Right Portal Vein Ligation Combined With In Situ Splitting Induces Rapid Left Lateral Liver Lobe Hypertrophy Enabling 2-Staged Extended Right Hepatic Resection in Small-for-Size Settings

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Objective: To evaluate a new 2-step technique for obtaining adequate but short-term parenchymal hypertrophy in oncologic patients requiring extended right hepatic resection with limited functional reserve.

Background: Patients presenting with primary or metastatic liver tumors often face the dilemma that the remaining liver tissue may not be sufficient. Preoperative portal vein embolization has thus far been established as the standard procedure for achieving resectability.

Methods: Two-staged hepatectomy was performed in patients who preoperatively appeared to be marginally resectable but had a tumor-free left lateral lobe. *Marginal respectability* was defined as a left lateral lobe to body weight ratio of less than 0.5. In the first step, surgical exploration, right portal vein ligation (PVL), and in situ splitting (ISS) of the liver parenchyma along the falciform ligament were performed. Computed tomographic volumetry was performed before ISS and before completion surgery.

Results: The study included 25 patients with primary liver tumors (hepatocellular carcinoma: n = 3, intrahepatic cholangiocarcinoma: n = 2, extrahepatic cholangiocarcinoma: n = 2, malignant epithelioid hemangioendothelioma: n = 1, gallbladder cancer: n = 1 or metastatic disease [colorectal liver metastasis]: n = 14, ovarian cancer: n = 1, gastric cancer: n = 1). Preoperative CT volumetry of the left lateral lobe showed 310 mL in median (range = 197–444 mL). After a median waiting period of 9 days (range = 5–28 days), the volume of the left lateral lobe had increased to 536 mL (range = 273–881 mL), representing a median volume increase of 74% (range = 21%–192%) ($P < 0.001$). The median left lateral liver lobe to body weight ratio was increased from 0.38% (range = 0.25%–0.49%) to 0.61% (range = 0.35–0.95). Ten of 25 patients (40%) required biliary reconstruction with hepaticojejunostomy. Rapid perioperative recovery was reflected by normalization of International normalized ratio (INR) (80% of patients), creatinine (84% of patients), nearly normal bilirubin (56% of patients), and albumin (64% of patients) values by day 14 after completion surgery. Perioperative morbidity was classified according to the Dindo-Clavien classification of surgical complications: grade I (12 events), grade II (13 events), grade III (14 events, III a: 6 events, III b: 8 events), grade IV (8 events, IV a: 3 events, IV b: 5 events), and grade V (3 events). Sixteen patients (68%) experienced perioperative complications. Follow-up was 180 days in median (range: 60–776 days) with an estimated overall survival of 86% at 6 months after resection.

Conclusions: Two-step hepatic resection performing surgical exploration, PVL, and ISS results in a marked and rapid hypertrophy of functional liver tissue and enables curative resection of marginally resectable liver tumors or metastases in patients that might otherwise be regarded as palliative.

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In patients with primary or metastatic hepatic malignancies, surgical resection is the only potentially curative therapeutic option, especially if extrahepatic tumor manifestation is absent. Because of the impressive development of intra- and perioperative management within the past 2 decades, even major hepatectomy can be performed with acceptable morbidity and mortality. However, "resectability" of primary or metastatic liver cancer is not clearly defined so that, in many cases, the experience of the individual surgeon plays a pivotal role. One very important limiting factor for performing major liver resections is the remaining liver volume, referred to as *future liver remnant* (FLR). In case of normal hepatic function, an FLR of approximately 25% is considered to be sufficient to maintain liver function after resection. For patients with hepatic dysfunction or earlier liver injury (eg, due to chemotherapy), a higher FLR (approximately 40%) is recommended.[1–4] A good method for clinically estimating resectability in patients is to estimate FLR to body weight ratio, which should be greater than 0.5 to achieve good resectability.[5]

Several methods have been developed to increase resectability in patients undergoing major hepatic resection. In case of bilateral disease, a 2-staged resection can be performed.[1–3,6–11] This approach implies that one lobe of the liver is initially cleared of tumors by resection or local ablative therapies, followed by a period of recovery for approximately 4 to 6 weeks. Subsequently, after hypertrophy of the tumor-free lobe, tumor removal is completed by resection of the larger tumor mass in the contralateral liver lobe. Another technical option is occlusion of the portal vein in the tumor-bearing liver lobe.[12–23] The rationale behind this approach is to induce atrophy of the tumor-bearing lobe with subsequent hypertrophy in the contralateral lobe by diverting the portal venous flow into the liver section that is expected to remain. In general, 2 methods of portal vein occlusion can be employed: radiological portal vein embolization (PVE) or surgical portal vein ligation (PVL). However, neither technique has clear advantage so far.[12–14,24–26] Recent studies show that portal

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occlusion increases the FLR between 10% to 46% within 2 to 8 weeks and enables surgeons to perform an R0-resection in 70% to 100% of selected cases.[27–29] However, some patients show tumor progression after PVE, which can be detected either by diagnostic staging before the planned operation, or during the operation. It is still not clear whether this is just a matter of time (from portal vein occlusion to operation) or is due to growth stimuli to the tumor by the induced liver regeneration.

Here, we present a novel concept of 2-staged extended right hepatectomy with initial surgical exploration, right PVL, and in situ splitting (ISS) along the right side of the falciform ligament to induce rapid hypertrophy of the left lateral lobe in patients with marginally resectable or primarily nonresectable primary and metastatic liver tumors. After initially introducing this technique in one center (Regensburg), the method was also applied in several other German centers. The primary outcome measure of this analysis was to achieve resectability by rapid hypertrophy induction in the left lateral lobe over a short period of time by utilizing a new surgical concept, which combines PVL and ISS.

PATIENTS AND METHODS

Patients, Design, and Ethics

A retrospective review of 25 patients, who underwent a 2-staged hepatectomy with right PVL and ISS at the universities of Regensburg (n = 10), Göttingen (n = 7), Mainz (n = 3), Tübingen (n = 3), and Giessen (n = 2) between September 2007 and January 2011, was performed. Three patients underwent right trisectorectomy after ISS and right PVL due to hepatocellular carcinoma in Child A cirrhosis, 2 had intrahepatic cholangiocarcinoma, 2 patients had extrahepatic cholangiocarcinoma (ECC) Bismuth type 3a, and 1 patient each had a malignant epithelioid hemangioendothelioma and a gallbladder cancer. In addition, 14 patients were operated for colorectal liver metastasis (CRLM), 1 each for metastatic ovarian and gastric cancer. Preoperative left lateral lobe to body weight ratio was less than 0.5 in all patients. The Regensburg University Ethics Committee confirmed that no ethics approval was required for the application of the surgical technique and this retrospective analysis in accordance with the Bavarian State Medical Professional Regulations, because each patient was individually treated on the basis of the intention to heal and data were evaluated anonymously.

