A Two-Stage Hepatectomy Procedure Combined With Portal Vein Embolization to Achieve Curative Resection for Initially Unresectable Multiple and Bilobar Colorectal Liver Metastases

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Objective: To assess outcome after a 2-stage hepatectomy procedure (TSHP) combined with portal vein embolization (PVE) in the treatment of patients with unresectable multiple and bilobar colorectal liver metastases (MBCLM).

Background: Patients with MBCLM are often considered for palliative chemotherapy only, due to too small future remnant liver (FRL). Recently, right hepatectomy with simultaneous left liver wedge resections after previous right PVE has been reported in a curative intent. However, the growth of metastatic nodules in FRL after PVE can be more rapid than that of the nontumoral remnant hepatic parenchyma. Therefore, metastases located in the FRL should be ideally resected before PVE. Then, a right (or extended right) hepatectomy can be safely performed during a second-stage hepatectomy. Therefore, we analyzed our experience with the use of TSHP combined with PVE in treatment of MBCLM.

Patients and Methods: Between December 1996 and April 2003, 33 patients with unresectable MBCLM were selected for a TSHP. A right or an extended right hepatectomy was planned after treatment of left FRL metastases to achieve a curative resection. The first-stage hepatectomy consisted in a clearance of the left hemiliver by resection or radiofrequency destruction of metastases of the left FRL. Subsequently, a right PVE was performed to induce atrophy of the right hemiliver and hypertrophy of the left hemiliver. Finally, a second-stage hepatectomy was planned to resect the right liver metastases.

Results: There was no operative mortality. Post-PVE morbidity was 18.1%; postoperative morbidity was 15.1% and 56.0% after first- and second-stage hepatectomy, respectively. TSHP could be achieved in 25 of 33 patients (75.7%). The 1- and 3-year survival rates were 70.0% and 54.4%, respectively, in the 25 patients in whom the TSHP was completed.

Conclusions: In selected patients with initially unresectable MBCLM, a TSHP combined with PVE can be achieved safely with long-term survival similar to that observed in patients with initially resectable liver metastases.

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Liver resection has been recognized as the treatment of choice for patients with colorectal liver metastases (CLM), offering long-term survival and the only hope for cure.[1–3] However, hepatectomy can be performed only in approximately 10% to 20% of patients with CLM.[4] In the majority of cases, liver surgery is contraindicated due to too small future remnant liver (FRL).[5–7] During the last years, new multidisciplinary therapies have been proposed to increase safely the resectability rate in patients with initially nonresectable CLM. They include portal vein embolization (PVE),[8–10] systemic or arterial hepatic neoadjuvant chemotherapy,[11,12] transarterial neoadjuvant immunochemotherapy,[13] and local tumoral destruction.[14,15] However, these adjuvant therapies do not allow to achieve a curative resection in all patients and particularly in patients with multiple bilobar CLM (MBCLM). In these patients, the resection of MBCLM would result in a too small FRL. A 2-stage hepatectomy procedure (TSHP) without PVE was advocated to treat patients with unresectable multiple metastases.[16] However, after resection of MBCLM, high mortality (9%–15%) was reported.[16,17] Liver failure due to insufficient functional volume of the FRL is the main cause of postoperative mortality. Preoperative PVE has been proposed to induce compensatory hypertrophy of the FRL.[8,9] Some successful cases undergoing right hepatectomy and simultaneous left hemiliver wedge resections after PVE have been reported in patients with MBCLM.[18] However, growth of metastatic

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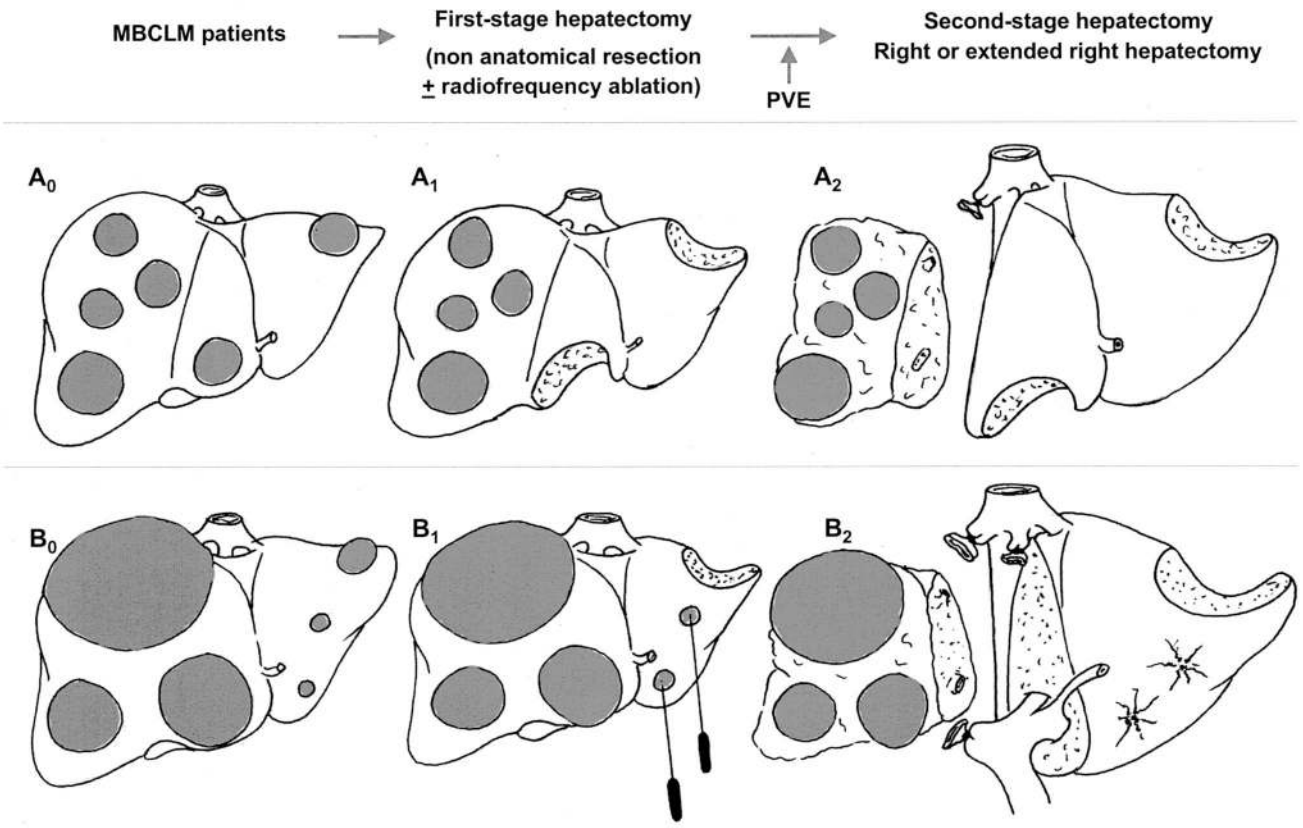

FIGURE 1. Patients with MBCLM (●) undergoing a TSHP. A_0, Patient with 2 metastases in the left hemiliver. A_1, First-stage: nonanatomic resection clearing the left liver of all metastases. A_2, Second-stage (right hepatectomy) after PVE (not shown): atrophy of the right and hypertrophy of the left liver. B_0, Patient with 4 metastases in the left hemiliver. B_1, First-stage: Radiofrequency destruction (●) and nonanatomic resection were associated to clear the left liver of all metastases. B_2, Second-stage (right hepatectomy) after PVE (not shown).

nodules in the FRL after PVE can be more rapid than that of the nontumoral remnant hepatic parenchyma.[19] Therefore, metastases located in the FRL should be ideally resected before PVE in a first-stage hepatectomy; a major hepatic resection can then be performed, after PVE, in a second-stage hepatectomy. Therefore, a new strategy design has been developed to treat patients with initially unresectable MBCLM. Our preliminary results were previously reported.[20]

The present study reports feasibility, surgical outcome, recurrence rate, and long-term survival of patients presenting initially unresectable MBCLM undergoing a TSHP combined with PVE.

