			0.661
0	59	51	
1	12	13	
Tumor size, mean ± SD, cm	6.36 ± 5.25	6.66 ± 3.75	0.620
Tumor multiplicity			0.849
Single	51	47	
Multiple	20	17	
Total bilirubin	0.90 ± 0.34	0.92 ± 0.65	0.671
AST	45.08 ± 45.18	45.32 ± 35.01	0.891
ALT	47.08 ± 66.85	40.43 ± 36.05	0.536
Portal vein embolic material			0.775
Gelatin sponge alone	39	30	
Embol-78 (liquid embolic material)	12	13	
Gelatin sponge with AVP	11	10	
Gelatin sponge with coils	9	11	

TACE transcatheter arterial chemoembolization, *PVE* portal vein embolization, *SD* standard deviation, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *LC* liver cirrhosis, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AVP* Amplatz vascular plug, *ECOG* Eastern Cooperative Oncology Group

RESULTS

Patient Characteristics before TACE and PVE

Comparative results of baseline patient and tumor characteristics in the TACE + PVE and PVE-only groups are summarized in Table 1. There was no significant difference between the two groups in terms of baseline tumor or patient characteristics.

Immediate Results and Changes of Liver Enzymes After PVE

TACE or right PVE was successfully performed in all patients. After PVE, complications occurred in only one patient (1.4%, 1/71) in the TACE + PVE group. In this patient, elevated liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT)] did not normalize during the 3 months following PVE, and right hepatectomy was not performed in this patient.

Figure 1 shows the changes in liver enzymes before and after TACE, PVE, and hepatectomy. In the TACE + PVE group, all liver enzymes were mildly elevated within 3 days following TACE but had returned to their baseline levels before PVE. After PVE and right hepatectomy, peak levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum bilirubin were similar in the two groups ($P = 0.535$, $P = 0.521$, and $P = 0.571$

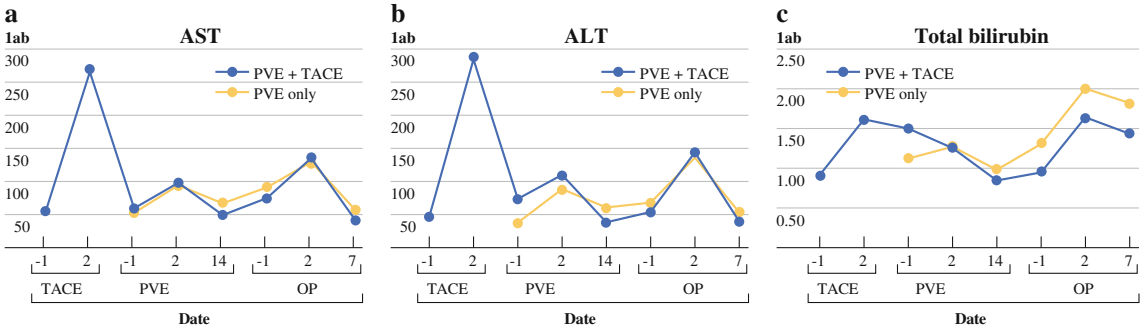

FIG. 1 Comparison of changes of aspartate aminotransferase (AST) (a), alanine aminotransferase (ALT) (b), and serum bilirubin (c) between the two groups. Laboratory data measured 2 days after the procedure were selected because most peak values were detected around this time

after PVE; $P = 0.720$, $P = 0.654$, and $P = 0.821$ after right hepatectomy, respectively) (Fig. 1).

Liver Volume Changes After PVE

Before PVE, the mean percentage of FLR volume to TELV in the TACE + PVE and the PVE-only groups was 34.1 ± 7.2% and 34.5 ± 7.6%, respectively. After PVE, the mean percentage of FLR volume in the TACE + PVE and PVE-only groups was 41.4 ± 7.3% and 40.3 ± 8.1%, respectively. The mean increase in percentage of FLR volume was statistically significantly ($P = 0.035$) higher in the TACE + PVE group (7.3 ± 3.6%) than in the PVE-only group (5.8 ± 4.5%).