Staging

Before resection, all patients underwent extensive radiologic evaluation with a 3-phase intravenous contrast CT scan of the abdomen and chest with oral contrast medium for staging, and for exclusion of nonresectable extrahepatic disease. In case the tumor extent was not clearly definable on CT scans, contrast-enhanced ultrasound and/or positron emission tomographic scans and magnetic resonance imaging were additionally performed. In case of tumor-free major vessels, hepatic tumor load sparing liver segments II and III, and lack of evidence for a nonresectable extrahepatic tumor, an exploratory laparotomy was performed.[30] No specific liver metabolism and no specific hemodynamic tests were done. Before the first operative procedure, a volumetry measurement for the left lateral liver lobe (segments II and III) was performed by one radiologist at every site using the Osirix MD CT volumetry processing program,[31,32] and the left lateral liver lobe to body weight ratio was calculated for every single patient.[5]

Primary and Secondary Endpoints, Data Collection

Standardized and routinely documented data were collected retrospectively from preoperative documentation (staging, demographics), intraoperative surgical protocols, and postoperative charts. The main focus of the new surgical technique was to achieve resectability. Therefore, the primary outcome measure of the retrospective analysis was the increase in volume of the left lateral lobe in mL represented by Δ-values of volume at the day before ISS and before completion surgery. In addition, the left lateral lobe to body weight ratio over time was evaluated. Secondary outcome measures were complications, development of liver parameters, coagulation status and renal function up to day 14 after completion surgery, persistence of ascites, and the influence of neoadjuvant chemotherapy on increase in volume. Moreover, disease free survival and overall survival (OS) were analyzed for the current period of follow up.

Intraoperative Ultrasound and Operative Procedure Step I

Exclusion of Nonresectable Undetected Metastases

During exploratory laparotomy, the liver tissue was assessed macroscopically and general resectability was defined on the basis of a tumor-free left lateral liver lobe and the surgeon's experience. The liver was mobilized by dissecting the round hepatic and falciform, and triangular and coronary, ligaments. Retroperitoneal adhesions were dissected and the caval vein identified and exposed. Furthermore, resectability was objectively confirmed and evaluated with intraoperative ultrasound—in some cases, also including contrast-enhanced ultrasound—using a linear ultrasound probe: by intraoperative ultrasound the proximity and position of the tumor in relation to major remaining vessels was reevaluated and a tumor-free left lateral lobe was reconfirmed.[33–35]

Definition of Remaining Hilar Structures

Relevant hilar structures (common bile duct, portal vein, and common hepatic artery) were exposed in a step-wise fashion close to their particular bifurcations, approaching from the right part of the hepatoduodenal ligament. After the right portal vein branch was identified, it was divided and oversewn. The left portal vein was then exposed centrally to identify segment I and/or IV branches. All portal, arterial, and biliary segment IV branches were identified along the right rim of the round ligament, divided, and were either clipped with metal clips or oversewn. Segment I-supplying or -draining structures were only divided when resection of the caudate lobe was necessary. Biliary and arterial structures and venous drainage of the right, subsequently resected liver tissue were not compromized.

For one of the ECC Bismuth type 3a tumors, first the parenchymal bridge between segments IV and III and left hilar structures were exposed proximally. The right portal vein was divided and ligated. The left portal vein had to be partially resected and was consequently reconstructed end-to-end. The left lateral biliary structures were identified during dissection of the liver tissue on the right side of the falciform ligament. The left biliary bifurcation then was identified. Further steps were analogous to the above-mentioned technique.

In Situ Splitting = First Operation

The right liver lobe was completely mobilized from the caval vein before ISS. Subsequently, total or nearly total parenchymal dissection was performed using an ultrasound dissector or Metzenbaum scissors, bipolar coagulation, and hemo-clips at the universities of Regensburg, Göttingen, and Mainz.[36] At the universities of Tübingen and Giessen, dissection was performed with a cavitron ultrasonic surgical aspirator. The central venous pressure was held below 5 mm Hg during dissection. After ISS, the right extended lobe was covered in a plastic bag to prevent adhesions in most patients, and the abdomen was closed. The extent of resected liver tissue is shown in Figure 1.

Postoperative Volumetry and Completion Surgery = Second Operation

After a median interval of 9 days (range: 5–28 days), a CT volumetry was performed and the procedure was completed on the same or following day by relaparotomy. The plastic covering was removed from the right-extended lobe, and the right artery was dissected and ligated. The bile duct and the venous drainage of the right and middle vein into the vena cava were divided. In addition, remaining parenchymal bridges of liver tissue were divided if present. In 3 patients, atypical resection of very small tumor nodules in segment II was additionally required. This was and performed with minimum loss of functional liver tissue by simply moving the resection line minimally toward segments II and III. The biliary system was reconstructed with Y-Roux hepaticojejunostomy in 10 of 25 cases. The left lateral lobe was then fixed to the anterior abdominal wall, usually along the remnant falciform ligament, to prevent malrotation. Finally, at least one 20 Chariere drain was placed at the resection surface, and the abdomen was closed.

Histology and Immunohistochemistry

To determine the histomorphological changes in liver tissue before right PVL and ISS, and during completion surgery after hypertrophy of the left lateral liver lobe, serial sections of representative specimens were available from some patients. Work-up included hematoxylin-eosin (HE) staining, and immunohistochemical analysis. In brief, 4-μm formalin-fixed paraffin-embedded tissue sections were deparaffinized and immunostained after antigen retrieval (60 minutes, 95°C, EDTA buffer, pH 8.4; primary antibody: Ki-67, clone MIB-1, Dako Cytomation, Hamburg, Germany, dilution 1:100, incubated at 36°C for 30 minutes) using the ultraView Universal DAB Detection Kit on a Ventana BenchMark ULTRA autostainer (Ventana, Tucson, AZ). Immunoreactivity for each liver specimen was scored semiquantitatively by calculating the number of nuclear positive hepatocytes compared to the total number of hepatocytes per high-power field.

