Original article

Associating portal embolization and artery ligation to induce rapid liver regeneration in staged hepatectomy

A. Dupré[1,2], M. Hitier[1], P. Peyrat[1], Y. Chen[1], P. Meeus[1] and M. Rivoire[1,2,3]

[1]Department of Surgical Oncology, Léon Bérard Cancer Centre , [2]Institut National de la Santé et de la Recherche Médicale, U1032, LabTau, and [3]Université de Lyon, Lyon, France

Correspondence to: Dr A. Dupré, Department of Surgical Oncology, Léon Bérard Cancer Centre, 28 Rue Laennec, 69008 Lyon, France (e-mail: aurelien.dupre@lyon.unicancer.fr)

Background: **Insufficient volume of the future liver remnant (FLR) is a major cause of unresectability in patients with bilobar colorectal liver metastases (CLM). The objective of this study was to evaluate the safety and efficacy of the novel associating portal embolization and artery ligation (APEAL) technique before extended right hepatectomy during a two-stage procedure for CLM.**

Methods: **All patients who had undergone extended right hepatectomy during two-stage surgery for CLM between 2012 and 2014 were identified retrospectively from a prospectively maintained database. In the first stage, right portal vein embolization, partial right hepatic artery ligation and devascularization of segment IVb along the round ligament without parenchymal transection were associated with clearance of the FLR and/or primary tumour resection. Liver volumetry was performed using OsiriX software on postoperative day (POD) 7 and 30.**

Results: **Ten patients underwent the APEAL procedure. During the first stage, APEAL was combined with colorectal resection in seven patients. The median (range) interval between the two stages was 45 (31–71) days. The FLR volume increased from 327 (214–537) cm^3 before surgery to 590 (508–1072) cm^3 on POD 7 and 701 (512–1018) cm^3 on POD 30. This corresponded to a FLR regeneration rate of 104 (42–185) and 134 (53–171) per cent respectively. There were no deaths. The overall morbidity rate was 60 per cent (6 of 10) after each procedure, with severe morbidity occurring in two and three of ten patients after the first and second procedures respectively.**

Conclusion: **APEAL induces fast, safe, reproducible and effective FLR growth when an extended right hepatectomy is scheduled in patients with multiple bilobar CLM.**

Paper accepted 18 June 2015

Published online 16 September 2015 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9900

Introduction

Liver surgery for colorectal liver metastases (CLM) has become increasingly common over the past two decades. This is explained in part by progress in chemotherapy and the use of targeted agents, but also by the fact that resection offers the possibility of cure in patients with metastases confined to the liver[1]. Equally, liver resection has become a safe procedure. Because response to medical therapy correlates with resectability[2], multidisciplinary management is the key. Although the assessment of resectability remains subjective[3], the major barrier to achieving an R0–R1 resection is insufficient volume of the future liver remnant (FLR). Several approaches have been used in attempts to overcome this limitation. These include combining radiofrequency ablation with surgery[4], portal vein embolization (PVE) and two-stage hepatectomy[5].

Achieving a sufficient volume of FLR is particularly problematic in multiple bilobar unresectable CLM because the FLR has to be cleared of metastases before inducing its regeneration by PVE. When the FLR consists of segments II and III (± segment I), right PVE may be insufficient to induce consistent FLR growth[6]. Two methods have been used in an attempt to deal with this problem. The first is postoperative percutaneous PVE of the right portal vein and segment IV branches, and then extended right hepatectomy at least 3 weeks later[7]. The second technique, published recently[8], is associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) 10 days before an extended right hepatectomy. These two options

are effective in inducing regeneration of the FLR. However, both have major drawbacks. Right + segment IV PVE is a technically demanding procedure even in the hands of a highly experienced radiologist, and ALPPS is associated with high rates of severe morbidity (40 per cent)[8] and mortality (up to 15 per cent)[9].

Techniques currently used to induce growth of the FLR are based on PVE. However, interrupting hepatic arterial blood flow before liver surgery to induce liver regeneration has also been explored using transarterial (chemo)embolization in hilar cholangiocarcinoma[10] and hepatocellular carcinoma[11–16].

This article reports a new method for inducing rapid growth of the FLR during two-stage hepatectomy requiring an extended right hepatectomy at the second stage. The novel concept is to associate, during the first stage, PVE with partial right hepatic artery ligation and ligation of the glissonian branches of segment IVb along the round ligament without parenchymal transection. The acronym APEAL (associating portal embolization and artery ligation) is proposed for this new procedure. The aim of this study was to evaluate the safety of the technique and to assess its effectiveness in inducing FLR growth.

Methods

All those who underwent a two-stage procedure with concomitant partial hepatic artery ligation and PVE in the first stage, and an extended right hepatectomy in the second stage, between December 2012 and April 2014, were identified from a prospective database of patients who received surgical management for liver metastases. This technique was proposed as an alternative to ALPPS for patients with at least two of the following criteria: very small FLR volume (segments II + III ± I), metastases in this FLR, and a primary tumour to be resected. These patients had unresectable bilobar liver metastases despite induction chemotherapy. During multidisciplinary team meetings that included at least one liver surgeon and one liver radiologist, unresectability was defined strictly as the inability to treat all metastases in a single procedure while leaving sufficient FLR. The main causes of unresectability were unfavourable location (tumour contiguous with at least 2 hepatic veins and the inferior vena cava or both sides of the liver hilum) and/or insufficient liver remnant and/or large multinodular metastases involving five or more liver segments. Pulmonary metastases, if fewer than three, were not a contraindication to two-stage hepatectomy. As this was a retrospective study, consent was not obtained from the patients. According to French law no formal ethics approval was required for this study.

