Original article

Outcome after associating liver partition and portal vein ligation for staged hepatectomy and conventional two-stage hepatectomy for colorectal liver metastases

R. Adam[1,2,4], K. Imai[1,2,5], C. Castro Benitez[1,2,4], M.-A. Allard[1,2,4], E. Vibert[1,3,4], A. Sa Cunha[1,2,4], D. Cherqui[1,3,4], H. Baba[5] and D. Castaing[1,3,4]

[1]Centre Hépato-Biliaire, Assistance Publique – Hôpitaux de Paris, Hôpital Universitaire Paul Brousse, [2]Institut National de la Santé et de la Recherche Médicale (INSERM) Unité 935, [3]INSERM Unité 785 and [4]Université Paris-Sud, Villejuif, France, and [5]Department of Gastroenterological Surgery, Graduate School of Life Sciences, Kumamoto University, Kumamoto, Japan

Correspondence to: Professor R. Adam, Centre Hépato-Biliaire Assistance Publique – Hôpitaux de Paris, Hôpital Universitaire Paul Brousse, 12 Avenue Paul Vaillant Couturier, F-94804 Villejuif, France (e-mail: rene.adam@pbr.aphp.fr)

Background: **Although associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been increasingly adopted by many centres, the oncological outcome for colorectal liver metastases compared with that after two-stage hepatectomy is still unknown.**

Methods: **Between January 2010 and June 2014, all consecutive patients who underwent either ALPPS or two-stage hepatectomy for colorectal liver metastases in a single institution were included in the study. Morbidity, mortality, disease recurrence and survival were compared.**

Results: **The two groups were comparable in terms of clinicopathological characteristics. ALPPS was completed in all 17 patients, whereas the second-stage hepatectomy could not be completed in 15 of 41 patients. Ninety-day mortality rates for ALPPS and two-stage resection were 0 per cent (0 of 17) *versus* 5 per cent (2 of 41) ($P = 0{\cdot}891$). Major complication rates (Clavien grade at least III) were 41 per cent (7 of 17) and 39 per cent (16 of 41) respectively ($P = 0{\cdot}999$). Overall survival was significantly lower after ALPPS than after two-stage hepatectomy: 2-year survival 42 *versus* 77 per cent respectively ($P = 0{\cdot}006$). Recurrent disease was more often seen in the liver in the ALPPS group. Salvage surgery was less often performed after ALPPS (2 of 8 patients) than after two-stage hepatectomy (10 of 17).**

Conclusion: **Although major complication and 90-day mortality rates of ALPPS were similar to those of two-stage hepatectomy, overall survival was significantly lower following ALPPS.**

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Introduction

Surgery is the treatment of choice for colorectal liver metastases. Only 20–30 per cent of patients are candidates for surgery[1,2]. Most patients are diagnosed with an extensive tumour burden in both lobes of the liver or have extrahepatic disease. In the past decade, more effective chemotherapy, portal vein embolization, local tumour ablation, resection of extrahepatic disease and two-stage hepatectomy, however, have increased the number of patients eligible for liver resection.

Two-stage hepatectomy was introduced in the year 2000 for patients with bilateral multinodular colorectal liver metastases[3]. Two-stage hepatectomy can achieve a 5-year survival rate of 32–64 per cent with acceptable morbidity and mortality[4–10]. However, nearly one-third of the patients in whom two-stage hepatectomy is planned do not proceed to the second stage, mainly owing to tumour progression[6–10]. Hence, survival of patients who fail to complete the second planned hepatectomy is poor and similar to that of patients treated with chemotherapy alone.

In 2012, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was reported as a novel form of two-stage hepatectomy[11]. Despite initial concerns about high morbidity and mortality, the procedure was adopted by many centres. ALPPS induces a rapid increase in volume of the future liver remnant, and shortens the interval between the first and second liver resection[12–15]. However, the optimal surgical technique and indications for ALPPS have not yet been determined, and the oncological outcome is still uncertain. The aim of

this study was to compare the outcome of ALPPS with that of two-stage hepatectomy.

