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Right Portal Vein Ligation is as Efficient as Portal Vein Embolization to Induce Hypertrophy of the Left Liver Remnant

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Abstract
Background Aim of this retrospective study was to compare induction of left liver hypertrophy after right portal vein ligation (PVL) and right portal vein embolization (PVE) before right hepatectomy for liver metastases.
Materials and Methods Between 1998 and 2005, 18 patients underwent a PVE, whereas 17 patients underwent a PVL during a first stage laparotomy.
Results There was no complication related to PVE or PVL. After a similar interval time (7±3 vs 8±3 weeks), the increase of the left liver volume was similar between the two groups (35±38 vs 38±26%). After PVE and PVL, right hepatectomy was performed in 12 and 14 patients, respectively. Technical difficulties during the right hepatectomy were similar according to duration of procedure (6.4±1 vs 6.7±1 h, $p=0.7$) and transfusion rates (33 vs 28%, $p=0.7$). Mortality was nil in both groups, and morbidity rates were respectively 58% for the PVE group and 36% for the PVL group ($p=0.6$).
Conclusion Right PVL and PVE result in a comparable hypertrophy of the left liver. During the first laparotomy of a two-step liver resection, PVL can be efficiently and safely performed.

Keywords Portal vein occlusion · Portal vein ligation · Liver metastasis · Liver hypertrophy

Abbreviations
PVL portal vein ligation
PVE portal vein embolization
FLR future liver remnant

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Introduction

In patients with primary liver tumors or selected liver metastases, complete resection is often the only chance of potential curative treatment to expect a long-term survival.[1,2] In case of extended hepatic lesions, liver resection may be hampered by the small volume of the residual liver, which is associated with a risk of postoperative life-threatening liver failure.[3,4] Moreover, many patients with advanced metastatic disease are referred to surgeons after a neoadjuvant chemotherapy, which has allowed downsizing of initially unresectable liver metastases,[5] or when there is a documented chemosensitivity.[6,7] Now, it has been well established that chemotherapy induces liver parenchyma changes, which may worsen postoperative morbidity.[8,9] In patients considered for liver resection of metastasis, both small volume of the future remnant liver and neoadjuvant chemotherapy increase the postoperative morbidity and mortality risk.

To overcome this risk and to increase resectability, more aggressive surgical treatment procedures have been proposed using the regenerative capacity of the liver.[10,11] Among them, occlusion of one branch of the portal vein

results in the atrophy of the ipsilateral and hypertrophy of the contralateral liver segments. This phenomenon was initially observed in patients with cholangiocarcinoma, which induced portal vein occlusion by tumor invasion.[12] Including portal vein occlusion in a strategy of scheduled sequential liver resections allowed to increase the number of patients amenable to curative surgery, while they were initially deemed unresectable.[10,11,13] Portal vein occlusion may be achieved by either percutaneous embolization or surgical ligation during a first-step laparotomy. Right portal vein ligation (PVL) has been considered to be less efficient than right portal vein embolization (PVE) before a right hepatectomy.[14,15]

The present study aimed to compare PVL and PVE before a right hepatectomy in patients with liver metastases in terms of safety, efficacy for hypertrophy of the left liver remnant, resectability rates, and technical impact on liver resection.