Preoperative evaluation

All patients were evaluated before operation with chest and abdominal CT, liver MRI and PET–CT (at initial referral) to complete evaluation and to exclude extrahepatic disease. Response to chemotherapy was evaluated by CT every four to six cycles.

Chemotherapy

Perioperative chemotherapy included interval chemotherapy between the two stages. At the time of initial referral to the authors' institution, patients had the opportunity to enrol in a clinical trial testing conversion chemotherapy associated with targeted therapies (NCT01442935). The possibility of any form of surgery was envisaged in this trial. The regimens comprised use of folinic acid and 5-fluorouracil (5-FU) combined with oxaliplatin (FOLFOX), irinotecan (FOLFIRI) or both (FOLFIRINOX or FOLFOXIRI). These regimens could be given in combination with bevacizumab or cetuximab, depending on *RAS* status. All patients with rectal cancer received neoadjuvant radiotherapy with 25 Gy over 5 days after induction chemotherapy.

Surgical procedure

Operations were performed through a right J-shaped laparotomy or midline incision. Antibiotics were administered following guidelines on antimicrobial prophylaxis. After dissecting the round hepatic and falciform ligaments, palpation and intraoperative liver ultrasonography were used to detect occult liver tumours, and to assess the relationship between liver tumours and intrahepatic vascular structures.

The first stage consisted of clearing the FLR with non-anatomical parenchyma-sparing resection. Focal destruction of small and deeply located metastases was associated with resection. The right portal vein was embolized with *n*-butyl-2-cyanoacrylate glue (Histoacryl®; Braun Medical, Aesculap, Tuttlingen, Germany) mixed with iodized oil (Lipiodol®; André Guerbet, Aulnay-sous-Bois, France) before being ligated and transected. The right hepatic artery was dissected up to its bifurcation by an extrahepatic hilar approach, without parenchymal transection, and its branches were taped. The artery for segments V–VIII or segments VI–VII was ligated depending on the predefined strategy. Ligation of the right anterior artery was favoured, unless there was a huge tumour burden in segments VI–VII. The right hepatic artery remained taped to facilitate its identification during the second stage. An additional procedure was undertaken to devascularize segment IV. The segment IVb glissonian branches (portal and

