Portal Vein Ligation as an Efficient Method of Increasing the Future Liver Remnant Volume in the Surgical Treatment of Colorectal Metastases

Lorenzo Capussotti, MD; Andrea Muratore, MD; Filippo Baracchi, MD; Bernard Lelong, MD; Alessandro Ferrero, MD; Daniele Regge, MD; Jean Robert Delpero, MD

Objective: To compare the volumetric increase of segments 2 and 3, segment 4, and the caudate lobe after portal vein ligation (PVL) and portal vein embolization (PVE).

The small size of the remnant liver and chemotherapy-induced liver injury increase the risk of postoperative hepatic insufficiency after major hepatic resection for colorectal liver metastases. Portal vein ligation has been suggested to be less effective than embolization in inducing hypertrophy of the remnant liver.

Design, Setting, and Patients: We retrospectively reviewed 48 patients with colorectal liver metastases who underwent PVL (n=17) or PVE (n=31) at the Istituto per la Ricerca e la Cura del Cancro or the Institut Paoli-Calmette from March 1, 2000, through August 31, 2006.

Main Outcome Measures: To compare the volume increase of segments 2 and 3, segment 4, and of the caudate lobe in patients who have undergone PVL or PVE in preparation for a major hepatic resection.

Results: There were no deaths related to PVE or PVL. Portal vein ligation was associated with resection of synchronous colorectal cancer in 16 patients. Resection of a liver metastasis in the remnant liver was performed in 11 patients. The median estimated baseline volume of segments 2 and 3 was 17.7% in the PVL group and 17.5% in the PVE group (P = .72). After PVL or PVE, it increased to 26.9% and 24.7%, respectively (P = .95), for volumetric increases of 43.1% and 53.4%, respectively (P = .39). The volumetric increases of segment 4 and the caudate lobe were similar.

Conclusion: Portal vein ligation is as effective as PVE in inducing hypertrophy of the remnant liver volume.

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Despite advances in chemotherapy regimens and ablative techniques, liver resection remains the best treatment for colorectal liver metastases, with good 5-year survival rates.1,2 Unfortunately, at the time of diagnosis, most patients have multiple hepatic lesions, which often preclude the possibility of an up-front complete resection. The introduction of oxaliplatin- or irinotecan hydrochloride–based chemotherapy in the preoperative setting has changed the prognosis of these patients, allowing high rates of response and downstaging to surgery.3,4 However, preoperative chemotherapy is associated with pathologic changes of the liver parenchyma. Recent studies have shown that such chemotherapy-induced liver injuries may translate into adverse clinical outcomes after hepatic surgery.5 Moreover, because these patients usually require major hepatectomies to achieve clear resection margins, the small size of the remnant liver and chemotherapy-induced liver damage increase the risk of postoperative hepatic insufficiency and morbidity.6,7 To minimize this risk, embolization (PVE) or ligation (PVL) of the portal branches feeding the liver to be resected have been used to increase future liver remnant volume (FLRV), thereby expanding the number of patients with resectable disease.8 However, it has been reported that PVL results in a significantly less efficient increase of the FLRV.9,10

The aim of this study was to compare the volumetric increases of segments 2 and 3, segment 4, and the caudate lobe in patients who underwent PVL or PVE in preparation for a major hepatectomy. We included for analysis a series of 48 consecutive patients with colorectal liver metastases and small remnant liver volumes.

METHODS

PATIENTS

From March 1, 2000, through August 31, 2006, 48 patients with colorectal liver cancer under-
went right PVL (n=17) or right PVE (n=31) at the tertiary care referral centers Istituto per la Ricerca e la Cura del Cancro or Institut Paoli-Calmette. Indications for ligation or embolization were an FLRV of 25% or less of the total liver volume in patients with normal liver and 30% or less of the total liver volume in patients treated with prolonged neoadjuvant chemotherapy. The mean age of the 48 patients was 62.6 (range, 32-63) years. Twenty-four were men.

