Sequential Transcatheter Arterial Chemoembolization and Portal Vein Embolization for Hepatocellular Carcinoma: The University of Tokyo Experience

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ABSTRACT

When undertaking portal vein embolization (PVE) in patients with hepatocellular carcinoma (HCC), the following possibilities should be considered: (1) failure to induce hypertrophy of the nonembolized segments due to the underlying liver disease, (2) acceleration of tumor growth by occlusion of the portal venous flow because HCC is a hypervascular tumor fed exclusively by hepatic arterial flow, and (3) poor efficacy of PVE due to the presence of arteriportal shunts frequently observed in cases of liver cirrhosis and HCC. With these in mind, we performed sequential transcatheter arterial chemoembolization (TACE) and PVE in 45 patients with HCC undergoing major liver resection. This double preparation was well tolerated, enhanced the hypertrophy process in the nonembolized segments, and suppressed the tumor growth during the preparation period. Furthermore, PVE also functioned as a preoperative test to select patients for major liver resection. Sequential TACE and PVE is an effective preoperative intervention in patients with HCC scheduled for major liver resection.

KEYWORDS: Portal vein embolization, hepatocellular carcinoma, transcatheter arterial chemoembolization, liver resection

Objectives: Upon completion of this article, the reader should understand the rationale and indications of sequential transcatheter arterial chemoembolization and portal vein embolization as a preoperative intervention in patients with hepatocellular carcinoma undergoing liver resection.

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Extensive liver resection often results in > 70% of the functioning liver parenchyma being removed and leads to an abrupt increase in the portal venous pressure. These changes can contribute to increased postoperative morbidity and eventually culminate in fatal liver failure. Portal vein embolization (PVE), first performed by our group in 1982 for patients with hilar bile duct carcinoma, is a preoperative intervention applied to induce atrophy of the embolized liver segments to be resected and compensatory hypertrophy of the nonembolized future remnant liver (FRL) segments and to induce transient elevation of the portal venous pressure in the FRL segments.¹⁻³ Due to its technical simplicity, PVE has become a standard preoperative intervention worldwide, and its indications have been expanded to include patients with hepatocellular carcinoma (HCC).⁴⁻¹⁰

Liver resection remains the mainstay of treatment for HCC, especially for patients with large HCCs and those with portal venous tumor thrombi, because neither liver transplantation nor ablative therapy can be undertaken in these patients. In addition, segment-oriented anatomical resection is recommended even for small HCCs to prevent postoperative recurrence.¹¹⁻¹⁴ These considerations inevitably signify that major liver resection is often required in patients with HCC. In addition, most HCC patients have impaired liver functional reserve because of hepatitis B and/or C virus-associated or alcoholic liver fibrosis/cirrhosis. Likewise, they often have elevated portal venous pressure, albeit at a subclinical level. All these adverse influences may lead to an increased rate of morbidity after major liver resection, providing the rationale for the application of PVE in these patients.

SEQUENTIAL PVE FOLLOWED BY TACE

While conducting PVE in patients with HCC, the following issues must be considered: (1) the underlying liver disease in the majority of patients with HCC may impair the capacity for FLR hypertrophy after PVE^{4,15-17}; (2) cessation of portal flow may induce a compensatory increase in the arterial blood flow in the embolized segments¹⁸ and result in the rapid growth of the tumors after PVE because most HCCs are hypervascular tumors fed mainly by arterial blood flow. This concern should not be ignored because the tumor doubling time of HCC¹⁹ is thought to be lesser than that of hilar bile duct carcinoma, a prototype of slow-growing tumors, and the interval between PVE and liver resection is often prolonged in patients with HCC because of the slow process of liver regeneration^{10,17,20}; and (3) arteriportal shunts are frequently found in cirrhotic livers and HCC tumors, and these shunts may attenuate the effects of PVE. Bearing these concerns in mind, we have been combining selective transcatheter arterial chemoembolization (TACE) with PVE before carrying out major liver resection in patients with HCC. This

double preparation is aimed at enhancing the process of hypertrophy of the FRL segments after PVE, preventing tumor progression during the interval between the PVE and the planned liver resection by TACE, and strengthening the effect of the PVE by first embolizing any arteriportal shunts that may exist using TACE.