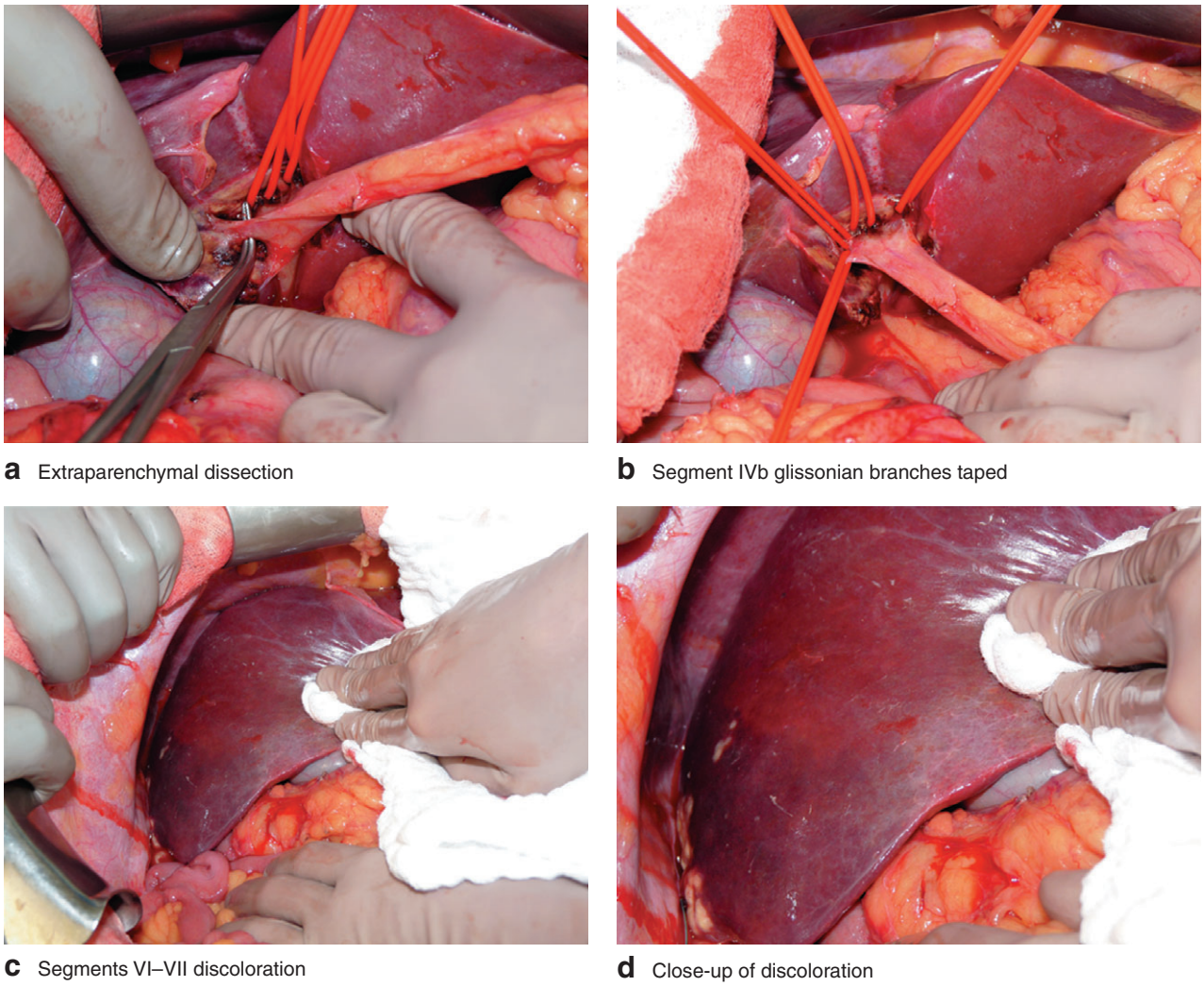

Fig. 1 Operative view of segment IV devascularization in the associating portal embolization and artery ligation technique: **a** dissection of segment IVb glissonian branches arising from the right side of the round hepatic ligament, without any transection; **b** the branches are taped close to their origin (before ligation); **c** and **d** discoloration of segments VI and VII

arterial branches, and biliary duct) arising from the right side of the round hepatic ligament were ligated close to their origin. As many branches as possible were ligated without any liver transection (*Fig. 1*).

Digestive procedures were performed after liver surgery. A diverting loop ileostomy was created in patients with postradiotherapy proctectomy. Before wound closure, four sheets of hyaluronic acid and carboxymethylcellulose membranes were applied around the liver[17].

The second stage was undertaken 1–2 months later with the intent to achieve an R0 resection. Transection of the liver parenchyma was carried out using the crushing Kelly clamp technique, clips and water bipolar forceps. Finally, intermittent clamping of the liver pedicle for 15 min, interrupted for 5 min (Pringle manoeuvre), was used to reduce blood loss.

Liver volumetry and assessment of liver regeneration

Liver regeneration was assessed by volumetry and measurement of biochemical variables (prothrombin time (PT) and total bilirubin). Preoperative hepatic functional reserve was not assessed.

Liver volumetry was performed on CT images with the image processing software OsiriX (Pixmeo, Bernex, Switzerland). The FLR volume, tumour volume and whole liver volume were determined. Total liver volume (TLV)

referred to whole liver volume minus tumour volume. The ratios of FLR (segments II and III ± segment I) to TLV and bodyweight (BW) were calculated for each patient. Liver regeneration after the first stage was assessed on postoperative day (POD) 2, POD 7 and POD 30. At each time point, the FLR and BW ratios, the increase in volume and FLR regeneration rate were calculated. The FLR regeneration rate was calculated as: increase in volume/initial FLR volume.

Outcomes and follow-up

Clinical and surgical findings during the first and second procedures were recorded. Preoperative and postoperative laboratory tests included complete blood cell count, levels of aspartate (AST) and alanine (ALT) aminotransferase, blood urea nitrogen, serum creatinine, C-reactive protein and bilirubin, and coagulation. Postoperative 30- and 90-day morbidity and mortality were recorded, and postoperative complications were graded using the classification of Dindo *et al.*[18]. Fever under 38·5°C was not considered a complication provided samples for bacteriological testing were negative and no antibiotics were administered. Acute renal injury was defined by a twofold increase in serum creatinine level, and acute renal failure by a threefold increase[19]. Postoperative liver failure was defined by a PT value below 50 per cent and a serum bilirubin concentration exceeding 50 μmol/l on POD 5[20], and/or by a postoperative peak bilirubin value of at least 120 μmol/l[21], and/or by grade C liver failure as defined by the International Study Group of Liver Surgery[22]. The first outpatient visit was scheduled at 1 month after the second operation. Follow-up consisted of physical examination and blood sampling with CT, every 3 months.

Statistical analysis

Continuous data are presented as median (range). Overall survival was calculated from the date of the second procedure to the date of death from any cause or date of last follow-up (censored observation). The Wilcoxon matched-pairs signed-rank test was used to evaluate differences from baseline in each patient and for comparison of median volumetry values. $P < 0{\cdot}050$ was considered significant. Statistical analysis was carried out using R software version 2.11 (R Project for Statistical Computing, Vienna, Austria).

Results

During the study interval, ten consecutive patients required right hepatectomy extended to segment IV ± I during a two-stage procedure (*Table 1*). All patients had concomitant partial interruption of arterial and portal blood flow and devascularization of segment IVb at the first procedure.

Table 1 Patient demographics and tumour characteristics

	No. of patients* ($n = 10$)
Age (years)†	60 (43–74)
Sex ratio (M : F)	9 : 1
Body mass index (kg/m^2)†	26·7 (20·3–32·1)
Primary tumour site	
Right colon	2
Left colon	4
Rectum	3
Pancreas (neuroendocrine tumour)	1
Node-positive primary	9
CEA level (μg/l)†	31 (2–979)
Timing of metastases	
Synchronous	9
Metachronous (>12 months)	1
No. of metastases†	9 (1–20)
Size of largest metastasis (mm)†	80 (20–140)
No. of metastases in FLR†	1 (0–6)
Size of largest metastasis in FLR (mm)†	29 (10–70)
Extent of disease in segment IV	
No. of metastases†	1 (0–2)
Contiguity with 2 hepatic veins and IVC	4
Total size of isolated metastases (mm)†	11 (0–50)
Patients with metastases no longer visible on imaging	4
Lung metastases	2

*Unless indicated otherwise; †values are median (range). CEA, carcinoembryonic antigen; FLR, future liver remnant; IVC, inferior vena cava.