PATIENTS AND METHODS

Patient Selection

From December 1996 to April 2003, 33 of 398 patients (8.2%) presenting MBCLM were selected for a TSHP combined with PVE.

Inclusion Criteria

We included patients with MBCLM in whom the left hemiliver could be cleared of metastases during a first-stage hepatectomy respecting the left hepatic pedicle and/or at least segments 2 and 3. In these patients, at least 30% of the functional liver volume (as estimated by a preoperative three-dimensional CT scan) could be preserved after right PVE and a second-stage right or extended right hepatectomy.

Exclusion Criteria

We excluded patients with MBCLM presenting obstructive jaundice, invasion of vena cava, invasion of FRL hepatic vein, or with altered hepatic functional reserve (evaluated by an indocyanine green retention rate after 15 minutes [ICG 15] of more than 20%).[21] We also excluded patients in whom the disease progressed under chemotherapy administered before referral to our institution.

TABLE 1. Patient and Tumor Characteristics

	Two-Stage Procedure Planned	Two-Stage Procedure Achieved
No. of patients	33	25
Age (years)*	63 ± 9 (44–80)[63]	61 ± 9 (44–80)[60]
Older than 70 years	8	4
Sex ratio M/F	22/11	17/8
Weight (kg)*	72 ± 12 (51–101)[70]	72 ± 12 (51–101)[70]
Primary tumor site		
Right colon	8	4
Left colon	13	10
Rectum	12	11
pTNM stage (M excluded)		
Stage I	2	1
Stage II	4	3
Stage III	27	21
Metastases		
Synchronous	22	19
Metachronous (>6 months)	11	6
No. of metastases in whole liver*	7 ± 4 (2–23)[7]	8 ± 4 (3–23)[7]
No. of metastases in the left FRL*	3 ± 2 (1–11)[3]	3 ± 2 (1–11)[3]
Size of largest metastases in whole liver (mm)*	69 ± 33 (25–160)[60]	71 ± 34 (35–160)[60]
Size of largest resected metastases in the left FRL (mm)*	27 ± 20 (3–90)[21]	29 ± 22 (3–90)[22]
Simultaneous primary and left liver metastases resection		
Yes	10	7
No	23	18
Volume of the FRL before PVE (mL)*	429 ± 191 (208–802)[390]	430 ± 191 (208–802)[390]
Ratio between volume FRL/body weight*	0.6 ± 0.2 (0.3–1.1)[0.5]	0.6 ± 0.2 (0.3–1.0)[0.5]
Volume of the FRL after PVE (mL)*	564 ± 263 (280–1148)[480]	564 ± 263 (280–1148)[480]
Ratio between volume FRL/body weight*	0.8 ± 0.3 (0.4–1.5)[0.7]	0.8 ± 0.3 (0.4–1.5)[0.7]
Chemotherapy		
Before first-stage hepatectomy	27	21
Between PVE and second-stage hepatectomy	3	3
Biopsy of normal liver parenchyma (first-stage hepatectomy)		
Normal	13	9
Macrosteatosis	15	11
Steatofibrosis	5	5
Extrahepatic disease (first-stage hepatectomy)		
Localized resectable carcinomatosis	4	0
Pulmonary resectable metastases	6	4
Spleen metastases	1	0
Extrahepatic disease (second-stage hepatectomy)		
Contiguous involvement of the diaphragm	2	2
Localized resectable carcinomatosis	1	1

*Values are expressed as mean ± SEM (range)[median].

Preoperative Investigations

Preoperative evaluation include thoracoabdominal CT scan with 3-dimensional volume evaluation of the liver and MRI of the liver with coronal views. The primary tumor site was assessed for recurrence with a total colonoscopy and ultrasound rectal endoscopy or MRI of the pelvis for rectal primaries.

Two-Stage Hepatectomy Procedure

First-Stage Hepatectomy

The first-stage hepatectomy was the key step of the planned procedure. It consists in a complete clearance of the metastases located in 1 hemiliver. In all our patients, the FRL

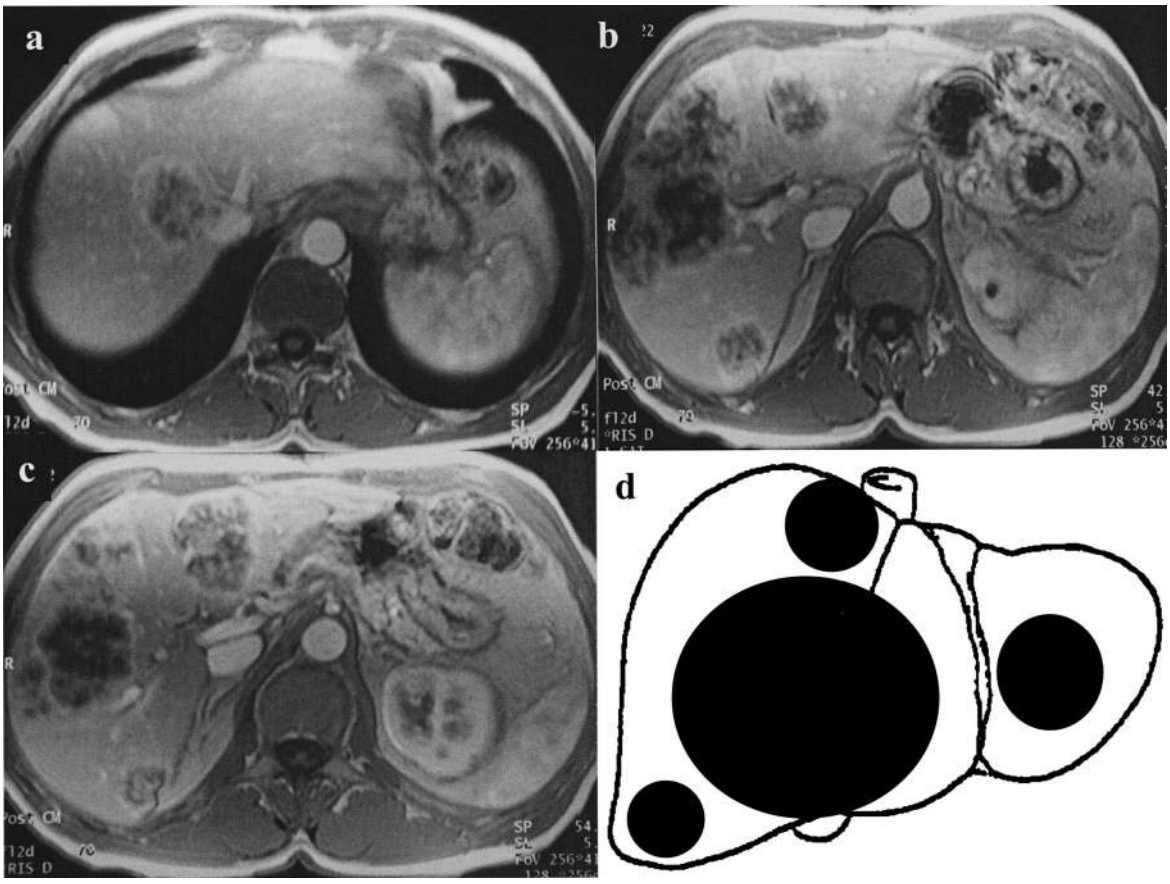

FIGURE 2. A case of MBCLM managed by a TSHP: preoperative MRI (A-C), a diagram representing topography of the metastases (D).

was the left hemiliver. In some cases, the first-stage hepatectomy was associated with resection of the primary colorectal tumor.[22] The first-stage hepatectomy consisted of nonanatomic liver resections in case of less than 3 metastases (Fig. 1A), and in nonanatomic resection associated with radiofrequency (RF) destruction in case of 3 or more metastases (Fig. 1B). Parenchymal dissection was performed either without pedicle clamping or under selective left hilar clamping.