Materials and Methods

Patients

Between 1998 and 2005, 35 patients with multiple colorectal or neuroendocrine liver metastases underwent a right portal branch obstruction before "high risk" right hepatectomy because of a future liver remnant (FLR) volume less than 30% of the total liver volume or because of a post-chemotherapy liver parenchyma. Eighteen patients underwent a percutaneous PVE because metastases were considered resectable in one stage. Seventeen patients had a PVL during a first-stage laparotomy when the metastatic disease in the left liver was judged too extensive to be safely resected along with the right liver (n=10) and/or when the resection of the primary tumor was also required (n=10). Patients and tumors characteristics are given in Table 1. In the PVE group, patients were older than in the PVL group (51±10 vs 61±14 years, respectively, p=0.023), and all patients had colorectal metastases, whereas ten (59%) patients had neuroendocrine metastases in the PVL group (p=0.02). There were more hepatic lesions, and they were bigger in the PVL group. Liver function assessed by prothrombin time, and bilirubin was normal and comparable in both groups (data not shown). Neoadjuvant chemotherapy consisting in the combined use of 5-fluorouracil and either oxaliplatin or irinotecan was administrated to all patients before PVE and to eight (47%) patients before PVL (p=0.001). Mean time between the end of chemotherapy and portal vein occlusion was 2.2±1.7 months and was not significantly different between groups.

Right Portal Vein Embolization

Right PVE was performed using the contralateral transhepatic approach as previously described.[16] In brief, a collateral vein of the left branch of the portal vein was punctured under light general anesthesia and ultrasound guidance. After control venous portography, the right anterior and posterior portal branches were embolized with a mixture of cyanoacrylate (Histoacryle; Braun Lab, Hamburg, Germany) and lipiodol (Lipiodol Ultrafluide; Guerbert Lab, Paris, France). In none of them, branches to segment 4 were embolized. Control portography was performed at the end of the procedure.

Right Portal Vein Ligation

Ligation of the right branch of the portal vein was performed as part of a two-stage procedure.[10] During the first stage, the resection of the primary tumor was performed in ten patients (one left colectomy, two ileocolic resections, and seven left pancreatectomies), and enucleation of the left-sided liver metastases, with at least a 5-mm margin, was achieved in 16 patients. Extraparenchymal ligation of the right portal branch was performed using a nonabsorbable suture. Its efficacy was checked by preoperative Doppler ultrasounds. Cholecystectomy was performed in the same time in ten patients.

Table 1 Characteristics of Patients Who Underwent PVE or PVL Before Right Hepatectomy for Liver Metastases

	PVE (n=18)	PVL (n=17)	p value
Gender (F/M)	7/11	10/7	0.3
Age (year)	61±10	51±14	0.023
Primary tumor			
Adenocarcinoma	18	7	0.001
Neuroendocrine	0	10	
Hepatic tumor location unilobar/bilobar	12/6	1/16	0.03
No. of tumors/patient			
Right liver	4.5±6	7±3	0.05
Left liver	0.5±0.7	3.2±2	0.001
Preoperative chemotherapy (%)	18 (100)	8 (47)	0.001

Continuous variables expressed as mean±SD

Right Hepatectomy

Right hepatectomy was performed 7 to 8 weeks after portal vein occlusion. All patients underwent liver resection by three senior liver surgeons, using a standardized technique for right hepatectomy.[16] Parenchymal transection was performed by either the clamp-crush technique or with an ultrasound aspiration dissector (Dissectron™; Satelec Medical, Merignac, France), with intermittent clamping of the hepatic pedicle. Patients were routinely transferred to the intensive care unit and returned to the wards at the discretion of the intensive care consultant. After right hepatectomy, the resected specimens were examined pathologically, paying attention to the disease-free margins and to the extent of necrosis of tumor. Tumor necrosis was defined as complete if no viable cells were observed in any nodule.

Follow-up and End Points

The primary end point of the analysis was the hypertrophy of the FLR induced by the right portal vein occlusion. All patients underwent volumetric helicoidal computed tomographic (CT) scan estimation of their liver volumes before the obstruction and 4–6 weeks thereafter. Measurements were performed for the whole liver and for the FLR using the middle hepatic vein, gallbladder bed, and umbilical portion of the left portal vein as landmarks. The FLR volume was expressed as a percentage of the total liver volume, excluding the tumor volume. Its hypertrophy after portal vein occlusion was calculated as follows: (FLR volume 4 to 6 weeks after portal vein obstruction−FLR volume before portal vein obstruction)×100/FLR volume before portal vein obstruction.