With the exception of one patient, with liver metastases from a pancreatic neuroendocrine tumour, all had CLM. If the primary tumour was still in place (7 patients), it was resected during the first stage of liver surgery. One patient had a suspected splenic metastasis not confirmed at pathological examination of the spleen.

All patients underwent preoperative chemotherapy. One patient had preoperative rectal radiotherapy before the first procedure. Three patients were included in a clinical trial testing conversion chemotherapy. None of the patients had progressive disease before surgery. Nine patients with CLM had received FOLFOX (5 patients), FOLFIRI (2), and FOLFIRINOX (2), associated with targeted therapy (bevacizumab in 7 patients and cetuximab in 2). The median number of cycles of preoperative chemotherapy was 15 (7–59). The patient with the neuroendocrine tumour had two cycles of 5-FU with streptozotocin before the first procedure and no further chemotherapy. Three patients had more than one line of chemotherapy. Seven patients had one cycle of interval chemotherapy with a mean delay of 20 (13–26) days after the first stage. The main reasons for not giving interval chemotherapy

Table 2 Perioperative data

	First stage ($n = 10$)	Second stage ($n = 10$)
Metastasectomy/minor hepatectomy	5	0
No. of resected metastases in FLR*	2 (1–5)	0
Extended right hepatectomy		
Right hepatectomy + IV		4
Right hepatectomy + IV + I		6
Resected liver weight (g)*	54 (20–75)	912 (570–2400)
Ablation in FLR	2	1
No. of ablations*	2 (1–6)	1
Hepatic artery ligation		–
Segments VI–VII	3	
Segments V–VIII	7	
Duration of operation (min)*	412 (180–585)	290 (180–540)
Total pedicle occlusion	0	9
Duration of occlusion (min)*	–	19 (8–35)
Blood loss (ml)*	150 (20–1000)	900 (300–3000)
Perioperative red blood cell transfusion	1	9
Primary tumour resection	7	0
90-day mortality	0	0
Duration of hospital stay (days)*	13 (8–26)	11 (7–29)
Interval between the two stages (days)*	45 (31–71)	

*Values are median (range). FLR, future liver remnant.

in the other three patients were extensive preoperative chemotherapy leading to asthenia, postoperative complications and primary neuroendocrine tumour. Seven patients received postoperative chemotherapy. No postoperative complication prevented the administration of chemotherapy after the second stage. Two patients did not have chemotherapy after the second stage because of the large number of cycles already received. Five patients did not undergo tumour resection inside the FLR during the first stage (*Table 2*). In the remaining five patients, a median of 4 (2–6) metastases were located in the FLR, with a total tumour size of 54 (40–125) mm. During the second stage, an additional procedure was undertaken in three patients: one loop ileostomy closure, one adrenalectomy and one inferior vena cava partial resection.

Liver volumetry

The FLR consisted of segments II + III in six patients, and segments II + III + I in four. Before operation, the TLV was 1855 (1165–2374) cm^3 and the FLR measured 327 (214–537) cm^3. Segment IV volume was 169 (106–236) cm^3, which represented 8 (7–12) per cent of the TLV. The FLR/TLV and FLR/BW ratios were 21 (9–25) and 0·46 (0·23–0·77) per cent respectively. On POD 7, the FLR measured 590 (508–1072) cm^3, corresponding to