PVE

A right PVE (± branches of segment IV) was performed 2 to 5 weeks after the first-stage hepatectomy. A percutaneous approach through the left portal branch was routinely used. Left liver hypertrophy was evaluated with three-dimensional CT scan 5 to 8 weeks after PVE. When the estimated volume of the left FRL was considered insufficient, a second evaluation at 3 to 4 weeks later was performed before excluding the patient from the second-stage hepatectomy.

Second-Stage Hepatectomy

A right- or an extended right hepatectomy was performed in all cases; resection of caudate lobe was associated in case of involvement. The dissection of liver parenchyma was achieved without clamping or under selective right pedicle clamping. In case of development of further metastases in the left FRL, iterative nonanatomic resection or RF destruction was performed during the second-stage hepatectomy.

Hepatoduodenal Ligament Lymph Nodes Dissection

During the first-stage hepatectomy, a picking of lymph nodes was routinely performed (around portal vein and common hepatic artery). During the second-stage hepatectomy, a hepatic pedicle lymph node dissection was performed according to the preference of the surgeon. The procedure of lymph node dissection was performed as described previously.[23]

Follow-up

Patients were followed with a physical examination, liver biochemistry, carcinoembryonic antigen and CA 19–9 serum levels, liver ultrasonography, and CT scan every 3 months. No patient was lost during the follow-up period.

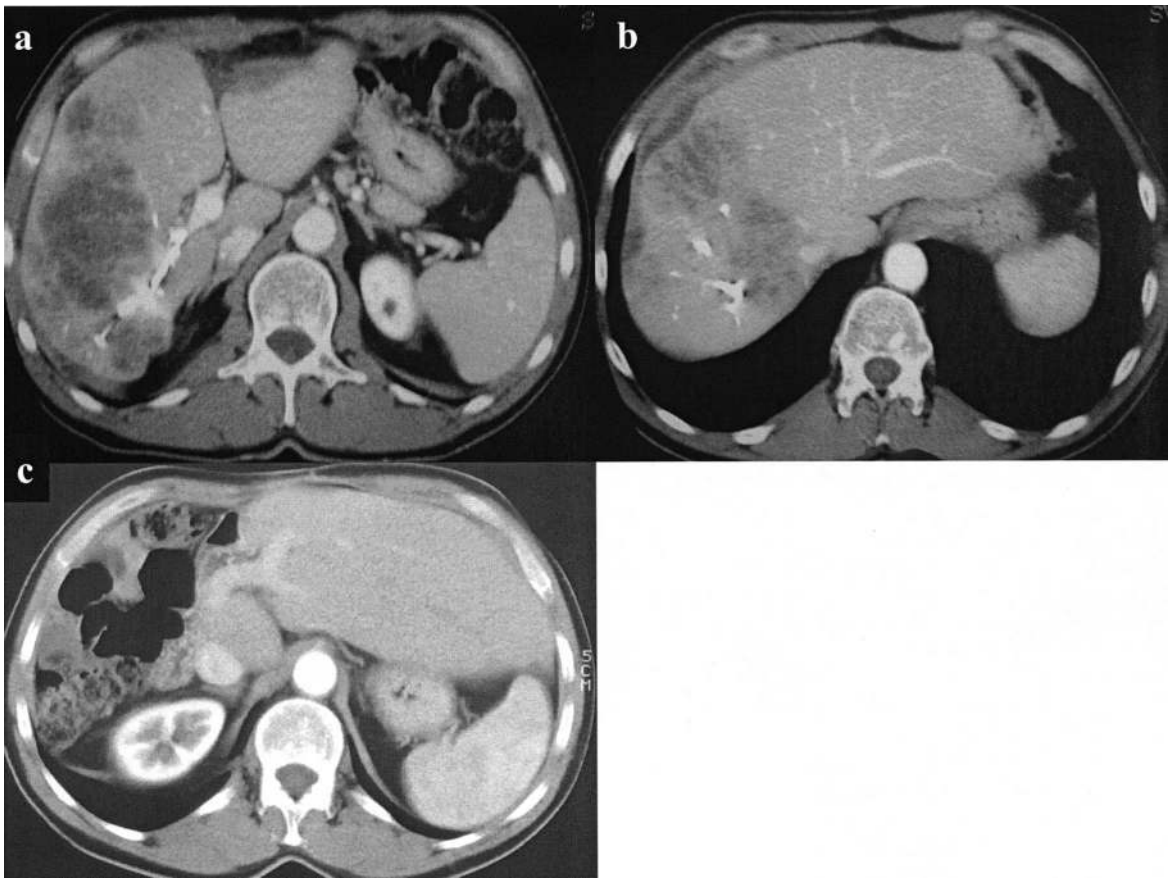

FIGURE 3. The same case as in Figure 2. CT scan showing nonanatomic resection of segment 3 during the first-stage hepatectomy and coils in the right liver parenchyma as evidence of right portal vein embolization (A), left FRL hypertrophy and patent left hepatic vein after PVE (B), and CT scan 1 year after extended right hepatectomy performed during the second-stage hepatectomy (C).

Statistics

Mean values are expressed with standard error of mean. χ^2 and Fischer exact test were appropriately used. Survival was calculated from the date of the second-stage hepatectomy with Kaplan-Meier method, and significant differences were examined with log-rank test. Survival for patients in whom the procedure has not been achieved was calculated from the date of the first-stage hepatectomy. A difference was considered significant when the P value was less than 0.05.

RESULTS

Patient Characteristics

The sex ratio (male/female) was 2. The mean (±SD) age was 63.2 ± 9.3 years (range, 44–80 years; median, 61 years). Eight patients were older than 70 years. Patients characteristics are shown in Table 1. The primary tumor was located in the colon in 21 patients (63.6%) and in the rectum in 12 patients (36.4%). All the patients presented with asymptomatic liver metastases. After first-stage hepatectomy and PVE, 8 patients could not undergo a second-stage hepatectomy and received palliative chemotherapy, while the other 25 patients achieved the TSHP. A demonstrative case was summarized in Figures 2 and 3. No patient had any macroscopic sign of lymph node involvement. Among the 7 patients who underwent hepatic pedicle lymph node dissection, 2 presented lymph nodes metastases.

Twenty-three patients were referred to our institution after primary tumor resection, with mean interval of 17 ± 14 months (range, 3–52 months; median, 14 months). Metastases in the liver were synchronous in 22 patients (66.7%), and 10 of these patients underwent simultaneous first-stage hepatectomy at the time of primary tumor resection in our institution. Tables 1 and 2 summarize the metastases characteristics and surgical details of the TSHP. The number of metastases located in the left FRL was 1 in 11 patients, 2 in 5 patients, 3 in 7 patients, and more than 3 in 10 patients, respectively.

