Monosegment ALPPS hepatectomy: Extending resectability by rapid hypertrophy

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Background. Liver remnant function limits major liver resections to generally leave patients with ≥2 Couinaud segments. Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) induces extensive hypertrophy and allows surgeons to perform extreme liver resections.

Methods. The international ALPPS registry (NCT01924741; 2011–2014) was screened for novel resection type with only 1 segment remnant. The anatomy of lesions and indications for ALPPS, operative technique, complications, survival, and recurrence were evaluated.

Results. Among 333 patients, 12 underwent monosegment ALPPS hepatectomies in 6 centers, all for extensive bilobar colorectal liver metastases. All patients were considered unresectable by conventional means, and all had a response to or no progression after chemotherapy before surgery. In 2 patients, the liver remnant consisted of segment 2, in 2 of segment 3, in 6 of segment 4, and in 2 of segment 6. Median time to proceed to stage 2 was 13 days and median hypertrophy of the liver remnant was 160%. There was no mortality. Four patients experienced liver failure, but all recovered. Complications higher than Dindo-Clavien IIIa occurred in 4 patients with no long-term sequelae. At a median follow-up of 14 months, 6 patients are tumor free and 6 patients have developed recurrent metastatic disease.

Conclusion. ALPPS allows systematic liver resections with monosegment remnants, a novelty in liver surgery. Because such resections are difficult to conceive without rapid hypertrophy, we propose to name such resections after the segments constituting the liver remnant rather than the segments removed. (Surgery 2015;■:■-■.)

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SINCE THE INTRODUCTION OF THE RIGHT HEPATECTOMY "RÉGLÉE" by Lortat-Jacob[1] in 1952, major liver resections have become standard procedures.[2] Whereas young patients with no underlying liver disease may undergo resection of ≤75% of the total liver volume, patients with chronic liver disease have less reserve.[3,4] Poor clinical outcomes and high mortality in patients with small liver remnants after resection confirmed these limits.[3,5,6]

In 1957, Claude Couinaud described a modular structure of the liver comprising

initially 8 segments ("S").[7] The segmental division of the liver enables liver surgeons to perform liver resections following "anatomic lines"[7] Couinaud's initial description includes 7 major segments (S2–S8) and the additional dorsal segment S1, with less well-defined anatomic boundaries and lower volume. The 8 individual segments 1–8 constitute 5–15% of the total liver volume each. The current paradigm of liver resectability is defined as the removal of tumor with negative margins, preserving ≥2 contiguous, functional liver segments with intact portal and arterial inflow, as well as venous outflow and biliary drainage. According to the Brisbane 2000 terminology of hepatic anatomy and resections, the 2 most extensive liver resections are the right trisectionectomy of segments 4–8 (±S1), leaving S2 and S3 as remnants, and the left trisectionectomy of segments 1, 2, 3, 4, 5, and 8, leaving S6 and S7 as remnants.[8] The remnant segments in these trisectionectomies encompass a volume of 20–30% and have been shown to be associated with an increased morbidity and mortality,[9,10] presumably owing to varying degrees of posthepatectomy liver failure (PHLF).[6]

In an attempt to reduce the risk of PHLF, portal vein embolization (PVE) and portal vein ligation were introduced as novel methods to induce hypertrophy of the future liver remnant (FLR) > 30 years ago.[11] Even though PVE and portal vein ligation brought significant advancements to the field of complex liver surgery, liver growth after PVE is moderate, with an increase of liver volume of 2% per week.[12] In addition, the extent of liver hypertrophy after PVE is unpredictable and sometimes not sufficient for safe liver resections. Furthermore, about 30% of patients develop progression of disease in post PVE interval waiting time.[12-17]

The fundamental principle that the liver remnant should encompass ≥2 Couinaud segments, generally S2 and S3, has remained unchanged, even in the era of hypertrophy induction through portal vein manipulation. Up to now, single segment liver remnants have only been obtained after 2-stage hepatectomies with intervals of several months, procedures that should rather be called "repeated liver resections,"[16,18] or in other exceptional conditions.[19]

Recently, however, the field of inducing liver hypertrophy before resection has fundamentally changed with the advent of a new operative technique.[20,21] The procedure, introduced as "in-situ-splitting of the liver parenchyma"[20] and later given the eponym "associating liver partition and portal vein ligation for staged hepatectomy" (ALPPS)[21] is a transection of the liver parenchyma added to the ligation of the portal vein in stage 1 of a 2-stage hepatectomy. ALPPS allows an approximately 20% increase of the entire liver volume within 1 week, achieving a FLR volume increase of 80%,[22] a near doubling of the volume of a small remnant within a short period of time. ALPPS has opened the prospect of basing the FLR on only 1 Couinaud segment, thus expanding the scope of curative resection in livers with extensive tumor load. As such, near monosegmental liver surgery was possible only with very high risk to patients before the era of aggressive liver volume enhancement through ALPPS.[23] Before efficacious chemotherapy for colorectal liver metastases (CRLM), hepatectomies with monosegment remnants were also hampered because of limited disease control and restrictive oncologic indications. Both limitations have now been challenged.[20,24]

The objective of this study was to systematically explore the feasibility and safety of these novel, "extended" trisectionectomies in a worldwide registry of patients undergoing ALPPS.

MATERIALS AND METHODS

Study design. The ALPPS registry (www.alpps.net), registered at ClinicalTrials.gov (NCT01924741), was analyzed from initiation in October 2012 to April 2014 with follow-up until October 2014 for all patients with resections leaving only 1 Couinaud segment or 1 segment plus S1. All registry centers with high volume were contacted to confirm that no ALPPS monosegment procedures were missed. This series of patients was examined retrospectively.

Disclosure. Monosegment 4 ALPPS in patient 7 has been published previously as a case report.[25]

Participants. The study was conducted in accordance with the requirements of the institutional review boards of the centers participating in the international ALPPS registry and of the ethics committee of the Kanton Zurich, Switzerland, where the registry is located. Informed consent was obtained from each patient for the presentation and depiction of the surgical treatment. All surgeons who decided on indications and performed these resections collaborated in data collection, description of planning, technique, and management.