INDICATIONS OF PVE IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

In general, the indications for PVE are determined taking into account the balance between the ratio of the FRL volume to the total liver volume (TLV) and the extent of liver function impairment. Patients with advanced liver pathology (e.g., fibrosis or cirrhosis) clearly require a larger FRL volume than those with a normal liver.³ As a rule, we calculate the segmental liver volume in all patients with HCC scheduled to undergo liver resection based on computed tomographic (CT) images (Fig. 1A). Also, we evaluate the liver functional reserve in these patients according to the Child-Turcotte-Pugh (CTP) classification and indocyanine green retention rate at 15 minutes (ICGR15).²¹ ICGR15 is pharmacologically equivalent to the ICG elimination rate constant from the blood to the liver and represents the degree of sinusoidal capillarization, intrahepatic portovenous shunting, and alterations of the liver blood flow.²² The ICGR15 value provides more precise information on the magnitude of the liver functional impairment in patients who have conventionally been lumped together as CTP class A (score 5 to 6).²² Typically, we perform PVE for (1) patients with normal liver function, that is, an ICGR15 of $\leq 10\%$, if the FRL volume/TLV is $< 40\%$, and (2) even those with an impaired liver functional reserve, that is, $10\% < \text{ICGR15} \leq 20\%$, if the FRL volume/TLV is $< 50\%$. If the ICGR15 $> 20\%$, we consider major hepatectomy as contraindicated, even after PVE.²³

SEQUENTIAL TACE AND PVE

Once the indication for PVE is determined, we first carry out selective TACE for liver segments that bear the HCC tumor(s) (Fig. 1B).⁹ Following intra-arterial injection of epirubicin hydrochloride (Farmorbicin; Pfizer, Tokyo, Japan) and iodized oil (Lipiodol Ultra-Fluide; Guerbet Japan, Tokyo, Japan), the arterial branches of the segments to be resected are embolized with porous gelatin particles with a diameter of 1 to 2 mm (Gelfoam; Pfizer, Tokyo, Japan). In the case of large HCCs, the tumor(s) are often also fed by other arterial branches, such as a branch of segment 4 or right inferior phrenic artery, and these arterial branches are also embolized. The latter possibility should always be borne in mind because large HCCs in the right lobe, which frequently constitute an indication for PVE, are often adjacent to the diaphragm, which makes the right

Figure 1 Imaging studies of a 75-year-old man with hepatocellular carcinoma undergoing right hemihepatectomy after sequential transcatheter arterial chemoembolization (TACE) and portal vein embolization (PVE). (A) Computed tomography (CT) scan image before TACE and PVE, portal phase. A $6.6 \times 4.5 \times 3.6$ cm tumor is located in the right hemiliver from beneath the right diaphragm to the right anterior and posterior portal bifurcation (arrows). No portal vein tumor thrombosis was found. Right hemihepatectomy was indicated. Indocyanine green retention rate at 15 minutes (ICGR15) was 11%, and calculated left liver volume was 46% of total liver volume. (B) Selective TACE images. Tumor was fed by hepatic arterial branches to S8 dorsal + S5 (arrow) and S8 ventral (short arrow). These branches were selectively embolized. Branches to S7 (thin arrow), S6 (arrowhead), and right inferior phrenic artery were not embolized because no tumor stain was found from these branches. (C) Images of PVE performed 25 days after TACE. Dense accumulation of iodized oil in the tumor was confirmed (arrow). PVE was performed through ipsilateral approach by puncturing portal venous branch to S6. Portal branches to S5/8 (short arrow) and S6/7 (arrowhead) were embolized. Contrast medium and coils in these branches were visualized after PVE. (D) CT scan images on 14 days after PVE. Dense accumulation of iodized oil in the tumor (arrows) and coils in portal venous branches (arrowheads) were visualized. Calculated left liver volume at this time point was 60% of the total liver volume. ICGR15 value at the corresponding time point was 12%. AFP (α -fetoprotein) and des- γ -carboxy prothrombin (DCP) values before TACE and after PVE were as follows: 378 ng/mL and 3957 AU/mL (before TACE) and 19 ng/mL and 14 AU/mL (after PVE), AFP and DCP values, respectively.