The secondary end points of the analysis were the resectability rate and the postoperative course. Operative mortality was defined as death occurring within the same hospital stay or within 30 days of surgery. Postoperative complications, recorded prospectively, were defined as follow: (a) liver failure was defined by a prothrombin time of less than 50% (of normal) and serum bilirubin level greater than 50 μmol/l on postoperative day 5,[17] (b) significant ascites (abdominal drain output more than 500 ml/day), (c) biliary leak as the presence of bile in the abdominal drainage or abdominal collections greater than twice the serum level, (d) postoperative pulmonary complications included all clinically symptomatic pleural effusions, atelectases, and infections, and (e) renal insufficiency (serum creatinine level greater than 150 μmol/l).

Statistical Analysis

Summary statistics are expressed as mean±SD unless otherwise stated. Continuous variables were compared using the Fisher's exact *t* test, and categorical variables were compared using the Mann–Whitney test. A *p* value of less than 0.05 was considered as statistically significant. All the calculations were performed with the Statistical Package for the Social Sciences (SPSS) 14.0 statistical package (SPSS, Chicago, IL, USA).

Results

Liver Hypertrophy

Right portal vein occlusion was complete in all the cases in both groups. The mean interval time between portal vein occlusion and liver resection was similar in both groups (7±3 after PVE vs 8±3 weeks after PVL, $p=0.6$). The left liver volume increased from 509±222 ml to 641±220 ml after PVE ($p<0.001$) and from 477±179 to 638±192 ml after PVL ($p<0.001$). After portal vein occlusion, the increase of the left liver volume was not significantly different between the two groups (35±38% after PVE vs 38±26% after PVL, $p=0.7$; Fig. 1). None of the tumor but one in the left lobe increased until surgery (see below).

There was no complication after PVE and postoperative hospital stay was 2±1 days. In group PVL, four patients had postoperative complications (one left pleural effusion, two pancreatic fistulae, and one intra-abdominal abscess), which were all related to primary tumor resection, and postoperative hospital stay was 13±6 days.

Resectability

After PVE, six (30%) patients were not eligible for right hepatectomy because of insufficient hypertrophy of the left liver ($n=2$) or tumor progression ($n=4$). Two patients had peritoneal implants at laparotomy, one patient developed mediastinal metastatic lymph nodes, and in the last patient, diameter of the left lobe metastasis increased from 4 to 7.5 cm.

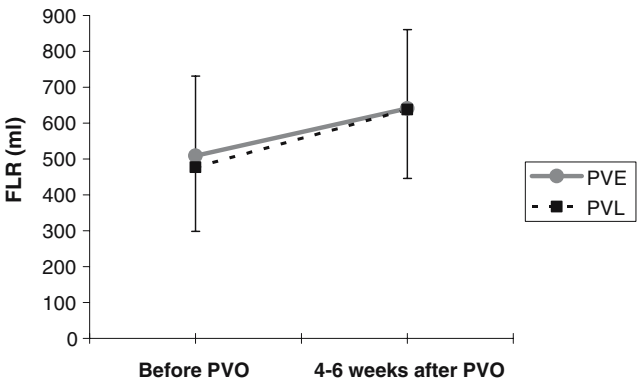

Figure 1 Volume of the future liver remnant (*FLR*) before and 4–6 weeks after portal vein embolization (*PVE*) or portal vein ligation (*PVL*). *PVO* Portal vein occlusion.

After PVL, three (18%) patients were not eligible for resection. Two patients developed tumor progression, which were lung metastases and metastatic lymph nodes in the hepatic ligament. One patient died from cardiac infarction before the second-step laparotomy. The difference of resectability between groups was not significant.

According to the pathologic examination, the maximum tumor diameter was measured as 6.5±4 cm in the PVE group and 4.8±3.7 cm in the PVL group (p=0.5). The amount of tumor necrosis was 47±29% in group PVE and 43±43% in group PVL (p=0.6). Liver parenchyma lesions induced by chemotherapy (sinusoidal dilatation, steatosis, and nodular regenerative hyperplasia) were found in six patients after PVE and in five patients after PVL (p=0.72).

