Sequential Preoperative Arterial and Portal Venous Embolizations in Patients With Hepatocellular Carcinoma

Taku Aoki, MD; Hiroshi Imamura, MD, PhD; Kiyoshi Hasegawa, MD, PhD; Akira Matsukura, MD; Keiji Sano, MD, PhD; Yasuhiro Sugawara, MD, PhD; Norihiro Kokudo, MD, PhD; Masatoshi Makuuchi, MD, PhD

Hypothesis: Hepatic resection is the only curative treatment for large hepatocellular carcinoma (HCC). Sequential, preoperative, selective transcatheter arterial chemoembolization (TACE) and portal vein embolization (PVE) allow feasible and safe major hepatic resections to be performed in HCC patients with chronic liver disease.

Design: Retrospective cohort study.

Setting: University hospital.

Patients: Seventeen HCC patients who underwent preoperative PVE following selective TACE for planned major hepatic resections were enrolled. The indications for PVE were determined using the volumetric ratio of the future remnant liver parenchyma and the indocyanine green retention ratio at 15 minutes.

Intervention: Preoperative TACE and PVE.

Main Outcome Measures: Tumor characteristics and blood test results before and after TACE and PVE, changes in the volumes of the liver segments after PVE, the feasibility of major hepatic resections, and short- and long-term patient prognoses.

Results: The liver function test results transiently worsened after TACE and PVE but returned to baseline levels within 1 (after TACE) or 2 (after PVE) weeks. Within 2 weeks after PVE, 22% ± 4% hypertrophy of the nonembolized segments was obtained; subsequent major hepatic resections were feasible in 16 patients. Four minor complications (25%) were experienced postoperatively; however, liver failure did not occur. The 3-year overall and disease-free survival rates after curative resection were 55.6% and 46.7%, respectively.

Conclusions: Sequential TACE and PVE contribute to both the broadening of surgical indications and the safety of major hepatic resections performed in HCC patients with damaged livers. The long-term outcome of this treatment strategy is satisfactory.

Arch Surg. 2004;139:766-774

Currently, hepatic resection is considered to be the only curative treatment for large hepatocellular carcinoma (HCC), because liver transplantation or ablative therapy is not indicated for these tumors. However, most patients with HCC have impaired hepatic functional reserves because of hepatitis B or C virus–associated liver cirrhosis. Consequently, the amount of liver parenchyma that can be safely resected in these patients is extremely limited. Major hepatic resections (the resection of 3 or more Couinaud segments), which are often required in patients with large HCC, are often contraindicated in many HCC patients because of the increased risk of postoperative liver failure. This dilemma limits the number of HCC patients who can benefit from hepatic resections and results in a low resectability rate. This concern is further underlined by the fact that HCC frequently metastasizes via the portal venous system and that anatomic hepatic resections are therefore advantageous in terms of long-term survival and a cure. Preoperative portal vein embolization (PVE) has been introduced in an attempt to extend the indications for major hepatic resections and to increase the safety of this procedure. First reported by Makuuchi et al., the aim of PVE was to induce the atrophy of the segments to be resected and encourage a compensatory hypertrophy of the remaining segments. This technique was first applied to patients with hilar bile duct tumors (Klatskin tumors) and its indications were subsequently extended to patients with metastatic liver tumors.

Some previous reports have also documented the application of preoperative PVE in patients with HCC. However, the indications for PVE in patients with HCC continue to be debated for the following reasons: (1) the livers of most HCC patients are com-
promised by an underlying liver disease, and the capacity for liver regeneration after hepatic resection is thought to be impaired under such conditions,16-18 making it difficult to predict whether sufficient hypertrophy of the future remnant liver segments can be achieved after PVE; (2) because most HCCs are hypervascular tumors fed mainly by arterial blood flow, cessation of the portal flow induces a compensatory increase in arterial blood flow in the embolized segments,19 resulting in the rapid progress of the tumors after PVE; and (3) arteriportal shunts are frequently found in cirrhotic livers and HCC tumors, and these shunts may attenuate the effects of PVE.