inferior phrenic artery the major extrahepatic collateral artery, although this cannot be recognized unless selective angiography of this branch is performed.²⁴ Finally, iodized oil is administered intra-arterially into the branches of the nonembolized segments to enable intrahepatic metastases to be detected by subsequent CT.²⁵

We perform PVE when the conventional liver function test results (i.e., the serum aspartate transaminase [AST], alanine transaminase [ALT], and total bilirubin levels) stabilize after the TACE, usually 7 to 10 days after the procedure in most cases (Fig. 1C). A transhepatic ipsilateral approach under local anesthesia is

Figure 1 (Continued) (E) Finding of the liver surface at operation performed 7 days after confirmation CT scan. Embolized right liver (arrow) was dark and shrunken; the nonembolized left liver (arrowhead) was enlarged. (F) Finding of the resected right hemiliver. Massive necrosis of the tumor (arrows) was observed although viable lesion was also found, especially in the subcapsular area (arrowhead). No necrosis was found in the nontumorous liver parenchyma.

the approach of first choice.²⁶ When this approach is thought to be impossible due to the presence of tumor(s) in the puncture line, either the transhepatic contralateral approach or transileocolic approach is chosen.^{17,27} The embolization material consists of a mixture of porous gelatin particles with a diameter of 1 to 2 mm, thrombin (Thrombin-YOSHITOMI; Benesis Corporation, Osaka, Japan), iohexol (OMNIPAQUE; Daiichi-Sankyo, Tokyo, Japan), coils (Boston Scientific, Tokyo, Japan), and tobramycin (Tobracin; Towa-pharmaceutical, Osaka, Japan). Portal venous pressure is measured

before and after the procedure, but this measurement is technically impossible in the case of the transhepatic ipsilateral approach.³

In some particular cases, we adopt a modified method for PVE. For example, when HCC tumor(s) located in segments 6/7 are associated with portal venous thrombi in the common portal branch of segments 6/7 that extends to the right portal trunk, segments 6/7 are usually already atrophied due to the decrease in portal flow caused by the tumor thrombi, whereas segments 5/8, along with the left hemiliver, show compensatory hypertrophy. Right hepatectomy is indicated and thus PVE to segments 5/8 should be performed. From the viewpoint of conducting PVE, the transileocolic or transhepatic contralateral approach is contraindicated in these patients due to the presence of tumor thrombi in the right portal trunk. In addition, only portal tributaries to segments 5/8 should be embolized. In these particular cases, we usually perform a percutaneous transhepatic puncture of these portal venous tributaries under ultrasound guidance and directly inject 1 to 5 mL of absolute ethanol to occlude these tributaries. Occlusion of the portal tributaries after the ethanol injection can be confirmed by Doppler ultrasound.

FOLLOW-UP AFTER TACE AND PVE

Hepatic function after PVE is assessed based on the serum levels of AST, ALT, total bilirubin, and prothrombin time. Because the liver does not have an intrinsic ability to modulate portal flow, which is a function of splanchnic and systemic factors, the total portal flow is thought to remain unchanged after PVE.²⁸ Therefore, the same volume of portal flow as that before the PVE is assumed to enter the nonembolized liver segments exclusively. In view of these concerns, the portal venous flow in the embolized and nonembolized segments is examined every 2 to 3 days after PVE using Doppler ultrasound. Theoretically, only the hepatic arterial flow, which is increased by a compensatory mechanism, can be detected in the embolized segments. Detection of portal venous flow in the corresponding hepatic segments signifies recanalization of the portal vein. We usually inject absolute ethanol into these branches as described earlier.