Intra- and Postoperative Course

Technical difficulties during surgical procedure were similar in both groups according to duration of procedure, blood loss, and transfusion rates after PVE and PVL, respectively (Table 2). Before resection, CT scan showed stigmata of portal cavernoma in three patients of each group. However, these vein dilatations did not make right hepatectomy more difficult. After PVL, previous cholecystectomy was not associated with more technical difficulties to perform right hepatectomy. There was no significant difference between patients with (n=8) or without cholecystectomy (n=6) in terms of duration of procedure (6.1±1.6 vs 6.3±0.5 hours, p=0.8), blood loss (775±872 vs 1025±464 ml, p=0.6) and transfusion rates (33 vs 25%, p=0.9).

The mortality after right hepatectomy was nil in both groups. The overall morbidity rate was 33%. Morbidity rates were respectively 58% for the PVE group and 36% for the PVL group (p=0.6), and the numbers of complications were 11 for the PVE group and 8 for the PVL group (Table 2). Hospital stay was not significantly different between both groups (24±20 vs 19±13 days after PVE and PVL, respectively, p=0.5).

Discussion

Results of the present study, which confirms that preoperative right portal occlusion induces significant hypertrophy of the future left remnant liver, showed that right PVL is as efficient than right PVE for inducing preoperative hypertrophy. Furthermore, PVL did not result in more preoperative difficulties during the second-step hepatectomy or more postoperative morbidity.

Serial CT scans allowed to establish well that PVE leads to macroscopic atrophy of the embolized liver and hypertrophy of the contralateral lobe. At the cellular level, some studies in humans support that both hypertrophy and replication are responsible for volume enlargement of the non-embolized liver after PVE, whereas both hepatocyte atrophy and apoptosis, predominantly in the perivenular area, lead to a decrease in volume of the embolized liver.[18–20] As the portal flow is presumed to have a hepatotrophic effect,[21,22] there is rational to get the most complete occlusion of a portal territory to expect the most effective hypertrophy of the contralateral liver lobe.

In patients with synchronous bilobar liver metastases that could not be completely resected within a single hepatectomy because of a small-anticipated residual liver volume, a two-step liver resection has been proposed.[10,11,13] The first step includes resection of metastases located in one liver lobe followed, several weeks later, by a second procedure with, in most cases, a contralateral liver lobe resection (Fig. 2). This strategy allows curative resection in patients who would otherwise be contraindicated for liver surgery.[11,13] The safety of the second procedure is facilitated by the hypertrophy of the FLR, which could be enhanced by a PVL during the first-step procedure or by a PVE after the initial procedure. In our previous experience of two-step strategy including PVL during resection of the primary tumor and/or clearance of left liver metastasis, we experienced evident volume increase of the non-ligated liver allowing us to perform safely right

Table 2 Intraoperative Characteristics and Postoperative Complications After Right Hepatectomy in PVE (n=12) and PVL (n=14) Groups

	PVE (n=12)	PVL (n=14)	p value
Intraoperative course			
Operating time (hours)	6.3±1.8	6.1±1.3	0.8
Intraoperative blood loss (ml)	1354±1837	900±660	0.5
Transfused patients (%)	4 (33)	4 (28)	0.7
No. of cavernoma	3	3	0.8
Postoperative complications			
No. of patients with complications (%)	7 (58)	5 (36)	0.6
Ascites	4	2	
Hepatocellular failure	2	2	
Pulmonary complications	3	2	
Renal failure	1	0	
Intraabdominal collections	1	2	