Extrahepatic Metastases and First-Stage Hepatectomy

Preoperative imaging studies revealed isolated resectable pulmonary metastases in 4 patients, and in 1 patient an

TABLE 2. Surgical Data

	First-Stage Hepatectomy (n = 33)	Second-Stage Hepatectomy (n = 25)
Type of liver resection	25	5*
Future left liver remnant	8	1*
Nonanatomic resection		
Radiofrequency ablation ± nonanatomic resection		
Right liver		
Right hepatectomy		12
Right hepatectomy extended to segment IV		10
Right hepatectomy extended to segment I and IV		3
Operative duration (minutes)	263 ± 88 (135–420)[225]	356 ± 69 (245–480)[360]
Blood transfusion requirement		
No. of patients	3	17
No. of RBC (units)	1.6 ± 0.5 (1–2)[2]	5.4 ± 3.4 (1–14)[5]
Hepatic inflow occlusion		
No. of patients	6	14
Duration (minutes)	22 ± 13 (10–43)[19]	29 ± 13 (5–48)[32]
Hospital stay (days)	12 ± 5 (6–33)[11]	17 ± 8 (8–34)[12]
Associated resection of extrahepatic disease		
Localized resectable carcinomatosis	4	1
Contiguous involvement of the diaphragm	0	2
Spleen metastases	1	0

Note: Values are expressed as mean ± SEM (range)[median].
*Patient is undergoing a right hepatectomy and either nonanatomic resection or radiofrequency ablation for de novo metastases in the left remnant liver.

isolated spleen metastases that required splenectomy. At the time of laparotomy, a localized carcinomatosis was detected and resected in 4 patients. Two of these patients had also resectable pulmonary metastases. None of the 5 patients presenting with intraabdominal extrahepatic disease completed the TSHP. Among the 4 patients presenting with isolated pulmonary metastases, 2 were resected after completion of TSHP and 2 others are planned for pulmonary resection.

Extrahepatic Metastases and Second-Stage Hepatectomy

In 3 patients, extrahepatic intraabdominal metastases were detected and resected during the second-stage hepatectomy. Two of them had contiguous involvement of the diaphragm and 1 had limited right perinephric carcinomatosis.

Chemotherapy

Six patients presenting with synchronous MBCLM did not received chemotherapy. The other 27 patients received a different regimen of systemic chemotherapy before the first-stage hepatectomy and before they were referred to our institution. The chemotherapy regimens included a combination of 5-fluorouracil and acid folinic alone (n = 5), or associated to either oxaliplatin (n = 14) or irinotecan (n = 8). The number of cycles ranged from 3 to 12 for each drug. In 8 patients, a second line of chemotherapy was administered with a shift from irinotecan to oxaliplatin (n = 2) or from oxaliplatin to irinotecan (n = 6). All 27 patients had at least stabilization of the metastatic liver disease.

Three patients received chemotherapy (2 to 3 cycles) after PVE and before the second-stage hepatectomy. The different regimens included 5-fluorouracil + folinic acid + irinotecan (n = 2) and Xeloda (n = 1). These 3 patients had more than 5 metastases in the left FRL resected or ablated by radiofrequency during the first-stage hepatectomy.

Outcome After PVE

According to the location of the metastases, the right portal vein was embolized in all cases. The segment IV portal branches were embolized in 5 (15%) patients. PVE was carried out successfully in 33 patients. PVE was performed 28 ± 22 days after the first-stage hepatectomy (range, 5–109 days; median, 22 days). The mean hospital stay after PVE was 4 ± 2 days (range, 2–14 days; median, 4 days). Table 1 summarizes the volumetric measures of FRL before and after

PVE. Postembolization course was uneventful in 27 patients. However, complications occurred in 6 patients (18.1%) including a hematoma of the left FRL ($n = 1$), an arterial hypotension during the procedure ($n = 1$), a transitory fever ($n = 3$) and a mesenterico-portal venous thrombosis ($n = 1$). The later patient did not undergo the second-stage hepatectomy and died 6 months following the PVE from disease progression. In 2 patients (6%), hypertrophy of the left FRL was considered insufficient and they received palliative chemotherapy only after PVE.

Operative Outcome

There was no operative mortality. Postoperative morbidity rates were 15.1% and 56.0% after first- and second-stage hepatectomy, respectively. However, 11 patients only (44%) presented complications related to liver surgery. The other 3 patients developed medical complications: urinary tract infection ($n = 1$) and central catheter infection ($n = 2$). The feasibility of the TSHP was 75.7% (25 of 33 patients). The second-stage hepatectomy was not performed because insufficient left FRL hypertrophy ($n = 2$, 6%), disease progression ($n = 5$, 15%) and a mesenterico-portal vein thrombosis ($n = 1$, 3%) complicating PVE. Postoperative complications after each hepatectomy are summarized in Table 3. Reoperation was required in 1 patient only for evisceration.

Survival and Recurrence

The mean and median follow-up after the second-stage hepatectomy were 19 ± 21 and 12 months, respectively (range, 4–76 months). The 1- and 3-year survival rates were 70.0% and 54.4%, respectively, in the 25 patients in whom the TSHP was completed. The 1- and 3-year disease-free survival rates were 35.2% and 14.1%, respectively. Sixteen patients (64%) developed recurrences and their characteristics are shown in Table 4. Among them, 6 patients died of recurrences after a mean follow-up of 13 ± 10 months (range, 5–33 months; median, 8 months), 6 were alive with recurrent disease, and 4 were alive and disease-free after resection of their recurrent disease with a mean follow-up of 47 ± 21 months (range, 26–72 months; median, 33 months). Nine of 25 patients did not developed any recurrence after a mean follow-up of 13 ± 10 months (range, 4–31 months; median, 5 months). Therefore, 13 patients were disease-free after a mean follow-up of 19 months (range, 4–72 months; median, 11 months).

The 1- and 3-year survival rates were 72.9% and 0%, respectively, in the 8 patients in whom the TSHP has not been completed (Fig. 4). Their median survival was 14 months with a mean follow-up of 10 ± 8 months (range, 4–26 months; median, 9 months). The survival rate was significantly higher in patients in whom the TSHP was completed

TABLE 3. Postoperative Complications

	First-Stage Hepatectomy ($n = 33$)	Second-Stage Hepatectomy ($n = 25$)
Mortality	0	0
Reoperation	1	0
Morbidity	5	14*
Type of postoperative complications		
General complications		
Sepsis	1	5
Urinary infection	1	2
Arrhythmia	2	0
Hemodynamic instability	0	1
Lower limb thrombophlebitis	0	1
Specific complications		
Deep wound infection	1	2
Subphrenic collection	0	3
Transitory liver failure	0	3
Angiocholitis	0	1
Pleural effusion	0	4
Atelectasia	0	3
Ascitis	0	1

Note: Values are number of patients.
*There were 26 complications in 14 patients.

TABLE 4. Site, Treatment, and Outcome of Recurrences After Two-Stage Hepatectomy Procedure for Initially Unresectable Colorectal Liver Metastases

Patient No.	Recurrence Site	Intervals After Second-Stage Hepatectomy (months)	Treatment of Recurrences	Outcome (months)*	Disease-Free
Univisceral recurrence					
1	Liver	65	Chemotherapy	A 76	N
2	Liver	6, 30	Repeat hepatectomy (2 times)	A 72	Y
3	Liver	13	Chemotherapy	A 21	N
4	Liver	2	Chemotherapy	D 5	—
5	Liver	5	Chemotherapy	A 8	N
6	Lung	9	Surgery	A 56	Y
7	Lung	9	Chemotherapy	A 13	N
8	Locoregional at the primary tumor site	13	Surgery + chemotherapy	A 33	Y
9	Bone	7	Radiotherapy	D 8	—
Multivisceral recurrence					
10	Lung, liver	9	RF + chemotherapy	D 33	—
11	Lung, liver	8	Chemotherapy	A 24	N
12	Lung, liver, bone, brain	4	Chemotherapy	D 8	—
13	Lung, liver	18	Surgery + chemotherapy	A 26	Y
14	Lung, liver	3	Chemotherapy	D 11	—
15	Lung, liver	7	Chemotherapy	D 12	—
16	Lung, liver	11	Chemotherapy	A 13	N

A, alive; D, dead; RF, radiofrequency; N, no; Y, yes.
*Numbers indicated intervals after second-stage hepatectomy.