Definition of monosegmental resection. Segments were defined according to the classic division of the liver based on the anatomy of the glissonian inflow as described by Couinaud in 1957,[7] but considering S1 as an accessory segment. "Monosegmental resection" is defined as a liver resection leaving a remnant constituted of 1 single segment ± S1. Although S4 with its multiple glissonian inflow structures along the umbilical fissures has been subdivided into subsegments 4a and 4b, we consider it one segment along the lines of Couinaud's anatomy.

Data sources and measurement. Photographic documentation of all procedures during ALPPS stages 1 and 2 was evaluated and anatomic sketches of resections were prepared. Cross-sectional imaging studies before stages 1 and 2 and after hypertrophy of the remnant liver were evaluated.

Patient demographics, comorbidities, and tumor characteristics were retrieved from the registry. The tumor load in each liver segment was evaluated. Liver volumetry was performed by each center and expressed as remnant liver volume in milliliters; standardized FLR volume (sFLR)[26] and growth kinetics were expressed as increase in liver volume per day.[26] Intraoperative data and postoperative outcomes were extracted from the registry and confirmed by the centers. Complications were extracted from the registry. Two commonly used definitions of PHLF were used; definition of PHLF by 50–50 criteria[27] and the definition of PHLF of the International Study Group of Liver Surgery (ISGLS).[28] Perioperative outcomes, complications, survival, and recurrence were followed to October 2014 in all patients.

Statistics. Descriptive statistics were performed with JMP 10.0.2. (Mac; SAS, Cary, NC).

RESULTS

Patient characteristics. Between October 2012 and April 2014, 333 patients undergoing ALPPS were entered into the registry. Among those, 12 patients were identified in whom the liver remnant consisted of only 1 segment ± S1. Two patients had a potential liver remnant consisting in segment 2, 2 patients in segment 3, 6 patients in segment 4, and 2 patients in segment 6. In 5 patients, segment 1 was preserved, either in contiguity with the monosegment remnant (patients 4, 7, 8, and 9) or at distance (patient 12). Detailed patient and tumor characteristics are displayed in Table I.

The median age of all patients was 58 years (range, 28–77). All patients had multifocal bilobar CRLM. Six of the 12 patients had lesions in all liver segments and the other 6 had lesions in all segments except in the future remnant. All patients underwent preoperative chemotherapy using Folfox in 6 patients, Capox, Xelox, Folfoxiri in 1 patient each, and Folfiri in 5 patients. Two to 12 cycles of chemotherapy were given, and 5 patients received biological agents additionally, bevacizumab in 4 patients and cetuximab in 1 patient. Ten patients demonstrated partial response according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria[29] and 2 patients had stable disease. Partial response after chemotherapy of target lesions according to RECIST criteria is a ≥30% decrease in the sum of the largest diameter of 5 target lesions, taking as reference the baseline sum largest diameter. Stable disease after chemotherapy of target lesions (5 largest liver lesions) according to RECIST criteria shows neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD since the treatment started. No patient in this series showed progression under chemotherapy (Table I). Progressive disease after chemotherapy of target lesions (5 largest liver lesions) according to RECIST criteria is a ≥20% increase in the sum of the largest diameter of target lesions, taking as reference the smallest sum largest diameter recorded since the treatment started or the appearance of ≥1 new lesions.

Why was ALPPS chosen? The main inclusion criteria of the surgeons responsible for monosegmental ALPPS resections were Eastern Cooperative Oncology Group performance status 1 of the patient, the expected freedom of disease for the FLR, irrespective of volumetric considerations, and response to chemotherapy (Fig 1). Alternative treatment modalities, such as further chemotherapy, conventional 2-stage hepatectomy with or without PVE or portal vein ligation, multiple wedge resections, and locoregional treatments like ablation or drug-eluting beads embolization and radioembolization, were considered by the institutional tumor boards and were ruled out in favor of a liver resection with curative intent. In all patients, potential FLRs of extended hepatectomies, the posterior right sector (S6 + S7) or the left lateral sector (S2+3), could not be retained in contiguity or at all, requiring to sacrifice 1 of the 2 segments of the FLRs. A conventional 2-stage trisectionectomy with tumor clearance of remnant was thus impossible. Multiple wedges and or metastasectomies[17,18] were considered inadequate either from the oncologic or from the technical standpoint,

Table I. Patient and tumor characteristics for associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) monosegments for colorectal liver metastases (CRLM)

Patient ID	ID ALPPS registry*	FLR segment	sFLR at baseline	Age (y)	Gender (F/M)	Total no. of lesions	Size of largest lesion (cm)	Type CRLM sync/ met†	T, N, and G stage, primary	Preoperative CEA (ng/mL)	Liver first (Y/N)‡	Preoperative CTx	Preoperative CTx, no. of cycles	Preoperative doses biological§	RECIST‖
1	AR01_341	2	0.10	55	F	10	1.5	Sync	T3N2	175	N	FOLFOX	6	No	PR
2	AR01_082	2 (+1)	0.16	62	M	3	3.5	Sync	T3N1	4	N	FOLFIRI	5	5 CETUX	NP
3	BR01_117	3	0.21	28	F	21	15	Sync	T3N1G2	700	Y	FOLFOXIRI	2	No	PR
4	BR01_187	3 (+1)	0.14	57	F	9	7	Sync	T3N2G2	7	N	FOLFIRI	7	No	PR
5	CND01_108	4	0.15	63	F	10	4.5	Sync	T3N1G1	154	Y	XELOX	6	5 BEVA	PR
6	AR01_095	4 (+p3)	0.13	68	M	6	2.8	Met	T3N0G2	150	N	CAPOX/ FOLFIRI	4/2	2 BEVA	PR
7	AR01_094	4 (+1)	0.20	77	M	12	4.5	Met	not known	113	N	FOLFOX	6	No	PR
8	UK02_322	4 (+1)	0.15	34	M	6	11.5	Sync	T3N0G2	7.6	Y	FOLFIRI	12	12 BEVA	PR
9	DE05_333	4 (+1)	0.20	51	M	12	3.1	Sync	T3N2G2	104	N	FOLFOX/ FOLFIRI	8/2	RAMI	NP
10	LB01_357	4	0.22	58	M	6	5.5	Sync	T3N2G2	18	N	FOLFOX	7	7 BEVA	PR
11	BR01_310	6	0.08	66	F	12	4.6	Sync	T3N2G1	207	N	FOLFOX	6	No	PR
12	BR01_188	6 (+1)	0.13	58	M	19	6.1	Sync	T3N2G3	319	N	FOLFOX	6	No	PR
Summary			Median, 0.15	Median, 58	F, 5; M, 7	Median, 10	Median, 4.6	Sync, 10; Met, 2			Y, 4; N, 8		Median, 6		SD, 2, PR,10

