

Monosegment ALPPS hepatectomy preserving segment 4 for colorectal liver metastases: literature review and our experience

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Abstract: Monosegment 4±1 Associating Liver Partition and Portal Vein ligation for Staged hepatectomy (ALPPS) for bilateral colorectal liver metastases decreases the risk of drop-out of two stage hepatectomy, triggering a rapid and significant increase in future liver remnant (FLR) with promising oncological outcomes. We report two cases of segment 4±1 monosegment ALPPS for multiple colorectal liver metastases performed at our institution. In the literature, seven similar cases have been reported. Short and long term outcomes of our two patients were reported along with a review of data from the literature. Our patients showed a FLR increase from 13% to 37% and from 14% to 41% of total liver volume, respectively. This was compared to a median growth from 19% at baseline to 34% before stage 2, in the literature. After 20 and 27 months since resection both patients are alive and disease-free. In the literature, median overall survival and disease free survival were 13 months (range, 5–24 months) and 5 months (range, 3–23 months), respectively. Segment 4±1 ALPPS is associated with promising oncological outcomes and a significant FLR growth. It may be safely performed in selected patients as a salvage procedure, reducing the risk of the dropout of two-stage hepatectomy.

Keywords: Associating Liver Partition and Portal Vein ligation for Staged hepatectomy (ALPPS); liver resection; colorectal liver metastases

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Introduction

Monosegment Associating Liver Partition and Portal Vein ligation for Staged hepatectomy (ALPPS) was defined by Schadde *et al.* as a liver resection leaving a remnant constituted of one single segment ± segment 1 (S1) (1). This variation of the ALPPS technique represents a substantial change to the traditional paradigm of liver resectability, which is defined as the removal of tumour with negative margins, preserving ≥2 contiguous liver segments along with their inflow, outflow and biliary drainage. Various reports and reviews have been published, describing advantages and limitations of ALPPS (1-3). ALPPS induces a rapid hypertrophy of the liver remnant compared to portal vein embolization or ligation with a rate of completion of

second stage between 95% and 100%. However, concerns are mainly due to the high morbidity (up to 44% of Clavien-Dindo grade III or more) and mortality rates up to 29%, as well as the possible relationship between a rapid hypertrophy and tumour progression (3). Therefore, ALPPS is still a debated topic. Monosegment ALPPS hepatectomy overcomes left and right trisectionectomy, which are the most extensive liver resections according to the terminology introduced by the IHPBA (4), with the intent of offering an oncological resection and a lower incidence of post-hepatectomy liver failure (PHLF). Prior to the introduction of ALPPS, the treatment of bilobar borderline resectable liver metastases with single segment remnants could only be achieved by the means of two-stage hepatectomies (TSH),

but often requiring very long intervals to achieve a sufficient FLR. Alternatively, the option of ultrasound-guided multiple wedge resections aimed to maximize parenchymal-sparing and to allow curative resection in one stage (5,6).

However, the ALPPS technique has not yet been standardized. Different types of monosegment ALPPS hepatectomy have been described by Schadde *et al.*, who proposed a nomenclature based on the segment of the liver remnant rather than the segments of resected liver (2). In this report, we present our preliminary experience on segment 4+1 monosegment ALPPS hepatectomy and a review of the literature of published similar cases.

Methods

Literature search

PubMed database was searched from inception to 23/10/2016. The following search terms were used: Text words [monosegment*] AND [ALPPS*] OR [Associating Liver Partition and Portal Vein ligation for Staged hepatectomy*]. Three results were yielded in total from the initial search.

Definitions

Segments were defined according to the classic Couinaud's anatomical division of the liver (7). Monosegment resection was defined as a liver resection leaving a remnant constituted of 1 single segment \pm S1 (2). The cut-off for the minimal safe size of the liver remnant after single stage hepatectomy was set as $>30\%$ of the TLV for patients with chemotherapy-related liver injury (8). Post-hepatectomy liver failure (PHLF) was defined according to the International Study Group of Liver Surgery (ISGLS) classification (increased INR or need of clotting factors to maintain normal INR and hyperbilirubinemia on or after postoperative day 5) (9). Postoperative complications were graded according to the Clavien-Dindo classification (10).

Patients

Two patients underwent segment 4+1 ALPPS hepatectomy at Aberdeen Royal Infirmary (UK). The first patient was a 61-year-old female with no comorbidities. She presented with adenocarcinoma of the right colon with synchronous bilobar liver metastases. The preoperative

CT and MRI liver showed 7 lesions in segments 5, 7 and 8 and in the left lobe, where the largest, measuring 3.4 cm, was at the passage between S2 and S3. She underwent right hemicolectomy, and the primary was staged as Duke's D pT3N1. After chemotherapy with four cycles of Capecitabine and Oxaliplatin (XELOX), a partial response was observed. Technically, the right hemiliver and the left lateral sector could not be preserved due to the involvement of the right hepatic vein and the large lesion in S2–3. The preoperative FLR volume for segments 4+1 was 199 cm^3 , 13% of total liver volume (TLV), which was deemed too small for a single stage procedure (*Figure 1*).

