Transcatheter management for unresectable hepatocellular carcinoma with marked arterioportal shunts: TACE during portal vein occlusion.

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Background

Hepatocellular carcinoma (HCC) is frequently associated with arteriovenous shunts—mainly arterioportal (AP) shunts . Although the presence of small AP shunts does not necessarily preclude transcatheter arterial chemoembolization (TACE) therapy for unresectable HCC, larger AP shunts do interfere with TACE, because anticancer drugs, either alone or mixed with iodized oil, easily pass through the shunts.

Attempts have been made to treat marked AP shunts by the embolization of hepatic arteries with materials such as gelatin sponges or coils, and good short-term results have been obtained. However, such treatment does not eradicate HCC and therefore contributes only marginally to patient survival. A safe and effective therapeutic protocol for HCC with marked AP shunts remains to be established.

Purpose

- To assess the clinical effects of TACE during the corresponding portal vein occlusion (TACE-PVO) in patients with hepatocellular carcinoma (HCC) and marked arterioportal (AP) shunts.

Patients and Methodsl

The eligibility criteria

1) diagnosis of HCC based on histologic, or CT/MRI findings, and/or laboratory data;

2) presence of AP shunts in the arterial phase confirmed by hepatic arteriography;

3) no indications for other surgical interventions;

4) no tumor thrombus in the portal vein trunk;

5) an apparent increase in tumor size despite TACE therapy mainly because of AP shunts;

6) adequate liver and bone marrow function (bilirubin<3.0 mg/dl, leukocyte>3000 cells/mm3, platelet>50,000 cells/mm3);

7) controllable, or no, ascites.

Patients and MethodsII

Patients (Table 1)

- Between June 2002 and May 2007, 651 patients with unresectable HCCs were treated by TACE at our hospital.
- The subjects were 21 patients with unresectable HCC and marked AP shunts who underwent shunt embolization with the use of coils and/or gelatin-sponge particles (group A: n=7) or by TACE-PVO (group B: n=14).

Table 1. Baseline characteristics

	Standard TAE (group A: n=7)	TACE-PVO (group B: n=14)	*p*
Demography			
Age, years	67 (56-79)	72(47-79)	0.329
M/F	4/3	14/0	0.008
Hepatic virus			
non/B/C	1/0/6	0/1#/14	0.283
Child-Pugh classification			
Grade A/B/C	0/7/0	1/13/0	0.480+
PT* (normal/abnormal)	2/5	7/7	0.350
Ascites			
non/small/large	4/3/0	8/6/0	1+
Performance status			
0/1/2	1/5/1	6/6/2	0.322
Previous treatments			
RFA** or PEIT***	5	4	0.513
standard TACE	7	14	1
Tumor			
$\leq$3 / >3 (number)	1/6	2/12	1
Unilateral lobe/bilateral lobe	1/6	3/11	0.694
Other information			
gastric varices	7	12	0.293
distant metastasis	1	1	0.599

*, prothrombin time, **, radiofluquency ablation, ***, percutaneous ethanol infusion therapy
#, One patient had both B & C virus +, Mann-Whitney U test, others; Chi-squared test

Patients and MethodsIII

Embolization technique

- **Group A (Standard TAE group):**
  Embolization with coils and/or gelatin sponge particles.

- **Group B (TACE-PVO group):**
  A balloon catheter was advanced into the portal vein branch showing the AP shunt, and the balloon catheter was inflated, and a mixture of Lipiodol (up to 15 mL) and epirubicin emulsion (30 mg/m2) was injected via the target feeder artery. Next, gelatin sponge particles were immediately injected into the feeder artery until it was occluded.