*ID as recorded in the International ALPPS Registry.
†Type of colorectal liver metastasis: Syn, synchronous; Met, metachronous.
‡"Liver first approach": to first resect colorectal liver metastasis followed by the primary tumor.
§Antibody therapy used for preoperative chemotherapy.
‖RECIST, Response Evaluation Criteria In Solid Tumors

BEVA, Bevacizumab; *CEA*, carcinoembryonic antigen; *CETUX*, cetuximab; *RAMI*, Ramicirumab; *CTx*, chemotherapy; *FLR*, future liver remnant; *PR*, partial response (after chemotherapy of target lesions according to RECIST criteria: a ≥30% decrease in the sum of the largest diameter of 5 target lesions, taking as reference the baseline sum largest diameter); SD, Stable disease after chemotherapy of target lesions (5 largest liver lesions) according to RECIST criteria shows neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD since the treatment started; sFLR, standardized future liver remnant.
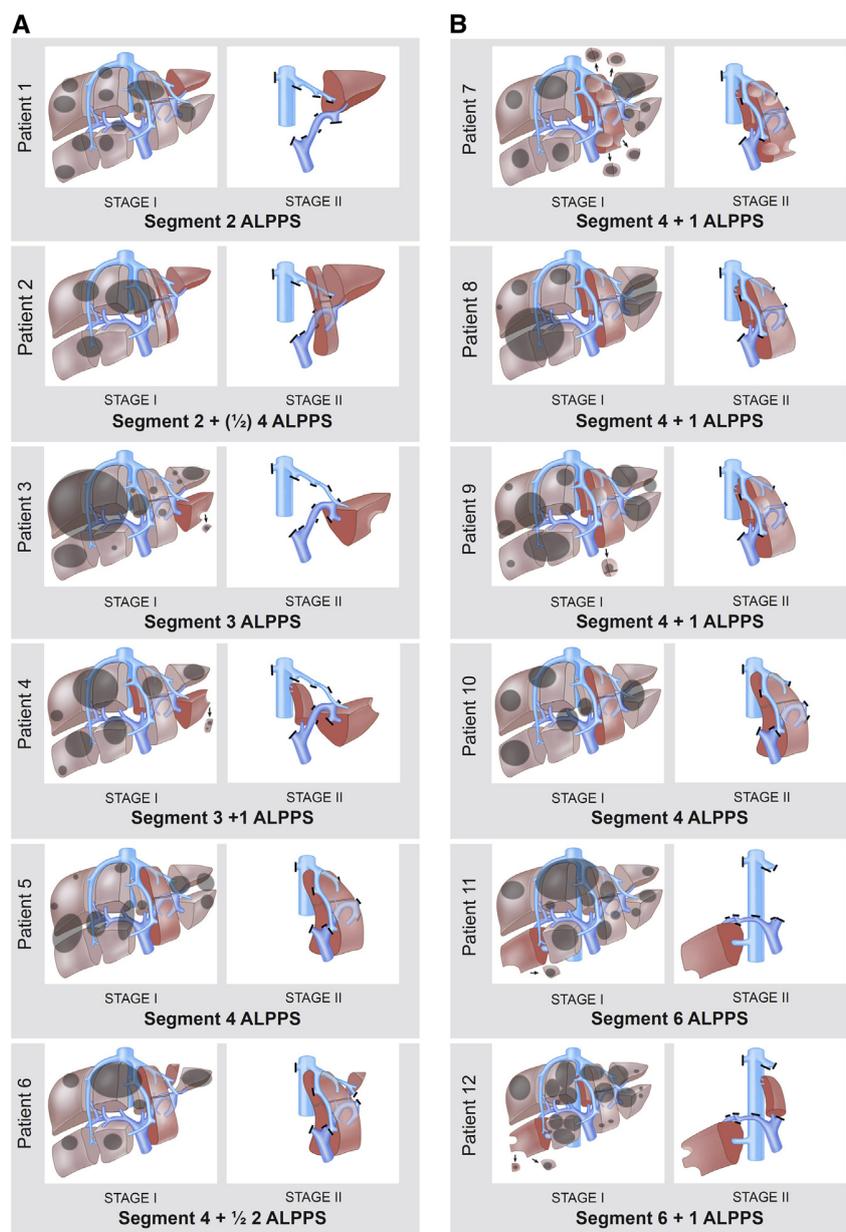
Fig 1. The 12 monosegment Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) hepatectomies showing the tumor status before stage 1 with the future liver remnant marked in dark red and the tumorectomies marked by arrows. At stage 2, the diseased liver is removed leaving the hypertrophied monosegment remnant liver behind.

exposing patients to risk of recurrence and/or surgical complications.

In patient 1, S3 could not be preserved owing to tumor invasion of the inflow pedicle. It was felt that in order to achieve sufficient hypertrophy of S2 alone, ALPPS had to be performed. In patient 2, S3 and S7 had previously been resected and a right trisectionectomy was necessary owing to middle and right hepatic vein involvement.