PREOPERATIVE WORKUP

All patients underwent evaluation using abdominal computed tomography (CT) performed 3 to 7 days before PVE or PVL. Portal-phase CT was used to assess the FLRV in view of its ability to best depict the hepatic venous anatomy. The region of interest was traced manually by a hepatobiliary radiologist (D.R.) with a cursor on each CT section, and the area was determined automatically. The volume was obtained by the sum of the areas of each region of interest multiplied by the scan interval. Volumes of the caudate lobe, segment 4, and segments 2 and 3 were obtained individually. The FLRV was calculated using the following formula:

\[
\text{FLRV} = \left( \frac{\text{Remnant Liver Volume} \times 100}{\text{Entire Liver Volume} - \text{Tumor Volume}} \right) \times 100
\]

The volumetric increase of the future liver remnant (FLR) was calculated with the following formula:

\[
\text{FLR Increase} = \left( \frac{\text{Remnant Liver Volume Before Surgery} - \text{Remnant Liver Volume before PVE}}{\text{Remnant Liver Volume Before PVE}} \right) \times 100
\]

The volume measurements were repeated 3 to 4 weeks after the procedure in the PVE group. In the PVL group, because an associated surgical procedure was performed in all of the patients, the hypertrophy of the remnant liver was evaluated about 2 weeks later than in the PVE group. The delay of the CT volume measurement allowed more improvement of the performance status in preparation for the reoperation.

PORTAL VEIN LIGATION

Right PVL was indicated in patients with colorectal cancer and synchronous multiple liver metastases requiring a major hepatic resection, in the presence of a small remnant liver volume. Ligation of the right portal branch was performed during resection of the colorectal primary tumor with or without clearance of the FLR.

Intraoperative liver ultrasonography was routinely performed before ligation of the right portal branch to stage the liver metastases and to check the presence of anatomic variants of the right portal vein. Isolation of the right portal branch or of the right sectorial branches, if a portal trifurcation was present, was performed by means of selective dissection on the right side of the hepatic pedicle. Ligation of the right portal branch was usually controlled by Doppler ultrasonography to ensure the complete ligation of the right portal vein and the patency of the main portal trunk and left portal vein. The gallbladder was always left to reduce the extent of postoperative adhesion formation and to ensure an anatomic guide to the hepatic pedicle during the second operation.

PORTAL VEIN EMBOLIZATION

Portal vein embolization was performed in all cases under fluoroscopic guidance during conscious sedation. At the Department of Surgical Oncology of the Istituto per la Ricerca e la Cura del Cancro, the ipsilateral approach was used whenever possible; in patients with large lesions of the right liver narrowing or obstructing the posterior right portal branch, PVE was performed with a contralateral approach. At the Institut Paoli-Calmette, the preferred approach was contralateral.

The portal vein was punctured with a 22-gauge Chiba needle under ultrasonographic guidance. A 4F hydrophilic catheter (Radiofocus Glidecat; Terumo Europe, Leuven, Belgium) was used to catheterize the portal system. Digital subtraction portography was performed in the anteroposterior projection to visualize the portal segmental anatomy. Embolization was performed in all cases by injecting a mixture of cyanoacrylate (Glubran 2 [GEM, Viareggio (Lucca), Italy] or Histoacryl blue [Braun-Dexon GmbH, Spangenburg, Germany]) and iodized oil (Lipiodol UF; Guerbet, Roissy, France) in a 1:10 ratio through a 3F hydrophilic microcatheter (Radiofocus Glidecat). Embolization of the proximal part of the main right portal branch was avoided to minimize the periportal inflammatory reaction that might hamper surgical isolation of the hepatic pedicle. Control portography was performed at the end of the procedure.

STATISTICAL ANALYSIS

Results are expressed as median (5th-95th percentile). Continuous variables were compared using the Mann-Whitney test; categorical variables were compared using the χ² or the Fisher exact test as appropriate. All analyses were performed using commercially available statistical software (Statistica 6.1 for Windows; StatSoft Italia, Vigonza, Italy). Differences were considered statistically significant at P < .05.

CHARACTERISTICS OF THE PVE AND PVL GROUPS

The preocclusion characteristics of the PVL and PVE groups are summarized in Table 1. None of the examined features was significantly different in either group. Liver function was good, as evidenced by the prothrombin times and the albumin and bilirubin levels. No patients had hepatitis B or C virus infection.

Forty-three patients underwent neoadjuvant systemic chemotherapy, including 15 in the PVL group and 28 in the PVE group (P = .59). The neoadjuvant protocol used infusional fluorouracil combined with oxaliplatin in 30 patients (70%) or with irinotecan in 11 patients (25.6%) or both in 2 patients. Six patients received a second-line chemotherapy (fluorouracil combined with oxaliplatin or with irinotecan according to the type of first-line chemotherapy).