Patients and MethodsIV

Data analysis

1) Technical and clinical effectiveness in treatment of AP shunts:
   Efficacy of the therapies for AP shunts (classified into three groups)
   i) Technical success (verified by post-embolization angiography)
      a) excellent (AP shunt had disappeared),
      b) acceptable (AP shunt appeared only in the venous phase),
      c) insufficient (AP shunt appeared in the arterial phase).
   ii) Clinical success (subsequent angiography 3 to 4 weeks after)
      classified into three groups according to the above-mentioned method.
2) Antitumor response:
   Assessment was by two methods:
   i) response evaluation criteria in the solid tumor (RECIST)
   ii) the area of Lipiodol accumulation was defined as the area of tumor necrosis.
      The area of Lipiodol accumulation (classified into three groups)
      a) excellent (more than 80%),
      b) acceptable (50% to 80%),
      c) insufficient (less than 50%).

Patients and MethodsⅣ'

Data analysis

3) Complication events:

In accordance with the criteria of the Society of Interventional Radiology.

4) Follow up and survival:

Survival rates were calculated by the Kaplan-Meier Method (median follow-up 18.7 months, 10.6 months in group A, 22.8 months in group B).

5) Statistical analysis:

Results were compared by Chi-squared test and Mann-Whitney's U test. Differences at $P < 0.05$ were considered statistically significant.

SPSS ver. 14 (SPSS Japan Inc., Tokyo, Japan)

Table 2. Results of embolization for HCC with AP-shunts

	Standard TAE (group A: n=7)	TACE-PVO (group B: n=14)	*p*
Embolization materials			
Lipiodol+GS*/Coils	3/7	14/1	0.002/<0.001
Effectiveness for AP-shunts			
Excellent	2	11	
Acceptable	1	3	0.009+
Insufficient	4	0	
TACE for HCCs			
yes/no	3/4	14/0	0.002
Accumulation of Lipiodol in the target area			
Excellent (more than 80%)	2	12	
Acceptable (50% to 80%)	0	2	0.343+
Insufficient (less than 50%)	1	0	
Tumor response assessed by RECIST			
CR	0	0	
PR	0	7	0.002
SD	2	5	
PD	5	1	
no evaluation	0	1	
Tumor marker			
AFP (normal/abnormal)**	2/5	3/11	0.186
up/NC/down***	2/3/2	0/6/7	0.148+
PIVKA II (normal/abnormal)	3/4	5/9	0.743
up/NC/down	2/4/1	1/7/5	0.116+

*, gelatin sponge, **, before therapy, ***, 3 to 5 weeks after therapy
+, Mann-Whitney U test, others; Chi-squared test

Table 3. Subsequent angiographic findings and procedures

	Standard TAE (group A: n=7)	TACE-PVO (group B: n=14)	*p*
Subsequent angiography			
yes/no	5/2	13/1**	0.186
AP-shunts			
Excellent	1	9	
Acceptable	1	3	0.028+
Insufficient	3	1	
Subsequent TAE for AP-shunts			
yes/no	3/2	1/13	0.017
(sessions*)	1-3 (2)	1	
Subsequent treatments for HCCs			
standard TACE	2	13	0.002
(sessions*)	2-4 (3.0)	1-9 (3.4)	0.020+
conservative	5	0	0.350
infusion port	0	4	0.116

*, Mean, **, One patient died of aspiration pneumonia 35 days after TACE-PVO.
+, Mann-Whitney U test, others; Chi-squared test