To increase the size of the FLR, a nonanatomic small medial aspect of S4, drained by the left hepatic vein, was also preserved. In patient 3, all segments of the liver carried tumor and the lesion in S2 required complete removal because 3 lesions occupied the entire volume of segment 2. In patient 4, S2 had to be resected owing to a large volume tumor, but S1 could be preserved. In patient 5, the right hemiliver had to be resected

Table II. Intraoperative variables and hypertrophy of patients with associating liver partition and portal vein ligation for staged hepatectomy monosegments for colorectal liver metastases

Patient ID	FLR segment	Time stage 1 (min)	Time stage 2 (min)	Pringle stage 1 (Y/N)*	Pringle time (min)	Anterior approach, stage 1†	Blood loss, stage 1 (mL)	Blood loss, stage 2 (mL)	Units of blood, stages 1 + 2
1	2	300	110	No	—	No	<100	<600	2
2	2 (+1)	360	120	Yes	7	No	<600	<100	0
3	3	300	260	No	—	No	<1,000	<600	2
4	3 (+1)	208	180	No	—	No	<100	<600	0
5	4	327	124	No	—	No	<600	<100	0
6	4 (+p3)	270	170	Yes	34	No	<600	<600	2
7	4 (+1)	300	90	Yes	10	Yes	<600	<600	0
8	4 (+1)	400	95	Yes	20	No	<1,000	<600	0
9	4 (+1)	310	160	Yes	60	No	>1,000	<1,000	0
10	4	660	110	Yes	100	No	>1,000	<100	5
11	6	240	100	Yes	55	No	<1,000	<100	0
12	6 + 1	400	240	No	—	No	<1,000	<600	2
Summary		Median, 305; range, 208–660	Median, 122; Range, 90–160	Yes: 7 No: 5	Median, 34; range, 7–100	Yes: 1 No: 11	<100: 2 >1,000: 2	<100, 4; >1,000,0	Median 0; Range, 0–5

BW, Body weight; *FLR*, future liver remnant; *KGR*, kinetic growth rate (may be expressed in mL/d or %sFLR/d; in this table it is expressed as %sFLR/wk); *sFLR*, standardized future liver remnant.
*Pringle maneuver = arterial and portal venous inflow occlusion.
†Anterior approach = liver transection without prior mobilization of the right lobe.

owing to involvement of both the right hepatic vein and the right glissonian structures, and S1–3 had to be removed as well. In patient 7, the right hepatic vein was involved with tumor and the left lateral segment had inflow involvement with multiple large lesions. Despite 4 tumors in S4, preservation seemed to be possible. In patient 8, only S4a and S1 were free of tumor; an en bloc resection of the anterolateral portion of S4b + S2+S3 in proximity of S4 glissonian inflow was required. In patient 9, there were large lesions in both the right lobe and the left lateral segment, but S4 could easily be cleared of a single lesion. In patient 10, the right hepatic vein, left hepatic vein, and right portal vein were encased with tumor. This patient had previously had PVE of the right portal vein, but S4 failed to grow significantly. ALPPS was chosen as a rescue approach (Fig 3). In patient 11, there were dense lesions in all segments, but only 1 peripheral lesion in S6 and an accessory right hepatic vein of large caliber and a sFLR volume of 0.08. This allowed for S6 ALPPS with S6 metastasectomy. In patient 12, the tumor involved the hepatic venous outflow of all 3 veins, but a S6 ALLPS was possible thanks to an accessory right hepatic vein and 2 peripheral lesions that could easily be wedged (Fig 1*A* and *B*).

Monosegment 2 ALPPS: technical details (patients 1 and 2). S3 is resected with careful preservation of the glissonian pedicle to S2 followed by resection of the caudate lobe S1

(Fig 1). The right portal vein is identified, transected, and the anterior and posterior branch of the right glissonian pedicle is marked. ALPPS transection at the falciform ligament then performed. In stage 2, the right glissonian pedicles are ligated and the right hepatic vein is transected and oversewn and the extended right lobe is removed.

Monosegment 3 ALPPS: technical details (patients 3 and 4). S2 is resected, identifying the glissonian pedicle to S2 using ultrasound guided intrahepatic glissonian technique (Fig 1). The left glissonian pedicle going to S3 is carefully protected. Then the right portal vein is ligated. Subsequently, the ALPPS transection between S3 and S4 is performed and carried superiorly along the left hepatic vein, ligating all venous braches draining S4 superiorly and thereby leaving the left hepatic vein skeletonized. The glissonian pedicle to S4 is divided during liver transection, but arterial supply preserved. S1 is removed en bloc during stage 2 in patient 3, thereby excluding S1 from the FLR, but left in place with the FLR in patient 4. In stage 2, the right portal pedicle is followed by transection of the middle and right hepatic vein, and the extended right liver is removed.

Monosegment 4 ALPPS: technical details (patients 5, 6, 7, 8, 9, 10). All accessory hepatic veins on the anterior aspect of the vena cava are divided (Fig 1). The right portal vein is ligated. The left lateral S2 and S3 are then resected and removed. Care is taken to identify S4 artery and

Table II. *(Continued)*

Transfusion overall (yes/no)	sFLR baseline	FLR/BW ratio baseline (mL/kg)	sFLR before stage 2	FLR/BW ratio before stage 2	Days	Degree of hypertrophy (%)	KGR (sFLR/wk)
Yes	0.10	0.24	0.26	0.54	6	160	0.19
No	0.16	0.33	0.49	0.97	14	206	0.17
Yes	0.21	0.43	0.53	1.12	21	152	0.07
No	0.14	0.30	0.36	0.77	20	157	0.07
No	0.15	0.33	0.28	0.62	6	93	0.15
Yes	0.13	0.48	0.34	0.75	10	161	0.15
No	0.20	0.42	0.50	1.09	12	150	0.18
No	0.15	0.32	0.33	0.69	13	120	0.10
No	0.20	0.40	0.34	0.69	10	170	0.10
Yes	0.22	0.45	0.41	0.76	6	190	0.22
No	0.08	0.18	0.28	0.59	21	250	0.07
Yes	0.13	0.28	0.41	0.89	21	215	0.09
Yes: 5 No: 7	Median, 0.15; range, 0.08–0.22	Median, 0.33; range, 0.18 -0.48	Median, 0.35; range, 0.26–0.53	Median, 0.75; range, 0.54–1.12	Median, 13; range, 6–21	Median, 160; range, 93–250	Median, 0.13; range, 0.07–0.22

the S4 glissonian pedicle at the umbilical ligament, aiming at careful preservation of the umbilical glissonian structures to S4. Thereafter, the ALPPS partition is carried through Cantlie's line, and the right glissonian structures are encircled and marked. In stage 2, the right glissonian pedicles and the right hepatic vein are transected and the right hemiliver is removed. The remnant is drained by the middle hepatic vein.

