Sequential Arterial and Portal Vein Embolization in Patients with Cirrhosis and Hepatocellular Carcinoma: The Hospital Beaujon Experience

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ABSTRACT

When feasible, hepatic resection is the treatment of choice for large hepatocellular carcinoma (HCC). Because HCC is often developed on chronic liver disease, which is known to have limited regeneration capacity, major hepatic resections are often contraindicated. Portal vein embolization (PVE) has been introduced to extend the indications for major hepatic resection and to increase the safety of the surgical procedure. However, hypertrophy after PVE is often less than in normal liver. It has been suggested that preoperative sequential arterial embolization and PVE have a strong anticancer effect and could increase the rate of hypertrophy more than PVE alone. In our experience, sequential arterial embolization and PVE effectively increase the future liver remnant and induce a high rate of complete tumor necrosis. This combined procedure should broaden the indication for major resection in chronic liver disease.

KEYWORDS: Liver—HCC, liver—intervention, liver—portal vein embolization

Objectives: Upon completion of this article, the reader should understand the indications for performing sequential arterial and portal vein embolizations in patients with hepatocellular carcinoma.

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Therapeutic embolization of portal venous branches or of hepatic arteries has been developed and utilized during the past two decades.¹ Portal vein embolization (PVE) is applied mainly preoperatively to induce hypertrophy of the anticipated remnant liver and thus,

used to increase the safety of major resection in patients with liver malignancy while transcatheter arterial chemoembolization (TACE) is one of the most widely used treatments for patients with unresectable hepatocellular carcinoma (HCC). This article presents an overview of a

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combined approach for patients with HCC who are considered marginal candidates for hepatic resection utilizing a strategy of sequential arterial and PVE based on our experience at the Hospital Beaujon in France.

RATIONALE

Portal Vein Embolization

Preoperative PVE has been used to induce compensatory hypertrophy of the future liver remnant (FLR) before major liver resection and is usually indicated in patients with liver metastases or hilar bile duct cancer before extended resection. However, a great proportion of patients with chronic liver disease continue to present with advanced large tumors requiring major resection. Although some concern exists about the regenerative capacity of fibrotic or cirrhotic liver parenchyma after technically successful PVE, it has been shown that preoperative PVE induces significant hypertrophy of the FLR even in patients with chronic liver disease.² Furthermore, it has been shown that preoperative PVE improves the safety and tolerance of major liver resection in patients with chronic liver disease.^{3,4} A direct antitumoral effect of PVE on HCC was initially suspected when used to control tumor thrombus spread within the portal vein but that has not been confirmed.⁵ Conversely, researchers have shown that there is a compensatory increase in arterial flow in the embolized lobe after PVE that could accelerate the growth of the HCC.^{6,7}

Transcatheter Arterial Chemoembolization

Transcatheter arterial chemoembolization (TACE) involves the administration of a chemotherapeutic agent (e.g., doxorubicin, mitomycin C, and/or cisplatin) into the hepatic artery followed by hepatic artery embolization. Because liver tumors preferentially receive their blood supply from the hepatic artery, occlusion of this artery induces selective ischemia of the tumor and enhances the cytotoxicity of the chemotherapeutic agent. Two prospective studies and two meta-analyses reported earlier this decade showed a significant survival benefit with TACE in unresectable HCCs.⁷⁻¹¹ However, there has been no clear evidence that neoadjuvant TACE procedures prolong overall survival or disease-free survival after curative resection of HCC.^{12,13}

Combining TACE and PVE

It has been speculated that performing preoperative selective TACE and PVE in a standardized sequential manner could increase the rates of hypertrophy and resection, mainly by decreasing the arterial flow to the liver that will subsequently be treated with PVE, by

suppressing arterioportal shunts that may negatively affect regeneration and by having a strong anticancer effect on the HCC.