The second patient was a 61-years-old male presenting with mid rectum adenocarcinoma treated with neoadjuvant pelvic radiotherapy, chemotherapy with XELOX and anterior resection with loop ileostomy (stage pT2N1 Duke's C). He received postoperative Capecitabine alone and unfortunately developed serious drug-induced neuropathy and pulmonary embolism (PE), which required therapeutic dose anticoagulation and contraindicated any further chemotherapy. Six months after resection of the primary tumor, he developed a total of 7 bilobar liver metastases, located in segments 2, 3, 5, 6 and 8. The maximum diameter of the largest lesion was 3cm, deep in S6 close to the sectorial division of the right portal vein. Only segment 7, 4 and 1 were clear from lesions. He could not receive further chemotherapy, and he was offered ALPPS as a rescue approach. The preoperative FLR volume for segments 4 and 1 was 255 cm^3 , 14% of TLV, which was deemed insufficient to undergo one-stage hepatectomy (*Figure 2*). For both patients, alternative treatment strategies were evaluated in our institutional Hepatobiliary and Pancreatic Multidisciplinary Meeting (HPB-MDT). Both patients were informed about surgical and nonsurgical options and gave informed consent to undergo two-stage hepatectomy with ALPPS technique.

Technique

First stage consisted in a left lateral sectionectomy with intra-glissonian dissection of the vascular elements assuring the preservation of the artery for segment 4 and its glissonian pedicle. The right portal vein was then ligated and the Cantlie line used as the mark for the right-sided transection. Parenchymal transection was performed using Thunderbeat[®] (Olympus) device, whereas clips and ligatures were used for vascular and bile ducts larger than