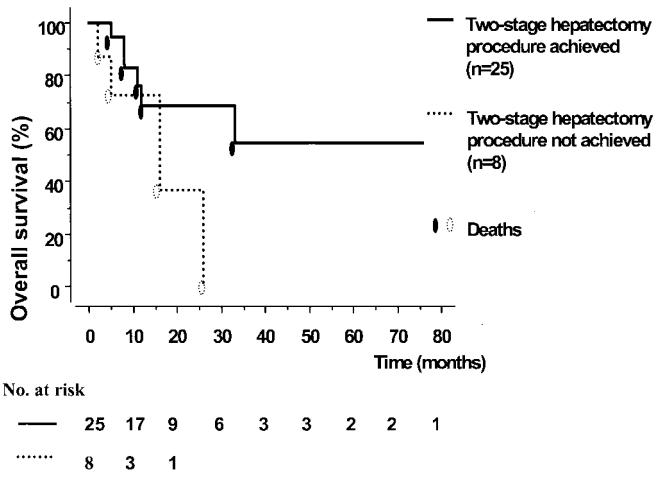

FIGURE 4. Kaplan-Meier survival of 33 patients with and without completion of the 2-stage hepatectomy procedure.

compared with those in whom the TSHP was not completed (Fig. 4; $P = 0.02$).

Prognostic Factors for Survival

Univariate analysis of parameters for overall and disease-free survival are shown in Table 5. The 3-year survival rate for patients presenting ≤ 2 metastases in the left FRL was higher but did not significantly differ from those with ≥ 2 metastases (59.3% vs. 40.0%; $P = 0.11$; Fig. 5). On the other hand, presence of ≥ 2 metastases located in the left FRL was associated with an increased risk of recurrence ($P = 0.004$; Table 5). Liver resection or RF during the first-stage hepatectomy did not appear to influence overall and disease-free survival ($P = 0.13$ and 0.15, respectively; Table 5).

Univariate Analysis of Prognostic Factors That Affect Completion of the Procedure

The results of univariate analysis showed that only the presence of intraabdominal extrahepatic disease, even limited and resectable at the first-stage hepatectomy, was significantly associated with increase rate of failure to achieve the TSHP (62.5% and 0%, $P < 0.0001$, respectively; Table 6).

DISCUSSION

The TSHP combined with PVE for initially unresectable MBCLM can be achieved safely without mortality. Analysis of our series suggests that this strategy represents currently a treatment, which can offer a real hope of long-term remission.

TABLE 5. Univariate Analysis of Overall and Disease-Free Survival After TSHP

		Overall Survival			Disease-Free Survival		
	No.	3 year (%)	Median (months)	*P*	1 year (%)	Median (months)	*P*
Gender							
Male	17	55.4	—	0.75	40.2	9	0.38
Female	8	60.0	—		22.2	7	
Age							
≤65 years	17	46.9	33	0.64	30.1	8	0.25
>65 years	8	68.6	—		42.9	10	
Primary site							
Colon	14	54.5	—	0.42	33.8	7	0.44
Rectum	11	58.3	—		37.5	9	
Primary tumor stage							
I and II	4	50.0	33	0.85	33.3	7	0.58
III	21	63.5	—		35.4	8	
Synchronous							
No	6	75.0	—	.58	27.8	11	0.59
Yes	19	50.0	33		22.1	8	
No. of metastases in whole liver							
<7	17	51.9	—	.89	36.8	8	0.94
>7	8	80.0	—		32.8	7	
No. of metastases in left remnant liver							
<2	12	59.3	—	0.11	60.6	12	0.004
>2	13	40.0	11		0.0	6	
Largest tumor size in whole liver							
<5 cm	8	50.0	33	0.64	30.0	7	0.87
>5 cm	17	61.4	—		36.7	9	
Largest tumor size in left remnant liver							
<3 cm	14	51.4	—	0.95	38.7	9	0.45
>3 cm	11	64.3	—		31.8	9	
Type of liver resection during first-stage hepatectomy							
Resection	20	58.0	—	0.13	38.3	8	0.15
Radiofrequency	5	0.0	—		33.3	6	
Transfusion							
No	8	0.0	31	0.31	42.9	9	0.77
Yes	17	76.4	—		32.6	8	
Extrahepatic disease							
No	19	50.0	33	—	34.6	8	0.34
Yes	6	100.0*	9	—	33.3	9	

*Two-year survival rate.

Recently long-term survival has been reported in patients with MBCLM after multimodal therapies combining induction chemotherapy followed by surgical resection associated or not with local ablation (radiofrequency, microwave)[24,25]; however, postoperative mortality due to liver failure still remained a drawback. In the present series, the majority of the patients were referred to our institution after a first or a second line chemotherapy; nevertheless, they were considered unresectable according to our selection criteria. Among these patients, a safe complete resection was only possible by TSHP. Our results suggest that PVE was an effective treatment to prevent postoperative mortality due to liver failure.

In the present series, univariate analysis did not show any impact of chemotherapy administration before TSHP on

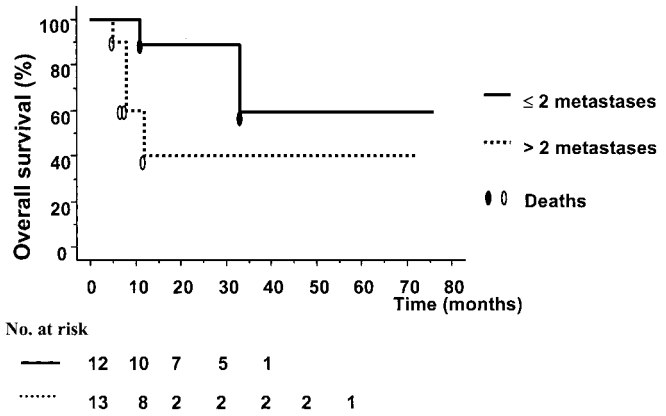

FIGURE 5. Kaplan-Meier survival of 25 patients in whom the strategy has been achieved according to the number of metastases in the future left remnant liver.

feasibility of the procedure and on survival. However, the design of this study does not allow conclusion on neoadjuvant chemotherapy efficiency. Indeed, most of the patients were referred after first or second line chemotherapy; at that time, the referring oncologist estimated that further medical treatment could not be helpful. However, in case of early referral neoadjuvant chemotherapy can be proposed to patients with MBCLM in attempt to down-stage the disease and eventually spare some patients from a TSHP in favor of a 1-stage procedure.[11,24]

The first-stage hepatectomy included nonanatomic resection, RF destruction or both techniques. This combination increased the feasibility of TSHP by 20% (5 of 25 patients) with similar overall and disease-free survival compared with patients undergoing nonanatomic liver resection alone (Table 5). Therefore, the percutaneous approach could be considered as an alternative to laparotomy to perform RF destruction. However, a percutaneous approach could overlook either small metastases in the FRL or peritoneal carcinomatosis, which can be both easily detected during laparotomy.