Methods

Patients who underwent ALPPS or two-stage hepatectomy for colorectal liver metastases at Paul Brousse Hospital between January 2010 and June 2014 were identified from an institutional database. Two-stage hepatectomy and ALPPS were indicated in patients who presented with bilobar colorectal liver metastases that were not amenable to single-stage hepatectomy with or without portal vein embolization or local ablation therapy. ALPPS was favoured in patients with an estimated smaller liver remnant volume, compared with that in conventional two-stage hepatectomy, irrespective of other tumour or patient characteristics. Additional data on patient characteristics, treatment and morbidity were obtained from the medical records.

Two-stage hepatectomy

Details of the two-stage hepatectomy procedure have been described previously[3,8,10]. During the first stage, all metastases from the least affected liver lobe were treated and portal vein embolization was performed. Radiofrequency ablation was used only in combination with hepatectomy to treat unresectable tumours that were located in the remnant liver. In principle, the second stage was scheduled around 2 months after the first-stage hepatectomy, with chemotherapy in between to ensure control of the tumour. The second stage was postponed in patients who presented with disease progression after the first-stage hepatectomy. In these patients, systemic chemotherapy was restarted using another regimen, and the response was again evaluated to assess the possibility of performing the second-stage hepatectomy. Second-stage hepatectomy was undertaken when curative resection was deemed possible, the remaining disease was stable with chemotherapy, and the volume of future liver remnant was thought to be sufficient, as described previously[10].

Associating liver partition and portal vein ligation

During the first stage, complete clearance of tumour in the future liver remnant was performed by partial hepatectomy. The hemiliver to be resected was mobilized. After exposure of the portal vein and the artery of the liver to be removed (usually the right hemiliver), transection of the liver parenchyma was undertaken with an ultrasonic dissector and bipolar coagulation in the plane of the future hepatectomy (usually to the right of the falciform ligament). Intraoperative ligation of the portal branch and embolization was performed using dehydrated ethanol, and a Silastic® (Dow Corning, Midland, Michigan, USA) loop was placed around the remnant hepatic pedicle. After confirming sufficient hypertrophy of the future liver remnant by CT and volumetric analysis 7 days after the first stage (at least 30 per cent of non-tumoral liver parenchyma, and remnant liver to bodyweight ratio exceeding 0·5), the second stage was generally performed around 10 days after the first stage. The right hepatic artery, right biliary duct, previously ligated right portal vein and the right hepatic vein (with the middle hepatic vein if needed) were transected, and the tumour-bearing liver was removed.

Perioperative chemotherapy

All patients with initially unresectable tumours were treated with preoperative chemotherapy and the response to chemotherapy was evaluated with CT using Response Evaluation Criteria in Solid Tumors (RECIST) after every four cycles[16]. In patients scheduled for two-stage hepatectomy, interval chemotherapy was generally administered 3 weeks after the first hepatectomy, using the same regimen as before surgery when a tumour response had been observed. In patients who had signs of disease progression after the first-stage hepatectomy, the second stage was postponed and chemotherapy initiated using another regimen, followed by a re-evaluation. The second-stage hepatectomy was undertaken only if complete tumour resection was feasible, the remaining disease was controlled by chemotherapy (complete/partial response or stable disease), and the volume of the future liver remnant was sufficient.

Postoperative chemotherapy was recommended after a completed two-stage hepatectomy and ALPPS. Treatment strategies were discussed in a weekly multidisciplinary tumour board meeting including surgeons, medical oncologists, pathologists and radiologists.

Follow-up

Postoperative complications were classified according to Dindo and colleagues[17]. A major complication was defined as any complication of grade III or higher. After discharge, all patients were seen at the outpatient clinic at regular intervals, and CT of chest and abdomen were done every 4 months. Recurrences were amenable to surgery in selected patients, only when curative treatment was deemed possible often in combination with chemotherapy. The last date of follow-up and survival status was checked by contacting the patient's general practitioner.