Right Hepatectomy and Postoperative Course

The mean interval between PVE and right hepatectomy was similar in the TACE + PVE and PVE-only groups (29 and 31 days, respectively, $P = 0.320$). Right hepatectomy could not be performed in six of the PVE-only group patients because of inadequate remnant liver hypertrophy ($n = 4$) or aggravation of HCC ($n = 2$), and right hepatectomy could not be performed in three of the TACE + PVE group patients because of inadequate remnant liver hypertrophy ($n = 2$) or deterioration of liver function ($n = 1$). The resection rate was higher in the TACE + PVE group (96%, 68/71) than in the PVE-only group (91%, 58/64), but not statistically significantly so ($P = 0.307$).

Right hepatectomy was performed in 58 and 68 patients in the PVE-only and the TACE + PVE groups, respectively. Pathologic tumor-node-metastasis (TNM) stage was not significantly different between the two groups who received surgery ($P = 0.323$) (Table 2).[26] After surgery, incidence of hepatic failure was higher in the PVE-only group (12%, 7/58) than in the TACE + PVE (4%, 3/68) group, but not statistically significantly so ($P = 0.185$). Five of seven patients with hepatic failure in the PVE-only group eventually recovered with medical management, while the remaining two patients in the PVE-only group eventually died of hepatic failure, despite medical management, 35 and 62 days after surgery, respectively, whereas all of the three patients with hepatic failure in the TACE + PVE group recovered with medical management. Incidence of postoperative mortality was higher in the PVE-only group (3%, 2/58) than in the TACE + PVE group (0%), but not statistically significantly so ($P = 0.210$).

TABLE 2 Pathologic TNM stage in the two groups who underwent surgery

Stage	TACE + PVE group	PVE-only group	*P*-value
Stages according to TNM category			0.323
Stage I (T1N0M0)	8	3	
Stage II (T2N0M0)	41	34	
Stage IIIA (T3N0M0)	19	21	

TACE transcatheter arterial chemoembolization, *PVE* portal vein embolization

Overall and Recurrence-Free Survival Periods

The current study ended in April 2010. During the follow-up period until the end of this study, 44 patients died, 6 were lost to follow-up, and 85 remained alive. In the TACE + PVE group, the cumulative survival rates at 1, 3, 5, and 10 years were 97%, 83%, 72%, and 58%, respectively. In the PVE-only group, the survival rates at 1, 3, 5, and 10 years were 89%, 73%, 56%, and 31%, respectively. The cumulative survival period was significantly longer in patients in the TACE + PVE group than in those in the PVE-only group ($P = 0.028$) (Fig. 2a).

During the follow-up period after PVE, there was HCC recurrence in 25 patients (35%, 25/71) in the TACE + PVE group and in 35 patients (55%, 35/64) in the PVE-only group. In the TACE + PVE group, the cumulative