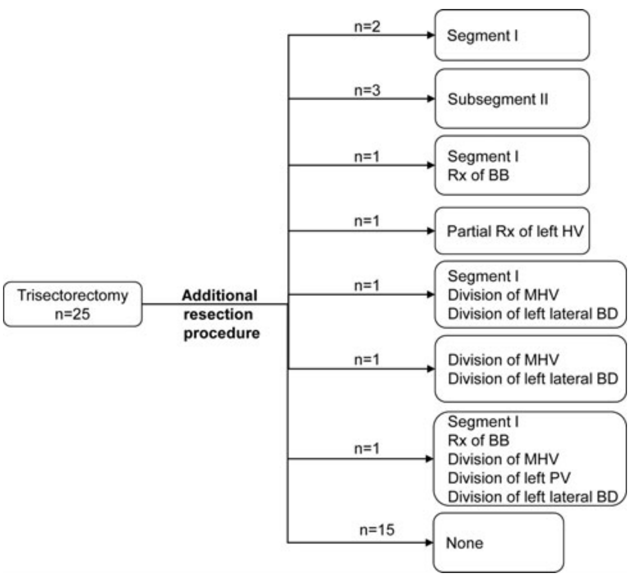

FIGURE 1. Extent of liver resection and additional surgical procedures performed in the 25 patients. BB indicates biliary bifurcation; BD, bile duct; HV, hepatic vein; MHV, middle hepatic vein; Rx, resection.

Statistics

The increase in liver volume was presented as Δ-volume, and percentage of hypertrophy was calculated as Δ-volume/volume before first surgical procedure. Statistics were applied as a *t* test where applicable. *OS* was defined as the time interval from completion surgery until date of death, whereas *DFS* was defined as the time interval from completion operation of the 2-staged hepatectomy until the time point of first suspicion of tumor recurrence. Differences between the first and second volumetric evaluations were statistically calculated with the *t* test. The OS curve was calculated with the "survival for a single group" estimation. Statistics were performed using Sigma Stat 11.0 (Systat Software Inc, Richmond, CA).

RESULTS

Patient Demographics and Preoperative Data

A total of 25 patients (14 men, 11 women) underwent right PVL and ISS with 2-staged hepatectomy. Median age was 63 years (range = 32–75 years). Patients had normal liver function before resection (INR: 1.0, range = 0.9–1.7 and albumin: 41 g/dL, range = 29–52 g/dL). Cholestatic values and transaminases were within normal ranges in median (Table 1). Three patients had a relevant cholestasis (total bilirubin: 4.4, range = 5–14 mg/dL) before surgery. Two patients underwent endoscopic retrograde cholangiography and placement of plastic stents, and one patient underwent percutaneous transhepatic cholangiography and drainage. None of the patients had Child B or C cirrhosis; 3 hepatocellular carcinoma patients had Child A cirrhosis, and 22 were noncirrhotic. Tumors were localized to the right and central liver in 20 patients, with additional spreads into segment I in 5 cases and into medial parts of segment II in 3 cases. Eleven patients with CRLM and 1 patient with hepatic metastasis from gastric cancer (44% of all patients) had received preoperative chemotherapy with different regimens/cycles per patient. In all cases, chemotherapeutic treatment was stopped at least 6 weeks before scheduled resection. The preoperative chemotherapeutic treatments are shown in Table 2.

Preoperative Volumetry, Precompletion Volumetry, and Hypertrophy Time

The median volume for the left lateral liver lobe was 310 mL (range = 197–444 mL). The left lateral liver lobe to body weight ratio (LLLL/BW ratio) was 0.38 in median (range = 0.25–0.49), indicating increased risk of resection without hypertrophy induction.[5] After a median time interval of 9 days (range = 5–28 days), the median liver volume of the left lateral liver lobe had increased to 536 mL (range = 273–881 mL). The median Δ-volume was 225 mL (range = 54–490 mL) indicating a median increase in volume of

TABLE 1. Demographics and Baseline Liver Function of all Patients (n = 25)

	Median	Minimum	Maximum
Age (yrs)	63	32	75
Body weight (kg)	83	72	112
Bilirubin (mg/dL)	0,7	0,3	14,0
INR	1.0	0.9	1.7
Albumin (g/dL)	41	29	52
GOT(U/l)	35	17	150
GPT (U/l)	42	14	120
yGT (U/l)	69	37	952
AP (U/l)	98	35	436

AP indicates alkaline phosphatase; GOT, glutamat-oxalat-transaminase; GPT, glutamat-pyruvat-transaminase; INR, International normalized ratio; yGT, gamma-glutamyltransferase.

TABLE 2. Preoperative Chemotherapeutic Strategies Before Liver Surgery

Patients	Diagnosis	Regimen	Cycles (n)
11	Colorectal liver metastasis	7x FOLFOX	3, 6, 7, 9,10, 12, 38
		1x FOLFOX + Cetuximab	12
		1x FOLFOX + Bevacizumab	6
		1x XELIRI + Cetuximab	14
		1x XELOX	1
1	Hepatic metastasis of gastric cancer	1x FLOT3	12

FLOT: 5-Fluorouracil, Oxaliplatin, and Docetaxel; FOLFOX: Folinic Acid, 5-Fluorouracil, and Oxaliplatin; XELIRI: Capecitabine, Irinotecan.

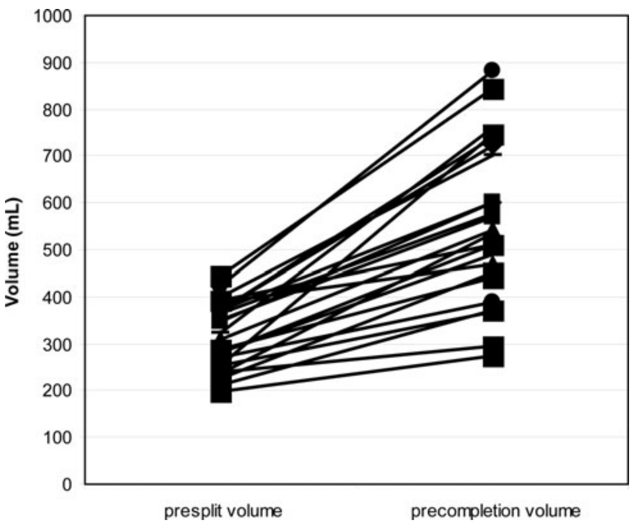

FIGURE 2. Computed tomographic volumetry results of left lateral liver lobe before ISS and before completion surgery. Data for all included patients are depicted.