In view of these concerns, we combined selective transcatheter arterial chemoembolization (TACE) with PVE before performing major hepatic resections in HCC patients with chronically diseased livers. This double preparation aimed at (1) using TACE to prevent tumor progression during the period between the PVE and the planned hepatectomy and (2) strengthening the effect of the PVE by first embolizing any arteriportal shunt that may exist using TACE. In this study, we describe the preoperative biological and clinical course of 17 HCC patients who underwent sequential TACE and PVE and also investigated the postoperative patient prognosis. We paid special attention to (1) the effect of TACE and PVE on the baseline hepatic functional reserve, (2) the hypertrophy of the future remnant liver segments after selective TACE and PVE, (3) the risk of tumor progression after PVE, and (4) the postoperative short- and long-term clinical outcomes.

METHODS

CRITERIA FOR SEQUENTIAL TACE AND PVE

In our department, all HCC patients who have been scheduled to undergo surgery first receive an indocyanine green (ICG) test to evaluate their baseline hepatic functional reserve. In addition, the volumes of the liver segments to be resected and the volumetric ratio of the future remnant liver parenchyma (including intrahepatic portal anatomy and to check for the presence of portal venous tumor thrombus. Embolization was separately performed under fluoroscopic control for each portal branch feeding a Couinaud segment. After the embolization of all the planned portal branches, a portogram was repeated to confirm the presence of portal venous tumor thrombus. The levels of α-fetoprotein (AFP; reference range, <20 ng/mL) and des-γ-carboxy prothrombin (DCP) (reference range, <40 arbitrary units [AU/mL]) were also measured before TACE and during the period between TACE and PVE.

TACE AND PVE PROTOCOLS

Selective TACE of the segments to be resected and intra-arterial injection of iodized oil (Lipiodol Ultra-Fluide; Andre Guerbet, Aulnay-Soubois, France) in the future remnant segments were performed before PVE. Following the intra-arterial injection of epirubicin hydrochloride (Farmorubicin; Pharmacia, Tokyo, Japan) and iodized oil, the arterial branches of the segments to be resected were embolized with gelatin cubes (Spongé; Yamamoto, Tokyo, Japan). When the HCC tumors were fed by other arterial branches, such as the arterial branch of segment 4 or the right inferior phrenic artery, these arterial branches were also embolized. Only the intra-arterial injection of iodized oil was performed in the branches of nonembolized segments to enable IM to be detected by subsequent CT.21

The PVE was performed once the liver functional test results had stabilized, usually 7 to 10 days after the TACE procedure in most cases. The PVE was performed using a previously described technique while the patient was under general anesthesia.22 A transileocolic approach was used in 16 patients, but a transhepatic approach was selected in 1 patient who had previously undergone surgery of the lower abdomen, resulting in severe adhesions in that area. The embolization material consisted of a mixture of gelatin powder (Gelfoam Powder, Pharmacia), thrombin (Mochida, Tokyo, Japan), diatrizoate sodium meglumine (60% Urografin; Schering AG, Berlin, Germany), and gentamicin. As of April 1998, stainless steel embolization coils (COOK Inc, Bloomington, Ind) were used to maintain the PVE effect. A portogram was obtained to assess the intrahepatic portal anatomy and to check for the presence of portal venous tumor thrombus. Embolization was separately performed under fluoroscopic control for each portal branch feeding a Couinaud segment. After the embolization of all the planned portal branches, a portogram was repeated to confirm the efficacy of the embolization. In addition, the portal venous pressure (PVP) was measured before and after the procedure.