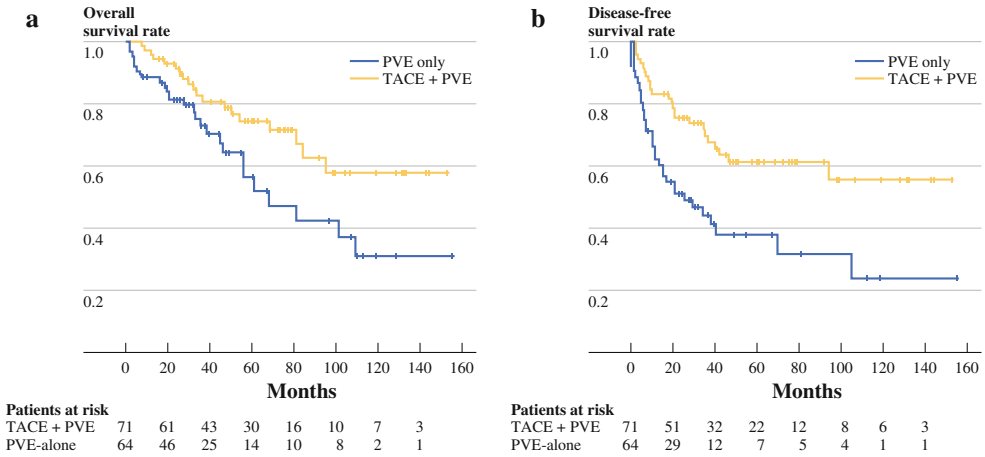

FIG. 2 Overall and disease-free survival rates after PVE: **a** Kaplan–Meier curves showing overall survival rates in the TACE + PVE group and in the PVE-only group. **b** Kaplan–Meier curves showing the disease-free survival rates in the TACE + PVE group and in the PVE-only group

recurrence-free survival rates at 1, 3, 5, and 10 years were 83%, 70%, 61%, and 56%, respectively. In the PVE-only group, the recurrence-free survival rates at 1, 3, 5, and 10 years were 62%, 51%, 38%, and 24%, respectively. The cumulative recurrence-free survival period was significantly longer in the TACE + PVE group patients than in the PVE-only group patients ($P = 0.001$) (Fig. 2b).

DISCUSSION

The basic hypotheses of the current study are: (1) that preoperative TACE + PVE may increase the rate of hypertrophy more than PVE alone in HCC patients with chronic liver disease by decreasing the compensatory increased hepatic arterial flow to the embolized lobe and by suppression of arterioportal shunts, and (2) that preoperative TACE + PVE may decrease the risk of rapid tumor progression prior to major hepatic resection by blocking the compensatory hypertrophied feeding arteries. According to these hypotheses, preoperative TACE + PVE may increase the probability of resectability for major hepatectomy and may decrease the risk of postoperative hepatic failure.

In the present study, the mean increase in percentage FLR volume was significantly higher in the TACE + PVE group ($n = 71$) (7.3 ± 3.6%) than in the PVE-only group ($n = 64$) (5.8 ± 4.5%) ($P = 0.035$), thus indicating that sequential TACE and PVE is more efficient than PVE alone for increasing FLR volume in HCC patients with chronic liver disease. Ogata et al. also observed similar results, i.e., the mean increase in percentage FLR volume was significantly higher in 18 patients who underwent sequential TACE and PVE (12 ± 5%) before right hepatectomy than in 18 patients who underwent PVE alone (8 ± 4%) ($P = 0.044$).[17]

After PVE, changes in liver function are usually minor and transient in both normal and chronic liver disease.[8,10,12,15] However, sequential TACE and PVE may have the theoretical drawback of increased risk of liver damage caused by double occlusion of the blood supply. However, in the present study, this complication occurred in only one patient (1.2%, 1/71) in the TACE + PVE group, in whom the planned hepatectomy was abandoned due to deterioration of liver function after PVE. Furthermore, the changes of liver enzymes after PVE noted in this study were similar in the TACE + PVE and PVE-only groups. In addition, Aoki et al. found that necrosis of noncancerous liver parenchyma was minimal in most cases, even though necrosis of HCC tumors was marked in the resected specimens of their study patients ($n = 17$) who underwent preoperative sequential TACE and PVE.[3] Therefore, we believe that preoperative sequential TACE and PVE can be safely performed in HCC patients and with similar safety in patients who undergo PVE without TACE before surgery.

Parenchymal damage caused by TACE in embolized liver, which is reflected by changes in liver enzymes including AST, ALT or total bilirubin, may differ according to the interval between TACE and PVE. In other words, shorter interval between TACE and PVE can lead to more damage to embolized liver and therefore presents a greater risk, particularly in patients with liver cirrhosis.[17] For instance, Aoki et al. found that AST and ALT levels were significantly elevated after sequential TACE and PVE (with median interval of 9 days) in 17 patients, even though these changes were transient and there was only a mild increase in bilirubin level.[3] In a report by Ogata et al., the mean interval between TACE and PVE in 18 patients was 3.6 weeks.[17] After PVE, peak levels of AST and ALT were significantly higher in the TACE + PVE group than in the PVE-only group ($P = 0.026$ and $P = 0.031$,

respectively).[17] However, mean peak levels of AST and ALT in the study by Ogata et al. were less than half those reported by Aoki et al.[3,17] However, we found that mean peak levels of AST, ALT, and total bilirubin after PVE were mildly elevated and were similar in the TACE + PVE and the PVE-only groups. The mean interval between TACE and PVE in our study was 1.2 months, and the mean peak levels of AST and ALT were less than half those reported by Ogata et al.[17]