There were no deaths related to the procedure used for portal vein occlusion. In 1 patient, the CT scan obtained 3 weeks after PVE showed a small cyanoacrylate thrombus fluctuating in the main portal trunk bifurcation. No other significant complications were observed after PVL or PVE. The median hospital stay was 10 (range, 5-31) days after PVL and 3 (range, 1-5) days after PVE (P < .001). Portal vein ligation was associated with resection of synchronous colorectal cancer in 15 patients (anterior resection of the rectosigmoid cancer in 10 patients and resection of the right colon in 5 patients) and with resection of a pelvic recurrence in 1 patient. In 1 patient, PVL was associated with wedge resection of a liver metastasis in segments 3 and 4.

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Intraoperative Findings

In 1 patient in the PVE group, a small cyanoacrylate thrombus was found fluctuating in the main portal trunk bifurcation and was removed during surgery without further complications. In 2 patients in the PVL group, during the second operation, it was not possible to perform extraperitoneal ligation of the right hepatic artery because of the presence of important adhesions at the hepatic pedicle.

Comment

Patients with large or multiple colorectal liver metastases often require extended hepatic resections to achieve a radical resection.4,11 In patients treated with neoadjuvant chemotherapy and expected to have a small or borderline remnant liver volume after the planned liver resection, occlusion of the portal vein to the liver to be resected has been shown to reduce postoperative morbidity.3 Hypertrophy of the remnant liver may be induced by PVE or PVL. The role of PVL in inducing hypertrophy of the liver has been clearly demonstrated in an experimental study.12 However, a recent report10 has suggested that PVL was significantly less efficient than PVE in inducing hypertrophy of the left lateral segments. In the present series, the rate of volumetric increase of segments 2 and 3, segment 4, and the caudate lobe was similar irrespective of the type of portal vein occlusion performed (PVE or PVL). It has been suggested that the failure of PVL to induce adequate hypertrophy might be owing to the formation of intrahepatic portoportal collaterals9; however, inadequate hypertrophy and the presence of intrahepatic collaterals observed in the patient described in that report were shown for the first time by CT performed 6 months after systemic chemotherapy. Moreover, an experimental study13 has shown that the increase in the volume of the liver’s left lobe after PVL was not restrained by

Volumetric Assessments

The median time between occlusion of the right portal vein and CT was 40 (range, 13-135) days in the PVL group vs 29 (range, 18-42) days in the PVE group (P = .01). The median (5th-95th percentile) baseline and post-PVE/PVL volumetric increase for segments 2 and 3, segment 4, and the caudate lobe are reported in Table 2. There were no statistically significant differences between the 2 study groups regarding the baseline and postocclusion volumes. The median estimated baseline volume of segments 2 and 3 was 17.7% in the PVL group and 17.5% in the PVE group (P = .72); after PVL or PVE, the volume of segments 2 and 3 increased to 26.9% and 24.7%, respectively (P = .95). The percentage of increase in segments 2 and 3 was similar at 43.1% in the PVL group vs 53.4% in the PVE group (P = .39). Similarly, PVE did not induce a significantly greater percentage of the volumetric increase for segment 4 and or the caudate lobe volumes.

Table 1. Clinical Characteristics of the Study Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PVE Group (n=31)</th>
<th>PVL Group (n=17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of men</td>
<td>15</td>
<td>9</td>
<td>.50b</td>
</tr>
<tr>
<td>Age, y</td>
<td>64 (37-75)</td>
<td>63 (52-76)</td>
<td>.29c</td>
</tr>
<tr>
<td>BMI</td>
<td>22.5 (17.7-29.0)</td>
<td>23.6 (18.3-31.6)</td>
<td>.41c</td>
</tr>
<tr>
<td>No. with diabetes mellitus</td>
<td>1</td>
<td>1</td>
<td>.57c</td>
</tr>
<tr>
<td>AST level, U/Ld</td>
<td>32 (19-116)</td>
<td>38 (19-58)</td>
<td>.96c</td>
</tr>
<tr>
<td>ALT level, U/Ld</td>
<td>33 (15-185)</td>
<td>26 (9-60)</td>
<td>.17c</td>
</tr>
<tr>
<td>GGT level, mg/dL</td>
<td>56 (21-217)</td>
<td>51.5 (20-302)</td>
<td>.83c</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>1 (0.4-1.8)</td>
<td>0.8 (0.4-1.5)</td>
<td>.50c</td>
</tr>
<tr>
<td>PT, %d</td>
<td>94 (81-110)</td>
<td>96 (71-144)</td>
<td>.91c</td>
</tr>
<tr>
<td>Albumin, g/dLd</td>
<td>0.39 (0.33-0.53)</td>
<td>0.38 (0.23-0.42)</td>
<td>.24c</td>
</tr>
<tr>
<td>No. receiving neoadjuvant CHTh</td>
<td>28</td>
<td>15</td>
<td>.59b</td>
</tr>
<tr>
<td>No. of CHT cycles</td>
<td>10 (4-20)</td>
<td>8 (2-15)</td>
<td>.37c</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHT, systemic chemotherapy; GGT, γ-glutamyltransferase; PT, prothrombin time; PVE, portal vein embolization; PVL, portal vein ligation.