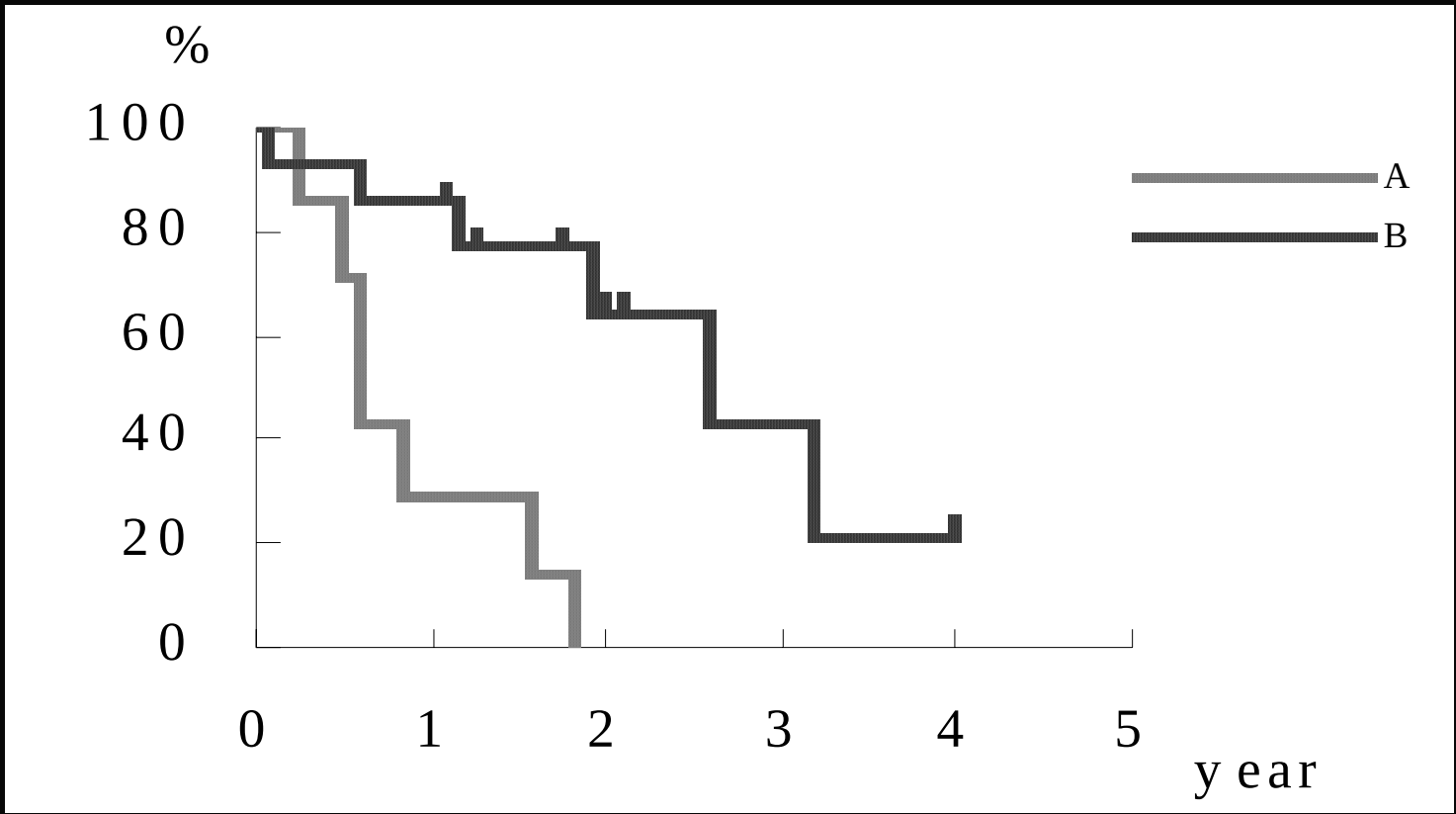
Results

Complications: No major procedure-related complication occurred in either group.

AP-shunts: Effectiveness for AP-shunt treatment was significantly better in group B than in group A in terms of both immediate results ($P = 0.009$) and subsequent results ($P = 0.028$).