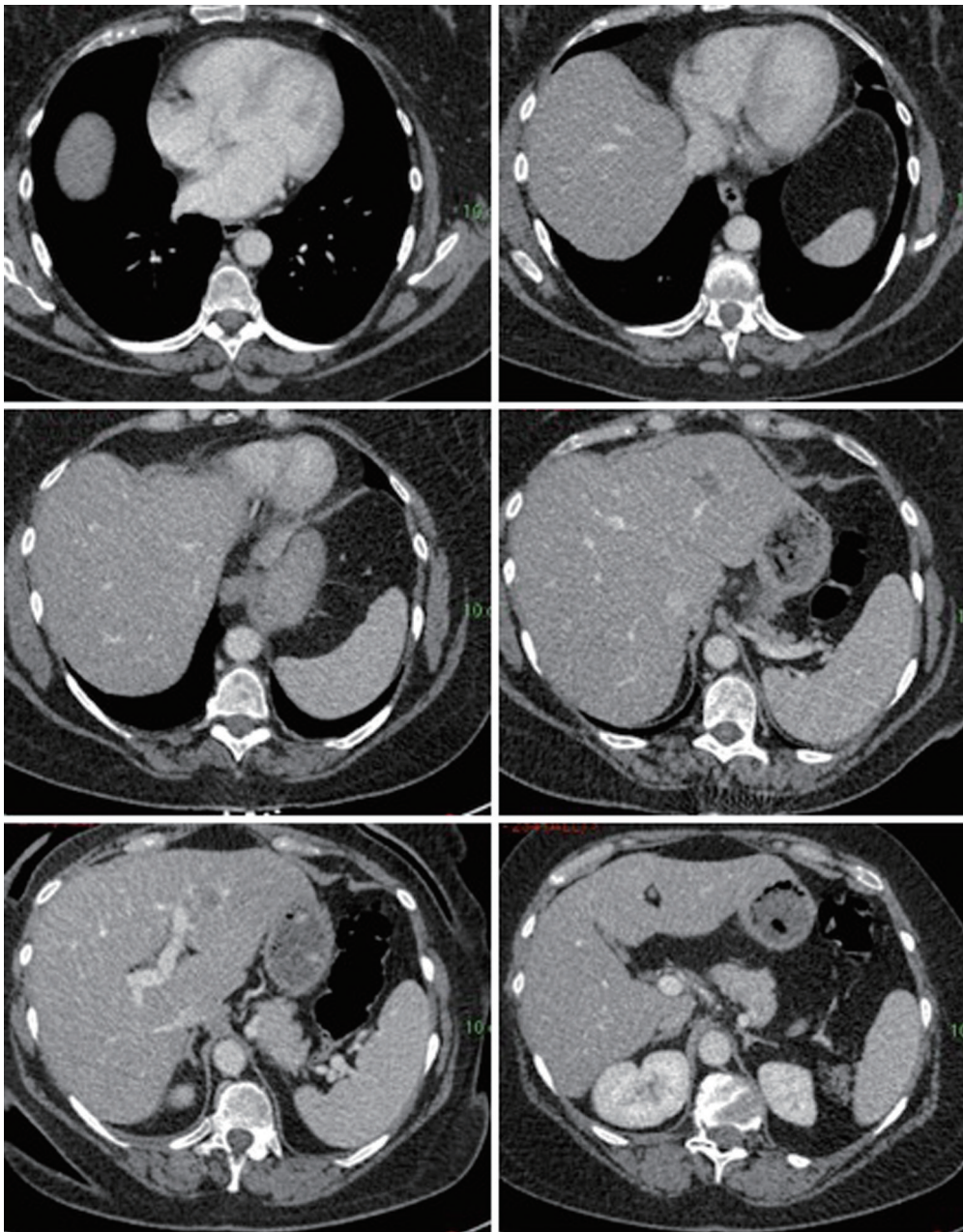


Figure 1 Preoperative triple phase CT liver in patient 1.

2 mm in diameter. No vascular occlusion was performed. A fibrin sealant patch (TachoSil®) was used to cover the transection area.

Second stage consisted of the division of right hepatic vein (RHV) and artery (RHA) and right glissonian pedicle with Vascular Endo GIA™ with removal of the right hemiliver.

Imaging

Patients were investigated with a preoperative MRI, a triple phase CT and liver volumetry preoperatively, after first stage and postoperatively as part of the follow up. Liver volumes were calculated using FIJI® CT volumetry software on the portal phase.

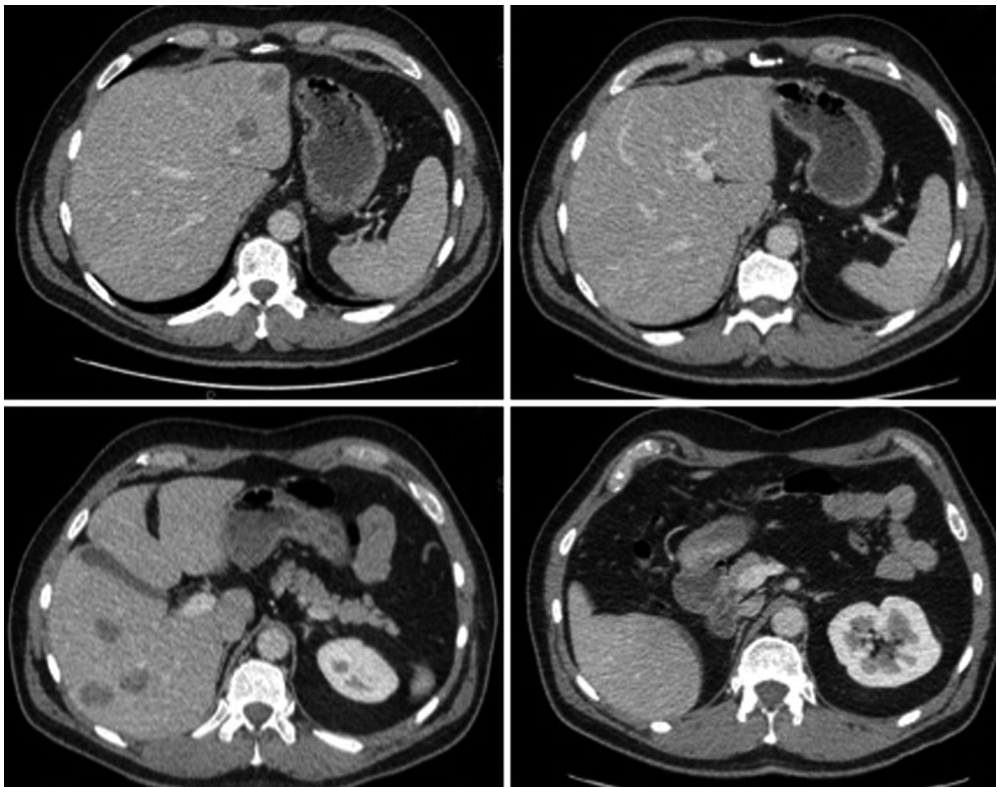


Figure 2 Preoperative triple phase CT liver in patient 2.

Results

Institutional experience

The preoperative volumetry showed total liver volumes of 1,840 and 1,634 cm³. The volume of the FLR, constituted of segment 4+1, was 255 cm³ (patient 1) and 199 cm³ (patient 2). After first stage, a significant FLR growth was observed in both patients: the CT scan prior to stage 2 showed an increase by 165% (255 to 677 cm³) and 241% (199 to 679 cm³), respectively. Second stage was performed after 9 and 14 days, respectively (*Figures 3,4*). First-stage lasted 6 and 5.5 hours in patient 1 and 2, and both had blood losses above 2,000 mL, requiring intraoperative blood transfusions. Between stages, both patients developed grade A PHLF, not requiring any change in their management. After second-stage both developed mild ascites, which recovered with conservative treatment. Both patients developed a subphrenic intraabdominal collection after second stage, and they required percutaneous drainage. These complications were scored grade IIIa Clavien-Dindo. No 90-day mortality was observed. Histopathology showed a complete resection (R0) in both cases. Both patients are

still alive after 20 and 27 months, respectively, with no evidence of recurrent disease (*Figures 5,6*).