Table 1 Clinicopathological characteristics

	ALPPS ($n = 17$)	TSH ($n = 41$)	P‡
Age (years)*	58 (23–75)	58 (32–75)	0·905§
Sex ratio (M : F)	12 : 5	23 : 18	0·299
ASA fitness grade			0·376
I	2	4	
II	11	33	
III	4	4	
T category of colorectal tumour			0·529
T1–2	1	4	
T3–4	15	30	
Missing	1	7	
N category of colorectal tumour			0·962
N0	3	6	
N1–2	13	27	
Missing	1	8	
Site of primary tumour			0·419
Colon	13	27	
Rectum	4	14	
Timing of liver metastases			0·593
Synchronous†	15	38	
Metachronous	2	3	
No. of liver lesions at diagnosis*	10 (3–20)	10 (2–35)	0·368§
Tumour size at diagnosis (mm)*	40 (13–145)	50 (10–150)	0·383§
Tumour number at hepatectomy*	8 (3–32)	10 (3–30)	0·391§
Tumour size at hepatectomy (mm)*	38 (8–140)	43 (10–140)	0·263§
CEA at diagnosis (ng/ml)*	82 (3–10 271)	88 (2–37 270)	0·527§
CEA at hepatectomy (ng/ml)*	8 (1–1195)	7·9 (0·5–940)	0·856§
ICG-R15 (%)*	8·5 (1·3–21)	9·3 (2·1–31)	0·704§
Preoperative chemotherapy	17	41	
No. of chemotherapy cycles*	8 (4–37)	11 (4–32)	0·884§
No. of chemotherapy lines*	1 (1–4)	1 (1–4)	0·882§
First-line regimen			
Oxaliplatin	11	24	
Irinotecan	4	14	
Both	2	3	
Other	0	0	
Second-line regimen			
Oxaliplatin	1	4	
Irinotecan	3	8	
Both	1	4	
Other	1	1	
Third-line regimen			
Oxaliplatin	1	1	
Irinotecan	1	2	
Both	1	1	
Other	0	1	
Use of biological agents	15	39	0·367
Disease progression during first line	2	4	0·586
Disease progression during final line	0	0	1·000
Concomitant extrahepatic disease	6	12	0·654
Lung	3	8	
Lung + lymph node	1	1	
Lung + ovary	1	0	
Lymph node	1	2	
Peritoneum	0	1	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Diagnosed before, during or within 3 months after colorectal resection. ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; TSH, two-stage hepatectomy; CEA, carcinoembryonic antigen; ICG-R15, indocyanine green retention rate at 15 min. ‡χ^2 test, except §Mann–Whitney U test.

Statistical analysis

Continuous variables are expressed as median (range), with analysis using the Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test. Survival curves were computed by the Kaplan–Meier method and groups compared using Cox regression. Overall survival was calculated by using the date of diagnosis of liver metastasis or the date of first-stage hepatectomy until death (event) or date of last follow-up (censored). Disease-free survival was defined as the time between the date of last hepatectomy and the first recurrence or death. For the analysis, the two-stage hepatectomy group included patients who completed two-stage hepatectomy as well as those who underwent only the first stage. All statistical analyses were carried out using the JMP® software program (SAS Institute, Cary, North Carolina, USA). $P < 0{\cdot}050$ was considered statistically significant.

Results

Between January 2010 and June 2014, 248 patients underwent surgery for colorectal liver metastases. Some 17 patients underwent ALPPS and 41 patients had a two-stage hepatectomy (including 15 who did not undergo the second stage) (*Table 1*). There were no significant differences