Triple-phase enhanced CT is conducted 2 weeks after the PVE (Fig. 1D). In the first phase of the CT performed without a contrast medium (Lipiodol-CT), we check for the presence of any tumor nodules in the nonembolized segments.²⁵ The presence of iodized oil deposition, which is compatible with HCC nodules, that could not be detected in the initial contrast-enhanced CT scans obtained before PVE indicates a high likelihood of intrahepatic metastasis, and therefore curative resectional surgery may be difficult to expect.²⁵

Then, we recalculate the volumes of the embolized and nonembolized segments and of the tumor(s). The ICGR15 value and the changes in the serum levels of α -fetoprotein (AFP) and des- γ -carboxy prothrombin (DCP) are reassessed also.

If the FRL volume and ICGR15 value satisfy the criteria of liver resection as described earlier, liver resection is scheduled (Fig. 1E). If the degree of hypertrophy of the nonembolized segments is considered insufficient, the volumetric changes of the liver segments are followed by a subsequent CT conducted 1 to 2 weeks later, and the indications for liver resection are reevaluated.⁹

TOLERANCE OF SEQUENTIAL TACE and PVE

Table 1 shows the characteristics of the 45 patients with HCC undergoing TACE followed by PVE during the 13 years between 1995 and 2007. The first concern of this double occlusion of the arterial and portal venous systems is the possible infarction of noncancerous liver parenchyma and resultant intolerance of the procedure. Fig. 2 demonstrates the chronological changes in the standard liver function test results. The maximum serum levels of AST and total bilirubin and the minimum value of the prothrombin time during the respective periods are shown. As expected, marked elevation of the AST together with a significant febrile episode was noted after TACE, reflecting the inflammatory reaction (Fig. 2A). It has been reported that occlusion of the portal vein alone by PVE does not evoke a necrotic or inflammatory reaction and the serum AST and ALT levels remain stable after PVE.²⁷ By contrast, patients undergoing sequential PVE following initial TACE showed a significant elevation of the serum AST and ALT, suggesting the occurrence of an inflammatory reaction in the liver parenchyma (Fig. 2A). Nevertheless, this change

Table 1 Patient Characteristics

Male/Female	39/6
Age (y)	61 (19–80)
Viral hepatitis: positive	32/45 (71%)
HBV: positive	16/45 (36%)
HCV: positive	19/45 (42%)
Median tumor size (cm)	7.8 (1.1–15)
< 10 cm	26 (58%)
≥ 10 cm	19 (42%)
Portal venous tumor thrombi: positive	11/45 (24%)
Pretreatment ICGR15	
< 10%	21 (48%)
10–20%	20 (45%)
≥ 20%	3 (7%)
Repeated liver resection	7/45 (16%)

Values are expressed as median (range).

HBV, hepatitis B virus; HCV, hepatitis C virus; ICGR15, indocyanine green retention rate at 15 minutes.

Figure 2 Chronological alterations in the (A) serum aspartate transaminase, (B) serum total bilirubin, and (C) prothrombin time during periods of sequential transcatheter arterial chemoembolization (TACE), portal vein embolization (PVE), and hepatectomy (Hx). The maximum (A and B) and minimum (C) values during the respective periods are shown. Data are expressed as mean $\pm$ standard error of mean. * $p < 0.0001$, † $p < 0.001$, and § $p < 0.05$ compared with the values before TACE. Paired t test.

was transient. Symptoms of the postembolization syndrome that occurs frequently after TACE, such as pain, nausea, and vomiting, were minimal. The increase in total bilirubin level and decrease in the prothrombin time after PVE were mild and transient, suggesting the liver functional impairment was minimal, if present (Figs. 2B and C). In addition, examination of the resected specimens obtained at the time of the scheduled liver resection revealed that the necrosis of the noncancerous liver parenchyma was minimal in most cases, whereas that of the HCC tumors was marked. The absence of parenchymal necrosis is most likely explained by the recanalization of the hepatic arterial tributaries

Figure 3 Increment in the portal venous pressure after portal vein embolization (PVE). The values in 30 patients in whom the measurement was possible are shown. Paired *t* test.

after TACE because parenchymal necrosis, albeit partial, was observed in anecdotal cases where repeated TACE was performed after PVE. All these results strongly indicate that sequential TACE followed by PVE can be tolerated well by HCC patients with underlying liver diseases. In this context, we argue against the proposal of others to carry out PVE after a minimum interval of 2 weeks after the initial TACE.¹⁰