74% (range = 21%–192%) ($P < 0.001$, Fig. 2). The LLLL/BW ratio before completion surgery was 0.61 in median (range = 0.35–0.95). In case of an LLLL/BW ratio greater than 0.45, completion resection was performed (Fig. 3). The presence or absence of preoperative chemotherapy did not influence the induction of hypertrophy. In 1 patient, the LLLL/BW ratio before completion surgery was 0.35, reflecting a poor hypertrophy of 21% in 15 days. However, for this 51-year-old, very well-informed female patient with a diagnosis of ICC and lacking alternative treatment options, it was decided to perform the second step of the procedure, which resulted in a further uneventful clinical course.

Intraoperative Data

Intraoperative data including incision-to-suture times for both of the surgical procedures, estimated blood loss, and extent of resection are given in Table 3. Notably, 2 patients required mass transfusion because of an inadequately controllable central venous pressure exceeding 15 mm Hg during initial surgery, which led to an estimated blood loss of 7500 mL in both cases. Hilar inflow occlusion was

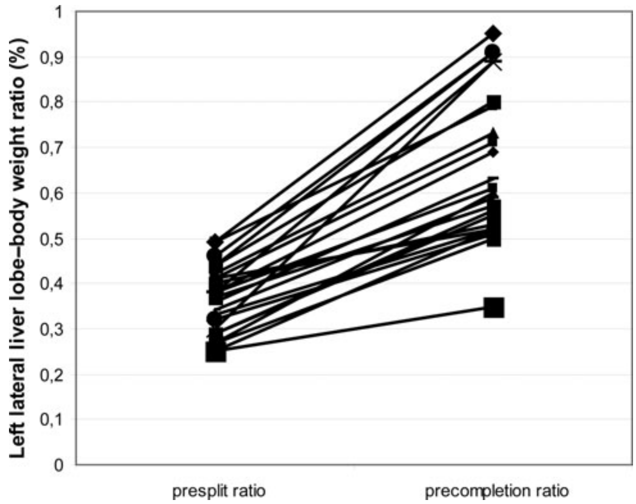

FIGURE 3. Individual increase in left lateral liver lobe-volume to body weight ratio (LLL/BW ratio). The red line marks a LLL/BW ratio of 0. 5%, which was regarded as the resectability cut-off.

TABLE 3. Intraoperative Parameters (n = 25)

	Median	Mean	Minimum	Maximum
Incision-suture time in situ split surgery (min)	210	252	157	500
Incision-suture time completion surgery (min)	117	152	64	364
Estimated blood loss (mL)	320	810	150	7.500
Packed red blood cell transfusions (Units)	0	1.3	0	15

performed in 6 of 25 cases for a median of 32 minutes (range = 16–42 minutes) during first surgery. Figs. 4A–E show representative intraoperative pictures of the initial in situ split and pictures of the completion surgery. Notably, all 25 patients in this series who underwent exploration and ISS with nearly total parenchymal dissection received completion surgery in the second step.

Histology

Histology reports of all resected right-extended hepatectomy specimens revealed negative resection margins in all but 1 patient who had an R1 situation (CRLM) due to close proximity of the tumor to the left hepatic vein. Representative specimens of liver tissue collected intraoperatively as a biopsy with a Biocut needle of the remaining liver segments II and III before right PVL showed regular patterns of portal tracts and terminal venules, and hepatocytes arranged in single-cell plates (Figs. 5A,B). During completion surgery, an intraoperative needle biopsy with a Biocut needle was performed in 1 patient from the remaining left lateral lobe showing liver tissue with both increased proliferative activity (by Ki 67 staining) and formation of twin-cell plates and polyploid binucleated hepatocytes regarded as (morphological) characteristics of hyperplasia (and regeneration), respectively (Figs. 5C, D).

Postoperative Liver Function and Ascites

None of the patients developed irreversible liver failure after surgery. Liver function improved significantly by day 14 after completion surgery. INR values of median 1.7 (range = 1.0–2.3) on day 2 after completion surgery decreased to almost normal values