In case of synchronous MBCLM, the resection of the primary colorectal tumor can be combined with the first-stage hepatectomy. Candidates for simultaneous resection were reported previously.[22]

The TSHP was designed to achieve a curative resection in patients presenting MBCLM with predominant involvement of 1 hemiliver. In our series, all patients with MBCLM had predominant right liver metastases. However, in 1 case (not included in this study) of multiple and bilobar endocrine metastases with predominant left hemiliver involvement, we performed left PVE after clearance of the right liver metastases during the first-stage hepatectomy and a left hepatectomy during the second-stage hepatectomy. This experience suggests that TSHP combined with PVE could be adequate for patients presenting MBCLM, even with predominant location in the left hemiliver using left PVE followed by a left or an extended left hepatectomy. In case of involvement of segment 4, the volume of the FRL (left hemiliver or segments 2 and 3) was determined according to the extent of the disease. Indeed, for massive involvement of segment 4, clearance of segment 2 and 3 only was performed at the time of the first-stage hepatectomy. Then, a right extended hepatectomy was performed as a second-stage hepatectomy provided that the portal branches of segment 4 were embolized during right PVE procedure. In case of limited resectable involvement of segment 4, a complete clearance of the 3 segments (2, 3, and 4) was achieved at the time of the first-stage hepatectomy.

After resection of MBCLM, a high mortality (9%–15%) has been reported in recent series mainly due to postoperative liver failure developed in patients who did not receive PVE.[16,17] In our experience, lethal postoperative liver failure was avoided by contraindicating the second-stage hepatectomy in patients with insufficient hypertrophy.

Recently, a prospective clinical trial demonstrated that systematic right portal vein embolization before right hepatectomy had no beneficial effect on the postoperative course in patients with normal liver.[26] In their series, the authors excluded patients with less than 2 months' delay between preoperative systematic chemotherapy and surgery. In our series, only 9 of 25 patients had a normal FRL liver parenchyma, and chemotherapy was administered to the majority of the patients with delay of less than 2 months from the first-stage hepatectomy. The remaining 16 patients had macrosteatosis ($n = 11$) or steatofibrosis ($n = 5$) as demonstrated by liver biopsy at the time of first-stage hepatectomy. Moreover, half of the patients required extended right hepatectomy after PVE. Functional reserve and volume of FRL were a major concern in our patients; our results suggest that PVE contributed to avoid postoperative mortality due to liver failure.

Even if in some cases the limited number of left FRL metastases (≤ 2) might have allowed proposal of a 1-stage hepatectomy, preservation of an adequate functional FRL volume was problematic because of size and/or location of the left FRL metastases and/or to the steatofibrosis of the FRL parenchyma subsequent to chemotherapy increasing the expected risk of postoperative mortality. Indeed, despite PVE and adequate left FRL hypertrophy (FRL $> 30\%$ of the functional liver volume after PVE), 3 patients developed transitory liver failure that might have been lethal without PVE.

Ligation of the right portal vein during the first-stage hepatectomy could be an alternative to PVE.[27] However, this attitude may induce postoperative liver failure due to simultaneous nonanatomic resection in the FRL and right portal vein ligation. Moreover, the occurrence of collateral circulation may reduce the efficiency of portal vein ligation, and

TABLE 6. Impact of Clinicopathologic Characteristics on Feasibility of the TSHP

	Two-Stage Procedure Achieved ($n = 25$)	Two-Stage Procedure Not Achieved ($n = 8$)	*P*
Gender			0.77
M	17	5	
F	8	3	
Primary tumor site			0.10
Colon	14	7	
Rectum	11	1	
pTNM stage (M excluded)			0.57
Stage I and II	4	2	
Stage III	21	6	
Metastases			0.08
Synchronous	19	3	
Metachronous	6	5	
No. of metastases in whole liver			0.70
≤7	17	6	
>7	8	2	
No. of metastases in the left remnant liver			0.92
≤2	12	4	
>2	13	4	
Size of largest metastases in whole liver			0.77
<5 cm	8	3	
≥5 cm	17	5	
Size of largest resected metastases in the left remnant liver			0.91
<3 cm	14	6	
≥3 cm	11	2	
Chemotherapy before first-stage hepatectomy			0.61
Yes	21	6	
No	4	2	
Simultaneous primary and left liver metastases resection			0.61
Yes	7	3	
No	18	5	
Intraabdominal extrahepatic disease (first-stage hepatectomy)			<0.0001
Yes	0 (0)	4 (62.5)	
No	25 (100)	4 (37.5)	
Pulmonary resectable metastases			0.56
Yes	4	2	
No	21	6	
Procedure during the first-stage hepatectomy			0.31
Resection	20	5	
Radiofrequency	5	3	

Numbers in parentheses are percentage.

development of portal cavernoma around the hepatic pedicle could increase the difficulty of the second-stage hepatectomy.

There was a mean period of time of 4 to 6 weeks between PVE and second-stage hepatectomy. However, Uesaka et al reported that the functional gain is more rapid and of greater magnitude than the volume gain.[28]

A right- or extended (segment 4 + caudate lobe) right hepatectomy was performed in all cases. In our series, 6 patients (24%) required, during the second-stage hepatectomy, further surgical treatment of left FRL metastases, which were undetectable at the time of the first-stage hepatectomy (Table 2).

The rationale for chemotherapy before right PVE would be to avoid progression of liver metastases in FRL. Indeed, the main cause of failure to achieve the TSHP was progression of the disease in the left FRL. The administration of chemotherapy after PVE in a subgroup of high-risk patients (with more than 5 metastases in the left FRL) could have contributed to increase the feasibility of the TSHP. The feasibility of the TSHP was 75.7%. Mortality was nil despite the 2 consecutive hepatectomies. Postoperative and long-term outcomes were similar to those reported by Adam et al for initially unresectable MBCLM.[16] However, interestingly, our series included more patients with a longer follow-up and 5-year survivors. As half of the study patients were included in the last part of the study, the median follow-up was of 12 months (range, 4–76 months).

Intrahepatic recurrences were observed in 12 patients (48%, Table 4). These recurrences could be resected in 4 patients (25%) with a disease-free survival of 26, 33, 56, and 72 months, respectively (Table 4). The analysis of our results showed that only the number of metastases in the left FRL ($\leq$ 2 vs. $>$ 2) was a risk factor for recurrence (Table 5; P = 0.004).

During the last decade, several groups tried to increase the number of patients who could benefit from the resection of CLM. Their approach, more aggressive, included resection of extrahepatic disease, resection in elderly patients, and resection of MBCLM with small FRL.[17,29] To extend the surgical indications of the TSHP, intraoperative RF destruction in association with nonanatomic liver resection has been performed in patients with more than 2 metastases located in the left FRL. Moreover, the same procedure has been also used during the second-stage hepatectomy to treat the recurrent metastases in the left FRL.

Elias et al recently reported that resectable peritoneal carcinomatosis should no longer be considered as an absolute contraindication to hepatectomy.[29] The 5-year survival rate following simultaneous resection of liver metastases and extrahepatic disease ranged from 18% to 20%.[29,30] In our series, 4 patients presented with localized resectable peritoneal carcinomatosis and 1 patient with a single splenic metastasis; extrahepatic disease was resected, but all these patients developed disease progression and could not undergo the second hepatectomy. Univariate analysis showed that the presence of intraabdominal extrahepatic disease diagnosed during the first-stage hepatectomy, even when "completely" resected, negatively affected the completion of the TSHP. Therefore, the presence of extrahepatic disease, detected during the first-stage hepatectomy, should currently be considered as a contraindication to the TSHP. The accuracy of detection of extrahepatic intraabdominal involvement should be improved either preoperatively (PET scan)[31] or intraoperatively before starting the first-stage hepatectomy. Staging laparoscopy could be used as an alternative approach to detect intraabdominal extrahepatic disease.[32,33] At the opposite, in our series the presence of resectable pulmonary metastases did not constitute an obstacle for completion of the TSHP.