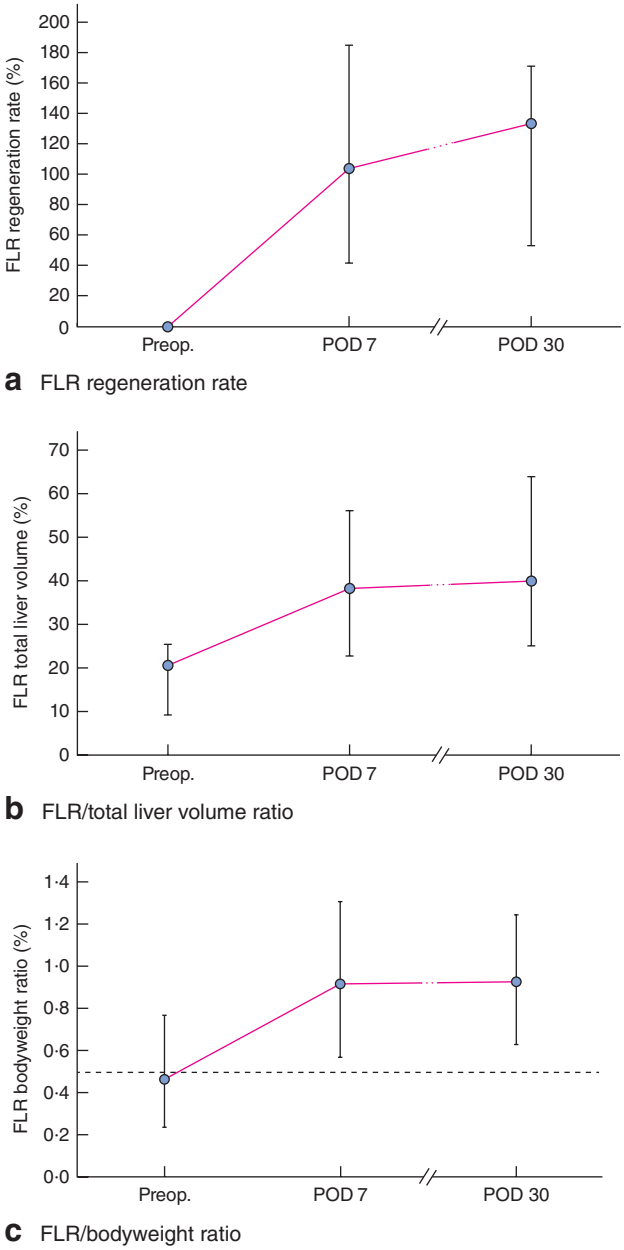

Fig. 2 Liver regeneration by postoperative day (POD) 7 and 30 after associating portal embolization and artery ligation in ten patients. **a** Future liver remnant (FLR) regeneration rate defined by the increase in volume divided by the initial FLR volume. **b** FLR to total liver volume ratio. **c** FLR volume to bodyweight ratio; the dashed line indicates the critical FLR to bodyweight ratio of 0·5 per cent[23]. Values are median (range).

an increase in volume of 300 (225–696) cm^3 and a FLR regeneration rate of 104 (42–185) per cent ($P = 0·005$ *versus* preoperative value). The FLR/TLV and FLR/BW ratios were 38 (23–56) and 0·92 (0·56–1·31) per cent

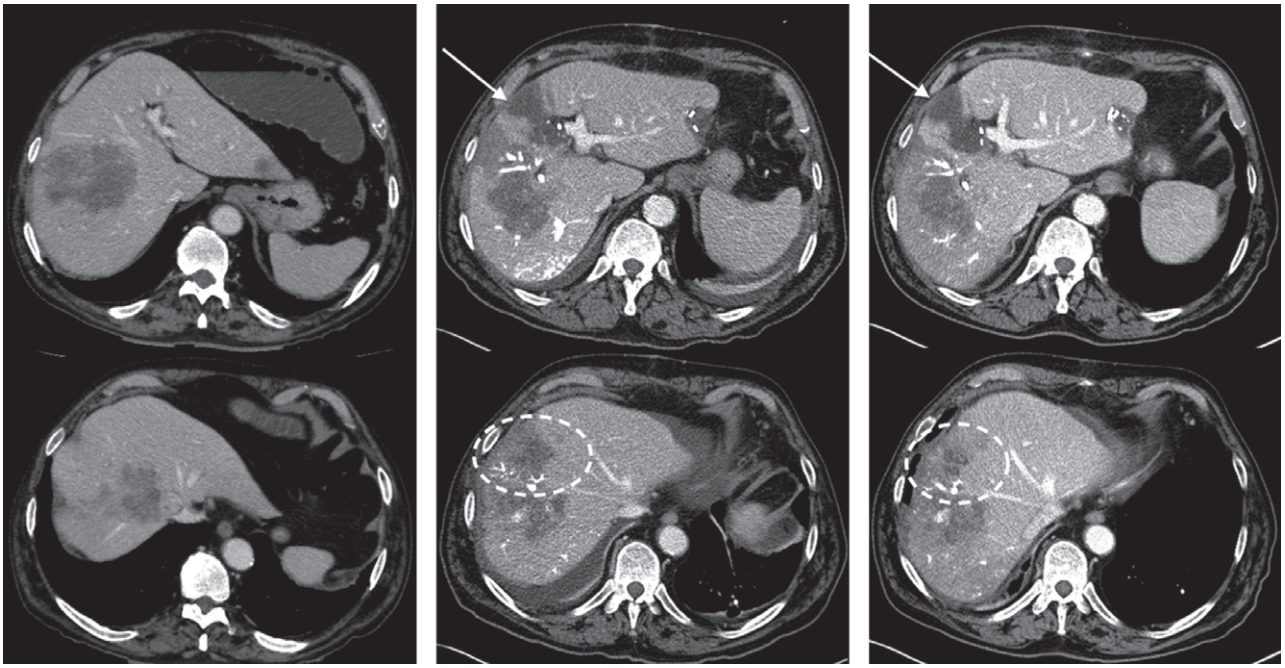

Fig. 3 CT images **a** before and on **b** postoperative day (POD) 7 and **c** POD 30 after associating portal embolization and artery ligation with devascularization of segment IVb and ligation of the right anterior hepatic artery. Images show hypodensity of segment IVb (white arrow) and segments V–VIII (white dashed circle). **a** Future liver remnant (FLR) volume 347 ml, FLR/total liver volume (TLV) ratio 25 per cent; **b** FLR volume 754 ml, FLR/TLV ratio 54 per cent; **c** FLR volume 892 ml, FLR/TLV ratio 64 per cent

respectively (*Fig. 2*). On POD 30, the FLR measured 701 (512–1018) cm^3, corresponding to an increase in volume of 367 (238–642) cm^3 and a FLR regeneration rate of 134 (53–171) per cent ($P = 0{\cdot}005$ *versus* before operation and $P = 0{\cdot}028$ *versus* POD 7). The FLR/TLV and FLR/BW ratios were 40 (25–64) and 0·93 (0·62–1·24) per cent respectively (*Fig. 2*).