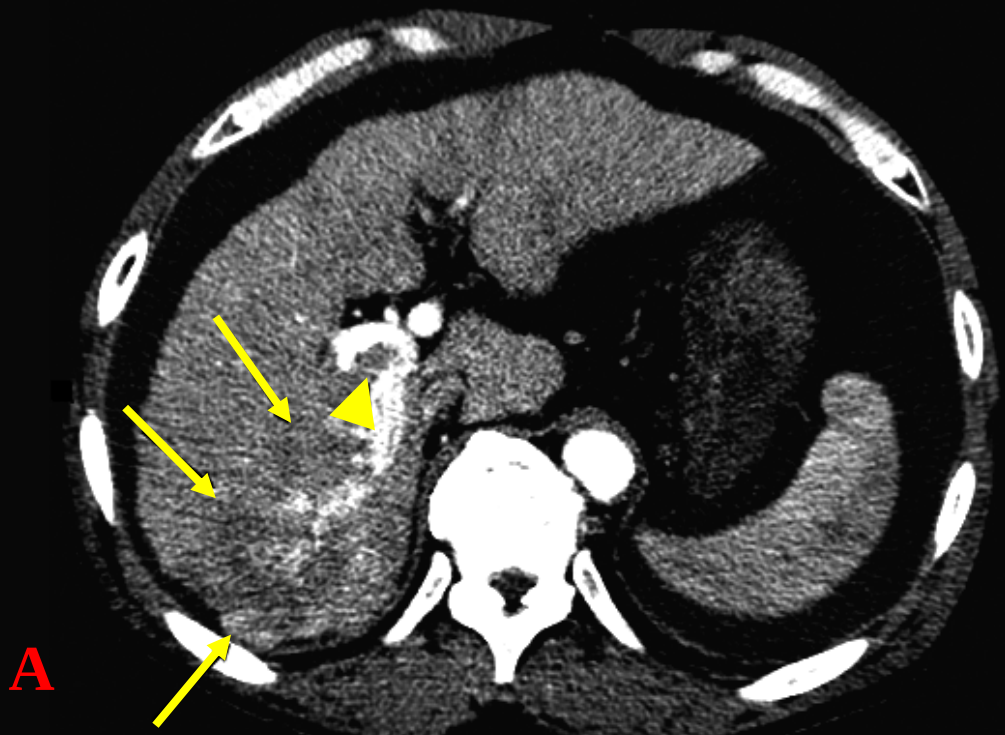
Efficacy: Tumor response ($P = 0.002$) in the therapeutic target area and survival ($P = 0.008$) was significantly better in group B than in group A.