FOLLOW-UP AFTER TACE AND PVE

Hepatic function after TACE and PVE was respectively assessed by blood tests for aspartate aminotransferase (AST) (reference range, 9-38 U/L), alanine aminotransferase (ALT) (reference range, 4-36 U/L), and total bilirubin (reference range, 0.3-1.3 mg/dL [5.13-22.23 µmol/L]). In addition, the ICG R15 value and the changes in the levels of AFP and DCP were reassessed approximately 2 weeks after PVE. Both the

PATIENTS

Between October 1, 1994, and December 31, 2002, a total of 592 hepatic resections were performed for the treatment of HCC in the Hepato-Biliary-Pancreatic and Transplantation Surgery Division of the University of Tokyo, Tokyo, Japan. Among them, 65 were major hepatic resections (3 or more Couinaud segments), and 16 of the 65 patients received hepatic resections following sequential preoperative TACE and PVE based on the criteria described herein. In addition, another patient who had been scheduled for right hepatectomy received preoperative TACE and PVE but eventually did not undergo a hepatic resection. As a whole, 17 patients who received sequential, preoperative TACE and PVE were enrolled in the present study. All the patients were male, with a mean age of 61 years (range, 36-81 years). Results of tests for hepatitis B surface antigen and the anti–hepatitis C virus antibody were positive in 4 and 10 patients, respectively. Preoperative evaluations of the HCC tumors (number of tumors, tumor location, size of tumor, macroscopic vascular invasion [VI], macroscopic intrahepatic metastasis [IM], and distant metastases) were conducted using various imaging modalities, including abdominal ultrasound, enhanced CT, and abdominal angiography. The levels of α-fetoprotein (AFP; reference range, <20 ng/mL) and des-γ-carboxy prothrombin (DCP) (reference range, <40 arbitrary units [AU/mL]) were also measured before TACE and during the period between TACE and PVE.
Table 1. Preoperative Characteristics of Patients With PVE

<table>
<thead>
<tr>
<th>Patient No./ Age, y/sex</th>
<th>HCV Ab</th>
<th>ICG R15, %</th>
<th>AFP, ng/mL</th>
<th>DCP, AU/mL</th>
<th>Tumors, No.*</th>
<th>Tumor Location</th>
<th>Tumor Size, cm</th>
<th>Macroscopic VI</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/63/M 63 – M + − 8 37 92 861.0 3 S6-7, S8-5-4, S7 14.0</td>
<td>– – – 3 S6-7, S8-5-4, S7 14.0</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>2/63/M 63 – M + − 9 56 414 62.5</td>
<td>2 S6-7, S8 6.0</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>3/60/M 60 – M + – 17 30 681 167 317.0</td>
<td>4 S5-8, S9, S7, S2 12.0</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>4/62/M 62 – M – – 16 38 18 468 2295.0</td>
<td>2 S5-6-7, S8, S7 11.0</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>5/57/M 57 – M – + 40 191 139.0</td>
<td>3 S5-6, S6, S2 5.2</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>6/42/M 42 – M – – 5 36 11 18.0</td>
<td>3 S4-5-8, S5, S6 10.5</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>7/65/M 65 – M – + 14 41 9 25.0</td>
<td>Multiple Right liver 5.0</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>8/65/M 65 – M + – 9 33 2079 309.0</td>
<td>2 S5-8, S7 10.0 PVTT (S8)</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>9/68/M 68 – M – + 13 57 48 10.0</td>
<td>2 Hepatic hilum, S7 7.5</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>10/42/M 42 + – 11 56 759 600 10 239.0</td>
<td>3 S5-6-7, S5, S3 14.0 PVTT (S5, S8), TT in LHD</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>11/64/M 64 – M + – 8 36 3 328.0</td>
<td>2 Hepatic hilum, S5 4.3</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>12/78/M 78 – M – + 16 40 121 123 4223.0</td>
<td>1 S7-8 9.5 RHV invasion</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>13/61/M 61 – M – + 12 46 329 119 140 289.0</td>
<td>1 S5-6-7-8, S7 13.0 TT in RHV</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>14/54/M 54 + – 20 40 38 586 1555.0</td>
<td>1 S5-6-7-8 14.5 TT in LHV</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>15/64/M 64 – M – – 8 46 19 13 010.0</td>
<td>1 Hepatic hilum 9.5</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>16/36/M 36 + – 7 37 25 038 18 1913 423 3.0</td>
<td>1 Multiple Right liver 5.0</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>17/72/M 72 – M – – 11 45 77 63.0</td>
<td>1 Hepatic hilum 12.0</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HCV Ab, hepatitis C virus antibody; ICG R15, indocyanine green retention ratio at 15 minutes; LHD, left hepatic duct; MHV, middle hepatic vein; minus sign, negative; plus sign, positive; PVTT, portal venous tumor thrombus; RHV, right hepatic vein; TT, tumor thrombus; VI, vascular invasion; VR, volumetric ratio.