Biological parameters

After the first stage of surgery the total bilirubin level increased slightly relative to baseline over the first few days, reaching a median of 23 (7–39) μmol/l on POD 2. Values were 20 (8–56) μmol/l on POD 3 and 17 (7–45) μmol/l on POD 5. The PT was at its lowest level of 58 (range 40–69) per cent on POD 1–2 and then rose to 79 (44–100) per cent on POD 5. The serum creatinine concentration showed a transient increase in two patients, rising to 136 and 199 μmol/l on POD 2 and 3 respectively. All parameters had normalized before the second stage. Aminotransferase levels peaked on POD 2 when the ALT level was 3191 (807–8612) units/l and the AST level 2911 (417–9506) units/l. The results were similar when ALT and AST values from the patients who received additional ablation were excluded.

After the second stage, the serum creatinine concentration did not vary significantly except in the patient who underwent reoperation for haemorrhage a few hours after hepatectomy. Bilirubin, aminotransferases and PT had kinetic profiles similar to those seen after major hepatectomy. On POD 5, median total bilirubin was 22 (4–83) μmol/l and PT was 64 (49–69) per cent. One patient had a total bilirubin level over 50 μmol/l with PT lower than 50 per cent. At 2 months after operation, the total bilirubin concentration was 13 (3–30) μmol/l and PT was 78 (60–100) per cent.

Imaging findings

In all but two patients, sectoral hepatic ischaemia was noted on CT 7 days after the first procedure. All patients had marked cytolysis. Hypodense parenchyma suggesting hepatic ischaemia was visualized better on POD 7 than on POD 2 (*Fig. 3*). At 1 month, there was no sign of hepatic ischaemia in seven of the ten patients. Two patients had segment V–VIII parenchymal ischaemia, which was less pronounced than on POD 7. Ischaemia disappeared

Table 3 Postoperative complications

	First stage ($n = 10$)	Second stage ($n = 10$)
No. of patients with complications	6	6
No. of patients with severe complications	2	3
Grade of most severe complication*		
I	1	1
II	3	2
IIIa	2	0
IIIb	0	2
IVa	0	1
IVb	0	0
V	0	0
Related specifically to treatment of primary tumour	3	0
Related specifically to treatment of liver metastases	2	7
Hepatobiliary complication	0	5

*Dindo–Clavien classification.

proximally (around the hilar plate). One patient had atrophy of segments VI–VII. Ischaemia of segment IVb was observed in eight of ten patients on POD 2 and POD 7, and in six of ten on POD 30.

Postoperative outcomes and complications

There was no death by 90 days after the first procedure or by 90 days after the second operation. Six patients experienced morbidity after the first procedure (*Table 3*). There were no liver-specific complications. Three patients had severe complications after the second procedure: postoperative haemorrhage, reoperated on within 2 h (2 patients) and pneumonia requiring 3 days of intensive care (1). There were no complications related to histological changes in the resected lobe

Recurrences and survival

The median follow-up was 14·5 (3·1–20) months. Nine of ten patients were alive at 1 year, although seven had developed recurrences. Three patients were treated with curative intent and were disease-free at latest follow-up. One patient had disseminated disease progression 7 months after the second procedure and died within 2 months of resuming chemotherapy.

Discussion

This study evaluated the feasibility and effectiveness of the APEAL technique, consisting of right PVE, hepatic artery ligation and devascularization of segment IVb, in ten consecutive patients requiring an extended right hepatectomy during two-stage surgery for bilobar metastases. All patients had an extremely low FLR volume and/or had received extensive preoperative chemotherapy. The novel APEAL technique described here resulted in rapid and extensive hypertrophy of the FLR (over 100 per cent at 1 week). No previously published procedure has achieved such high regeneration rates using a standard technique in consecutive patients. Indeed, with right portal vein + segment IV embolization, the regeneration rate is about 62 per cent at 4 weeks[7]. With ALPPS, the regeneration rate is about 74 per cent after 9 days[8].

A potential consequence of concomitant PVE and hepatic artery ligation is hepatic necrosis. To date, there have been no published descriptions of concomitant PVE and hepatic artery ligation or embolization. However, reports[11–16] of sequential PVE and hepatic artery embolization/chemoembolization have shown encouraging results. In the present study, sectoral hypodensity on CT at POD 2 and POD 7 and/or raised levels of aminotransferases on POD 2 were noted in all but one patient. However, only two had imaging signs of sectoral hepatic necrosis. Interestingly, four patients had revascularization of segment IVb, which confirms that hepatic ischaemia is most often transient. Angiographic studies of the collateral arterial supply after hepatic artery ligation showed that revascularization occurred within a few hours through the hilar plate, interlobar collaterals and perihepatic collaterals[24].

There was no postoperative clinical complication related to hepatic necrosis. The only consequences were transient acute renal injury in two patients. In ALPPS, necrosis of segment IV was associated with infection and bile leakage. By avoiding parenchymal transection along the falciform ligament, the APEAL technique avoids these complications, even if colorectal surgery is associated, provided that a sectoral-only hepatic artery is ligated (not the right hepatic artery).