Table 2 Operative details

	ALPPS ($n = 17$)	TSH ($n = 41$)	P‡
Percentage of estimated FLR before first stage (%)*	24 (11–38)	30 (19–53)	0·056§
Percentage of estimated FLR before second stage (%)*	36 (26–49)	40 (25–55)	0·122§
Portal vein embolization	17	38	0·143
First stage	$n = 17$	$n = 41$	
RFA	1	6	0·323
Anatomical resection	1	10	0·024
Vascular clamping	16	23	0·002
Duration of clamping (min)*	18 (11–66)	33 (14–61)	0·358§
Duration of surgery (min)*	404 (260–668)	337 (190–700)	0·054§
Blood loss (ml)*	600 (300–2000)	200 (100–1700)	< 0·001§
Red blood cell transfusion	4	2	0·044
No. of tumours treated*†	2 (0–7)	4 (1–18)	0·040§
Liver resection margin			0·104
R0	9	10	
R1	7	25	
R_{rfa}	1	6	
Interval chemotherapy	0	35	< 0·001
Time interval between stages (days)*	12 (9–39)	103 (19–450)	< 0·001§
Second stage	$n = 17$	$n = 26$	
RFA	0	1	0·312
Anatomical resection	17	25	0·312
Vascular clamping	1	22	< 0·001
Duration of clamping (min)*	17 (17–17)	52 (12–100)	0·152§
Duration of surgery (min)*	243 (138–540)	385 (190–610)	0·002§
Blood loss (ml)*	500 (50–3100)	700 (170–4000)	0·170§
Red blood cell transfusion	4	8	0·602
No. of tumours treated*†	8 (1–25)	6 (2–15)	0·533§
Liver resection margin			0·423
R0	6	13	
R1	11	12	
R_{rfa}	0	1	
Total (completed)	$n = 17$	$n = 26$	
Duration of surgery (min)*	615 (488–1208)	655 (230–1062)	0·282§
Blood loss (ml)*	1100 (450–4800)	500 (100–4400)	0·012§
Red blood cell transfusion	5	9	0·721
No. of tumours treated*†	9 (2–32)	8 (1–30)	0·364§
Resection margin			0·668
R0	2	5	
R1	14	18	
R_{rfa}	1	3	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Including tumours treated with radiofrequency ablation (RFA). ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; TSH, two-stage hepatectomy; FLR, future liver remnant; R_{rfa}, treated with radiofrequency ablation. ‡χ^2 test, except §Mann–Whitney *U* test.

between the two groups in terms of clinicopathological characteristics, preoperative chemotherapy regimen and extrahepatic disease.

Operative details

The percentage of estimated functional liver reserve before the first- and second-stage operation was not significantly different between the groups (*Table 2*). At the first stage, anatomical resections were performed more frequently and vascular clamping less frequently, in the two-stage hepatectomy group. Longer operating times, greater blood loss and more red blood cell transfusions were seen in the ALPPS group. The median (range) number of tumours treated by resection or ablation at the first stage was significantly greater in two-stage hepatectomy group than in the ALPPS group: 4 (1–18) *versus* 2 (0–7) respectively ($P = 0{\cdot}040$).

Postoperative outcome

ALPPS was completed in all patients, whereas 15 of 41 patients in the two-stage hepatectomy group did not proceed to the second stage, mostly owing to disease progression, insufficient functional liver remnant, portal vein thrombosis or death (*Table S1*, supporting information). The rate of minor complications was significantly higher in the ALPPS than in the two-stage hepatectomy group: 59 per cent (10 of 17) *versus* 15 per cent (6 of 41) ($P = 0{\cdot}001$) respectively. There was no significant different in the percentage of major complications between groups: 41 per cent (7 of 17) after ALPPS *versus* 39 per cent (16 of 41) following two-stage hepatectomy ($P = 0{\cdot}999$) (*Table S1*, supporting information).

Recurrence

In the ALPPS group, six of 17 patients did not undergo complete hepatic and extrahepatic tumour removal (*Table 3*). Eight patients had a recurrence within 12 months after surgery. In the two-stage hepatectomy group, complete tumour resection could not be achieved in 18 of 41 patients, and 17 patients developed recurrence. Recurrence in the liver was more frequent after ALPPS than after two-stage hepatectomy (8 of 8 *versus* 9 of 17 patients respectively; $P = 0{\cdot}005$).