Monosegment 6 ALPPS: technical details (patients 11 and 12). All accessory hepatic veins on the anterior aspect of the vena cava are divided, except for the accessory segment 6 hepatic vein (Fig 1). In case 12, no mobilization of the caudate lobe from the vena cava is performed to allow segment 1 to stay adherent to the vena cava. The glissonian sheath going to the right hemiliver is then identified through an extraglissionan ultrasound-guided approach through the liver parenchyma and marked with a vessel loop. Using the same approach, the glissonian pedicle from the right posterior segment (S6–7) is identified and encircled with a vessel loop. The right anterior pedicle is identified and clamped. Surface demarcation of the limits between right anterior and posterior sector is marked with cautery. The liver is transected along this demarcation. At the division line of inferior and superior segments, the transection is moved 90° toward the right. The S7 pedicle portal vein is ligated inside the liver parenchyma. At this time, S6 is detached from the

rest of the liver. The left portal vein is dissected in the hilum of the liver, identified, and ligated. The right anterior portal vein is ligated. In stage 2, the glissonian pedicle to the left liver is transected, followed by transection of the glissonian pedicle to S5 and S8. All 3 hepatic veins are then clamped and transected and the surgical specimen consisting of S1, 2, 3, 4, 5, 7, and 8 is removed (Fig 4). In case 12, the glissonian pedicle going to S1 is isolated as well to preserve S1 artery and portal branches from the proximal left portal vein in stage 1 and in stage 2 S1 is maintained on the vena cava.

In patients 1, 3, 4, 7, 9, 11, and 12 nonanatomic wedge resections were additionally performed in the FLR during stage 1. Photographs of the operative site after stage 2 resection for each type of monosegment resection are shown in Fig.2.

Intraoperative data. The median duration was 5 hours 5 minutes for stage 1 procedures, and 2 hours 2 minutes for stage 2 (Table II). The longest case during stage 1 lasted 11 hours for a S4 ALPPS, the shortest 3 hours 30 minutes. Pringle maneuver was used in 7 of 12 patients, in 3 patients for <45 minutes and in 3 patients for >45 minutes cumulatively. The anterior approach was used in one S4 ALPPS. In 2 patients with S4 ALPPS, blood loss was >1,000 mL during stage 1; however, in stage 2 there was only 1 patient who lost >600 mL of blood. Five of the 12 patients received intraoperative blood transfusions, 2 units each in 4 patients and 5 units in 1 patient. Perioperative

regimen varied between centers. All patients were extubated after stage 1 ALPPS in the operating room and transferred to a monitored bed or intensive care unit after surgery. Patients 1, 2, 5, 6, 7, and 9 remained in the hospital between stages, and patients 3, 4, 8, 11, and 12 were discharged home between stages. All patients had intraperitoneal drains placed during stage 1 and in all cases they were kept until stage 2 and sometimes for weeks thereafter. All patients received perioperative prophylactic antibiotics, but did not receive antibiotics prophylactically between stages 1 and 2. All patients had oral feeding; in patients 6 and 7, total parenteral nutrition was provided in addition to oral feeding.

Postoperative outcomes and oncologic efficacy. After a median waiting time of 13 days, the sFLR increased from a median of 0.15 (range, 0.08–0.22) to a median 0.35 (range, 0.26–0.53; Table III). This represents a median increase of 160% increase compared with the starting volume (range, 93–250). Kinetic growth was at a median of 0.13 FLR per week (range, 0.07–0.22).

No mortality was observed among the 12 patients and all patients reached 90 days follow-up. Four of the 12 patients experienced liver failure according to the ISGLS criteria and 3 patients based on 50/50 criteria. All patients fully recovered from PHLF. In addition, 4 patients with PHLF according to the ISGLS criteria showed increased bilirubin levels at 5 times above baseline at 5 days after stage 2 and so did 2 patients who did not have PHLF according to aforementioned criteria. Six of 12 patients developed ascites postoperatively. Four patients experienced major surgical complications (>IIIA). In only 1 patient this was related to PHLF; in the other 3, it was due to reexploration because of a partial hepatic artery thrombosis in the deportalized lobe, debridement of a superficial wound infection, and insertion of a chest tube for a postoperative hydrothorax. There were no long-term consequences for the patients' health status from these complications. In all 4 patients, major complications correlated with a prolonged length of hospital stay. Median hospital stay was 22 (range, 10–49) days. Ten out of 12 patients were resected with an R0 status.

Median follow-up was 14 months (range, 5–34). At last follow-up, 6 of the 12 patients were free of tumor recurrence. Two hepatic recurrences were diagnosed 3 and 12 months after resection and were treated by radiofrequency ablation and chemotherapy, respectively. An ovarian metastasis occurred 2 months after resection and the patient died 3 months later; 1 brain metastases occurred

3 months after ALPPS and the patient died 5 months after surgery. A pulmonary metastasis occurred 10 and 16 months after surgery and were treated surgically. Another pulmonary metastasis was diagnosed 12 months after resection and the patient received chemotherapy again. Eight of 10 patients reaching 1-year follow-up are alive at 1 year (80%) and 5 of 10 patients reaching 1-year follow-up are disease free at 1 year (50%).