Review of the literature

The literature search provided three results, including an original article and two case reports. Schadde *et al.* (2) analyzed retrospectively the ALPPS Registry for all monosegment ALPPS. In this series 12 patients underwent monosegment ALPPS and 6 of them were segment 4+1 ALPPS. One of the two case reports was already been included within the series published by Schadde (11). Montalvá Orón *et al.* reported the case of a 65-year-old patient with CRLM who underwent segment 4+1 ALPPS (12). *Table 1* shows intraoperative details and volumetrics for the seven cases from the literature and our two patients for comparison. Our cases had a lower baseline FLR and a higher FLR before stage 2 compared to the median values from the literature. Likewise, there was an increase in FLR/BW ratio from 0.31 to 0.84 in patient 1 and from 0.22 to 0.76 in patient 2, compared to median values of 0.42 and 0.69 respectively at baseline and prior to stage 2

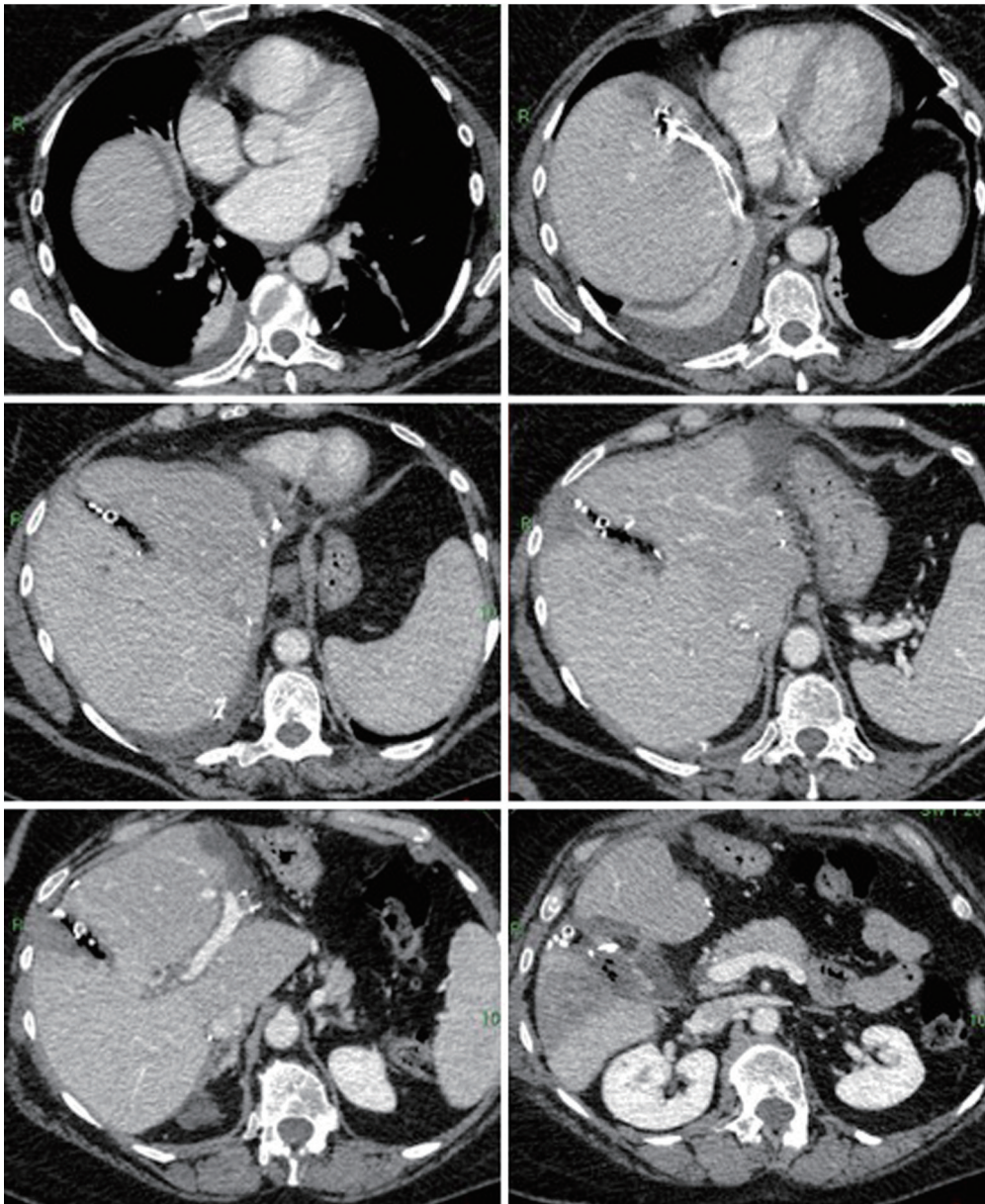


Figure 3 Before second stage triple phase CT liver showing increase of FLR in patient 1.