*Including macroscopic intrahepatic metastasis.

depletion of portal blood flow to the embolized segments and the patency of the nonembolized portal branches were evaluated repeatedly using color Doppler ultrasound (Multi-View 2000; Aloka, Tokyo, Japan) before hepatic resection. We regularly assessed the general status of each patient and recorded any complications. The volumes of the embolized and nonembolized segments and of the tumor(s) were recalculated using enhanced CT approximately 2 weeks after PVE. Hepatic resection was considered when (1) the volumetric ratio of the future remnant segments was approximately 40% (in cases with an ICG R15 of less than 10%) or 50% (in cases with an ICG R15 of 10%-20%) of the total liver parenchyma and (2) the liver function test results had returned to values that were comparable to those obtained at baseline. If the hypertrophy of the nonembolized segments was considered to be insufficient, the volumetric changes of the liver segments were followed by successive CT scans. Operations were reconsidered once the hypertrophy of the nonembolized segments became sufficient.

HEPATIC RESECTIONS AND PATIENT FOLLOW-UP

Our standard procedure for performing hepatic resections for HCC has been previously described.23 The location and number of tumors, as well as any suspicion of VI and IM, were determined using intraoperative ultrasonography as a final diagnostic procedure. During the dissection of the liver parenchyma, intermittent blood inflow occlusion was accomplished using the Pringle maneuver. All postoperative complications were recorded.

After operation, the resected specimens were examined pathologically, with special attention given to the extent of necrosis in both the HCC nodule and the noncancerous liver parenchyma. The tumor staging was determined based on the TNM classification according to the Union Internationale Contre le Cancer. Likewise, the staging of fibrosis was assessed according to the scoring system advocated by Desmet et al.24 Patient follow-up continued until May 30, 2003, ranging from 2.5 to 82.9 months for individual patients, with a median of 26.7 months.

STATISTICAL ANALYSIS

All data are expressed as the mean ± SEM. Survival curves were generated using the Kaplan-Meier method. The AST, ALT, and bilirubin values, as well as the AFP and DCP levels, were compared with those at baseline using analysis of variance for repeated measures. The AST, ALT, AFP, and DCP levels were compared after logarithmic transformation. Portal venous pressure, ICG R15, the volumetric ratio of the nonembolized liver segments, and the tumor volume after PVE were compared with pre-PVE values using paired t tests. Differences were considered to be statistically significant at P<.02 for the analysis of variance and at P<.05 for the other analyses.

RESULTS

PATIENT CHARACTERISTICS BEFORE TACE AND PVE

The baseline ICG R15 before TACE and PVE was less than 10% in 8 patients and between 10% and 20% in 9 patients. The volumetric ratio of the future remnant segments to the total liver parenchyma ranged from 30% to 57%, with a median of 40%. Six patients had solitary HCC tumors, whereas 11 patients had multiple tumors, regardless of multifocal tumors or IM; the size of the tumors ranged from 3.5 to 14.5 cm (median, 9.7 cm). Macroscopic VI was found in the segmental portal branch of 2 patients, in the major hepatic vein of 4 patients, and in the left hepatic duct in 1 patient using preoperative imaging modalities. One patient (No. 10) had comitant lung metastases, and a 2-staged lung resection operation was planned. The metastatic lesions became sufficient.
After PVE