Survival

By 1 January 2015, seven of 17 patients in the ALPPS group had died, seven were alive with disease and three were alive without disease (*Fig. S1*, supporting information). In the two-stage hepatectomy group, 11 of 41 patients had died, 20 patients were alive with disease and ten patients were alive without disease.

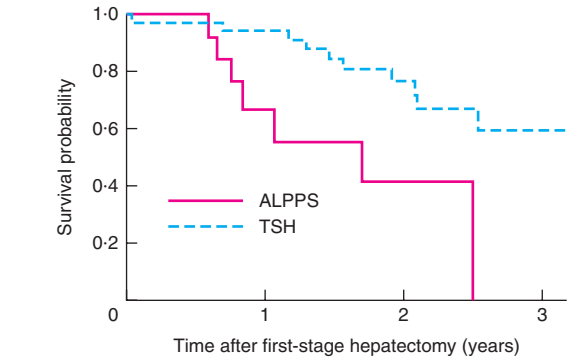
Table 3 Curability of surgery and recurrence

	ALPPS ($n = 17$)	TSH ($n = 41$)	P*
Complete tumour removal	11	23	0·542
Reason for non-curability			
Failure of second stage	0	15	
Concomitant extrahepatic disease not resected	4	2	
Primary tumour not resected	2	1	
Recurrence	8	17	
Recurrence within 12 months	8	12	
First recurrence (single or multiple sites)			0·289
Single site	5	14	
Liver	5	6	
Lung	0	6	
Colorectal local	0	1	
Peritoneum	0	1	
Multiple sites	3	3	
Liver + lung	1	2	
Liver + lymph node	1	1	
Liver + peritoneum	1	0	
Liver	8	9	0·005
Lung	1	8	0·077
No. of recurrent tumours	3	3	0·901†
Size of largest recurrent tumour (mm)	22	13	0·041†
Repeat surgery for recurrence	2	10	0·073
Hepatectomy	1	6	
Hepatectomy + lymphadenectomy	0	1	
Radiofrequency ablation	1	0	
Resection of extrahepatic recurrence	0	3	

ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; TSH, two-stage hepatectomy. *χ^2 test, except †Mann–Whitney *U* test.

Median (range) follow-up in the ALPPS and two-stage hepatectomy groups was 20 (6–50) and 30 (7–68) months respectively after diagnosis of liver metastases. Overall survival after the first-stage hepatectomy was significantly lower after ALPPS than two-stage hepatectomy group (2-year overall survival: 42 *versus* 77 per cent; median survival 20 *versus* 37 months; hazard ratio (HR) 3·73, 95 per cent c.i. 1·36 to 10·24; $P = 0{\cdot}006$) (*Fig. 1a*). Two-year overall survival after diagnosis of liver metastasis was also significantly lower in the ALPPS group: 72 per cent *versus* 95 per cent for two-stage hepatectomy (HR 3·42, 1·25 to 9·36; $P = 0{\cdot}017$) (*Fig. S2*, supporting information).

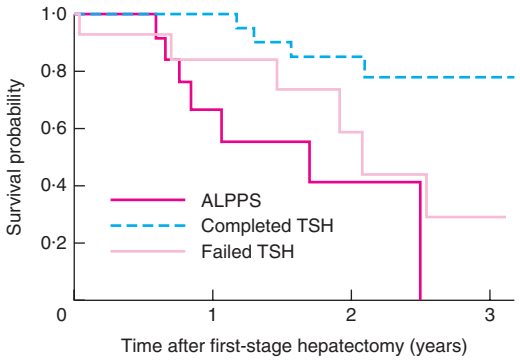
When the two-stage hepatectomy group was stratified into two-stage completed and two-stage failed, overall survival was significantly worse for the failed two-stage hepatectomy group than the completed group (HR 3·75, 1·05 to 13·39; $P = 0{\cdot}041$). Overall survival for the failed two-stage hepatectomy group was not significantly different from that for the ALPPS group (HR 1·91, 0·59 to 6·15;