in the data from the literature. Median overall survival (OS) for the 7 cases reported in the literature was 13 months (range, 5–24 months). Median disease free survival (DFS) was 5 months (range, 3–23 months), as shown in *Table 2*: three out of 7 patients did not present recurrence after 5, 13 and 23 months of follow up. Three patients recurred within 6 months: two to the liver and extrahepatic recurrence and one patient with brain metastases. Another patient presented recurrent disease only after 12 months of follow up.

Discussion

The two patients presented above had extensive multifocal bilobar CRLM, presenting with more than 6 lesions distributed in less than 6 segments, but with the possibility of a complete oncological resection with negative margins (R0). Therefore, they were considered technically resectable with a two stage hepatectomy (left lobe wedge resections and right hepatectomy) or a monosegment ALPPS. A two stage hepatectomy was technically feasible but, similarly

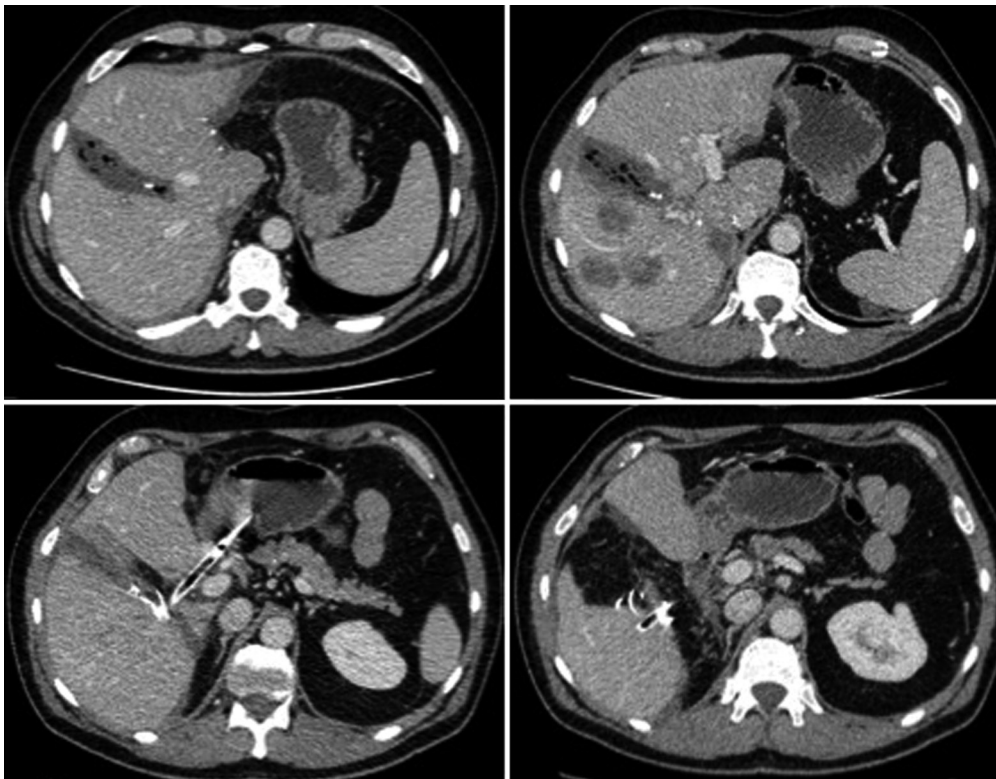


Figure 4 Before second stage triple phase CT liver showing increase of FLR in patient 2.

to the cases reported in the literature, the right hemiliver and the LLS could not be retained as part of the FLR and wedge resections of the LLS were considered oncologically inadequate. Monosegment ALPPS was chosen as a salvage procedure with the aim to avoid the risk of drop-out due to inadequate hypertrophy or progression between stages.

Monosegment 4+1 ALPPS hepatectomy in the two cases reported allowed obtaining an oncological clearance of the liver with acceptable costs in term of morbidity and good long-term outcomes.

In the literature, the technique of monosegment ALPPS resection was initially presented as a case report by De Santibanes *et al.*, and then described by Schadde *et al.* in a subanalysis of the ALPPS Registry (2,11). From a technical point of view, we used the same technique, avoiding the utilization of a plastic sheath on the transection plane and using TachoSil® instead. This decision was made to prevent the need for a surgical removal in case of impossibility to proceed to second stage.