Continuous variables expressed as mean±SD

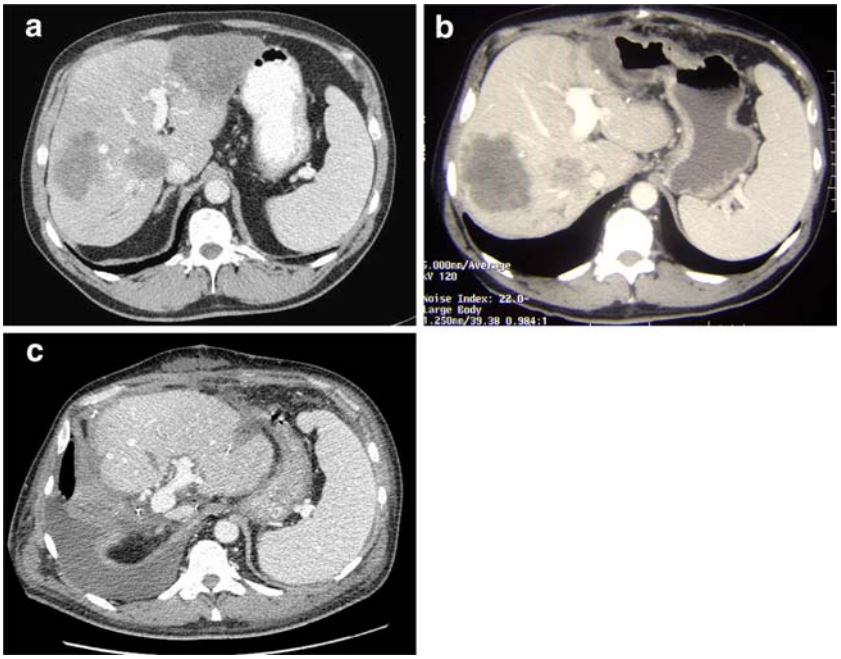

Figure 2 **a** A computed tomography scan in a 56-year-old patient who developed synchronous bilobar colorectal metastases and was treated by left colectomy and 6-month systemic chemotherapy. **b** Six weeks after resection of the left lobe tumor and right portal vein ligation, the volume of the left liver remnant increased while the right liver atrophied. **c** The residual liver 10 days after right hepatectomy.

hepatectomy.[10] As there is still a debate whether PVL is as efficient as PVE, this retrospective study aimed to compare PVL and PVE in terms of efficiency to induce hypertrophy of the FLR volume and impact on the planned liver resection after portal vein occlusion.

Broering et al.,[15] comparing PVE and PVL for induction of hypertrophy of the left lateral lobe before extended right hepatectomy, showed that PVE was more efficient. However, in the latter study, 60% of patients who underwent PVE had a partial or complete occlusion of the segment IV branches, whereas 29% in the PVL group (p=0.02). In our experience, we do not embolize segment IV branches to avoid migration of cyanoacrylate in the left portal branch, which would compromise the second-step hepatectomy. Results of the present study are consistent with those from Bouzari et al.[23] Their results confirm that PVL is as effective as PVE in inducing hypertrophy of the FLR volume. PVL was supposed to be less efficient than PVE because it may induce the formation of intrahepatic porto-portal collaterals leading to failure of liver hypertrophy.[14] However, in an experimental model, Krupski et al.[24] showed that the increase of liver volume after PVL was not restrained by the formation of porto-portal collaterals. The fortnight normalization of increased portal blood flow induced by portal vein occlusion in humans[25] and the early peak of hepatocyte proliferation after portal occlusion in rodents[26,27] suggest that liver hypertrophy is early induced after portal occlusion. Then, later formation of porto-portal collaterals would not impact on the induced liver hypertrophy. In this way, a recent experimental study in a non-human primate model supports that even a reversible portal vein occlusion may act as a starter for the liver hypertrophy.[28]

Another important result of the present study is that PVL did not result in more perioperative difficulties during the second-step hepatectomy or more postoperative morbidity. The second-step right hepatectomy were performed with a zero mortality rate and a 33% overall morbidity rate, which are consistent with the literature.[2,29,30] According to operating time, blood loss, and transfusion rates, perioperative technical difficulties during second-step hepatectomy in the PVL group were not affected by the presence of portal collaterals, previous liver resection, and cholecystectomy. We think that attention should be directed toward safe and complete left liver resection without unnecessary dissection or mobilization that could impact the difficulty of the second step. Excessive dissection of the porta hepatitis should be avoided to facilitate redissection at the second procedure. Cholecystectomy, which could be necessary to allow efficient control of the right branch of the portal vein, seems to have no impact on the technical difficulties.