Table 2. Perioperative Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Interval Before PVE and TACE, d</th>
<th>PVE Procedure</th>
<th>Changes in Volumetric Ratio of Nonembolized Segments After PVE, %</th>
<th>Changes in Portal Venous Pressure After PVE, cm H2O</th>
<th>Complications After PVE</th>
<th>Operative Procedure</th>
<th>Complications After Hepatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>TIPE</td>
<td>11.0→14.0</td>
<td>37→41</td>
<td>12</td>
<td>ERH</td>
<td>Biliary fistula</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>TIPE</td>
<td>17.5→21.5</td>
<td>56→60</td>
<td>16</td>
<td>RH</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>TIPE</td>
<td>26.0→29.0</td>
<td>30→45</td>
<td>43</td>
<td>RH</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>TIPE</td>
<td>22.4→26.1</td>
<td>38→58</td>
<td>43</td>
<td>RH</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>TIPE</td>
<td>16.5→20.5</td>
<td>40→49</td>
<td>19</td>
<td>ERH + wedge</td>
<td>Fluid collection</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>TIPE</td>
<td>13.5→17.0</td>
<td>36→39</td>
<td>33</td>
<td>ERH</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>39</td>
<td>TIPE</td>
<td>14.5→23.5</td>
<td>41→53</td>
<td>49</td>
<td>RH</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>TIPE</td>
<td>17.0→20.0</td>
<td>33→43</td>
<td>19</td>
<td>RH</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>TIPE</td>
<td>14.5→16.0</td>
<td>57→68</td>
<td>23</td>
<td>RH</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>TIPE</td>
<td>17.5→18.0</td>
<td>56→64</td>
<td>16</td>
<td>ERH + wedge</td>
<td>Pleural effusion</td>
</tr>
<tr>
<td>11</td>
<td>13</td>
<td>TIPE</td>
<td>10.5→15.5</td>
<td>36→50</td>
<td>30</td>
<td>RH</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>17</td>
<td>TIPE</td>
<td>16.5→21.5</td>
<td>40→52</td>
<td>21</td>
<td>RH</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>7</td>
<td>THPE</td>
<td>23.0→26.5</td>
<td>46→57</td>
<td>31</td>
<td>RH</td>
<td>Wound infection</td>
</tr>
<tr>
<td>14</td>
<td>9</td>
<td>TIPE</td>
<td>22.5→25.5</td>
<td>46→52</td>
<td>34</td>
<td>RH</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>38</td>
<td>TIPE</td>
<td>15.0→15.0</td>
<td>46→51</td>
<td>9</td>
<td>RH</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>9</td>
<td>TIPE</td>
<td>15.0→21.0</td>
<td>37→43</td>
<td>21</td>
<td>ERH</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>4</td>
<td>TIPE</td>
<td>15.5→18.0</td>
<td>45→48</td>
<td>17</td>
<td>ELH</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ELH, extended left hepatectomy; ellipses, no complication; ERH, extended right hepatectomy; ERH + wedge, extended right hepatectomy with wedge resection of segment 2 or 3; PVE, portal vein embolization; PVP, portal venous pressure; RH, right hepatectomy; TACE, transcatheter arterial chemoembolization; THPE, PVE via a transhepatic approach; TIPE, PVE via a transileocolic approach.

The median interval between the TACE and PVE procedures was 9 days (range, 4–48 days) (Table 2), and PVE was judged to be feasible in all 17 patients. Intraoperative measurements showed that the PVE induced a significant elevation in PVP (from 16.9±1.0 cm H2O to 20.5±1.0 cm H2O, P<.001) (Table 2). In 1 patient (No. 4), recanalization of the portal blood flow of the right lateral sector branch was observed 5 days after the PVE. Subsequent TACE and PVE of the right lateral sector branch were performed in this patient, because CT scans obtained 14 days after the initial PVE showed insufficient hypertrophy of the nonembolized left liver.

The chronological changes in AST, ALT, and bilirubin values after TACE and after PVE are shown in Figure 2. The average values for days 1 to 3 after TACE or PVE and the average values thereafter (from days 4 to 7 after TACE and days 4 to 14 after PVE) were compared with the baseline values for all 3 variables. All 3 variables increased significantly within 3 days after TACE (AST: P<.001; ALT: P=.004; bilirubin: P<.001) and returned to their baseline values after 1 week. The AST and ALT values increased again within 3 days after the PVE but returned to their pre-PVE values after 2 weeks. After the PVE, bilirubin values remained stable. Five patients experienced complications after the sequential TACE and PVE procedures. These complications consisted of fever as a result of cholecystitis, pleural effusion, an asthma attack, ascites, and a bowel obstruction (Table 2); all of these complications were treated conservatively.