Fig. Survival rates



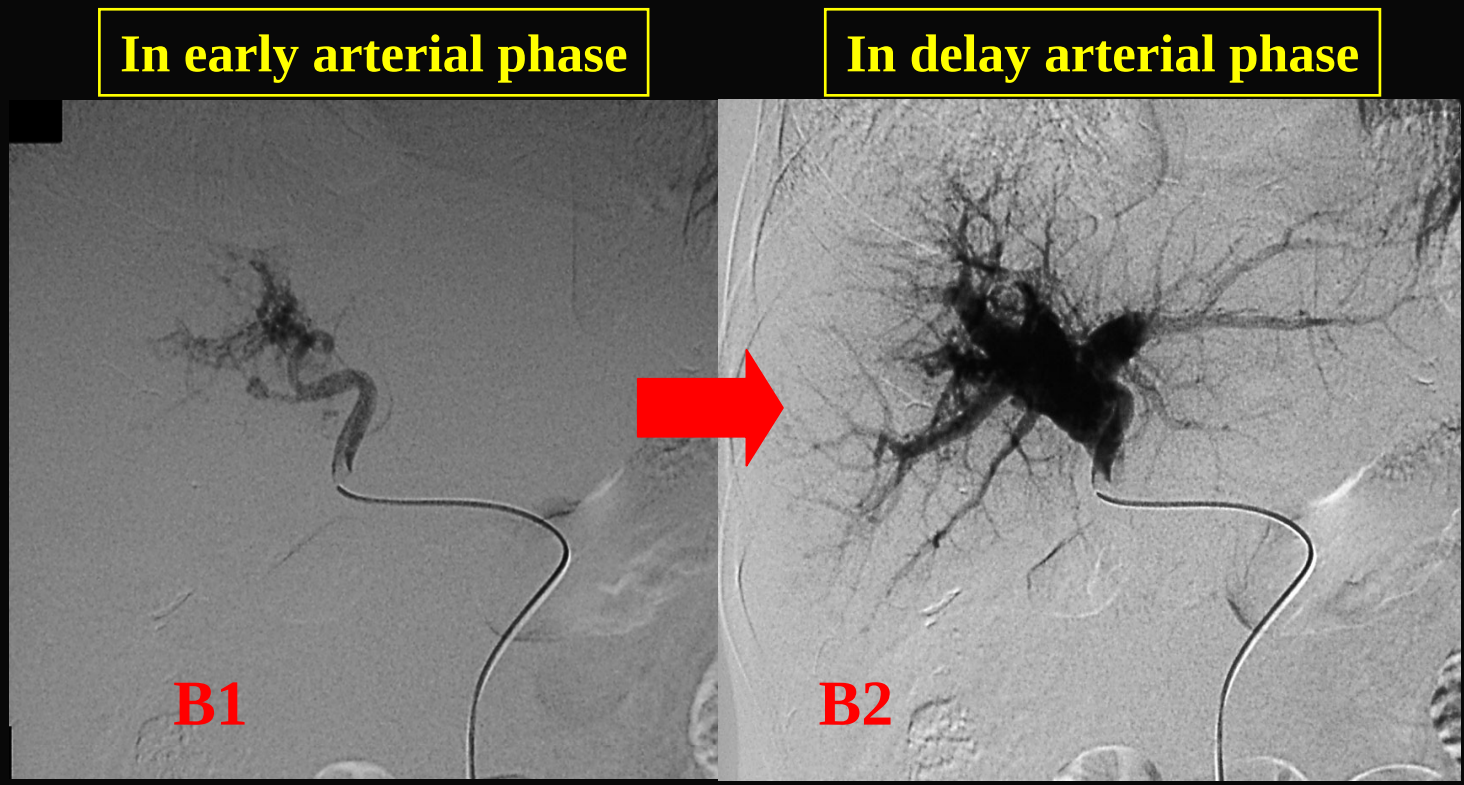
- In group A (standard TAE), 1- and 2-year survival rates were 28.6% and 0%, respectively. In group B (TACE-PVO), 1-, 2-, 3-, and 4-year survival rates were 85.7%, 64.3%, 42.9%, and 21.4%, respectively.
- The survival rates in group B were significantly (P = 0.008) higher than those in group A (generalized Wilcoxon test).

Case 1. A 65-year-old man with HCC and marked AP shunts due to portal vein tumor thrombus.



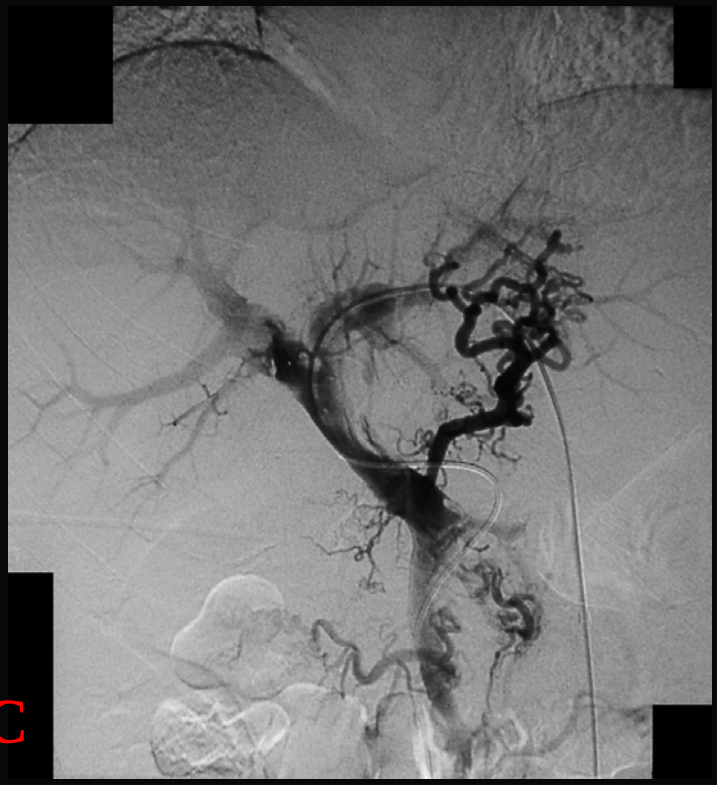
Enhanced CT in the early phase demonstrates heterogeneous enhancement in the posterior segment (A, arrows). The arrowhead indicates portal vein tumor thrombus.