In ALPPS the observed median kinetic growth is 0.02 sFLR per day (interquartile range, 0.01–0.03), which means that a patient with an initial FLR of 15% could achieve the

volume cut-off of 30% within 15 days after stage 1 (13). It would require about six weeks to get the same results after TSH, when the liver volume only increases by 2% per week. Furthermore, the risk of cancellation of second stage because of insufficient growth of FLR or further intra or extra-hepatic spread of the disease in the waiting time is more than 35% with TSH (2,4). Overall, ALPPS induces a growth of FLR of approximately 80% in 7 days (range, 6–13 days) with only 3% of patients not undergoing the second stage (13). In our experience of monosegment 4±1 ALPPS and in the literature, second stage was performed in all cases, achieving a complete oncological resection.

The present manuscript and the review of the literature report encouraging oncological outcomes for monosegmental 4±1 ALPPS. Considering all nine cases, overall median disease free survival was 8.5 months (3–27 months) and 5 out of 9 patients did not present any recurrence during their follow up. However, some patients recurred within 6 months with local or extrahepatic disease. Early postoperative recurrence or disease progression in less than 6 months might reflect both a failure of the treatment and a very aggressive biology of the tumor.

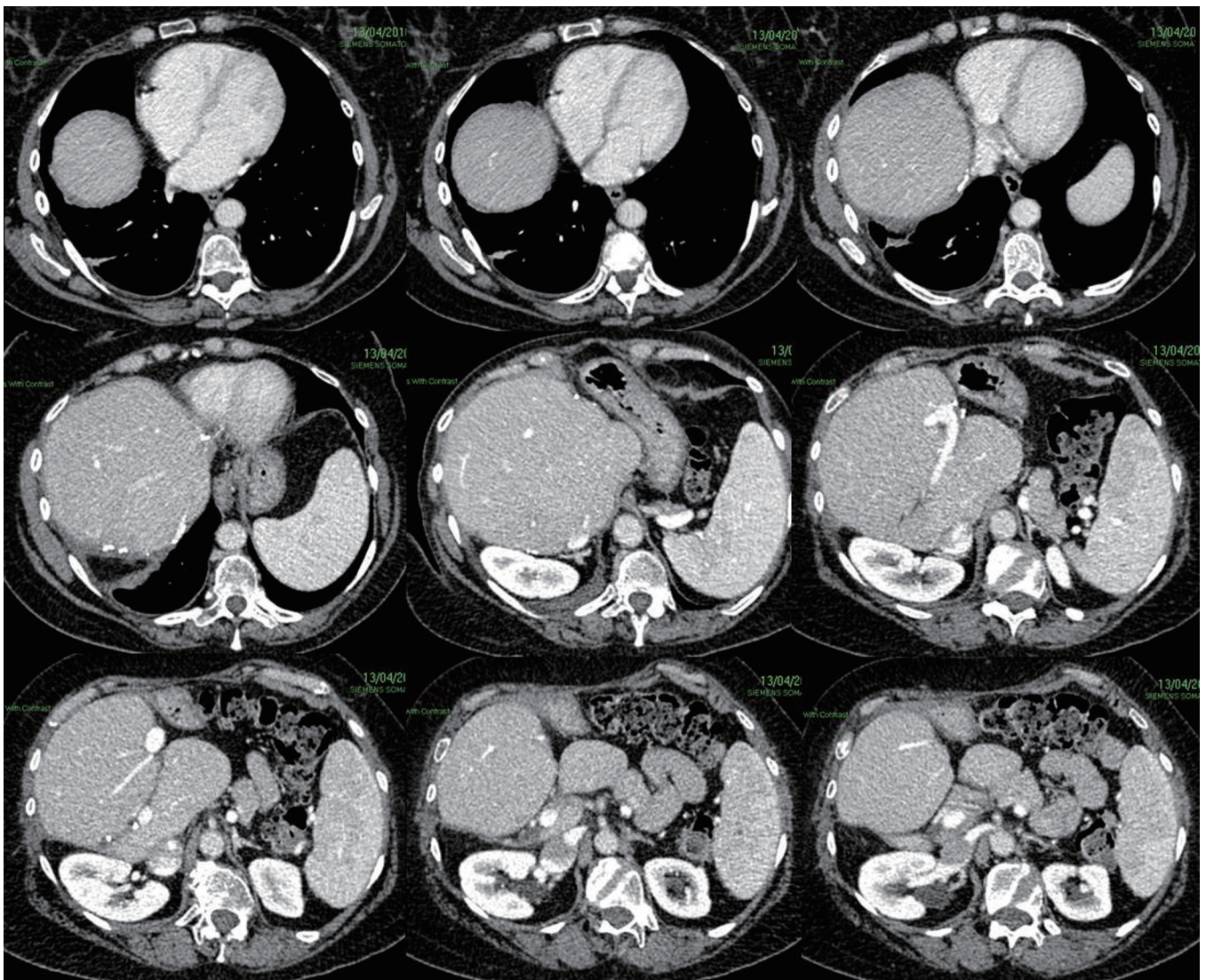


Figure 5 Patient 1 follow up triple phase CT with no evidence of recurrence.

