Kinetics of Liver Volume Changes in the First Year After Portal Vein Embolization

Danton Corrêa, MD; Lawrence Schwartz, MD; William R. Jarnagin, MD; Scott Tuorto, BA; Ronald DeMatteo, MD; Michael D'Angelica, MD; Peter Allen, MD; Karen Brown, MD; Yuman Fong, MD

Objective: To determine the time course of liver hypertrophy after portal vein embolization (PVE).

Design: In a cohort study, computed tomography volumetrics were calculated for livers during a 1-year period after PVE.

Setting: Tertiary liver cancer treatment center.

Patients: Ten patients who were subjected to PVE and were found subsequently to not be candidates for liver resection.

Intervention: Right PVE.

Main Outcome Measures: Left and right liver volumes.

Results: The left liver continued growing for the entire first year after PVE, while the right liver continued to atrophy. The total volume remained remarkably constant.

Conclusion: Early PVE during administration of a course of neoadjuvant therapy would be beneficial for enhanced growth of the liver before liver resection.


Liver resection has been shown to be a potentially curative therapy for primary malignant neoplasms of the liver and biliary tract and for certain metastatic tumors such as colorectal cancer. Improvements in surgical technique and perioperative care have made major liver resection a safe procedure. Mortality rates are below 5% in tertiary centers, and fatal liver failure after resection is rare.

Despite these advances, patients subjected to resection of more than 75% of functional parenchyma have more than 3 times the risk of postoperative hepatic dysfunction and a higher likelihood of liver failure and death.

See Invited Critique at end of article

Portal vein embolization (PVE) has been described as a means of reducing such complications by increasing the amount of functional liver mass after resection; it induces atrophy in the embolized lobe and compensatory hypertrophy of the future remaining lobe after hepatectomy. This minimally invasive procedure, performed transcutaneously, was originally proposed as a means of improving the safety of resection for hilar cholangiocarcinoma, in which a large piece of functional liver is often resected for a very small tumor. Recently, such a strategy has been performed to increase the pool of candidates selected for surgical treatment of hepatic colorectal metastasis. Empirically, most investigators using this technique wait approximately 3 to 4 weeks after the embolization to perform hepatectomy because of data indicating that, after liver resection, volumetric regeneration is accomplished in approximately 4 to 6 weeks. It is not known whether liver growth after PVE is the same as that after liver resection. Beyond this period, the kinetics of liver volume changes are not well documented. The present study addresses these issues by examining a group of patients who underwent PVE but were found to have unresectable cancer. These patients were followed up...
PORTAL VEIN EMBOLIZATION

The techniques of PVE at our institution have been described previously.\textsuperscript{19} We used an ipsilateral puncture of the portal vein to decrease the likelihood of iatrogenic damage to the liver intended to be the remnant after resection. Embolization was performed with the use of polyvinyl alcohol particles (200–300 µm).\textsuperscript{20} Metallic coils were avoided to prevent interference with a concurrent protocol that used magnetic resonance spectroscopy for assessment of liver function. The segment 4 portal vessels were not embolized.

METHODS

Patients with colorectal hepatic metastasis undergoing preoperative right PVE from January 1, 2000, through December 31, 2003, were identified from the Department of Surgery prospective database at Memorial Sloan-Kettering Cancer Center. From an initial pool of 74 patients, 19 were never submitted to tumor resection. Of these, 10 patients had more than 2 computed tomographic (CT) scans after PVE, allowing volumetric analysis and were included in the analysis.

VOLUMETRIC ASSESSMENTS

Analysis of liver hypertrophy and atrophy was performed with the use of CT volumetrics to compare scans obtained before PVE with scans performed later. All CT scanning was performed with a helical scanner, and the CT data were transferred to an independent workstation for assessment. Volumes of right and left livers were determined by semiautomated contouring of the scans. This was performed on serial axial images. On each section, the total liver was outlined and the sum of the sections was calculated by integrated software techniques using the density threshold. This was repeated solely for the right liver according to the plane of the middle hepatic vein. The difference between total liver volume and right liver volume was considered the left liver volume.

STATISTICAL ANALYSIS

Computed tomography was performed at monthly intervals. Results were recorded as the percentage of volume change of the right and left livers. The values from different patients were averaged as a percentage of the baseline value, and a single curve was created with standard error bars. Comparisons were performed by paired, 2-tailed t test and χ² test as indicated. Nonparametric factors were compared by the Mann-Whitney test.\textsuperscript{21}

Of the 10 patients included in the study, 8 were men and 2 were women. The median age was 57 years (range, 53–79 years), with a mean (SEM) age of 59(4) years. The median follow-up time was 747 days (range, 198–2247 days). The cancer diagnosis for these 10 patients included 9 cases of metastatic adenocarcinoma and 1 case of metastatic squamous cell carcinoma of the anus. Four of the patients had documented liver steatosis, and none had cirrhosis of the liver. These patients were not resected after embolization because of extensive bilobar tumor (n=4), vena caval invasion (n=1), and extrahepatic metastases to the lung (n=2), bone (n=1), celiac node (n=1), and omentum (n=1). All patients were treated with chemotherapy after the determination of unresectable disease (paclitaxel [n=1]; infusional fluorouracil [n=1]; a combination of levovorin calcium, fluorouracil, and oxaliplatin [n=2]; oxaliplatin plus irinotecan hydrochloride [n=1]; hepatic arterial infusional floxuridine [n=1]; hepatic arterial infusional floxuridine plus oxaliplatin [n=3]; or hepatic arterial infusional floxuridine plus irinotecan hydrochloride [n=1]).