Case 1. A 65-year-old man with HCC and marked AP shunts due to portal vein tumor thrombus.

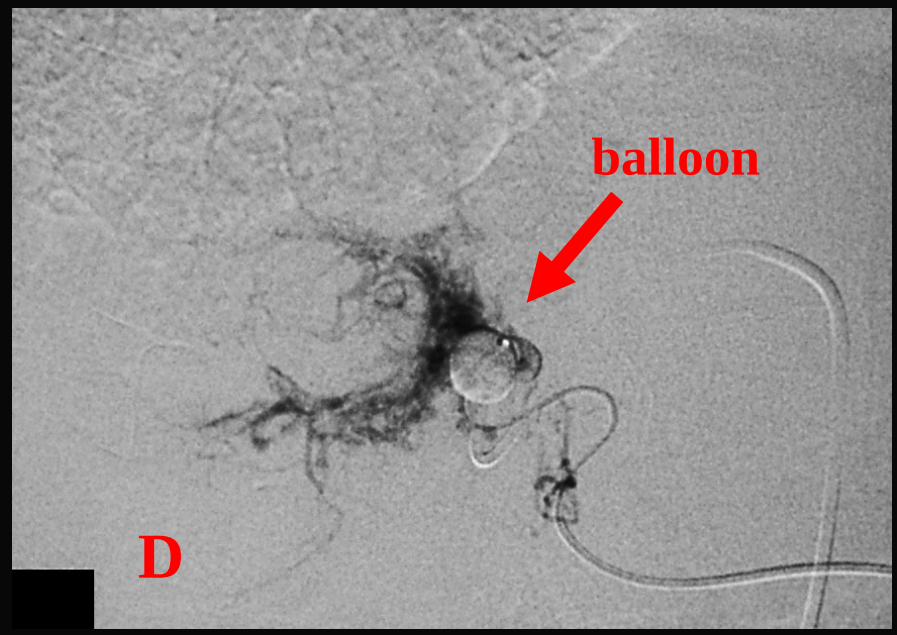


Proper hepatic arteriography in the arterial phase demonstrates the whole intrahepatic portal venous system and portal vein trunk owing to the presence of AP shunt (B1-2).

Case 1. A 65-year-old man with HCC and marked AP shunts due to portal vein tumor thrombus.