HISTORY

In the 1980s and early 1990s, three groups of investigators performed combined TACE and PVE in a small number of patients.^{5,14-16} Interestingly, most of the patients that have been treated in this fashion were considered nonsurgical candidates. Procedures were different in terms of materials used and the timing of the TACE and PVE procedures:

- Nakao et al¹⁴ performed embolization of both the hepatic artery and portal vein with Gelfoam sponge, while Yamakado et al¹⁵ used TACE with injection of a mixture of iodized oil and doxorubicin followed by administration of Gelfoam and transportal ethanol injection.
- Nakao et al¹⁴ performed simultaneous embolization of the hepatic artery and portal vein, while Kinoshita et al⁵ did the PVE 2 weeks after hepatic artery recanalization, and Yamakado et al¹⁵ performed the portal vein occlusion 1 to 4 weeks after TACE.

Results of these preliminary studies are summarized as follows:

1. Complete necrosis of the tumor assessed by histologic examination was observed in most cases (14 of 17 [82%]).
2. Simultaneous arterial and portal vein embolization led to hepatic infarction in many cases with an infarction ratio ranging from 5 to 35% and a recovery time after the combined procedure longer than after TACE alone.¹⁴ Nakao et al¹⁴ recommended "that combined embolization should be performed only in cases that involve relative small tumors and that are located in the subsegment region near the surface of the liver."
3. Some patients became resectable after the procedure.^{14,15}
4. Most of the nonresected patients (seven of the nine in the Yamakado study) showed no recurrence or intrahepatic metastasis during a follow-up of 7 to 42 months.¹⁵
5. TACE could be repeated in patients with incomplete response with mild liver damage.¹⁵

THE HOSPITAL BEAUJON EXPERIENCE

The purpose of our study was to investigate the tolerance and efficacy of preoperative sequential TACE and PVE before right hepatectomy in patients with chronic liver disease and HCC, and to compare perioperative

outcome with that of a matched group of patients undergoing PVE alone.¹⁷

Technique

TACE was performed before PVE. After arterial and portal venous flow assessment, the tip of the catheter (5-F or coaxially placed microcatheter depending on the difficulty of catheterization) was placed selectively into the right hepatic artery. A mixture of 10 to 15 mL iodized oil and 40 to 60 mg doxorubicin was injected under fluoroscopic control, followed by embolization with gelatin-sponge until complete stasis was achieved.

All patients underwent volumetric helical computed tomographic (CT) estimation of liver volume before PVE (but not before TACE) and before surgery. The interval between PVE and preoperative CT volumetry was 4 to 6 weeks and the interval between preoperative CT volumetry and surgery was 6 to 8 days. Measurements were performed for the whole liver as well as for the right and left lobes, 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 $\times$ 100)/total liver volume.

PVE was performed at least 3 weeks after TACE (mean interval 3.4 weeks) (Figs. 1 and 2). Right PVE was performed using the contralateral transhepatic approach. The left portal branch was punctured using sonographic guidance and with the patient under general anesthesia. Following portal venography, the right anterior and posterior portal branches were embolized with a mixture of ethiodized oil and n-butyl cyanoacrylate until complete stasis was achieved.

Right hepatectomy was performed 4 to 8 weeks after PVE. All patients underwent liver resection by one of two senior liver surgeons, using a standardized technique for right hepatectomy. After right hepatectomy, the resected specimens were examined pathologically, paying special attention to the extent of necrosis of HCC. Tumour necrosis was defined as complete if no viable cells were observed in any nodule.

Results of Sequential Arterial and Portal Vein Embolization

Sequential TACE and right PVE were feasible in all patients (18 of 18 [100%]) and they were discharged between 2 and 7 days after each procedure with no major complications noted. Results of liver function tests after TACE and after PVE showed peak levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) that were significantly higher than baseline but

returned to baseline before surgery (mean peak levels of AST and ALT after PVE were significantly higher in the TACE + PVE group than in the PVE alone group (303 U/L and 200 U/L versus 95 U/L and 100 U/L, respectively). The mean increase in percentage FLR was 12% (the mean increase in the TACE + PVE group was significantly higher than that in the PVE alone group [8%]). Sixty-seven percent of the patients had an increase of more than 10% but only 22% of the patients with F4 fibrosis had an increase of more than 10%.