None of the prognostic factors analyzed was significantly associated with an improved survival, except the completion of the procedure. Among patients in whom the TSHP has been completed, the overall and disease-free survivals were similar to that recently reported for patients with initially resectable CLM.[1,17,24,25,30,34,35] Several arguments could explain these favorable results. First, the design of our strategy allowed better selection of the patients based not only on preoperative investigations but also including a "test of time" of 2 to 3 months to evaluate tumoral behavior. Second, the combination of minor resections and RF destruction increased the number of patients who could undergo the whole procedure. Third, the recent introduction of chemotherapy after PVE in a subgroup of patients considered at high risk for disease progression could have contributed to increase the feasibility of the procedure by controlling recurrences occurring in the FRL between the 2 hepatectomies; however, further studies are needed to confirm this preliminary hypothesis.

CONCLUSION

This study provides further evidence that a TSHP combined with PVE for initially unresectable MBCLM can be performed safely in selected patients, with similar short- and long-term outcome compared with patients with initially resectable CLM.

REFERENCES

1. Nordlinger B, Jaeck D, Guiguet M, et al. Surgical resection of hepatic metastases: multicentric retrospective study by the French Association of Surgery. In: Nordlinger B, Jaeck D, eds. *Treatment of Hepatic Metastases of Colorectal Cancer*. Paris: Springer-Verlag, 1992:129–146.
2. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver: a prognostic scoring system to improve case selection, based on 1568 patients. *Cancer*. 1996;77: 1254–1262.
3. Jaeck D, Bachellier P, Guiguet M, et al. Long-term survival following resection of colorectal hepatic metastases. *Br J Surg*. 1997;84:977–980.
4. Scheele J, Stangl R, Altendorf-Hofmann A, et al. Resection of colorectal metastases. *World J Surg*. 1995;19:59–71.
5. Moertel CG. Chemotherapy for colorectal cancer. *N Engl J Med*. 1994;330:1136–1139.
6. Levi F, Zidani R, Misset JL, et al. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. *Lancet*. 1997;350:681–686.
7. Rougier P, Van Cutsem E, Bajetta E, et al. Randomized trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet*. 1998;352: 1407–1412.
8. Makuuchi M, Le Thai B, Takayasu K, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery*. 1990;107:521–527.
9. Azoulay D, Castaing D, Smail A, et al. Resection of non resectable liver metastases from colorectal cancer after percutaneous PVE. *Ann Surg*. 2000;231:480–486.

10. Elias D, Roche A, Vavasseur D, et al. Induction of hypertrophy of a small left hepatic lobe by preoperative right portal embolization, preceding extended right hepatectomy. *Ann Chir*. 1992;46:404–410.
11. Bismuth H, Adam R, Levi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg*. 1996;224:509–522.
12. Miyanari N, Mori T, Takahashi K, et al. Evaluation of aggressively treated patients with unresectable multiple liver metastases from colorectal cancer. *Dis Colon Rectum*. 2002;45:1503–1509.
13. Lygidakis NJ, Vlachos L, Raptis S, et al. New frontiers in liver surgery: two-stage liver surgery for the management of advanced metastatic liver disease. *Hepato-Gastroenterology*. 1999;46:2216–2228.
14. Adam R, Akpinar E, Johann M, et al. Place of cryosurgery in the treatment of malignant liver tumors. *Ann Surg*. 1997;225:39–50.
15. Curley SA, Izzo F, Delrio P, et al. Radiofrequency ablation of unresectable primary metastatic hepatic malignancy: results in 123 patients. *Ann Surg*. 1999;230:1–8.
16. Adam R, Laurent A, Azoulay D, et al. Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. *Ann Surg*. 2000;232:777–785.
17. Bolton JS, Fuhrman GM. Survival after resection of multiple bilobar hepatic metastases from colorectal carcinoma. *Ann Surg*. 2000;231:743–751.
18. Kawasaki S, Makuuchi M, Kakazu T, et al. Resection for multiple metastatic liver tumors after portal embolization. *Surgery*. 1994;115:674–677.
19. Elias D, de Baere T, Roche A, et al. During liver regeneration following right portal embolization the growth rate of liver metastases is more rapid than that of the liver parenchyma. *Br J Surg*. 1999;86:784–788.
20. Jaeck D, Bachellier P, Nakano H, et al. One or two-stage hepatectomy combined with portal vein embolization for initially nonresectable colorectal liver metastases. *Am J Surg*. 2003;185:222–230.
21. Kubota K, Makuuchi M, Kusaka K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology*. 1997;26:1176–1181.
22. Weber JC, Bachellier P, Oussoultzoglou E, et al. Simultaneous resection of colorectal primary tumour and synchronous liver metastases. *Br J Surg*. 2003;90:956–962.
23. Jaeck D, Nakano H, Bachellier P, et al. Significance of hepatic pedicle lymph node involvement in patients with colorectal liver metastases: a prospective study. *Ann Surg Oncol*. 2002;9:430–438.
24. Pawlik TM, Izzo F, Cohen DS, et al. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. *Ann Surg Oncol*. 2003;10:1059–1069.
25. Azoulay D, Castaing D, Smail A, et al. Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. *Ann Surg*. 2000;231:480–486.
26. Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. *Ann Surg*. 2003;237:208–217.
27. Kianmanesh R, Farges O, Abdalla EK, et al. Right portal vein ligation: a new planned two-step all-surgical approach for complete resection of primary gastrointestinal tumors with multiple bilateral liver metastases. *J Am Coll Surg*. 2003;197:164–170.
28. Uesaka K, Nimura Y, Nagino M. Changes in hepatic lobar function after right portal embolization: an appraisal by biliary indocyanine green excretion. *Ann Surg*. 1996;223:77–83.
29. Elias D, Ouellet JF, Bellon N, et al. Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. *Br J Surg*. 2003;90:567–574.
30. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. 1999;230:309–321.
31. Strasberg SM, Dehdashti F, Siegel BA, et al. Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma: a prospective database study. *Ann Surg*. 2001;233:293–299.
32. Metcalfe MS, Close JS, Iswariah H, et al. The value of laparoscopic staging for patients with colorectal metastases. *Arch Surg*. 2003;138:770–772.
33. Rahusen FD, Cuesta MA, Borgstein PJ, et al. Selection of patients for resection of colorectal metastases to the liver using diagnostic laparoscopy and laparoscopic ultrasonography. *Ann Surg*. 1999;230:31–37.
34. Yamaguchi J, Yamamoto M, Komuta K, et al. Hepatic resections for bilobar liver metastases from colorectal cancer. *J Hepatobiliary Pancreat Surg*. 2000;7:404–409.
35. Nordlinger B, Rougier P. Liver metastases from colorectal cancer: the turning point. *J Clin Oncol*. 2002;20:1442–1445.

Discussions

DR. ADAM: I think that we should congratulate your team for this extensive experience on 2-stage hepatectomy, a strategy that we proposed some years ago. We should congratulate you not only for the low mortality and morbidity and high rate of survival but also for showing that nonresectability of patients with colorectal liver metastases is not a fatality.

My first question regards the proportion of 50% of the patients who underwent a 2-stage hepatectomy article having only 1 or 2 lesions in the left liver. This would appear for most liver surgeons as a good indication of treatment by a single procedure using a combination of right hepatectomy and radiofrequency. What was the reason that prompted you to do a 2-stage hepatectomy rather than a single procedure?

The second question regards survival. You have really a fantastic 5-year survival of 55% in a group of patients for whom we would expect to observe a lower range of survival because they were initially unresectable with multinodular disease. How do you explain such a high survival rate in your risky population?