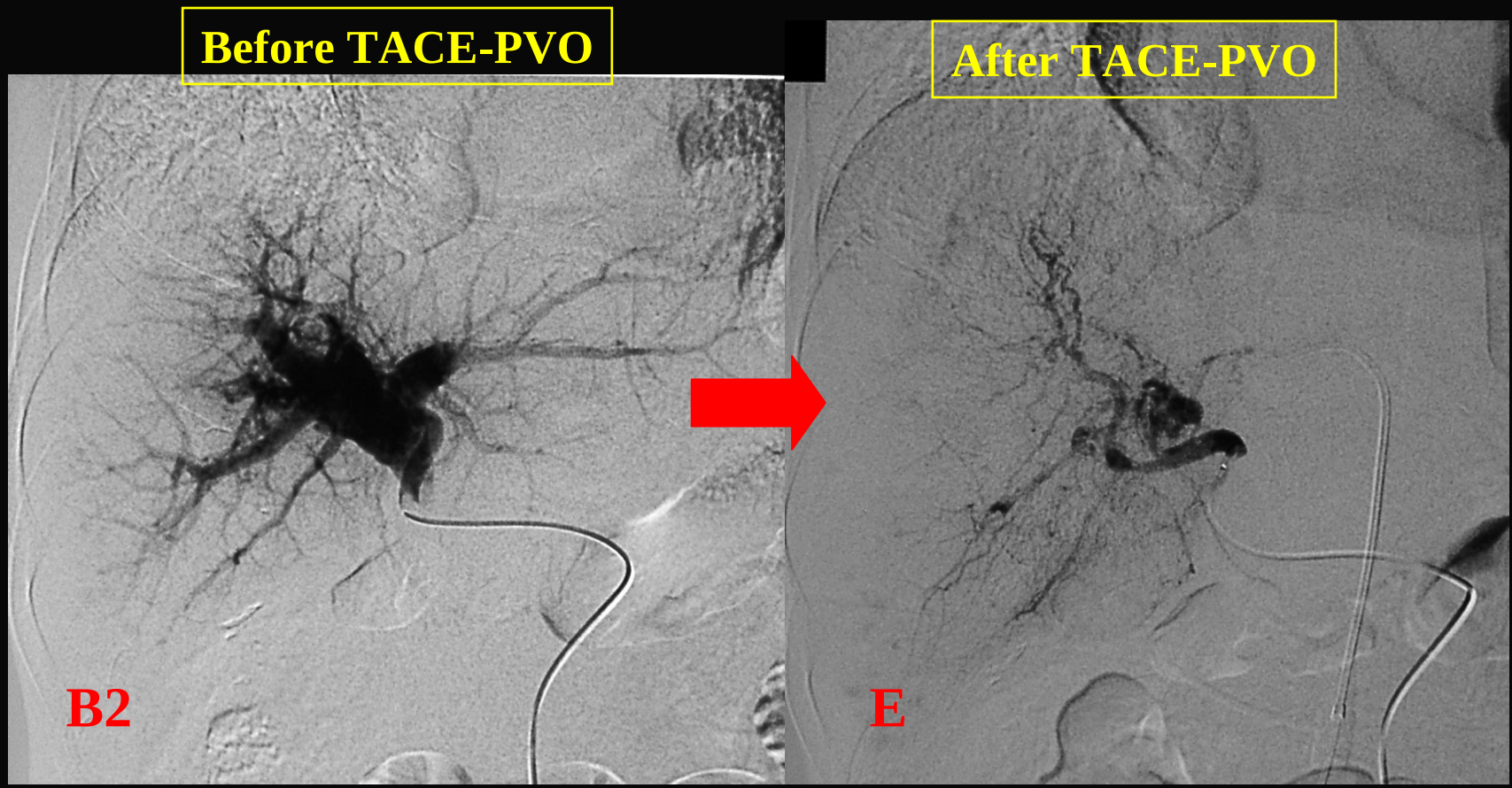


Portography via the balloon catheter in the posterior segmental branch.



The lateral superior branch of the left portal vein is punctured, and a 5-French sheath is inserted into the portal vein. Direct portography is performed to identify the portal vein branch showing the AP-shunts (C). A balloon catheter is advanced into the portal vein branch (posterior segmental branch) and inflated (D).

Case 1. A 65-year-old man with HCC and marked AP shunts due to portal vein tumor thrombus.