DISCUSSION

To date, right and left trisectionectomies have been regarded as the most extensive liver resections routinely performed. They typically leave 2 contiguous Couinaud segments as liver remnants, constituting between 20 and 40% of the total liver volume. This study shows that the anatomic borders of 1 single Couinaud (±S1) may suffice for patients to undergo a short interval 2-stage resection, as long as rapid hypertrophy is induced with ALPPS, and adequate vascular inflow, outflow, and biliary drainage are ensured. The routine preservation of only 1 liver segment (±S1) is a novelty in liver surgery. Four feasible resection types are reported here (Fig 5): S2 ALPPS with S3 resection in stage 1 followed by a right trisectionectomy in stage 2; S3 ALPPS with resection of S2 during stage 1 followed by a right trisectionectomy in stage 2; S4 ALPPS with removal of the left lateral segment during stage 1, followed by a right hemihepatectomy during stage 2; and S6 ALPPS in those patients who have an anatomic variation with a large inferior right hepatic vein draining S6, which was first described by Makuuchi et al.[30] Owing to limitation of the parenchymal mass of a single Couinaud segment, these resections would have been impossible without inducing an unparalleled amount of rapid liver hypertrophy with ALPPS, reaching a median liver volume increase of 160% (range, 93–250%). These extreme resections were performed systematically and resulted in postoperative outcomes comparable to complex liver resections[6] and 2-stage hepatectomies for CRLM.[31] Patients were carefully selected; all of them had undergone preoperative chemotherapy, half of them with addition of biological agents. There was no patient in this series with progression during preoperative chemotherapy. Although the follow-up is short, there has been no local recurrence occurrence to date. Clearly, most patients would have been considered unresectable, even with conventional 2-stage hepatectomies, owing to too extensive involvement of either S2 and S3 or S6 and S7.

Despite this, there are limitations to this report. First, the study is a small series so far, primarily

Table III. Perioperative outcomes and survival and recurrence of associating liver partition and portal vein ligation for staged hepatectomy monosegments for colorectal liver metastases

Patient ID	FLR segment	Liver failure ISGLS*	Liver failure 50–50 criteria†	Bilirubin baseline/day 5 after stage 2 (mg/dL)	Ascites after stage 2, yes/no	Highest compl Clavien/ Dindo	Type of highest compl	Hospital stay	90-Day mortality	Resection status	Restart chemotherapy after resection (mo)	OS (mo)	DFS (mo)	Type of recurrence	F/U time (mo)
1	2	Grade A	Yes	2.5/12.2‡	+	IIIa	Pleural effusion	31	No	R0	1	5	2	Ovarian§	5
2	2 (+1)	No	No	1.0/0.5	—	IIIb	HA thrombosis	20	No	R0	1.5	28	16	Lung‖	28
3	3	No	No	0.2/0.3	—	None	—	16	No	R0	2	34	12	Lung¶	34
4	3 (+1)	No	No	0.4/1.0	—	None	—	13	No	R0	1.5	24	24	—	24
5	4	No	No	0.6/6.8‡	—	IIIa	Wound infection	49	No	R1	2	23	23	—	23
6	4 (+p3)	No	No	0.8/1.4	—	None	—	10	No	R0	1	5	3	Brain§	4.7
7	4 (+1)	No	No	n.a.	+	IV	ARF dialysis	43	No	R0	2	13	13	—	13
8	4 (+1)	Grade B	yes	0.5/4.4‡	+	II	Liver failure medications	20	No	R0	4	10	3	Liver¶	10
9	4 (+1)	No	No	0.2/1.5‡	+	II	Ascites medications	20	No	R1	6	14	12	Liver, lung#	14
10	4	Grade A	yes	1.2/7‡	+	I	Ascites mediations	12	Not reached	R0	—	5	5	—	5
11	6	Grade A	No	0.8/4.0‡	+	II	Ascites medications	16	No	R0	4	8	8	—	8
12	3	No	No	1.2/7‡	—	None	—	13	No	R0	2	26	26	—	26
Summary		Yes, 4	Yes,3	Bilirubin increased, 6	Yes, 6	>IIIA, 4		Median, 18; range, 10–49	0/11	R1: 2		1-year OS, 8/10 (80%)	1-y DFS, 5/10 (50%)	Extrahepatic, 4; hepatic, 2	Median, 14; range, 5–34

*Liver failure by Criteria of the International Study Group for Liver Surgery (ISGLS).[29]
†Liver failure by 50–50 criteria.[28]
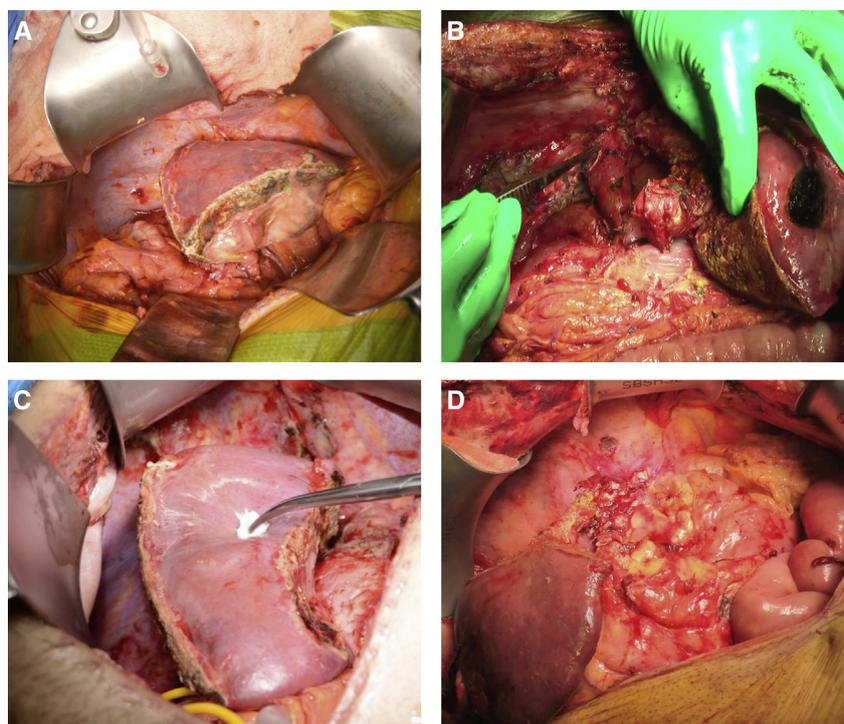‡Elevation of bilirubin >5 times baseline values.
§Died from recurrence.
‖Treated with lung resection, alive.
¶Treated with chemotherapy, alive.
#Treated with transcutaneous CT-guided radiofrequency ablation, alive.
R0, Microscopically free margins; R1, macroscopically involved margins; OS, overall survival; DFS, disease-free survival.