The volumes of the nonembolized and embolized liver segments evaluated by enhanced CT approximately 2 weeks after the PVE showed that PVE induced significant hypertrophy or atrophy of the segments (nonembolized segments: from 534±47 mL to 643±27 mL, P<.001; embolized segments: from 745±47 mL to 626±42 mL, P<.001) (Figure 3A). The median volumetric ratio of the future remnant segments to the total liver parenchyma after PVE increased to 51% (range, 39%–68%), and this difference was also statistically significant (P<.001) (Table 2 and Figure 3B). Tumor progression during the period when the TACE, PVE, and hepatic resection procedures were successively performed was evaluated by tumor volume, the serum AFP level, and the plasma DCP level (Figure 4). The tumor volume

CLINICAL COURSE AFTER PVE

The volumes of the nonembolized and embolized liver segments evaluated by enhanced CT approximately 2 weeks after the PVE showed that PVE induced significant hypertrophy or atrophy of the segments (nonembolized segments: from 534±47 mL to 643±27 mL, P<.001; embolized segments: from 745±47 mL to 626±42 mL, P<.001) (Figure 3A). The median volumetric ratio of the future remnant segments to the total liver parenchyma after PVE increased to 51% (range, 39%–68%), and this difference was also statistically significant (P<.001) (Table 2 and Figure 3B). Tumor progression during the period when the TACE, PVE, and hepatic resection procedures were successively performed was evaluated by tumor volume, the serum AFP level, and the plasma DCP level (Figure 4). The tumor volume

©2004 American Medical Association. All rights reserved.
tended to decrease after the PVE, although the difference did not reach statistical significance. Serum 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 ($P = .001$ and $.003$, respectively). The plasma DCP level between the TACE and PVE procedures decreased significantly ($P = .02$), whereas the DCP level between the PVE and the hepatectomy procedures showed a decrease of borderline significance ($P = .02$).

In most patients, the ICG R15 values after PVE were comparable to those obtained at baseline, and the planned hepatic resections were performed in 16 patients (Figure 5). In 1 patient (No. 3), however, the ICG R15 value deteriorated from 17% to 28%, with the emergence of persistent ascites and pleural effusion. Conse-
HEPATIC RESECTION AND POSTOPERATIVE COURSE

Planned hepatic resections were performed after PVE in all but 1 of the 17 patients (94%). The mean interval between PVE and hepatic resection was 24.5 days (median, 21 days; range, 9-49 days). A right hepatectomy was performed in 10 patients, an extended right hepatectomy in 3 patients, an extended right hepatectomy with wedge resection of segment 2 or 3 in 2 patients, and an extended left hepatectomy in 1 patient (Table 2). The maximum bilirubin value after hepatic resection ranged from 0.6 to 2.1 mg/dL (median, 1.2 mg/dL), and no postoperative deaths or liver failures occurred. Four complications in 1 patient each were experienced: a biliary fistula, fluid collection, wound infection, and pleural effusion (Table 2). All of these 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. On the other hand, the extent of the necrosis of the noncancerous liver parenchyma was minimal in 14 patients, although segmental infarction was found in the resected right liver in 2 patients. The TNM classification was stage II in 4 patients, stage IIIA in 7 patients, stage IVA in 4 patients, and stage IVB in 1 patient. Fibrosis of the underlying liver was classified as stage 1 in 3 patients, stage 2 in 8 patients, stage 3 in 3 patients, and stage 4 in 2 patients (Table 3). As a result, chronic hepatitis in 11 patients and advanced cirrhosis in 2 patients were confirmed.

One patient with concomitant lung metastasis (No. 10) did not undergo a planned 2-stage lung resection because of a rapid increase of the lung tumors; therefore, the hepatic resection was considered to be noncurative. The long-term outcomes of the patients who received curative resections are shown in Figure 6. The 2- and 5-year disease-free survival rates after curative resection in 15 of the 17 patients were 46.7% and 46.7%, respectively, whereas the cumulative overall 2- and 5-year survival rates were 63.6% and 55.6%, respectively.