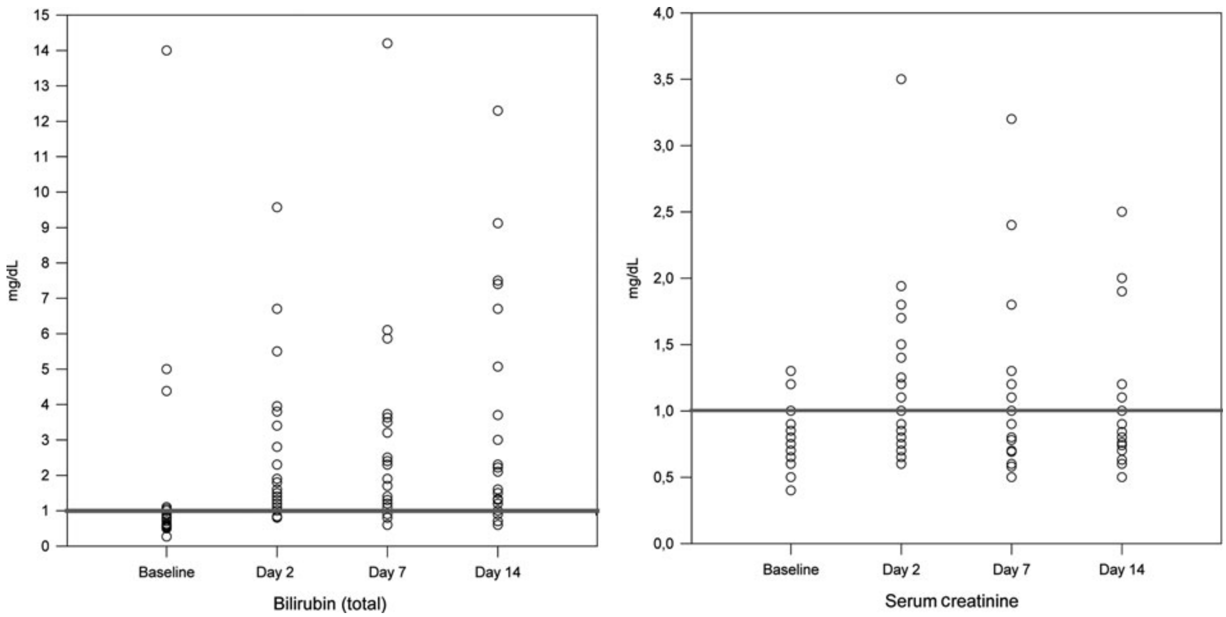

FIGURE 4. Operative Procedures. A, Situs during first surgical procedure before right portal vein ligation and ISS along the round ligament. *marks tumor inside the right liver lobe and in Segment IV. B, Situs after nearly total ISS and right portal vein division*. CBD indicates common bile duct; LHA, left hepatic artery; LPV, left portal vein; RHA, right hepatic artery. C, Segment IV A and B showing reduced perfusion after dissecting and closing supplying portal venous and arterial structures (*red arrow*) at the end of ISS procedure. D, Partially necrotic liver segment IV B during completion surgery after a hypertrophy interval of 9 days. E, Vital and hypertrophied left lateral liver lobe at the end of completion surgery.

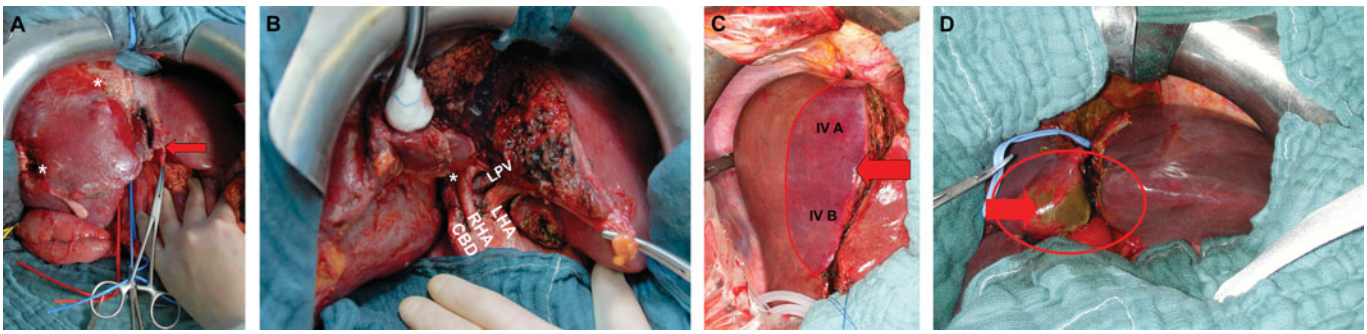

FIGURE 5. Histology and Immunohistochemistry. A, normal liver parenchyma during ISS surgery in conventional histology with HE-staining, 50× magnification; B, single hepatocyte Ki-67 nuclear positive representing liver parenchyma with low proliferation activity during first surgery (*arrow*) in immunohistochemistry with Ki-67 staining and 50× magnification. C, enlarged hepatocytes forming twin-cell plates (binucleated hepatocytes) during completion surgery (*cycles*) with conventional HE-staining, 60× magnification. D, numerous hepatocytes Ki-67 nuclear positive binucleated hepatocytes representing hyperplastic liver parenchyma with increased proliferation activity during completion surgery (*arrows*) in immunohistochemistry with Ki-67-staining, 60× magnification, insert: 370× magnification.

of 1.4 (range = 1.0–2.1) on day 14 ($P < 0.001$). Albumin, however, lagged behind and improved only slightly by day 14 after resection as shown in Table 3. Bilirubin values also increased slightly from day 2 after surgery until day 14 after surgery mainly because of 11 patients showing values of more than 2 mg/dL. Creatinine values, as a reflection of renal function, also decreased and normalized (median creatinine: 0.8 mg/dL; range = 0.6–2.5 mg/dL, $P = 0.34$) on day 14 after completion surgery, without any patient requiring renal replacement therapy, although 4 patients (16%) still had values of more than 1.5 mg/dL. Data for total bilirubin and serum creatinine are shown in Fig. 6.

Ascites was collected in 24-h intervals and documented in the patient charts. In case of less than 200 mL/d of fluid, drainages were removed and patients were regarded to be free of persisting ascites. In case abdominal fluid collection was more than 200 mL/d, patients received additional diuretic therapy with loop-diuretics, potassium-saving aldosterone antagonists, or thiaziddiuretics in accordance to center standards and requirements. A total of 5 of 25 patients (20%) presented with new onset ascites after completion surgery, which persisted for a median of 4 weeks and was then resolved in 2 cases. Three patients required continued diuretic treatment till the complete resolution of ascites (range: 2 to 6 weeks).