No. at risk

ALPPS	17	6	2	0
TSH	41	31	16	5

a ALPPS *versus* TSH

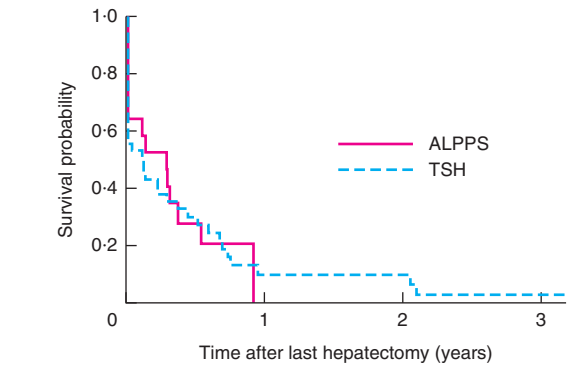


No. at risk

ALPPS	17	6	2	0
Completed TSH	26	22	12	4
Failed TSH	15	9	4	1

b ALPPS *versus* completed TSH *versus* failed TSH

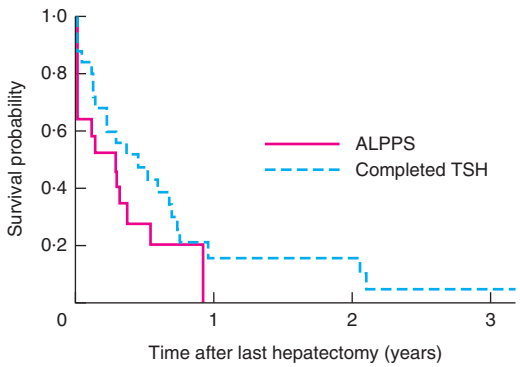
Fig. 1 Overall survival after first-stage hepatectomy: **a** patients who underwent associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) or two-stage hepatectomy (TSH); **b** patients who underwent ALPPS or TSH stratified by completed or failed TSH. **a** $P = 0{\cdot}006$; **b** $P = 0{\cdot}041$ (completed *versus* failed TSH), $P = 0{\cdot}004$ (ALPPS *versus* completed TSH), $P = 0{\cdot}269$ (ALPPS *versus* failed TSH) (Cox regression)



No. at risk

ALPPS	17	0	0	0
TSH	41	3	3	1

a ALPPS *versus* TSH



No. at risk

ALPPS	17	0	0	0
Completed TSH	26	3	3	1

b ALPPS *versus* completed TSH

Fig. 2 Disease-free survival: **a** patients who underwent associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) or two-stage hepatectomy (TSH); **b** patients who underwent ALPPS or completed TSH. **a** $P = 0{\cdot}843$; **b** $P = 0{\cdot}206$ (Cox regression)

$P = 0{\cdot}269$) (*Fig. 1b*). For ALPPS *versus* completed two-stage resection the HR was 6·17 (1·77 to 21·53; $P = 0{\cdot}004$).

Disease-free survival was not significantly different between the ALPPS and two-stage hepatectomy groups (1-year disease-free survival: 0 and 10 per cent respectively; HR 0·94, 0·51 to 1·73; $P = 0{\cdot}843$) (*Fig. 2a*). Disease-free survival for the ALPPS group was also comparable to that of the completed two-stage hepatectomy group (HR 1·56, 0·78 to 3·14; $P = 0{\cdot}206$) (*Fig. 2b*).

Discussion

Although the major complication and 90-day mortality rates of ALPPS were similar to those of two-stage hepatectomy, overall survival was significantly worse after ALPPS. Completion of the ALPPS procedure did not seem to translate into a better oncological outcome compared with the results of two-stage hepatectomy.

The main drawback of conventional two-stage hepatectomy is drop-out after the first stage. In the present study,

15 of the 41 patients in whom two-stage hepatectomy was planned eventually did not proceed to the second stage. As the main reason for this was disease progression, the way to prevent drop-out may be better patient selection and/or interval chemotherapy between the two stages. However, the role of interval chemotherapy is still unclear, and prolonged chemotherapy might cause liver injury leading to higher complication rates[18–20].