SI conversion factors: To convert albumin to grams per liter, multiply by 0.1. To convert total bilirubin and γ-glutamyltransferase to micromoles per liter, multiply by 0.0167. To convert prothrombin time to seconds, multiply by 10.

a Unless otherwise indicated, data are expressed as median (5th-95th percentile).
b Calculated by means of the χ² test or Fisher exact test as appropriate.
c Calculated by means of the Mann-Whitney test.
d Indicates pre-PVE or pre-PVL serum levels or measurement.
e Indicates pre-PVE or pre-PVL CHT.

and with closure of a loop ileostomy. Overall, resection of a liver metastasis located in the remnant liver was performed in 11 patients; intraoperative radiofrequency ablation of a nonresectable metastasis in the FLR was associated with liver resection in 2 patients.

Thirteen of the 48 patients (27%) did not undergo resection of the embolized or ligated liver, including 6 in the PVL group and 7 in the PVE group (P = .29). The decision was made preoperatively in 10 patients (6 in the PVL group and 4 in the PVE group), because the CT scan showed nonresectable disease progression in the remnant liver in 7 (3 in the PVE group), in the abdominal para-aortic lymph nodes in 1 (in the PVL group), and in the dorsal vertebrae in 1 (in the PVL group). The remaining patient underwent low anterior resection of the rectal cancer and right PVL after 12 cycles of fluorouracil combined with oxaliplatin and irinotecan; the subsequent CT scan revealed insufficient FRV increase. In 3 patients in the PVE group, the decision was made on the basis of intraoperative findings, including peritoneal dissemination, nonresectable metastases in the FLR, and para-aortic lymph node metastases in 1 patient each.

Thirty-five of the 48 patients (73%) underwent resection of the embolized or ligated liver. All the patients underwent right-sided hepatectomy, which was extended to segment 4 in 15 patients (in the PVL group). Associated resection of the caudate lobe was performed in 5 patients (3 in the PVL group). The median hospital stay was 18 (range, 6-54) days in the PVL group vs 15 (range, 6-30) days in the PVE group (P = .99). One patient in the PVE group who underwent right-sided hepatectomy extended to segment 4 died of sepsis on postoperative day 34. Nine patients had postoperative complications: 5 in the PVL group vs 4 in the PVE group (P = .10). No patients received intraoperative blood transfusions. Seventeen patients received postoperative blood transfusions, including 7 in the PVL group and 10 in the PVE group (P = .20).
the formation of collaterals. The efficient hypertrophy induced by PVL has been confirmed by a recent report analyzing the use of a 2-step surgical procedure that included right PVL as the first step in 20 patients with bilobar liver metastases. In none of those patients was the second step of the operation precluded by inadequate hypertrophy of the remnant liver. In the present series, only 1 of 17 patients in the PVL group did not undergo the second step of the liver operation because of inadequate hypertrophy of the FLR; that patient had received 12 cycles of chemotherapy with fluorouracil combined with oxaliplatin and irinotecan before undergoing right PVL. The association between irinotecan-based chemotherapy and steatohepatitis is well known.5 Steatohepatitis may affect liver regeneration.15

Some authors have suggested that extension of embolization to segment 4 branches induces greater hypertrophy of the remnant liver.16 A recent prospective study from our institution has shown no advantages in segment 4 embolization.17 From 2004 onward, because of the results of that study, we routinely have not embolized segment 4 branches. Moreover, in the present study, we deliberately chose to include only patients undergoing right portal vein occlusion in order to have 2 homogeneous groups. In the study by Broering et al., only 29% of patients undergoing PVL had additional occlusion of segment 4 branches, compared with 59% of those undergoing PVE (P = .002).

In the present series, the median time between occlusion of portal flow to evaluation of the FLRV was significantly longer than in our series because PVE was performed about 2 to 5 weeks after the first stage. Moreover, 1 patient developed a portomesenteric venous thrombosis after the embolization and did not undergo the planned second stage of the hepatectomy.