The concern of an abrupt increase in portal venous pressure after major hepatectomy causing liver damage appears to have been overlooked while performing PVE, although recent studies on living donor liver transplantation have focused on portal pressure and the small-for-size syndrome.^{29,30} In our previous series, the increase in portal pressure immediately after PVE in normal livers was 4.9 ± 2.7 mm H₂O.³¹ Despite the higher baseline portal pressure (18.6 ± 4.8 cm H₂O), the increase was similar in patients with cirrhosis and HCC 4.1 ± 2.8 cm H₂O (Fig. 3). No information on the chronological changes of the portal pressure after PVE is available yet, but the elevation is thought to be transient, with the pressure gradually returning to the baseline within 2 to 3 weeks, as indicated by the portal flow velocity (cm/sec) changes measured by Doppler ultrasound.³²

Figure 4 Volumetric change in the future remnant liver in patients with hepatocellular carcinoma (HCC) after sequential transcatheter arterial chemoembolization (TACE) and portal vein embolization (PVE). The data of patients with liver metastases undergoing PVE alone, as the control group, are also shown ($n=46$). HCC:ICGR15 $\leq 10\%$ ($n=19$), HCC:ICGR15 10 to 20% ($n=17$), and HCC:ICGR15 $> 20\%$ ($n=2$). White columns indicate values before TACE; the black columns indicate those after PVE. The volumetric gain after PVE (differences in values before and after PVE) in patients with HCC was not statistically significantly different from that in the patients with liver metastases. ICGR15, indocyanine green retention rate at 15 minutes. Data are expressed as mean $\pm$ standard error of mean. Dunnett test.

EFFICACY OF PVE IN A CHRONICALLY DISEASED LIVER

The second concern of applying PVE to patients with HCC is whether sufficient hypertrophy of the FRL can be achieved after PVE in a chronically injured liver because the capacity for liver regeneration after hepatic resection is reportedly impaired under such conditions.^{15,33} Our early experience revealed that the effect of PVE in inducing hypertrophy in the FRL segments was strengthened when the procedure was combined with preceding TACE,⁸ a finding consistent with that reported by Ogata et al.¹⁰ Fig. 4 depicts the volumetric changes of the FRL in patients undergoing right hemi-liver PVE. All of the patients with HCC underwent

Figure 5 Alterations of the tumor growth status during sequential transcatheter arterial chemoembolization (TACE) and portal vein embolization (PVE). (A) serum α -fetoprotein. (B) serum des- γ -carboxy prothrombin (DCP). Data are expressed as mean $\pm$ standard error of mean. $\ddagger p < 0.01$ and $\S p < 0.05$ compared with the values before TACE. Paired *t* test. Hx, hepatectomy.

initial TACE before the PVE. As the data from a control group, data of patients undergoing PVE alone for metastatic liver tumors, who are supposed to have a normal background liver, are shown. Data of anecdotal patients who underwent PVE despite not satisfying our criteria (i.e., those with an ICGR15 of $>20\%$) are also shown. According to our criteria, the more the liver functional impairment as evaluated by the ICGR15, the larger the minimum FLR volume indicated for PVE. Unexpectedly, the examination 2 weeks after PVE showed a similar degree of hypertrophy of the nonembolized FRL segments irrespective of their ICGR15 values. Taking into account the reported attenuation of the volume increase in larger FRL segments before PVE,^{27,34} this result might strongly suggest that a similar degree of hypertrophy of the FRL can be expected following PVE even in livers with impaired functional reserve when PVE is performed following TACE. In the present series, 14 patients in whom the degree of FRL hypertrophy was thought to be insufficient at this point (2 weeks after PVE) finally underwent the scheduled liver resection after a subsequent CT-based volumetric study was conducted after another 1 to 2 weeks.

TUMOR SUPPRESSION BY TACE

The third concern about applying PVE to patients with HCC is the possible growth of HCC tumors during the preparation period. Fig. 5 depicts the tumor status as assessed by two independent tumor markers, that is, the serum levels of AFP and DCP. As a whole, tumor growth was at least suppressed by the preceding TACE. Examination of the resected specimens also confirmed marked necrosis of the tumor tissues, although viable HCC cells were also observed, especially in the subcapsular region, in most cases (Fig. 1F).