The number of scans performed after embolization varied from 3 to 8 per patient. Eight patients were followed up for at least 210 days after PVE, and 5 were followed up for 360 days. The serial CT scans for 2 representative patients are shown in Figure 1 in which equivalent sections are seen for scans performed before PVE, as well as scans from 1, 3, 6, 9, and 12 months after PVE. The arrows indicate the middle hepatic vein and show the demarcation between the left and right lobes of the liver. It is clear that both hypertrophy of the left liver and atrophy of the right liver continue for at least a year.

METHODS

PORTAL VEIN EMBOLIZATION

The number of scans performed after embolization varied from 3 to 8 per patient. Eight patients were followed up for at least 210 days after PVE, and 5 were followed up for 360 days. The serial CT scans for 2 representative patients are shown in Figure 1.
Liver volume changes for a different representative patient are shown in Figure 2. The mean (SE) total liver volume remained at a remarkably steady $2.73 \times 10^6$ $\pm 0.04 \times 10^6$ cm$^3$ throughout the atrophy-hypertrophy process.

The summary data, presented as the mean (SE) percentage of liver atrophy and hypertrophy, are shown in Figure 3. In the first month, there was 23% (6%) growth in the left liver, while a 19% (6%) decrease in size occurred in the right liver. This is consistent with the changes presented in previously published series.3,11,12,15,18

During the ensuing year, the left liver grew a total of 83.4%. Of the total growth, 50% occurred by 90 days after PVE and 75% by 230 days. These data confirm that atrophy of the treated side and compensatory hypertrophy of the contralateral side occur continually until at least 360 days after PVE.

**COMMENT**

The first reported use of PVE to induce left lobe hypertrophy before major hepatectomy was published in 1990 by Makuuchi et al.14 After this initial report, a number of publications from Asian, European, and American authors described the safe use of this technique to improve the outcome of hepatectomy for primary and secondary hepatic and biliary malignant neoplasms.22 The mechanisms involved in liver growth are still not well understood,22,23 but there is no doubt that abrupt occlusion of 1 of the 2 branches of the portal vein results in drastic alterations in blood flow and redistribution of functional mass of the liver.24 The resultant hypertrophy of the future liver remnant improves immediate postoperative liver function and clinical outcomes for many patients subjected to liver resection for malignant neoplasms.10,25

The volume and functional capacity of the liver are measured in most studies around 30 to 40 days after PVE11-15,18,22,24,26,27 because most surgeons wait that long before performing liver resection. This is based on practicalities of how long an oncologist is willing to wait before resection of the tumor. It is also based on the observation that most volumetric liver hypertrophy occurs in the first 30 to 40 days after liver resection.3,11,12,15,18 After PVE, however, the liver is found to have hypertrophied only approximately 25% in the first 30 to 40 days.3,11,12,15,18 What happens after this period is mostly unknown. Our study confirms that, at 30 days after PVE, approximately 25% of the total possible liver growth has occurred. It further documents that the liver continues to grow after this point. Two practical implications of these data are apparent. First, the longer surgeons can wait before resection, the more volumetric growth will be evident. With current neoadjuvant therapeutic regimens for metastatic colorectal cancer,26 the option to wait 2 to 6 months before hepatectomy is possible. Second, if inadequate growth occurs in the first month, patients should be reassessed later for liver hypertrophy.

Liver function correlates with size, although the percentage of change in the 2 sides is not exactly the same.29 Assessment of function of the nonembolized lobe measured by technetium Tc 99m galactosyl human serum albumin scintigraphy is usually higher than what is expected by the change in size.27 The increased total amount of adenosine triphosphate and hepatic energy reserve of the lobe in which the portal vein was not embolized also exceeds its volume increase early after PVE.26 Thus, size changes are only an approximation of functional improvement. Nevertheless, liver volume is a measurement that is easily acquired, is widely available, and remains a useful guide to clinical outcome.

The kinetics of liver growth after PVE are very different from those after liver resection. Development of the atrophy-hypertrophy complex continues for at least the entire first year after embolization. Consideration should therefore be given to performing PVE early as an adjunct to neoadjuvant chemotherapy for those patients expected to subsequently undergo major hepatectomy.
Is Waiting Longer Better?

P reoperative PVE has become a well-established maneuver to reduce the risk of postoperative hepatic insufficiency following major hepatectomy. In the present study, Corrèa et al have shown in 10 patients who underwent PVE but did not undergo resection that the atrophy-hypertrophy complex that occurs following PVE continues for up to 1 year after embolization. Few long-term data exist for rates of hypertrophy at 1 year following PVE because most of these patients undergo resection within 4 to 8 weeks. Previous data have suggested that most hypertrophy of the future liver remnant will have occurred by 21 days after PVE. Longer-term data among patients who were not resected showed further hypertrophy beyond 2 months.

REFERENCES