COMMENT

In this study, we investigated the characteristics and clinical course of patients who underwent sequential TACE and PVE before scheduled major hepatic resections. Our concerns were to clarify (1) the extent of hypertrophy of the nonembolized liver segments after PVE in chronically diseased livers, (2) the effect of PVE combined with selective TACE on baseline hepatic functional reserve and HCC tumor(s), and (3) the impact of this strategy on short- and long-term survival outcomes.

Although the indications for preoperative TACE and PVE were determined by the imbalance between the volumetric ratio of the future remnant liver parenchyma and hepatic functional reserve evaluated by ICG R15, the 17 patients in our series had advanced HCC tumors (stage III and IV in 12 patients), as reflected by the presence of multiple tumors, a large tumor size, and VI. In particular, our results showed that preoperative TACE and PVE were often indicated for HCC patients with VI of the major portal or hepatic venous branches, probably because curative operations in these patients necessitate the removal of the tumor-bearing portal branches together with the corresponding hepatic parenchyma, requiring a major hepatic resection. We previously reported that hepatic resection with preoperative TACE was an effective combination therapy in selected patients with HCC and portal venous tumor thrombus. Therefore, preoperative TACE and PVE should be considered when a major hepatic resection is required for the complete removal of HCC tumor(s) and segmental portal venous tumor thrombus in injured livers.

In the present series, all patients undergoing PVE underwent selective TACE as an initial procedure. The main concern was the possible infarction of noncancer-
ous liver parenchyma induced by the double occlusion of the arterial and portal venous systems. Occlusion of the portal vein by PVE has been reported not to evoke a necrotic or inflammatory reaction, and AST and ALT levels have been reported to be stable after PVE.12 However, in the present series of patients who underwent an initial TACE, the AST and ALT levels were significantly elevated after PVE, suggesting that an inflammatory reaction had occurred in the liver parenchyma. Nevertheless, our results show that these changes were transient, and the increase in the bilirubin level after PVE was mild, consistent with previous reports.14,15 In addition, examination of the resected specimens revealed that the necrosis of the noncancerous liver parenchyma was minimal in most cases, although the necrosis of the HCC tumors was marked. Accordingly, we conclude that sequential TACE and PVE (with a median interval of 9 days) produced a remarkable antitumoral effect but caused only a transient inflammatory effect on the liver parenchyma.

The complications experienced after TACE and PVE were similar to those experienced after PVE without TACE and were reversible with conservative therapy.12 In 1 patient, the planned hepatic resection was abandoned because of deterioration in the ICG R15 value after the TACE and PVE procedures had been performed. In this particular patient, the PVP was remarkably high (26 cm H2O) before the PVE, suggesting that severe cirrhosis was present. In this case, the ICG R15 value before PVE may have underestimated the true hepatic functional reserve.

Our results show that PVE following selective TACE induced sufficient hypertrophy of the future remnant segments within approximately 2 weeks, even in chronically diseased livers, although the hypertrophy ratio (22% ± 4%) was less than that in a normal liver (approximately 30%).8,12 The similar ICG R15 values before and after the sequential TACE and PVE procedures in most cases showed that liver function was not adversely affected by the procedure. Moreover, the liver hypertrophy allowed us to safely perform major hepatic resections in patients with chronic liver disease. In our series, the median interval between PVE and hepatectomy was 21 days (range, 9-49 days), which was shorter than that reported in Western series of patients (mean, 32-84 days).11,14,26,27 In earlier reports, hepatic resections were attempted once complete hypertrophy of the nonembolized segments had been attained or once the time–liver volume curve of the nonembolized segments had reached a plateau. In contrast, our results show that moderate hypertrophy attained within 3 weeks of the PVE procedure was sufficient to enable safe major hepatic resections, even in injured livers. Liver failure after a major hepatic resection is thought to be induced by the small size of the remnant liver parenchyma, combined with sinusoidal damage caused by the sudden increase in portal flow and pressure immediately after resection.28

![Figure 4](https://archsurg.jamanetwork.com/)

**Figure 4.** Changes in (A) tumor volume before transcatheter arterial chemoembolization (TACE) and portal vein embolization (PVE) and before hepatectomy, and changes in (B) serum α-fetoprotein (AFP) and (C) plasma des-γ-carboxy prothrombin (DCP) before TACE, before PVE (after TACE), and before hepatectomy (after PVE). Data are expressed as mean±SEM, and the levels of AFP and DCP were compared after logarithmic transformation (P<.02 by analysis of variance).