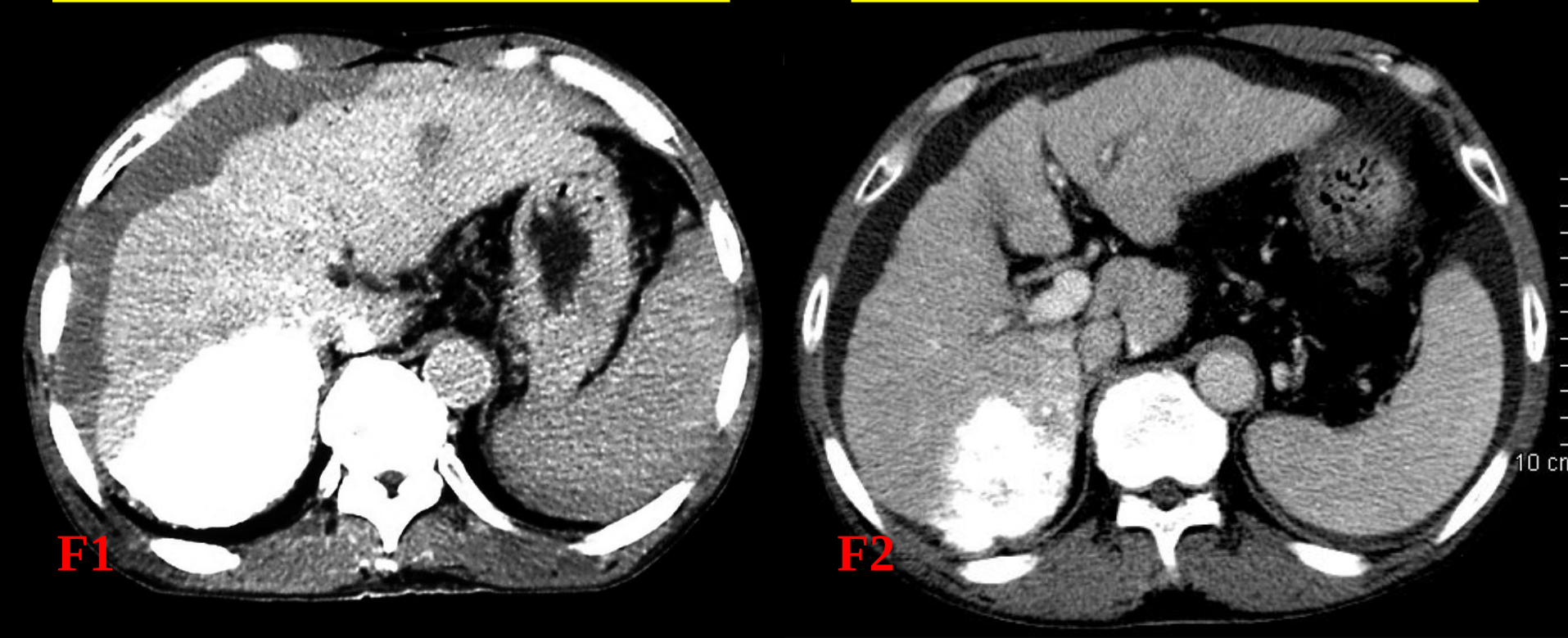


Proper hepatic arteriography after TACE-PVO demonstrates non-visualized AP shunts (E).

Case 1. A 65-year-old man with HCC and marked AP shunts due to portal vein tumor thrombus.

CT immediately after TACE-PVO

CT 4 weeks after TACE-PVO



Enhanced CT 4 weeks after TACE-PVO shows diminished portal vein tumor thrombus and a dense accumulation of Lipiodol in the tumors (F2).

Discussionl

- A major disadvantage of TACE for unresectable HCC with marked AP shunts is that TACE may cause liver failure as a result of the extensive embolization of portal veins, or pulmonary embolism.
- Embolization of the marked AP shunts using coils may prompt the development of tortuous and thin collateral anastomoses, and it becomes much hard to perform TACE. Consequently, embolization of the hepatic arteries for treatment of AP shunts contributes little to patient survival.

DiscussionII

- To overcome this disadvantage, we tried to perform TACE during portal venous occlusion. The effectiveness of TACE-PVO for AP shunts was ascribed to adequate embolization of the entire tumor, including the portions involving AP shunts, by portal venous occlusion. Consequently, TACE-PVO may prevent the development of collateral anastomoses to AP shunts.
- Our results on the effectiveness of AP shunt treatment indicated that TACE-PVO was significantly ($P = 0.009$) better than standard TAE, and subsequent angiographic findings ($P = 0.028$) suggested the superiority of TACE-PVO.

Conclusions

- TACE-PVO may be a safe and useful therapy for selected patients with unresectable HCC and marked AP shunts.