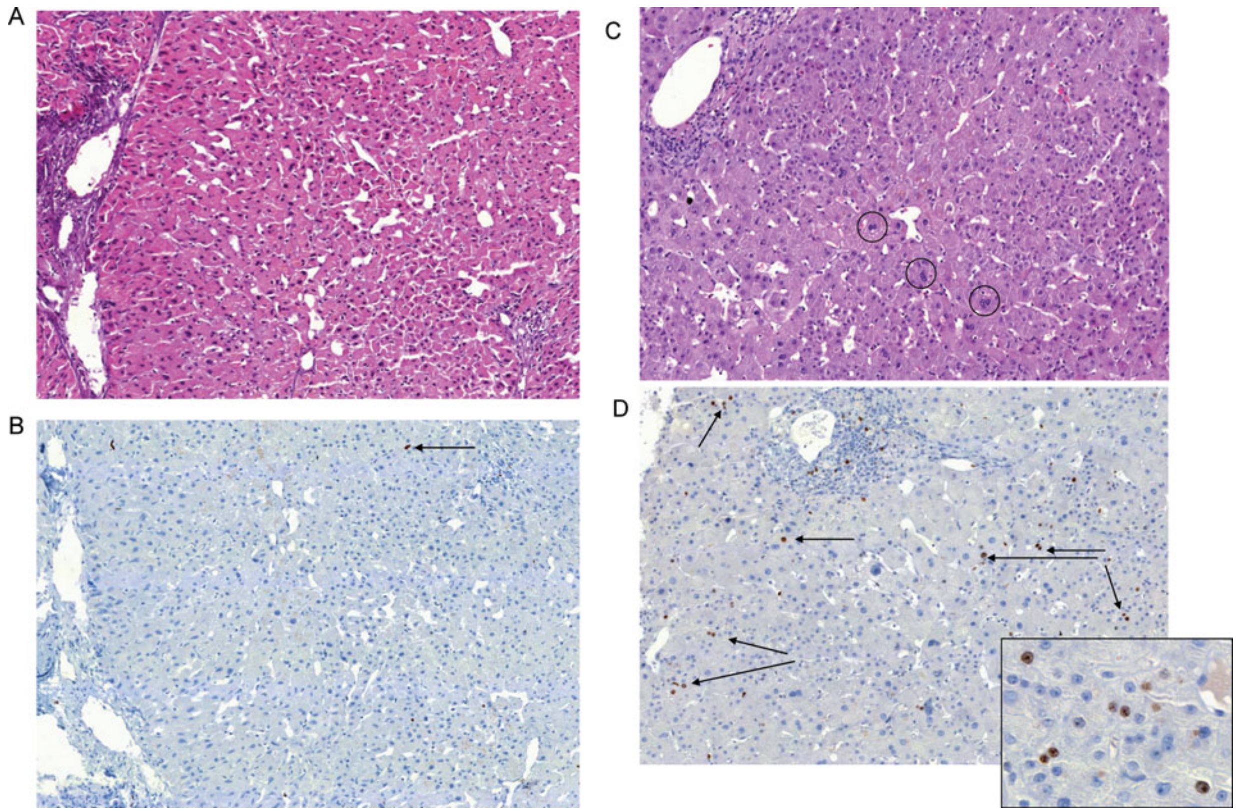

FIGURE 6. Total bilirubin and creatinine serum levels in mg/dL from baseline (before first surgery) until day 2, 7, and 14 after completion surgery for all patients.

Neoadjuvant Chemotherapy and Hypertrophy

Twelve patients (48% of all patients) received different regimens of neoadjuvant chemotherapeutic regimens, which are shown in Table 2. Patients with any kind of chemotherapy before ISS had a median Δ-volume between ISS and completion surgery of 186 mL (range = 76–490 mL) compared to 230 mL (range = 54 to 437 mL) in patients who did not receive chemotherapy.

Complications

Complications were classified according to the Dindo-Clavien classification of surgical complications.[37] Overall, 50 events in 16 patients (64% of patients) were documented. Fifty percent (25/50 events) of all events could be classified as grade I or grade II surgical complications requiring no intervention. Nine patients did not experience any complications. A total of 22 events (44% of events) were classified as grade III or IV, which required intervention or reoperation (grade III), or were life threatening including single- or multiorgan failure requiring intensive care unit treatment (grade IV). Five patients (20% of patients) experienced a biliary leakage, which had to be treated by percutaneous transhepatic cholangiography and drainage, or stenting via endoscopic retrograde cholangiography. Table 4 Two patients (8% of all patients) had a leakage at the hepaticojejunostomy and had to undergo reoperation.

Notably, 20 of 50 events (40% of all events) occurred in the 3 patients at 3 different sites (Regensburg, Giessen, and Göttingen) who died during the clinical stay. The first patient experienced septic bleeding from the hepatic artery and had to undergo reoperation. In the further clinical course, the patient experienced biliary leakage, which was persistently drained. However, the bleeding and biliary leakage triggered septic complications and the patient experienced cardiac arrest with consecutive cerebral hypoxia after reanimation in critical state of disease and died on day 62 after ISS. The other 2 patients, who died experienced septic complications related consecutively to biliary leakage and persisting cholestasis on days 61 and 50 after ISS. All patients had CRLM, and they received neoadjuvant chemotherapy (3, 6, and 10 cycles of FOLFOX) before ISS. Complications are presented according to classification in Table 5 and as number of complications per patient in Table 6.

TABLE 4. Hepatic and Renal Recovery Parameters: 2, 7, and 14 Days After Completion Resection (n = 25)

	Day 2 Median (Range: min–max)	Day 7 Median (Range: min–max)	Day 14 Median (Range: min–max)
INR	1.7 (1.0–2.3)	1.4 (1.0–2.1)	1.3 (1.0–2.1)
Albumin (g/dL)	24 (18–33)	27 (18–43)	28 (20–40)
Bilirubin (mg/dL)	1.6 (0.8–9.6)	1.7 (0.6–14.2)	1.6 (0.6–12.3)
Creatinine (mg/dL)	1.0 (0.6–3.5)	0.9 (0.5–3.2)	0.8 (0.5–2.5)

DFS and OS

Patients were followed up for a median of 180 days (range = 50–776 days). Perioperative mortality (in hospital) was 12% (3 of 25 patients). In the further course, 2 patients died because of recurrent disease 5 and 22 months after primary surgery. Six-month median OS was 86%; current median OS is 80% (see Fig. 7).

TABLE 5. Complications Classified in Accordance to Dindo and Clavien Classification of Surgical Complications

Grade	Number (n)	Event	Number (n)
I	12	Anemia	2
		Encephalopathy	1
		Fever	4
		Impaired wound healing	5
II	13	Depression	1
		Leg edema	1
		Persisting ascites	5
		Persisting cholestasis	2
		Pneumonia	2
		Pulmonary embolism	1
		Small-for-size-syndrome	1
III	14		
III a	6	Biliary leakage	5
		Pleural effusion	1
III b	8	Biliary leakage	2
		Fascial dehiscence	1
		Intraoperative hemorrhage	2
		Postoperative hemorrhage	2
		Volvulus	1
IV	8		
IV a	3	Cardiac arrest	1
		Cerebral hypoxia	1
		Septic bleeding from hepatic artery	1
IV b	5	Sepsis	5
V	3	In house lethality	3

Overall 50 complications occurred in 16 patients. Nine patients did not experience postoperative complications.

DISCUSSION

The only chance to obtain long-term survival in patients with hepatic tumor or metastasis from other primary cancers is complete tumor resection in the liver. However, in some patients with large tumors, or even with small tumors located close to central structures, the functional liver volume that would remain after radical resection might be too small to maintain liver function. Therefore, we have devised a new surgical strategy, using a combination of right PVL and total or nearly total ISS of the hepatic parenchyma along the falciform ligament, to enable a safe extended right hepatic resection in such patients. This procedure is a novel strategy, which leads to the induction of marked and rapid hypertrophy of about 75% of the left lateral lobe within a median of 9 days borderline.