Seven of the 18 patients had no perioperative or postoperative complications; two died of liver failure during the hospital stay. The most common complications were significant ascites, liver failure, and pulmonary complications.

Examination of the resected specimens showed that complete necrosis of the tumor induced by TACE combined with PVE occurred in 83% of the cases. Overall survival rates were 83%, 54%, and 43% at 1, 3, and 5 years, respectively. Recurrence-free survival rates were 78%, 37%, and 37% at 1, 3, and 5 years, respectively.

Comparison with Other Recent Series

Aoki et al¹⁸ reported their experience in 17 patients with HCC. Some findings were similar to our experience:

- TACE and PVE were feasible in all 17 patients.
- The AST and ALT values increased within 3 days after TACE and returned to their baseline value after 1 week. After PVE, the values increased again within 3 days and returned to their pre-PVE values within 2 weeks.
- No major complications occurred after sequential TACE and PVE. However, there were minor complications such as cholecystitis, pleural effusion, asthma attack, ascites, and bowel obstruction (all minor complications were treated conservatively).
- Examination of the resected specimens showed that the extent of the tumor necrosis was 50 to 60% in 4 patients, 70 to 80% in 2 patients, and 90 to 100% in 10 patients.
- All patients but one (94%) ultimately had major hepatic resection.
- The 5-year disease-free and overall survival rates after curative hepatic resections were 46.7 and 55.6%, respectively.

However, there were discrepancies and other findings:

- The median interval between the TACE and PVE procedures was only 9 days; this shorter interval could explain the higher rate of complications in the Aoki et al article (5 of 17 [29%]) versus no complication in our series.

Figure 1 Sequential arterial and portal vein embolization in a patient with hepatocellular carcinoma. (A) Arterial phase computed tomography (CT) showing a large hypervascular tumor in the right liver. (B) Portal venous phase CT shows a hypoattenuating tumor with central necrosis. (C) A more caudal section on portal venous phase CT showing the left portal vein. (D) Hepatic arteriogram shows that the tumor is hypervascular and supplied by the right hepatic artery. The lesion was treated with transcatheter arterial chemoembolization (TACE) (not shown). (E) Direct transhepatic portography from contralateral approach performed 3 weeks after TACE.

- The volumes of the nonembolized and embolized liver segments was evaluated by contrast-enhanced CT ~2 weeks after the PVE and showed that sufficient hypertrophy of the future remnant segments was achieved.
- Serum alpha-fetoprotein (AFP) levels between the TACE and PVE procedures and between the PVE and the hepatectomy procedures were significantly lower than the AFP levels before TACE.

Figure 1 (Continued) (F) Portography after embolization of the right portal vein. (G) Arterial phase CT after sequential arterial and portal vein embolization shows massive uptake of the Lipiodol by the tumor. (H) Portal venous phase CT after sequential arterial and portal vein embolization shows a dramatic decrease in size of the tumor compared with (B). (I) Portal venous phase CT obtained at the same level as (C) shows that the right portal branches are occluded and marked hypertrophy of the left lobe is seen. The patient had successful hepatic resection.

Comparison with PVE Alone in Patients with HCC

In our experience, the FLR and the mean increase in percentage FLR were significantly higher in the patients who had sequential TACE and PVE than in patients with PVE alone (12% versus 8%).¹⁷ Examination of the resected specimens showed that complete necrosis of the tumor induced by TACE combined with PVE occurred in 83%, compared with 5% following PVE alone.¹⁷

There was a clear relationship between the increase in percentage FLR volume and postoperative risk. The overall postoperative morbidity rate was 18%, 67%, and 100% if the increase in percentage FLR volume was > 10%, between 5 and 10%, and < 5%, respectively. The overall postoperative mortality rate was 0%, 13%, and 50% if the increase in percentage FLR volume was > 10%, between 5 and 10%, and < 5%, respectively.