Fig 2. Representative photographs of each type of monosegment associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) during stage 2 after removal of the diseased liver. (*A*) Segment 2 ALPPS. (*B*) Segment 3 ALPPS. (*C*) Segment 4 ALPPS. (*D*) Segment 6 ALPPS.

owing to the novelty of ALPPS in general and its controversies regarding its higher morbidity and mortality rate.[20,32-35] Nevertheless, in a recently performed first analysis of the ALPPS registry, we have demonstrated that the reported concerns are likely due to the application of ALPPS in patients with primary liver tumors and elderly patients.[22] As such, all patients included in this series, treated with monosegmental ALPPS, were hepatectomies for CRLM and 8 out of 12 patients were <60 years old.

A second limitation of this study is the short median follow-up time of 14 months (range, 5–34). A recent analysis of the ALPPS registry demonstrated a disease-free survival of 59% at 1 year and 41% at 2 years for all 141 patients with CRLM analyzed.[22] In this selected series of patients with very extensive tumor burden, 6 patients have been free from recurrence so far, 2 died from systemic recurrence, 2 developed liver recurrences (one of which could be treated by transcutaneous radiofrequency ablation), and 2 developed pulmonary recurrences (one of which was treated by resection).

Although patients with bilobar CRLM as extensive (Fig 1*A* and *B*) are not considered generally to be candidates for surgical cure by multidisciplinary

care teams, we highlight in this report that, in well-selected candidates, high tumor burden in all liver segments is resectable using this novel monosegmental ALPPS technique. This technical advancement may become even more important as chemotherapy and biological agents for the treatment of CRLM have become more effective.

The inaugural report by Schnitzbauer et al[20] established the ALPPS procedure to allow rapid and extensive hypertrophy of the left lateral segments S2 and S3 in extended right liver resections. Subsequent series demonstrated the use of ALPPS in right trisectionectomies with nonanatomic wedge resections of the FLR in S2 and S3.[36] Variations of ALPPS called "reversal ALPPS" followed suit, using the right posterior sector as the FLR.[36,37] Recently De Santibanes et al[25] presented the first report of monosegment 4 ALPPS procedure in the literature for a patient where extensive involvement of S2 and S3 did not allow to preserve them.
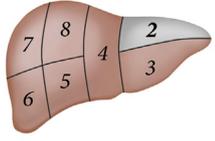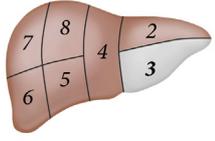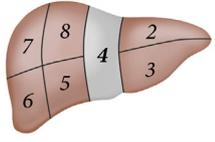
The present study evaluates this novel option in a series of situations in which the right or left lateral sectors cannot serve as the FLR either because the tumor burden in the remnant liver is too extensive, or owing to an involvement of the vascular inflow or outflow. In addition, this series
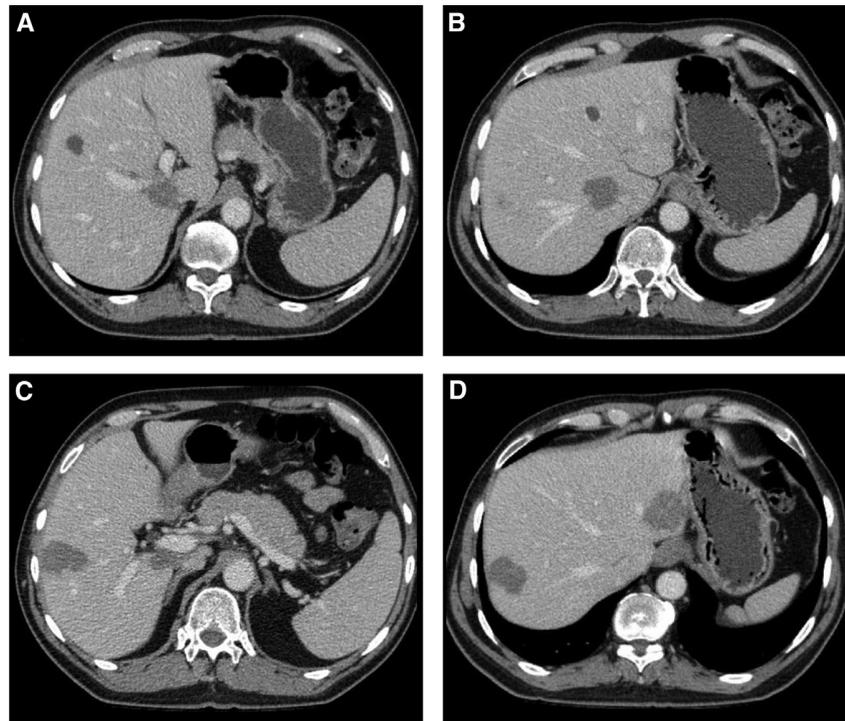
Fig 3. CT of typical tumor anatomy necessitating a monosegment remnant resection leaving only segment 4 with an standardized future liver remnant of 0.22. in patient 10. (*A*) Tumor at the interface of segments 1 and 6, involving the right glissonian inflow. (*B*) Tumor encasing the right hepatic vein. (*C*) Tumor at the interface between segments 8 and 5, making preservation of both difficult. (*D*) Tumor abutting the left hepatic vein, necessitating resection of segments 2 and 3.
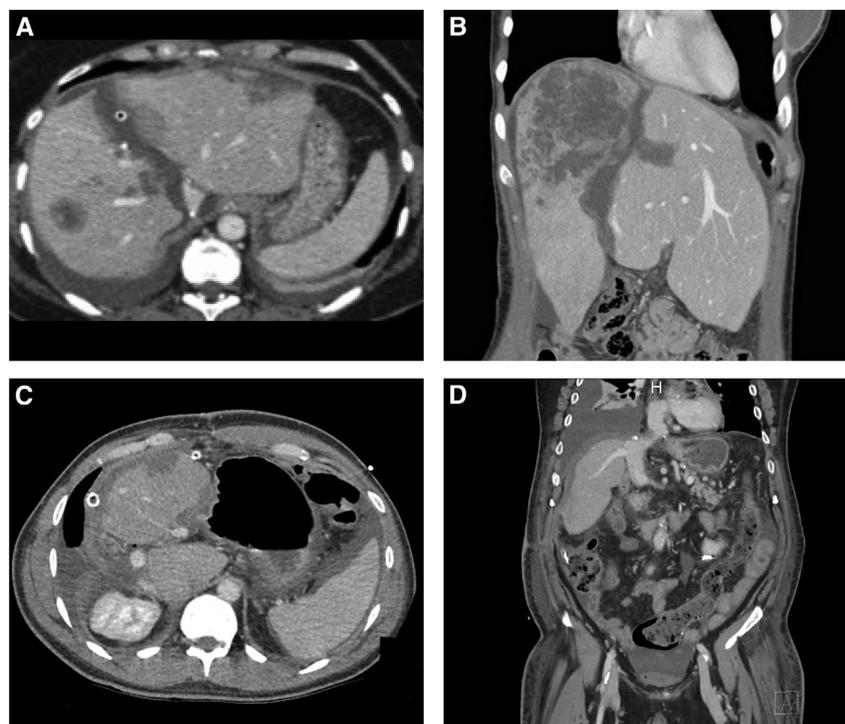
Fig 4. CT of each type of monosegment associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) after stage 2. (*A*) Segment 2 ALPPS. (*B*) Segment 3 ALPPS. (*C*) Segment 4 ALPPS. (*D*) Segment 6 ALPPS.