To date, strategies to induce hypertrophy of the FLR in patients with large uni- or bilateral liver tumors comprise interventional PVE or surgical PVL. In a recent review by Liu and Zhu, PVE using various methods of embolization has been described as leading to an increase in FLR of 10% to 46% after 2 to 8 weeks. The group of Belghiti and coworkers found hypertrophy induction of 38% 8 weeks after PVL, which was not inferior—but also not better–compared to PVE.[12] These data were confirmed by Capussotti et al,[14] who found a volumetric increase of 53% after PVL versus 43% after PVE after an interval of 4 to 6 weeks. The efficacy of PVL in comparison to PVE was also investigated by the group of Clavien and coworkers, who hypothesized that the impairment of liver regeneration after PVE may be a consequence of macrophage trapping in the occluded segment due to foreign body reaction.[24] In contrast, Broering et al showed inferiority of PVL (123 mL) versus PVE (188 mL) ($P = 0.012$) in inducing hypertrophy over 4 weeks, speculating that the formation of collaterals between the 2 liver lobes plays a significant role.[13,25] Moreover,

TABLE 6. Complications split up per patient: 16 of 25 (64%). Depicted are all 16 patients that experienced complications. A total of 16 patients experienced 50 complications. Three patients that died perioperatively experienced 20 of 50 events (40% of all events). Eight patients of 16 with complications experienced only 1 event

	Patients							
Number of complications	1	2	3	4	5	6	7	8
1	Septic bleeding from hepatic artery	Persisting ascites	Biliary leakage requiring surgery	Intraoperative hemorrhage	Pleural effusion	Leg edema	Biliary leakage	Persisting ascites
2	Biliary leakage	Impaired Wound healing	Persisting ascites	Biliary leakage requiring surgery	Pneumonia	Biliary leakage	Sepsis	Postoperative hemorrhage
3	Fever	Biliary leakage	Fever	Biliary leakage	Intraoperative hemorrhage	Impaired wound healing		Impaired wound healing
4	Cardiac arrest	Fever	Persisting cholestasis	Persisting ascites	Fever	Fascial dehiscence		
5	Cerebral hypoxia	Sepsis	Sepsis	Impaired wound healing				
6	Impaired wound healing	Death	Death	Anemia				
7	Sepsis			Small-for-size				
8	Death			Persisting cholestasis				
9				Sepsis				

	Patients							
Number of Complications	9	10	11	12	13	14	15	16
1	Postoperative hemorrhage	Volvulus	Persisting ascites	Pneumonia	Pulmonary embolism	Depression	Encephalopathy	Anemia

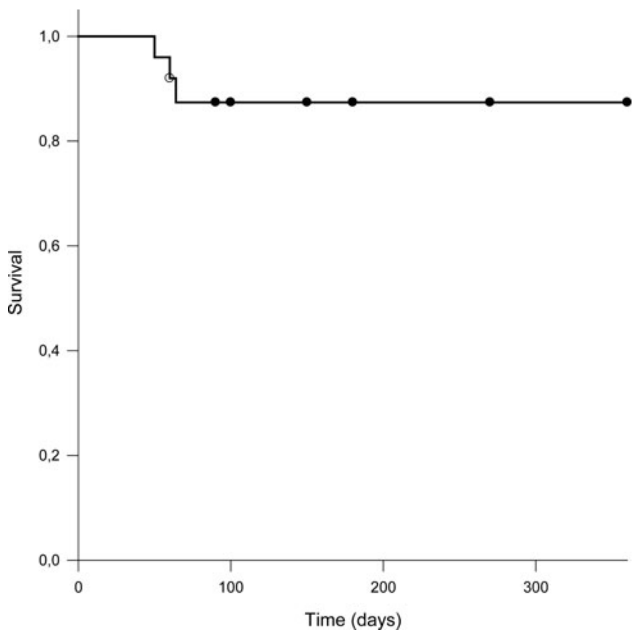

FIGURE 7. Estimated OS for all study patients.

the selective embolization or ligation of segment IV branches had a significant impact (66 mL vs 122 mL; $P < 0.0001$) on the hypertrophy of the FLR. However, the completeness of segment IV branch embolization requires optimal access and may frequently be incomplete. Broering et al[13] achieved a 90% segment IV embolization rate, whereas other authors do not give rates of unsuccessful segment IV embolization.[38–43] With regard to these data, our approach of combining PVL with ISS by nearly total parenchymal dissection induced a median hypertrophy of 74%, which is markedly above the range that can be achieved by PVL or PVE alone. Remarkably, our hypertrophic effect occurred after a median time interval of 9 days. In contrast, hypertrophy using PVL or PVE was generally described after 4 weeks (range = 2–8 weeks) and achieved a much lower degree of hypertrophy in the remaining liver tissue. Taken together, our approach led to a much more pronounced and more rapid increase in FLR in patients with marginally resectable liver tumors.

The critical procedure for the enormously accelerated hypertrophy effect observed with our newly described approach—as compared to PVL and PVE alone (even with inclusion of segment IV)—thus must be attributed to the ISS procedure. This procedure leads to a complete (ie, arterial and venous) devascularization of segment IV and also prevents formation of vascular collaterals between the left lateral and the right extended liver lobe. The combination of 2 procedures obviously induces a much stronger stimulus leading to rapid and marked hypertrophy of the left lateral lobe. Whether the surgical procedure or the surgical trauma also plays a role remains unclear. Animal models have shown that partial hepatectomy and PVL induce comparable regenerative responses especially when the FLR is tumor free.[44] The earlier occurrence of the hypertrophic effect may additionally be explained by an early liver regeneration rate peak in the FLR at 24 to 48 hours after hepatectomy (in our clinical model the nearly total parenchymal dissection) and a delayed effect 48 to 72 hours after PVL that was attributed to differential expression of activin and its receptor after PVL versus hepatectomy, as described by Tashiro.[45] Indeed, immunohistochemistry revealed Ki-67 positivity and typical histology for liver regeneration and hyperplasia in our patients. Moreover, Willms et al described the development of portal neocollaterals in the portal-occluded liver parts performing ex situ angiography after PVE and PVL, which may hinder hypertrophy.[25] In our technique, the neovascularization and persistence of interlobar perfusion are prevented by performing parenchymal dissection and complete devascularization of segment IV.