In patients with numerous unresectable liver metastases, extending right hepatectomy to segment IV ± I carries a major risk of liver failure owing to the small size of the FLR associated with the parenchymal toxicity of induction chemotherapy. Moreover, the need to clear liver metastases in the FLR during the first stage increases functional impairment. In this situation, two ways to induce optimal FLR hypertrophy and to decrease the risk of postoperative liver failure have been proposed: the ALPPS technique and percutaneous embolization of the right portal vein and segment IV branches. The use of hepatic vein embolization associated with PVE could be an option. However, this technique has been studied only as a salvage procedure for insufficient FLR growth after right PVE before a right

hepatectomy. ALPPS created enthusiasm among hepatobiliary surgeons because hypertrophy of the FLR was rapid enough to allow second-stage surgery within 2 weeks. The major drawback of this strategy is the high mortality rate of 12–15 per cent[8,9]. This rate is difficult to accept when dealing with isolated CLM, in which chemotherapy alone offers a median overall survival of 25–29 months[25].

Right portal vein + segment IV embolization has been proven effective with low morbidity[7]. However, the completion of segment IV embolization is technically demanding and incurs the risk of left portal vein thrombosis. Moreover, the efficacy and reproducibility of adding segment IV embolization to right PVE can be questioned[26]. This is explained by the anatomy and vascularization of segment IV, which has numerous anatomical variations. Segment IV is vascularized by both the umbilical part and the transverse (proximal) part of the left portal vein. Up to six branches arising from the umbilical part of the left portal vein have been described as supplying segment IVb alone[27]. With APEAL, only the glissonian branches to segment IVb were ligated without parenchymal transection. This induced arterial and venous interruption and resulted in necrosis, which might be more effective in inducing FLR growth. Moreover, by avoiding dissection of the transverse part of the left portal vein, this technique precluded the risk of left portal vein damage and thrombosis.

APEAL resulted in rapid FLR hypertrophy and would have allowed a shorter delay between the two procedures, as is the case with ALPPS. Nevertheless, in the present series, the second stage was performed after the same 1–2 months' delay used in conventional two-stage hepatectomy. This waiting period is useful for patients' recovery and to exclude those who will experience rapid disease progression[28]. In two-stage hepatectomy, extrahepatic disease progression is a major cause of patient drop-out; this would not be prevented by the rapid removal of liver tumour by the ALPPS approach. The second stage of ALPPS has to be undertaken quickly because technical problems arise owing to infection and necrosis of segment IV associated with perihepatic adhesions if more than 2 weeks elapse after the first stage.

The APEAL technique has the advantage of being less technically demanding because of the absence of extensive previous liver dissection and of postoperative fluid collections. It can be facilitated further by perihepatic placement of antiadhesion barriers[17] and systematic vessel taping with coloured silicone loops. Another advantage of this technique is that artery ligation not only increases FLR regeneration but also has potential antitumour effects by depriving cancer cells of oxygen, leading to necrosis and apoptosis[10,29].

As well as demonstrating rapid and extensive FLR hypertrophy, both surgical procedures were safe. There were no deaths at 90 days and morbidity rates were 60 per cent after both procedures. Despite the fact that the patients included had more extensive disease than those undergoing conventional two-stage hepatectomy, the morbidity rate was consistent with previous publications on two-stage hepatectomy. Morbidity rates of 0–26 per cent after the first stage and 20–59 per cent after the second stage have been reported, with severe morbidity rates of up to 10 and 30 per cent respectively[30]. After right portal vein + segment IV embolization, morbidity and severe morbidity rates were 58 and 33 per cent respectively[7]. Moreover, in the present study resection of the primary tumour was performed in 70 per cent of patients during the first stage of APEAL. This is important because two-stage hepatectomy is a frequent option in patients with synchronous CLM[17,30]. The combination of primary tumour resection with the first stage of liver surgery reduces the total number of procedures undertaken.

The lack of longer-term survival data is a limitation of this preliminary study, as is the small number of patients. Both prevent the drawing of any firm conclusions about oncological outcomes. Technically, APEAL requires an intraoperative approach by laparotomy and could appear more aggressive than percutaneous PVE. However, the surgical technique is simple, reproducible and consistently associated with major FLR hypertrophy. Furthermore, APEAL permitted full exploration of the peritoneal cavity, confirming the absence of peritoneal carcinomatosis and allowing removal of the primary tumour. It also permitted assessment of the FLR using intraoperative ultrasonography to check for the absence of liver metastases and for improved localization of metastases that may have been missed on the preoperative CT. This technique is still under investigation and the results require confirmation in a multicentre approach. Analysis of future registry data should be undertaken, and a trial of ALPPS or right portal vein + segment IV embolization *versus* APEAL may be warranted.

Acknowledgements

R. Stepney, medical writer, Charlbury, UK, assisted with editing.
Disclosure: The authors declare no conflict of interest.