In conclusion, the results of the present study have clearly demonstrated that PVL is a safe and efficient method of increasing the FLRV. Patients with synchronous colorectal cancer and multiple liver metastases requiring a 2-stage hepatectomy are the best candidates for PVL.

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Author Contributions: Drs Capussotti and Muratore had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Capussotti, Muratore, Regge, and Delpero. Acquisition of data: Muratore, Baracchi, Lelong, and Ferrero. Analysis and interpretation of data: Muratore. Drafting of the manu-

### Table 2. Variations of Liver Volume for Segments 2 and 3, Segment 4, and the Caudate Lobea

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline Volume, mL</th>
<th>Baseline FRLV, %</th>
<th>Post-PVE/PVL Volume, mL</th>
<th>Post-PVE/PVL FRLV, %</th>
<th>Rate of Volumetric Increase, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segments 2 and 3</td>
<td>PVE</td>
<td>204.5 (125.0-311.0)</td>
<td>17.5 (10.7-22.3)</td>
<td>302.5 (225.0-473.0)</td>
<td>24.7 (18.0-38.5)</td>
</tr>
<tr>
<td></td>
<td>PVL</td>
<td>204.0 (110.0-440.0)</td>
<td>17.7 (9.3-29.5)</td>
<td>265.0 (161.6-562.0)</td>
<td>26.9 (12.7-38.5)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>.82</td>
<td>.72</td>
<td>.85</td>
<td>.95</td>
</tr>
<tr>
<td>Segment 4</td>
<td>PVE</td>
<td>150.0 (81.0-310.0)</td>
<td>13.4 (6.8-22.2)</td>
<td>217.0 (95.0-336.0)</td>
<td>17.2 (8.4-28.6)</td>
</tr>
<tr>
<td></td>
<td>PVL</td>
<td>171.0 (65.0-330.0)</td>
<td>13.4 (7.6-25.4)</td>
<td>218.0 (76.0-337.0)</td>
<td>15.7 (8.3-24.0)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>.39</td>
<td>.60</td>
<td>.92</td>
<td>.54</td>
</tr>
<tr>
<td>Caudate lobe</td>
<td>PVE</td>
<td>28.0 (10.0-98.0)</td>
<td>2.8 (0.8-8.3)</td>
<td>39.0 (12.0-98.0)</td>
<td>3.0 (0.9-8.2)</td>
</tr>
<tr>
<td></td>
<td>PVL</td>
<td>44.0 (8.0-98.0)</td>
<td>3.4 (0.9-8.9)</td>
<td>47.0 (19.0-94.0)</td>
<td>4.1 (2.1-8.5)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>.16</td>
<td>.29</td>
<td>.13</td>
<td>.24</td>
</tr>
</tbody>
</table>

Abbreviations: FRLV, future remnant liver volume; PVE, portal vein embolization; PVL, portal vein ligation.

aUnless otherwise indicated, data are expressed as median (5th-95th percentile)
script: Muratore, Baracchi, and Ferrero. Critical revision of the manuscript for important intellectual content: Capussotti, Lelong, Regge, and Delpero. Statistical analysis: Muratore, Baracchi, and Ferrero. Administrative, technical, and material support: Lelong and Regge. Study supervision: Capussotti and Delpero.

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REFERENCES


INVIITED CRITIQUE

Of the most important technical developments in hepatic surgery is the use of portal venous interruption to maximize the size and function of the liver remnant. Capussotti and colleagues offer a retrospective comparison of 2 approaches to portal venous interruption. They demonstrate that a similar increase in remnant size occurs with surgical PVL vs percutaneous PVE. Both methods were safe, and both methods produced hypertrophy of the anatomic left liver.

Is there an optimal approach to portal venous interruption? Like most technical approaches in liver surgery, the details of the technique must be tailored to the specifics of the clinical situation. One concern that drives decision making is the potential for liver regeneration induced by portal venous interruption to enhance tumor growth in the remnant.1 As such, patients with disease in the planned remnant are ideal for a staged approach in which the disease in the planned remnant is resected and the portal vein is ligated. A later definitive resection is performed after hypertrophy.3

In contrast, patients who do not have a primary tumor in place or who have no disease in the planned remnant have no need for a surgical procedure before the definitive resection of their liver metastases. These individuals will be best served by a percutaneous embolization followed by extended hepatectomy.

With increasing use of preoperative chemotherapy, the role of portal venous interruption will be increasingly important in the treatment of patients with liver metastases. Both ligation and embolization will play a role. The challenge for surgeons will be to continue to refine methods of patient selection so that individuals will receive the treatment that is optimal for their unique clinical situation.

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