Morbidity after extended liver resection ranges between 20% and 50%, depending on extent of resection, and underlying disease, and liver and patient condition at the time of surgery.[46–48] In our patient cohort, morbidity was similar to data in the literature. A total of 50 events in 16 of the 25 patients were documented and classified according to the Dindo-Clavien classification of surgical complications.[37] Nine of 25 patients (36%) did not experience any complications. Grade III and IV complications occurred in 44% (22 events), which is higher than comparable reports from the literature. Breitenstein et al reported an overall grade III and IV complication rate in noncirrhotic patients undergoing liver resection of 26%. However, the complication rate for all patients undergoing major hepatic resection in their study was 32% (106 events in 329 patients).[49] Mullen et al reported a prevalence of grade III and IV complications of 17%. However, only 20% of their investigated noncirrhotic patients undergoing liver resection received a right or left extended resection, which prohibits general comparability of these data. Unfortunately, there has been no stratification of complications for patients after extended resection reported in the literature.[50]

Hospital lethality was 3 of 25 (12%), which is higher than the numbers from a systematic review from Asiyanbola et al[51] with a literature-based perioperative mortality rate of 5.6% worldwide in patients undergoing liver resection by Mullen et al.[50] Again, the main limitation in these 2 studies is that outcome reporting was not stratified with regard to the extent of hepatic resection, which reduces comparability. Lang et al[52] reported a perioperative mortality of 12% in patients undergoing left trisectorectomy, which is similar to data observed in our patient cohort.

Biliary leakage requiring radiologic or endoscopic intervention occurred in 6 of 25 patients (24%). Although this may at first appear to be a high number, it actually reflects the demanding technical challenges of the procedure. Extended resections demand a preparation of the bile ducts over a long distance, which then may result in lack of sufficient perfusion, which is a major risk factor for biliary complications. This secondary may lead to biliary necrosis and insufficiency of anastomosis or bile leakage at the remaining bile duct. Overall, these data correspond very well to the publications of Breitenstein et al[49] and Capussotti et al[53] who identified predictive factors for the occurrence of a biliary leakage such as major hepatectomies ($P = 0.03$), peripheral ECC ($P < 0.001$), and resection including segment I ($P = 0.001$) and segment IV ($P = 0.003$). Yamashita et al[54] reported a prevalence of more than 10% of bile leakages in patients undergoing right extended hepatectomies. Nagano et al[55] reported an incidence of 6% in patients undergoing extended lobectomies. A major risk factor in the publications of Yamashita and Nagano for an uncontrollable bile leakage was a proximal injury of the bile duct. All of our patients received major hepatectomy. Therefore, 2 independent risk factors were present also in our collective.

Apart from achieving resectability in primarily non- or marginally resectable patients, our technique of rapid and marked hypertrophy induction carries 2 hypothetical advantages concerning the aspects of tumor progression. First, our procedure starts with an exploration of the abdominal cavity so that intra- and extrahepatic disease, which might have escaped preoperative staging and might preclude resectability with a curative intent, can be reliably excluded. In particular, the use of intraoperative ultrasound (with contrast-enhancement if possible) was helpful in this respect.[35,56] Second, the time interval between first surgical procedure and the "completion surgery" is kept very short (9 days in median) compared to the "classic" PVE approach with an interval of 2 to 6 weeks. Relevant tumor progression is thus prevented during this interval. Clinically, none of our patients proved irresectable on "completion surgery" after hypertrophy induction. The 5 patients who experienced tumor recurrence had a median hypertrophy of 77% (range: 21%–94%) within a median time interval of 9 days (range: 7–28 days), which was not different from patients without tumor recurrence. The one patient who had an R1-resection of colorectal liver metastases at the liver margin did not experience local tumor recurrence but presented with pulmonary metastasis and a local recurrence of primary rectal cancer in the pelvis 9 months after completion surgery. Of course, the oncological results in this study are difficult, or even impossible, to interpret because of the heterogeneity of indications. In fact, the focus of this study was on the technical feasibility and on surgical aspects of the new approach. In spite of favorable short-term results, the concept of extended resection remains controversial because of increased morbidity, a potentially reduced quality of life (an aspect not addressed in our study), and the concern of increased tumor growth in the FLR during liver regeneration.[57] Clavien and coworkers described a mouse model in which PVL and partial hepatectomy induced similar regenerative responses in tumor-free mice, but in which mice with a tumor that underwent hepatectomy lacked adequate regenerative activities and had significantly higher intrahepatic tumor load in the FLR than in the PVL group.[44] These data were confirmed by other groups that found accelerated tumor growth in the remnant liver after hepatectomy, whereas PVE or PVL resulted in significant reduction of tumor growth in the nonembolized (nonligated) lobes.[45]. Furthermore, a recent study by Pamecha et al showed that one third of patients undergoing PVE turned out to be nonresectable because of rapid and significant proliferation of metastasis after PVE when compared with non-PVE patients ($P = 0.04$), and this finding was very recently confirmed by the group of Maggiori.[58] In addition, in this study, the long-term outcome for patients resected after PVE was less favorable than for those who underwent immediate surgery.[59] In our study, the short interval of hypertrophy induction enabled resection without signs of tumor progression and irresectability upon "completion surgery."

Various aspects of this study have to be considered for appropriate interpretation: One aspect is that the technique was initially developed at one center (Regensburg University, who also contributed the majority of patients) but was rather rapidly applied by several other German centers. On the one hand, this shows that this innovative technique quickly gained interest in the German surgical community and has been successfully applied in several experienced centers. On the other hand, by that the technique may have been subject to some center-specific variations, for example, different techniques of parenchymal dissection or the use versus nonuse of coverage of the right extended lobe in a plastic bag, anesthesia management, etc. Moreover, it has to be kept in mind that the study is based on a rather heterogeneous group of patients with respect to the underlying pathology and the use or nonuse of chemotherapy before surgery. Finally, this is a report on 25 initial patients in whom the procedure was applied. Thus, our data should serve to stimulate further basic scientific research on the interaction of this novel technique with liver regeneration and tumor biology on a molecular and biochemical level, which currently cannot be explained satisfactorily. Moreover, the data still necessitate an optimal definition for the selection of patients, who might benefit from this approach.

CONCLUSIONS

In conclusion, 2-staged hepatectomy with right PVL and ISS induces a marked and rapid hypertrophy of the left lateral liver lobe. Thus, it represents a new 2-step technique to provide curative therapeutic options for patients with advanced or unfavorably located hepatic tumors or metastasis.

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