In the current study, the recurrence-free survival period was significantly longer in the TACE + PVE group patients than in the PVE-only group patients ($P = 0.001$). The significantly longer recurrence-free survival period in the TACE + PVE group than in the PVE-only group can be explained by several factors. First, given that the combined treatment may induce higher tumor necrosis, there would be less chance of incomplete tumor excision or tumor cell dissemination during surgery.[17] TACE alone induces complete tumor necrosis in approximately 50% of patients.[27–29] Ogata et al. found that sequential TACE and PVE achieved complete tumor necrosis in more than 80% of their patients compared with only 5% after PVE alone.[17] Second, the combined treatment may decrease the rate of early recurrence, which usually develops due to undetected or residual microscopic tumor after resection.[30] Our findings support this assumption; the recurrence-free survival curve demonstrated in our study shows the beneficial effect of the combination therapy, particularly during the first year after surgery. Once recurrence occurs, survival is limited.[31] The longer recurrence-free survival period in the TACE + PVE group in the current study eventually led to longer overall survival period in the TACE + PVE group than in the PVE-only group ($P = 0.028$).

The principal limitation of our study is its nonrandomized and retrospective design, which involves some inherent flaws. A prospective and randomized control trial will be required to reach definite conclusions regarding the clinical efficacy of sequential TACE and PVE before surgery.

In conclusion, sequential TACE and PVE before surgery is a safe and effective method to increase the rate of hypertrophy of the future liver remnant; it also leads to longer recurrence-free survival in patients with HCC.

REFERENCES

1. Palavecino M, Chun YS, Madoff DC, et al. Major hepatic resection for hepatocellular carcinoma with or without portal vein embolization: perioperative outcome and survival. *Surgery.* 2009;145:399–405.
2. Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN. Portal vein embolization before major hepatectomy and its effects on regeneration, respectability and outcome. *Br J Surg.* 2007;94:1386–94.
3. Aoki T, Imamura H, Hasegawa K, et al. Sequential preoperative arterial and portal venous embolizations in patients with hepatocellular carcinoma. *Arch Surg.* 2004;139:766–74.
4. Hwang S, Lee SG, Ko GY, et al. Sequential preoperative ipsilateral hepatic vein embolization after portal vein embolization to induce further liver regeneration in patients with hepatobiliary malignancy. *Ann Surg.* 2009;249:608–16.
5. Abulkhir A, Limongelli P, Healey AJ, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann Surg.* 2008;247:49–57.
6. Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for respectable hepatic colorectal metastases. *Ann Surg.* 2008;247:451–5.
7. Yoo H, Ko GY, Gwon DI, et al. Preoperative portal vein embolization using an amplatzer vascular plug. *Eur Radiol.* 2009;19:1054–61.
8. Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. *Ann Surg.* 2003;237:208–17.
9. Azoulay D, Castaing D, Krissat J, et al. Percutaneous portal vein embolizationincreases the feasibility and safety of major liver resection for hepatocellular carcinoma in injured liver. *Ann Surg.* 2000;232:66–72.
10. Imamura H, Shimada R, Kubota M, et al. Preoperative portal vein embolization: an audit of 84 patients. *Hepatology.* 1999;29:1099–105.
11. Lee KC, Kinoshita H, Hirohashi K, Kubo S, Iwasa R. Extension of surgical indications for hepatocellular carcinoma by portal vein embolization. *World J Surg.* 1993;17:109–15.
12. Shimamura T, Nakajima Y, Une Y, et al. Efficacy and safety of preoperative percutaneous transhepatic portal embolization with absolute ethanol: a clinical study. *Surgery.* 1997;121:135–41.
13. Tanaka H, Hirohashi K, Kubo S, Shuto T, Higaki I, Kinoshita H. Preoperative portal vein embolization improves prognosis after right hepatectomy for hepatocellular carcinoma in patients with impaired hepatic function. *Br J Surg.* 2000;87:879–82.
14. Yamakado K, Takeda K, Matsumura K, et al. Regeneration of the unembolized liver parenchyma following portal vein embolization. *J Hepatol.* 1997;27:871–80.
15. Wakabayashi H, Yachida S, Maeba T, Maeta H. Indications for portal vein embolization combined with major hepatic resection for advanced-stage hepatocellular carcinomas. A preliminary clinical study. *Dig Surg.* 2000;17:587–94.
16. Gruttadauria S, Luca A, Mandala L, Miraglia R, Gridelli B. Sequential preoperative ipsilateral portal and arterial embolization in patients with colorectal liver metastases. *World J Surg.* 2006;30:576–8.
17. Ogata S, Belghiti J, Farges O, Varma D, Sibert A, Vilgrain V. Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. *Br J Surg.* 2006;93:1091–8.
18. Murata S, Tajima H, Nakazawa K, Onozawa S, Kumita S, Nomura K. Initial experience of transcatheter arterial chemoembolization during portal vein occlusion for unresectable hepatocellular carcinoma with marked arterioportal shunts. *Eur Radiol.* 2009;19:2016–23.
19. Kang BK, Kim JH, Kim KM, et al. Transcatheter arterial chemoembolization for hepatocellular carcinoma after attempted portal vein embolization in 25 patients. *AJR Am J Roentgenol.* 2009;193:W446–51.
20. Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. *Ann Surg.* 2006;243:364–72.