The next question regards an originality of your paper, that is, to propose a standardized 2-stage hepatectomy by primary clearance of the left liver and a further right hepatectomy. Sometimes we are faced with a central tumor or with metastases predominant on the left liver. So, how do you treat this type of patient?

Finally, my last question is on postoperative chemotherapy: are you performing it routinely or not, since this was not mentioned in your manuscript?

DR. JAECK: Thank you for your comments and questions. Concerning your first question, I agree with you that, in case of a limited number of metastases in the future remnant liver (FRL), which can be resected at the same time of a major hepatectomy, we would perform a 1-stage procedure. However, according to our inclusion criteria, the 2-stage hepatectomy (TSHP) was decided when the preoperative liver volume evaluation, estimated by a three-dimensional CT scan, showed that the FRL that could be preserved (after a right or extended right hepatectomy combined with a nonanatomic resection or radiofrequency ablation of left liver metastases during a 1-stage procedure) would be less than 30% of the initial functional liver volume without portal vein embolization. In fact, our study population cannot be defined

by a single criterion based on the number of metastases. Indeed, in our series, 50% of the patients required an extended right hepatectomy to clear right liver metastases. The mean size of the largest left liver metastases was 3 cm, so a major sacrifice of liver parenchyma would be necessary even in patients with only 1 or 2 metastases in the left FRL. Finally, 3 patients developed, despite portal vein embolization (PVE), transitory liver failure. All these data show that the major problem in these patients is a too small left FRL; the absence of mortality in our series was probably correlated with the routine use of PVE.

The second question is how we explain the good results concerning survival. The explanation for the improved results is directly related to the design of the strategy, which allows a high selection of the patients based not only on preoperative evaluation but also giving to the patient a test of time, of 2 to 3 months, between the first and the second-stage hepatectomy to accurately evaluate the tumor behavior and to better select the cases for surgery. In fact, our patients can be divided into three subgroups according to the aggressivity of the disease: the first subgroup is represented by a highly aggressive disease and includes the 5 patients in whom the disease progressed massively in the left FRL; they could not complete the TSHP. The second subgroup with an intermediate aggressive disease is represented by 6 patients who developed further metastases in the left FRL. However, these "de novo" left liver metastases were resected during the second-stage hepatectomy by combination of a right major hepatectomy to additional nonanatomic resection or radiofrequency ablation. Finally, a third subgroup with a low aggressive disease is represented by the 19 patients who completed the TSHP; that means with a second-stage hepatectomy resecting only the right liver metastases.

The third question is about a standardized TSHP in case of a centrohepatic lesion. In fact, patients presenting centrohepatic lesions or major involvement of segment IV were managed by a standardized TSHP considering only segments II and III as the FRL. Metastases in segment IV were left in place during the first-stage hepatectomy and we tried only to clear the left lateral lobe (segments II and III). Then, a PVE was performed and followed after adequate hypertrophy of the remnant liver, by an extended right hepatectomy.

The fourth question is about the postoperative chemotherapy. All the patients received postoperative chemotherapy. The chemotherapy that was started before the first-stage hepatectomy was continued, but now we also include chemotherapy between PVE and the second-stage hepatectomy.

Dr. Eggermont: My compliments for this presentation, but in view of the data that were just presented by Professor Adam, I wonder what the outcome was of the chemotherapy in the 21 patients in your series, before the first-stage hepatectomy. Do I understand correctly that they all responded or had at least stable disease after their chemotherapy, or were there any patients who actually progressed under chemotherapy before the first-stage hepatectomy?

Dr. Jaeck: In our series, only 27 of the 33 patients received preoperative chemotherapy and all the 27 patients selected for the TSHP showed, at least, stabilization of the disease.

Dr. Neuhaus: I enjoyed your paper. I would like to discuss the relevance of chemotherapy between the 2 operations. We all know that chemotherapy cannot cure the patient from a metastasis. It can only postpone the appearance or the growth. If a metastasis is in the future remnant liver, if it is very small and you missed it, then you have a chance at the second operation to take it out, but if you suppress it by chemotherapy you will not find it at the second operation. That might be a disadvantage even. We have this problem very often when patients are referred: you have the first CT scan and you have 4 metastasis, and then on the second CT scan only 1 is visible and some scars. Would you take out the scars or would you just take out the nodule then?

Dr. Jaeck: Thank you for your comment and, as you said, there is a need for a prospective study to elucidate the need of an extended liver resection after chemotherapy. Our policy is to resect liver metastases according to the initial preoperative CT scan evaluation performed before chemotherapy administration. In our series, only 3 patients received chemotherapy between the 2 operations, and it was decided to introduce chemotherapy as all of them presented with more than 5 left liver metastases. Moreover, our results showed that a repeat hepatectomy could be achieved after completion of the TSHP.

Dr. Senninger: My first question is, alluding to the chemotherapy given in between: did you do objective measurements of the volume incitement of the liver because we noticed that there are objective data that hypertrophy at least slowed down?

My second question is: in some patients, you did radiofrequency ablations in the liver for 2 reasons. Were these all 100% effective to control local disease. Or was it so that you, in the end, have considered to better resect it.

Dr. Jaeck: As we aimed to extend the indications in patients with several left liver metastases, we decided to combine nonanatomic resections with radiofrequency ablation in patients with more than 3 metastases in the FRL. We have already compared the impact of resection alone versus combination with radiofrequency ablation on survival. Our results suggest that the type of ablation by radiofrequency or by nonanatomic resections during the first-stage hepatectomy did not affect overall survival or recurrence of the disease.

Concerning your first question about liver volume and chemotherapy, I would answer that volumetric evaluation has been done after the first-stage hepatectomy and before the second-stage hepatectomy in only 3 patients who received chemotherapy between the 2 operations. Our results suggest that chemotherapy did not affect liver hypertrophy if introduced 10 days or more after PVE. This hypothesis is supported by a study reported by Uesaka et al (*Ann Surg*. 1996;223:77–83), showing that the functional gain is more rapid and of greatest magnitude than the volumetric gain.

DR. BISMUTH: I have 2 questions. First, did you study the possibility to replace the first-stage of hepatectomy for clearance of the left lobe by radiofrequency destruction of the nodule at the time of the portal embolization?

For the effect of chemotherapy between the 2 stages, I wonder if the chemotherapy does not impair the regenerative process. Did you study the change of liver function during this period of chemotherapy? In our experience, in our lab, when we take hepatocytes from the specimen of liver resection for tumor in a patient treated by chemotherapy, in order to culture these hepatocytes, there is no replication of these altered hepatocytes. Therefore, to continue the chemotherapy after the portal embolization may be an obstacle to the regenerative process.

DR. JAECK: Indeed, the alternative to the first-stage hepatectomy could be percutaneous radiofrequency ablation to clear the left liver metastases. But this alternative carries the risk of overlooking small liver metastases and also peritoneal carcinomatosis. Our results suggest that the presence of extrahepatic disease is a contraindication to complete the TSHP. Currently, we do not include patients with peritoneal carcinomatosis detected during the first-stage hepatectomy.

Concerning chemotherapy, I agree with you as we observed the same phenomenon with culture of hepatocytes. We evaluate routinely the liver reserve by an indocyanine-green (ICG) test before PVE and before the second-stage hepatectomy. Particularly in the 3 patients who received chemotherapy between the 2 hepatectomies, we did not observe any difference in liver function estimated by ICG test, and we did not contraindicate any of these patients for the second-stage hepatectomy. However, they received only 1 or 2 sessions of chemotherapy, and surgery was performed not earlier than 1 month after receiving chemotherapy.