Olthof *et al.* showed that ALPPS had the same outcomes as palliative chemotherapy in patients with at least 2 of the following criteria: ≥ 6 metastases, ≥ 2 future liver remnant metastases, ≥ 6 involved segments excluding segment 1 (14). These results might help in the selection of patients to exclude from ALPPS because of advanced disease, although our two patients met only one of the criteria. However, the number of cases is too small to draw any definitive conclusions regarding the oncological outcomes of monosegment ALPPS.

Monosegment ALPPS might prove of benefit in the future for patients with lesions in proximity of main vascular structures for which a progression in size between

stages would compromise the resection. In this group of patients, it seems reasonable to offer an operation with the highest rate of hypertrophy and a completion of stages in the shortest interval possible. Therefore, in our opinion monosegmental ALPPS may represent an appropriate option in a selected group of patients.

To date, monosegment ALPPS is not a standard technique in the treatment of bilateral CRLM. Pringle manoeuvre, diseased liver parenchyma (steatosis, fibrosis, chemotherapy-related changes) and age greater than 60 years may negatively affect kinetic growth (13) and consequently, postoperative outcomes. Bell and colleagues recently investigated the impact of advancing age on short

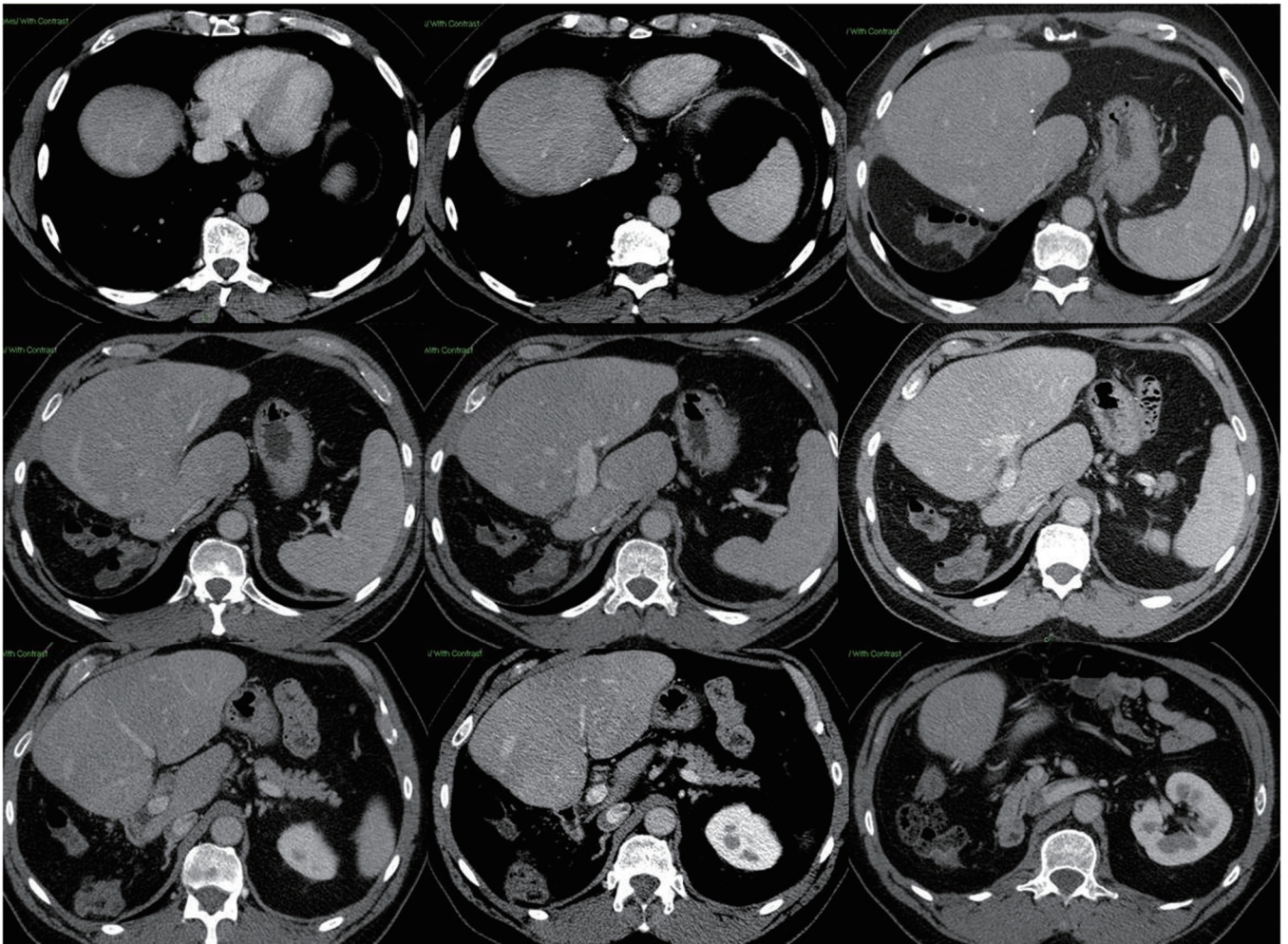


Figure 6 Patient 2 follow up triple phase CT with no evidence of recurrence.