The overall survival rates were not significantly different but 1-, 3-, and 5-year recurrence-free survival rates were higher in the TACE + PVE patients than in the PVE patients (83%, 54%, and 43% versus 72%, 31%, and 31%, respectively). 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%).¹⁷

Our study concluded that sequential TACE and PVE before hepatic resection increases the rate of hypertrophy of the FLR and leads to a higher rate of complete tumor necrosis associated with longer recurrence-free survival than PVE alone. Our results confirm Yamakado's results,¹⁶ which demonstrated that hypertrophy of the nonembolized liver parenchyma was greater with combined use of TACE and PVE than in the patients without TACE (57% versus 36%).

Figure 2 Sequential arterial and portal vein embolization in a patient with hepatocellular carcinoma. (A) Coronal reconstruction of portal venous phase CT shows a large hypervascular tumor of the right liver. (B) Coronal reconstruction of portal venous phase CT after sequential arterial and portal vein embolization. The tumor has decreased and is mostly necrotic. Note the occluded right portal branches. Compared with (A), there is a marked hypertrophy of the left lobe due to portal vein embolization. The patient had successful hepatic resection.

COMPLICATIONS

Although complications after sequential arterial and portal vein embolization were minor in the published series, one should remember that PVE in patients with chronic liver disease has a higher morbidity than in patients with normal underlying liver. The two most frequent complications are liver failure (6%) and portal vein thrombosis (5%); conversely to patients with normal liver where they are observed in less than 1% of the cases.^{2,19} Transient ascites may also be seen. The rate of complications is higher in patients with cirrhosis than with fibrosis.²⁰

PVE Alone versus Sequential Arterial Embolization and PVE for HCC

PVE alone is used in patients with HCC to extend the indications for and the safety of major hepatectomy, and is indicated in patients with a F3 fibrosis score or lower and/or a Child-Pugh A cirrhosis without severe portal hypertension with an anticipated inadequate FLR volume. According to different authors, this last criterion may be either a FLR volume less than 40%, a future liver volume less than 285 mL/m², or when a major resection is planned.^{2,12,21} In this indication, sequential arterial and portal vein embolizations seem even more adequate than PVE alone because they permit a tumor control and increase more the rate of hypertrophy of FLR. Therefore, at our institution, when a PVE is indicated in HCC patients with chronic liver disease, we systematically perform sequential arterial and portal vein embolization.

HCC may also develop in patients with non-alcoholic fatty liver disease. In these patients, HCC may be observed before cirrhosis is seen.²² The size of the tumor at diagnosis is often large because these patients are not enrolled in a screening program and major

resections are often required. Although not been extensively studied, patients with nonalcoholic fatty liver disease may have a limited regeneration capacity and present with at least some liver fibrosis on preoperative biopsy that could indicate the need for sequential arterial and portal vein embolization.

Another indication of PVE with or without TACE is to determine preoperatively the patients who are at higher risk for postoperative liver failure. Two studies have shown that those who do not exhibit significant left hypertrophy after PVE are at higher risk.^{21,23} We have also demonstrated that minimal or absence of hypertrophy after PVE alone or sequential arterial and portal vein embolization could be a prognostic factor. The overall mortality rate was 0% when the percentage FLR/total liver volume increased more than 10%, and was 50% if percentage FLR/total liver volume did not exceed 5%.¹⁷

Finally, in the future, sequential TACE and PVE may be indicated in unresectable patients with Evidence Medicine Level 1 showing an improvement in survival.¹³ Because complete necrosis of the tumor induced by TACE combined with PVE is achieved in the vast majority of the cases, there may be a role for sequential arterial and portal vein embolizations in unresectable patients.

CONCLUSION

Our experience corroborates other studies in showing that sequential arterial embolization and PVE effectively increase the FLR and induce a high rate of complete tumor necrosis. This combined procedure may replace the indication of PVE alone for major resection in chronic liver disease. Further studies are needed to evaluate the role of sequential arterial embolization and

PVE in other indications such as nonalcoholic fatty liver disease.

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