References

1 Adam R, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B *et al.* Patients with initially unresectable colorectal liver

metastases: is there a possibility of cure? *J Clin Oncol* 2009; **27**: 1829–1835.
2 Folprecht G, Grothey A, Alberts S, Raab HR, Köhne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2005; **16**: 1311–1319.
3 Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT *et al.* Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 2010; **11**: 38–47.
4 Evrard S, Rivoire M, Arnaud J, Lermite E, Bellera C, Fonck M *et al.* Unresectable colorectal cancer liver metastases treated by intraoperative radiofrequency ablation with or without resection. *Br J Surg* 2012; **99**: 558–565.
5 Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006; **13**: 1271–1280.
6 Mise Y, Aloia TA, Conrad C, Huang SY, Wallace MJ, Vauthey JN. Volume regeneration of segments 2 and 3 after right portal vein embolization in patients undergoing two-stage hepatectomy. *J Gastrointest Surg* 2014; **5**: 1–9.
7 Shindoh J, Vauthey JN, Zimmitti G, Curley SA, Huang SY, Mahvash A *et al.* Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. *J Am Coll Surg* 2013; **217**: 126–133.
8 Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA *et al.* 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. *Ann Surg* 2012; **255**: 405–414.
9 Schadde E, Ardiles V, Slankamenac K, Tschuor C, Sergeant G, Amacker N *et al.* ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors compared with conventional-staged hepatectomies: results of a multicenter analysis. *World J Surg* 2014; **38**: 1510–1519.
10 Vogl TJ, Balzer JO, Dette K, Hintze R, Pegios W, Maurer J *et al.* Initially unresectable hilar cholangiocarcinoma: hepatic regeneration after transarterial embolization. *Radiology* 1998; **208**: 217–222.
11 Yoo H, Kim JH, Ko GY, Kim KW, Gwon DI, Lee SG *et al.* Sequential transcatheter arterial chemoembolization and portal vein embolization *versus* portal vein embolization only before major hepatectomy for patients with hepatocellular carcinoma. *Ann Surg Oncol* 2011; **18**: 1251–1257.
12 Tanaka H, Honna T, Muto M, Fujino A, Kasahara M, Kitano Y *et al.* Selective ligation of portal vein and hepatic artery for ruptured hepatocellular carcinoma in a 13-year-old boy. *J Pediatr Surg* 2011; **46**: 973–977.
13 Ogata S, Belghiti J, Farges O, Varma D, Sibert A, Vilgrain V. Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. *Br J Surg* 2006; **93**: 1091–1098.
14 Kong D, Kusano M, Arase T, Nishino N, Jin Z, Kameyama S *et al.* Liver regeneration after portal vein plus hepatic artery ligation performed heterochronously in rats. *J Hepatobiliary Pancreat Surg* 2002; **9**: 86–92.
15 Kang BK, Kim JH, Kim KM, Ko GY, Yoon HK, Gwon DI *et al.* Transcatheter arterial chemoembolization for hepatocellular carcinoma after attempted portal vein embolization in 25 patients. *AJR Am J Roentgenol* 2009; **193**: W446–W451.
16 Gruttadauria S, Luca A, Mandala L, Miraglia R, Gridelli B. Sequential preoperative ipsilateral portal and arterial embolization in patients with colorectal liver metastases. *World J Surg* 2006; **30**: 576–578.
17 Dupré A, Lefranc A, Buc E, Delpero JR, Quenet F, Passot G *et al.* Use of bioresorbable membranes to reduce abdominal and perihepatic adhesions in 2-stage hepatectomy of liver metastases from colorectal cancer: results of a prospective, randomized controlled phase II trial. *Ann Surg* 2013; **258**: 30–36.
18 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–213.
19 Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet* 2012; **380**: 756–766.
20 Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D *et al.* The '50–50 criteria' on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg* 2005; **242**: 824–828.
21 Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S *et al.* Hepatic insufficiency and mortality in 1059 noncirrhotic patients undergoing major hepatectomy. *J Am Coll Surg* 2007; **204**: 854–862.
22 Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R *et al.* Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011; **149**: 713–724.
23 Truant S, Oberlin O, Sergent G, Lebuffe G, Gambiez L, Ernst O *et al.* Remnant liver volume to body weight ratio > or = 0·5%: as new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. *J Am Coll Surg* 2007; **204**: 22–33.
24 Koehler RE, Korobkin M, Lewis F. Arteriographic demonstration of collateral arterial supply to the liver after hepatic artery ligation. *Radiology* 1975; **117**: 49–54.
25 Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE *et al.* FOLFIRI plus cetuximab *versus* FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; **15**: 1065–1075.

26 Capussotti L, Muratore A, Ferrero A, Anselmetti GC, Corgnier A, Regge D. Extension of right portal vein embolization to segment IV portal branches. *Arch Surg* 2005; **140**: 1100–1103.
27 El Gharbawy RM, Nour BM. Segment 4 architecture and proposed parenchyma-wise technique for *ex vivo* graft procurement and implantation. *Liver Transplant* 2013; **19**: 1189–1201.
28 Aloia TA, Vauthey JN. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): what is gained and what is lost? *Ann Surg* 2012; **256**: e9.
29 van Lienden KP, Hoekstra LT, van Trigt JD, Roelofs JJ, van Delden OM, van Gulik TM. Effect of hepatic artery embolization on liver hypertrophy response in a rabbit liver VX2 tumor model. *Hepatobiliary Pancreat Dis Int* 2013; **12**: 622–629.
30 Lam VW, Laurence JM, Johnston E, Hollands MJ, Pleass HC, Richardson AJ. A systematic review of two-stage hepatectomy in patients with initially unresectable colorectal liver metastases. *HPB (Oxford)* 2013; **15**: 483–491.

If you wish to comment on this, or any other article published in the *BJS*, please visit the online Your Views section of the website (www.bjs.co.uk).