21. Madoff DC, Hicks ME, Abdalla EK, Morris JS, Vauthey JN. Portal vein embolization with polyvinyl alcohol particles and coils in preparation for major liver resection for hepatobiliary malignancy: safety and effectiveness—study in 26 patients. *Radiology.* 2003;227:251–60.
22. Ko GY, Sung KB, Yoon HK, et al. Preoperative portal vein embolization with a new liquid embolic agent. *Radiology.* 2003;227:407–13.
23. Hwang S, Lee SG, Sung KB, et al. Hepatectomy for patients with transient hepatic failure after preoperative portal vein embolization. *Hepatogastroenterology.* 2007;54:1817–20.
24. Kim YI, Chung HJ, Song KE, et al. Evaluation of a protease inhibitor in the prevention of ischemia and reperfusion injury in hepatectomy under intermittent Pringle maneuver. *Am J Surg.* 2006;191:72–6.
25. Balzan S, Belghiti J, Farges O, et al. The '50–50 criteria' on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg*. 2005;242:824–9.
26. Befeler AS, Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. *Gastroenterology.* 2002;122:1609–19.
27. Adachi E, Matsumata T, Nishizaki T, Hashimoto H, Tsuneyoshi M, Sugimachi K. Effects of preoperative transcatheter hepatic arterial chemoembolization for hepatocellular carcinoma. The relationship between postoperative course and tumor necrosis. *Cancer.* 1993;72:3593–8.
28. Gerunda GE, Neri D, Merenda R, et al. Role of transarterial chemoembolization before liver resection for hepatocaricnoma. *Liver Transpl.* 2000;6:619–26.
29. Clavien PA, Selzner N, Morse M, Selzner M, Paulson E. Downstaging of hepatocellular carcinoma and liver metastases from colorectal cancer by selective intra-arterial chemotherapy. *Surgery.* 2002;131:433–42.
30. Matsumata T, Kanematsu T, Takenaka K, Yoshida Y, Nishizaki T, Sugimachi K. Patterns of intrahepatic recurrence after curative resection of hepatocellular carcinoma. *Hepatology.* 1989;9: 457–60.
31. Cha C, Fong Y, Jarnagin WR, Blumgart LH, DeMatteo RP. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. *J Am Coll Surg*. 2003;197:753–8.