![Figure 5](https://archsurg.jamanetwork.com/)

**Figure 5.** Values of the indocyanine green retention ratio at 15 minutes (ICG R15) before transcatheter arterial chemoembolization (TACE) and portal vein embolization (PVE) and before hepatectomy. A scheduled hepatectomy was abandoned in 1 patient (asterisk) whose hepatic function deteriorated.
lar mechanism has been discussed in connection with the injury of small-for-size liver grafts in living-donor liver transplantations.

In the present series, PVE induced a rapid increase in PVP (Figure 2), causing an early change in portal hemodynamics similar to that observed after a major hepatic resection. Accordingly, PVE may improve the patient’s tolerance of major resections as a form of preconditioning, thereby minimizing hepatocellular damage after resection.

As a result, major hepatic resections can be safely performed after a relatively short waiting period, when the nonembolized liver segments are not yet fully hypertrophied.

Tumor progression while waiting for nonembolized liver segments to become hypertrophied is an important issue. Previous reports have shown that the volume of metastatic liver tumors increases more rapidly than the volume of the liver parenchyma after PVE, both in nonembolized and embolized liver segments. In our series, tumor progression (as evaluated by tumor volume and tumor markers) during the waiting period was inhibited by TACE, as previously reported.

In addition, TACE before PVE has been shown to have an independent contribution to the atrophy or hypertrophy effect of PVE. Such a comparison was not possible in our series, because all patients received TACE before PVE. Nevertheless, these previous findings may further justify our strategy.

Taken together, our findings show that sequential preoperative TACE and PVE induces a short-term increase in PVP before major hepatic resections and causes the volume of nonembolized segments to increase by approximately 20% within approximately 2 weeks of PVE, even in injured liver, with no deterioration in baseline hepatic functional reserve or tumor progression. Therefore, we conclude that this procedure contributes to both the broadening of surgical indications and the safety of performing major hepatectomies in HCC patients with chronic liver disease.

The overall and disease-free 5-year survival rates after curative hepatic resections for HCC in previous reports have ranged from 37% to 50% and 25% to 32%, respectively, whereas the 5-year survival rates of patients who have HCC with microscopic VI has been reported to be 17% to 28%. The 5-year disease-free and overall survival rates after curative hepatic resections in our series were 46.7% and 55.6%, respectively. Considering that most of our patients had macroscopic VI of major portal or hepatic venous branches or IM and that most of our patients had stage III or IV tumors, our results appear to be noteworthy. Our findings suggest that satisfactory long-term results can be anticipated when curative major hepatic resection is achieved after sequential TACE and PVE have been performed.

In conclusion, sequential preoperative TACE and PVE are useful treatment options for increasing the number of patients who can benefit from hepatic resections for HCC. The procedures are safe and can induce a satisfactory hypertrophy of nonembolized segments within
approximately 2 weeks, with no deterioration in basal hepatic functional reserve or tumor progression. The short- and long-term survival outcomes are satisfactory, although the patients who should undergo this procedure tend to have advanced tumors. We encourage the aggressive application of this treatment strategy in patients with large HCC and chronically injured livers.

Accepted for publication November 19, 2003. We thank Yutaka Matsuyama, PhD (Department of Biostatistics, School of Health Sciences and Nursing, University of Tokyo, Tokyo, Japan), for his critical advice regarding the statistical analyses.

Correspondence: Taku Aoki, MD, Division of Hepato-Biliary-Pancreatic and Transplantation Surgery, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan (AOKI-2SU@h.u-tokyo.ac.jp).

REFERENCES