The main advantages of ALPPS are the rapid and greater increase of future liver remnant volume, and therefore a shorter interval between the two stages. The percentage increased future liver remnant volume has been reported to range from 63 to 87 per cent[11], and the kinetic growth rate from 22 to 34·8 ml/day[13,15], with an interval of 7–13 days between the stages. Rapid future liver remnant hypertrophy and subsequent shorter intervals between the two stages lead to higher feasibility rates, reaching 97 per cent[21].

However, ALPPS is still evolving and the oncological long-term outcome after this procedure has not yet been determined. Previous studies[22–25] have demonstrated that stimulation of liver hypertrophy could also accelerate tumour progression after portal vein embolization. Oldhafer and colleagues[26] recently reported early tumour recurrence with disease progression after ALPPS for colorectal liver metastases. In the present study, overall survival was significantly worse after ALPPS than after two-stage hepatectomy. Of note, overall survival for the ALPPS group was comparable to that of patients who underwent two-stage hepatectomy but failed to complete the planned procedure.

The recurrence and disease-free survival rates after ALPPS and two-stage hepatectomy are comparable, and do not account for the worse survival after ALPPS. There are three possible explanations for this observation. The size of recurrent tumour was significantly larger after ALPPS than after two-stage hepatectomy, suggesting a more aggressive biological behaviour. Recurrence in the liver was more frequently observed after ALPPS than following two-stage hepatectomy. Conversely, lung metastases were more common after two-stage hepatectomy. Previous studies have shown that lung metastases are less aggressive compared with liver recurrence and could be associated with more favourable survival after hepatectomy[27,28] or liver transplantation[29] for colorectal liver metastases. Finally, in the ALPPS group only two of eight patients who developed recurrence were able to undergo repeat surgery (*Table 3*), whereas 10 of 17 patients in the two-stage hepatectomy group underwent salvage surgery. It might be more difficult to perform salvage surgery for recurrence after ALPPS, leading to worse survival of these patients. More rapid and aggressive recurrence after an ALPPS procedure could explain the poor survival in this group. In all patients with recurrence the disease recurred within 12 months after ALPPS. In contrast, only 12 of 17 patients in the two-stage hepatectomy group developed a recurrence within 12 months after surgery. The fast induction of hypertrophy of the liver that occurs after the ALPPS may trigger residual tumour cell progression, whereas the interval between the two stages in conventional two-stage hepatectomy may serve as a selection tool to identify patients who will not benefit from these aggressive strategies[30].

The high initially reported mortality rate of 12 per cent[11] led to the safety of the ALPPS procedure being challenged. The international ALPPS registry reported that the 90-day mortality rate was 9 per cent and the major complication rate (Clavien grade at least IIIa) was 40 per cent[31]. Recently, Alvarez and colleagues[32] reported the experiences of 30 series of ALPPS, with a major complication rate of 43 per cent and a 90-day mortality rate of 7 per cent. In the present study, there were no deaths within 90 days of ALPPS and the major complication rate was 41 per cent. These results are comparable to those of two-stage hepatectomy. The favourable postoperative short-term outcome of ALPPS suggests that it should no longer be considered a more risky procedure than two-stage hepatectomy, despite a higher minor complication rate.

The retrospective data analysis and small sample size from a single institution are the main limitations of the present study. In addition, as ALPPS is a recently introduced novel strategy, follow-up is still insufficient for conclusions to be drawn regarding long-term outcome. Furthermore, all the patients in this study had an extensive tumour load with a median of eight tumours and a median tumour size of 38 mm, even after intensive chemotherapy (median 8 cycles). This should be taken into account when comparing the results of the present study with those from other institutions.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Postoperative complications (Word document)

Fig. S1 Outcomes for patients who underwent associating liver partition and portal vein ligation for staged hepatectomy (Powerpoint file)

Fig. S2 Overall survival after diagnosis of liver metastasis for patients who underwent associating liver partition and portal vein ligation for staged hepatectomy and two-stage hepatectomy (Powerpoint file)