and long term outcomes after major surgery for colorectal liver metastases. Choosing a cut off of 75 years of age, they showed that the elderly group had greater morbidity ($P=0.048$), whereas marginally statistically significant. The 90-day mortality compared to the <75 group when performing a major hepatectomy of three or more segments was similar in both groups (15). Considering the increase in life expectancy in the western population and the good functional status of many people over 60 there is an open discussion about the differences between chronological and biological age (16). Our two patients were aged 61 at the time of surgery, which is one of the risk factors identified in the ALPPS Registry for poor postoperative outcomes, but they both had a good performance status, without major cardiovascular or respiratory comorbidities to contraindicate major surgery.

Several factors such as experience of each centre, age and patients' comorbidities should be considered before choosing between TSH and Monosegment ALPPS (17,18). A recent retrospective case-match analysis of ALPPS and TSH for CRLM showed that there was no difference in feasibility and completion of treatment. ALPPS patients had a shorter interval between stages, but at the expense of increased overall and major complications. Interestingly, patients undergoing TSH who matched out from the analysis had a higher ASA score, more lesions and received less chemotherapy than the subgroup used for the matched analysis (19). Those results may confirm that, to date, ALPPS is performed in patients with better performance status and fewer comorbidities and who required more chemotherapy to achieve resectability. Therefore, even though good results have been achieved so far, prospective

Table 1 Monosegment 4+1 ALPPS hepatectomy: intraoperative characteristics and volumetry results

Authors	Patient series ID	Time stage 1 (min)	Blood loss stage 1 (mL)	Transfusion overall (yes/no)	sFLR baseline	FLR/BW ratio baseline (mL/kg)	sFLR before stage 2	FLR/BW ratio before stage 2	Days
ALPPS registry (2)	CND01_108	327	<100	No	0.15	0.33	0.28	0.62	6
	AR01_094	270	<600	Yes	0.13	0.48	0.34	0.75	10
	AR01_095	300	<600	No	0.20	0.42	0.50	1.09	12
	UK02_322	400	<600	No	0.15	0.32	0.33	0.69	13
	DE05_333	310	<1,000	No	0.20	0.40	0.34	0.69	10
	LB01_357	660	<100	Yes	0.22	0.45	0.41	0.76	6
Montalvá Orón (12)	Case 1	-	-	-	0.19	0.42	0.29	0.59	10
Summary, median		318	<100: 2	Yes: 2	0.19	0.42	0.34	0.69	10
[range]		[310-660]	>1,000: 2	No: 4	[0.13-0.22]	[0.32-0.48]	[0.28-0.50]	[0.59-1.09]	[6.0-13.0]
Present series	Patient 1	360	>2,000	Yes	0.13	0.31	0.37	0.84	9
	Patient 2	330	>2,000	Yes	0.14	0.22	0.41	0.76	14

FLR, future liver remnant; BW, body weight.

Table 2 Monosegment 4±1 ALPPS hepatectomy: postoperative short and long term outcomes

Authors	Patient series ID	Monosegment ALPPS	Morbidity (Clavien/Dindo)	PHLF (ISGLS)	90-day Mortality	OS (mo)	DFS (mo)	Type of recurrence	F/U time (mo)
ALPPS Registry (2)	CND01_108	IV	Illa	No	No	23	23	-	23
	AR01_094	IV + I	IV	No	No	13	13	-	13
	AR01_095	IV + pIII	None	No	No	5	3	Brain	4.7
	UK02_322	IV + I	II	Grade B	No	10	3	Liver	10
	DE05_333	IV + I	II	No	No	14	12	Liver, lung	14
	LB01_357	IV	I	Grade A	NR	5	5	-	5
Montalvá Orón (12)	Case 1	IV	II	Grade B	No	24	4	Liver, extrahepatic	24
Summary, median [range]						13	5		13
Present series	Patient 1	IV + I	Illa	Grade A	No	20	20	-	20
	Patient 2	IV + I	Illa	Grade A	No	27	27	-	27

PHLF, post-hepatectomy liver failure; OS, overall survival; DFS, disease free survival; F/U, follow up; mo, months.

and randomized studies are needed to clarify the criteria to select the best candidate for ALPPS.

Conclusions

Our results, along with the review of the literature, suggest that the monosegment 4±1 ALPPS procedure is feasible and effective in selected patients. Therefore, it could be a rescue option decreasing the risk of drop-out of the two stage hepatectomy.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this Case report and any accompanying images.

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