PERFORMANCE OF SCHEDULED LIVER RESECTION AND PVE AS A TEST TO JUDGE THE SUITABILITY OF THE PATIENT FOR MAJOR LIVER RESECTION

Throughout the atrophy/hypertrophy process after PVE, the total liver volume reportedly remains unchanged.^{27,35} From the functional and hemodynamic viewpoints, the functional capacity of the total liver as assessed by antipyrine clearance and the total liver blood flow as evaluated by sorbitol clearance were not altered after PVE in the normal liver.³⁶ Fig. 6 depicts the ICGR15 values before and after PVE in patients with HCC. In 42 of 45 patients, ICGR15 values after PVE remained comparable to those obtained at baseline, and scheduled major liver resection could be performed after confirming a sufficient degree of hypertrophy in the FRL. The median interval between the PVE and hepatectomy in these patients was 29 days (range, 6 to

Figure 6 Future remnant liver (FRL) volume ratio (volume % of FRL) and the indocyanine green retention rate at 15 minutes (ICGR15) in 45 patients undergoing sequential transcatheter arterial chemoembolization (TACE) and portal vein embolization (PVE). (A) Values before TACE and PVE. (B) Values after TACE and PVE. Clear circles denote patients who underwent scheduled major liver resection, clear triangles denote patients who underwent downscaled liver resection, and filled circles denote those in whom liver resection was abandoned. (C) Alterations in the volume % of FRL and ICGR15 values following TACE and PVE in three patients in whom the scheduled major liver resection was abandoned.

100 days). In some of them, we decided to carry out liver resection even though the AST and ALT values did not return to baseline and/or the postembolization fever had not yet subsided because we judged that these inflammatory reactions occurred solely in the embolized segments that were to be resected.

But it is noteworthy that the ICGR15 values deteriorated in 3 of the 45 patients. This phenomenon can be more comprehensively understood by delineating the alterations in both the FRL volume and the ICGR15 values (Fig. 6). By our criteria of balancing the FRL volume with the extent of liver injury as evaluated by the ICGR15 value, major liver resection would be indicated for the patients (i.e., points, located in the upper left area of this graph [white zone]). Although most patients were initially located out of this area before PVE, they were successfully moved into this area after PVE (Figs. 6A and B); the 3 patients moved in a paradoxical direction (Fig. 6C). Some of them even developed ascites after PVE. These observations may be ascribed to the development of latent portosystemic collaterals that cannot be detected without conducting PVE. Scheduled major liver resection was abandoned in these patients: Downscaled liver resections (from left trisectorectomy to extended left hepatectomy and from extended S6/7 resection to extended S6 resection) were performed in 2 patients and liver resection was entirely abandoned in 1 patient. The fact that some patients do not respond favorably to PVE indicates another important aspect of PVE, that is, as a preoperative test to determine whether or not the patient would be a suitable candidate for major liver resection. A similar proposal was made by Farges et al.²⁰

OUTCOME FOLLOWING LIVER RESECTION CONDUCTED AFTER SEQUENTIAL TACE AND PVE

There was no operative mortality in the 44 patients who underwent liver resection following sequential TACE and PVE, including among the 42 patients who underwent major liver resection as scheduled. The median maximum total bilirubin level after liver resection was 1.4 (range, 0.4 to 2.8) mg/dL (Fig. 2B). The 1-, 3- and 5-year survivals of the patients with and without portal venous thrombi who underwent liver resection after sequential TACE and PVE were 54.6%, 27.3%, and 27.3% (n = 11), and 80.8%, 61.7%, and 61.7% (n = 33), respectively.

CONCLUSION

In conclusion, double preparation with initial TACE followed by PVE is an effective preoperative intervention in patients with HCC scheduled for major liver resection. This double preparation is well tolerated

and enhances the hypertrophy process of the FRL in patients with chronic liver injury. It also suppresses the tumor growth during the preparation period for the resection. Furthermore, PVE also functions as a preoperative test to select suitable candidates for major liver resection.

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