In the present study, we were able to perform the scheduled second-step right hepatectomy in 74% of the patients. This figure is comparable with other series of two-stage hepatectomy from the literature, which report 55–85% resectability rates.[13,15,31] This rate was 82% after PVL and 67% after PVE, but the difference did not reach significance. This difference could be explained by a more important severity of colorectal cancer than neuroendocrine cancer. Interestingly, no PVL patient was precluded

from second-step hepatectomy because of an inadequate left liver hypertrophy.

There is evidence to suggest that portal vein occlusion may stimulate tumor growth in both the embolized and non-embolized lobes of the liver.[31,32] Elias et al.[31] reported patients whom liver metastases of the non-embolized lobe grew more rapidly that the liver parenchyma. In our series, except for one patient, there was no significant increase of left liver metastases volume after PVE. No any new lesions appeared in the left liver after portal occlusion in both groups. In this context of suspicion of tumor growth induced by portal vein occlusion, patients with PVL may benefit from this procedure, as clearance of the contralateral lobe may be achieved in the same time. Thus, 16 of the 17 PVL patients had local resection of the left-sided liver metastases. Of note, the only patient in whom left-side metastasis growth precluded the second-step liver resection had a PVE.

We are aware that indications for portal vein occlusion could be debated and that the two groups are not similar. Indications for portal vein occlusion depend on factors that impact the FLR volume needed for adequate post-hepatectomy liver function in an individual patient. Presence or absence of underlying liver disease, patient size, and the extent and complexity of the planned resection must be considered in the setting of the patient's comorbidities, which may affect hepatic regeneration. As guidelines for portal vein occlusion are continuously evolving[33] and impact of intensive chemotherapy on postoperative course is still not very well known,[34] we chose to perform portal vein occlusion in patients who have received intensive chemotherapy and/or who were planned for significant resections in the left liver lobe before a right hepatectomy.

In the PVL group, the primary tumor was either a neuroendocrine tumor (59%) or a colorectal adenocarcinoma with advanced liver metastases (41%), whereas all patients in the PVE group were referred for colorectal liver metastases, the colorectal primary tumor being previously resected. That is the reason why the PVL patients were younger, and more patients in the PVE group received chemotherapy at the time of referral. We recently showed that continuing chemotherapy while portal vein obstruction is performed did not impair the hypertrophy of the FLR volume.[35] Furthermore, liver parenchyma lesions induced by chemotherapy were found in only six PVE and five PVL patients. Finally, the rate of liver hypertrophy in the PVE group (35%) correlates well with previous reports from literature,[3,4,11,32,35] which suggest that neither older age of patients nor chemotherapy administration would have minimized the effect of PVE and the difference with PVL-induced hypertrophy. The PVL patients were younger and had more numerous tumors, which were bigger and bilobar with a primary cancer to be resected, whereas PVE patients were referred with colorectal metastases in the context of a small-anticipated residual liver volume. This point particularly expresses the fact that the two procedures may be applied in different indications or strategies but with the same efficiency in term of hypertrophy of the liver. Patients with multiple liver metastases, an inadequate residual liver, and a synchronous primary cancer may benefit from PVL.

In conclusion, results of this study clearly showed that right PVL and PVE result in a comparable hypertrophy of the left liver. Therefore, during the first laparotomy of a two-step liver resection, PVL can be safely performed, as it induces efficient hypertrophy of the left liver and does not adversely impact postoperative course.

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