ALPPS Resections		
Resected Couinaud segments	**Term for surgical resection**	**Diagram** (resected area is shaded)
Sg 3-8 (+/- Sg 1)	Segment 2 ALPPS stipulate +/- segment 1	
Sg 2, 4-8 (+/- Sg 1)	Segment 3 ALPPS stipulate +/- segment 1	
Sg 2, 3,5-8 (+/- Sg 1)	Segment 4 ALPPS stipulate +/- segment 1	
Sg 2-5,7,8 (+/- Sg 1)	Segment 6 ALPPS stipulate +/- segment 1	
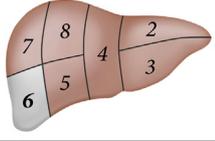
Fig 5. Proposal for a nomenclature of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) monosegment resections in based on the segment of the liver remnant rather than the segments of resected liver. *Sg*, Segment.

demonstrates that, if S2 has to be resected, S3 may serve as the only remnant segment. Likewise, if S3 has to be removed, S2 alone may support the patient after rapid hypertrophy. And extending the concept of reversal ALPPS with S6 and S7 as the liver remnant,[37] this report highlights that S6 alone may serve as a monosegment, as long as a venous outflow does not depend on the right hepatic vein but may be achieved by preserving an accessory right inferior hepatic vein, an anatomic variation first exploited by Makuuchi et al.[30] At last, because S4 extends along the entire craniocaudal axis in the middle of the liver, it may well become the most commonly used monosegment ALPPS procedure as long as its glissonian inflow through the left umbilical pedicle and its outflow through the middle hepatic vein can be preserved. Given its anatomic advantage, S4 has previously been described as a monosegment remnant in 2-stage hepatectomies, however, with long waiting time between stages.[16]

The Brisbane 2000 consensus on the nomenclature of liver anatomy and resections does not consider monosegmental resections resections in its synopsis (http://www.ahpba.org/index.php?option=com_content&view=article&id=35). This nomenclature offers the possibility to refer to any resection by use of its third-order term: just as a right trisectionectomy may be called a "resection S4-8," a resection of every segment except for S4 may be called "resection S1-3 and S5-8."[38]

A review of the existing literature on extreme liver resections, however, lead us to consider an alternative proposal: We found no reports on the systematic use of resections leaving only 1 Couinaud segment as FLR. Starzl et al[23] reported a 1-stage, extended trisectionectomy in 1975 in a 19-year-old woman with hepatocellular carcinoma, leaving only a nonanatomic part of S2 and S3 as a liver remnant, an estimated 85-90% liver resection before the era of cross-sectional CT volumetry. The patient experienced postoperative liver failure but eventually recovered.[23] Makuuchi et al[30] described the possibility to perform a left trisectionectomy extended to S7 based on the presence of a right inferior hepatic vein, later performed by Machado et al[30] as a "resection S1, 2, 3, 4, 5, 7, and 8" according to the Brisbane consensus. A report from Hungary described a sequential hepatectomy with a right trisectionectomy and then a resection of S2 and S3, leaving only a hypertrophied S1 as liver remnant.[18] However, the time between the 2 resections in this case was 4.5 months. Similarly, the 2 patients with single S4 liver remnants reported by Adam et al[16] have also had a long interval between stages.

A systematic use of resections with monosegment remnants in 2 procedures not farther apart, but 12 in days is, in our opinion, not possible without rapid hypertrophy as induced by ALPPS. We, therefore, propose to name such procedures leaving only 1 segmental remnant in the context of ALPPS according to the liver remnant, using third-order segment terms, for example, "S2 ALPPS," "S3 ALPPS," "S4 ALPPS," and "S6 ALPPS" (Fig 5).

It is conceivable to maintain the glissonian pedicle into S8 while preserving outflow through right and middle hepatic vein, so a "S8 ALLPS" may be feasible as well, but—to our knowledge—this procedure has not yet been reported. Owing to the difficulties of maintaining glissonian inflow in S7 and venous outflow in S5, it seems to be difficult theoretically, if not impossible to base extreme resections on only these monosegments.

However, with advanced parenchymal dissection techniques and increasing experience with rapid hypertrophy, we may expect further refinements of this technique.

In conclusion, extreme liver resections for CRLM based on a single segment liver remnants are feasible and safe using the novel monosegmental ALPPS technique. Metastases in every segment of the liver are not a contraindication for resection, even if only 1 segment can be preserved. Monosegmental ALPPS is a new surgical tool to add to advanced chemotherapy in the management of extensive CRLM. More experience and longer follow-up should determine the oncologic efficacy of this approach.

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