Imaging of ALPPS procedure: what the Radiologist should know

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Authors: M. Zerial, D. Iorenzin, A. risaliti, M. Bazzocchi, C. Zuiani, R. Girometti; Udine/IT
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Learning objectives

1) To review the indications and technique for Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) procedure; 2) to illustrate the role for imaging in the pre- and postoperative periods, with special emphasis on Computed Tomography (CT) and Magnetic Resonance Imaging (MRI).
Background

Liver resection and future liver remnant

Complete resection is the only treatment proved to achieve long-term survival in patients with malignant primary or metastatic focal liver lesions (FLL). Advances in surgical techniques, control of bleeding and intensive care improved the outcome of liver resection, leading to extend criteria for operability compared to the past.

However, hepatic resection should be planned after careful, multidisciplinary evaluation of lesion type and location, as well as patient's anatomy and the quality and volume of future liver remnant (FLR) after surgery. Preoperative estimation of FLR is of pivotal importance in assessing the feasibility of extended liver resection, i.e. in assessing whether FLR is capable to support adequate liver function after surgery. Indeed, post-hepatectomy liver failure (PHLF) caused by insufficient liver remnant function is a major postoperative complication, associated with high morbidity and mortality.

FLR should be no lower than 25-30% of preoperative liver volume in patients with normal liver function, and no lower than 40% in patients with underlying chronic liver disease or liver dysfunction (including the effects of chemotherapy) (1,2).

The ALPPS procedure

ALPPS has been introduced in 2007 by Schlitt et al (3). as a surgical approach to maximize the advantages related to preoperative portal vein embolization (PVE) or portal vein ligation (PVL). Relying on the regenerative properties of the liver, PVE/PVL aims to induce compensatory hypertrophy of an insufficient contralateral FLR, in order to make extended liver resection feasible. However, liver resection remains contraindicated in 10-30% of patients after PVE/PVL, because of insufficient FLR hypertrophy and/or disease progression occurring during the period of time needed to achieve it (2-6 weeks) (4). ALPPS can induce rapid growth of the FLR. Reportedly, the hypertrophy extent of FLR was 40%-80% within 6-9 days, in contrast to approximately 8%-27% within 2-60 days by PVL/PVE (1). Because of lower native volume, the FLR is almost invariably left liver lobe, whereas diseased hemiliver (DH) to be removed identifies with right liver lobe.
ALPPS is a two-stages hepatectomy designed to obtain FLR growth more rapidly and at a higher extent compared to PVE/PVL. The volume FLR can increase of 61-93% compared to baseline volume. The procedure is performed by following two stages\(^{(2)}\).

**Stage 1:** After cholecystectomy and lymphadenectomy of the hepatoduodenal ligament, complete tumor clean-up of the FLR is performed (if minor FLL involve it). Subsequently, right portal vein is sectioned and sutured (Fig. 1). Next step is hepatectomy, in order to separate the FLR from DH, i.e. the hemiliver showing bulky tumor volume.

At the end of the procedure, DH is left in situ after having being enveloped into a hermetic plastic bag (Fig. 2). The rationale for this stage is to induce hypertrophy of FLR (in which arterial and portal vascular supply is preserved) and hypotrophy of DH (in which portal supply is eliminated by portal vein transection). Two drains are placed: along the transection line up to the subphrenic space, and within the plastic bag, respectively.

**Stage 2:** patient undergoes second surgery after \#8 days from stage 1. Hepatic resection is completed by removing hypotrophic DH after transection of the hepatic artery, hepatic duct, portal vein and hepatic vein (Fig. 3-4). In the case of hilar cholangiocarcinoma, a Roux-en-Y biliodigestive anastomosis is also performed (Fig. 5).

**Indications to ALPPS**

ALPPS is indicated as a treatment to increase overall survival in patients showing locally advanced multiple liver neoplasia with borderline criteria for operability (insufficient FLR either in volume or quality). Treatable FLLs include metastases of colorectal carcinoma or breast cancer, Klatskin tumour, mass-forming or periductal infiltrating cholangiocarcinoma, gallbladder carcinoma, hepatocellular carcinoma (HCC) or neuroendocrine tumors. ALPPS can be offered as first-line surgical approach or salvage-strategy after failed PVE\(^{(5)}\). Prerequisites for undergoing the procedure are adequate FLR and patient's general status. It should be kept in mind that ALPPS is an "extrema ratio" procedure, with reported high operative morbidity (16%-64% of patients) and mortality (12%-23% of patients). Independent risk factors for severe complications were found to be blood cell transfusion on stage 1 > 300 min and age > 60 years. Thus, patients selection is essential in achieving a successful procedure.

Contraindications to ALPPS include: unresectable FLLs in the FLR, infiltration of the retrohepatic avascular space, severe portal hypertension, unresectable extrahepatic metastases, inoperable primary tumour, high anesthesiology risk, medical contraindications to major hepatectomy, together with serious comorbidities, impossibility to achieve negative margins, or unresectable primary tumor of other locations \(^{(6)}\). There...
is still debate whether cholestasis and the presence of biliary drainage contraindicate the procedure.
Fig. 1: After cleaning up of the future liver remnant (FLR) (arrows) (if needed), the right portal vein (RPV) is sectioned and sutured. Cholecystectomy is routinely performed (asterisk).

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**Fig. 2:** Hepatectomy is performed, usually along a line including or excluding segment IV (according to Couinaud classification)(A). After encircling its vasculobiliary pedicle and the draining hepatic vein(s) with black silks or vessel-loops, DH is enveloped with a plastic bag (B). The use of the bag leads to easier removal of DH on surgical stage 2, and better drainage or identification of collections, through a drain inserted within the bag itself.
Fig. 3: During the second stage of ALPPS, hypertrophy of the future liver remnant (FLR) is seen (blue arrowheads), as well as hypotrophy of the diseased hemiliver (DH) (black arrows). The resection of the DH is usually achieved using vascular staplers.

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Fig. 4: A) First intraoperative findings during stage 1, with evidence of resection line on the right side of ligamentum falciforme. B) Resected liver with right hepatic vein (asterisk) and right hepatic artery (arrow) encircled by vessel loop to simplify their identification during stage 2. It is of pivotal importance to avoid any injury to right hepatic artery during parenchymal transection, because this is the only vascular inflow for DH. Any arterial damage would translate into DH necrosis. C) Right Diseased Hemiliver showing multiple focal liver lesions (cholangiocarcinoma) before wrapping in the plastic bag. D) Pronounced hypertrophy of FLR during intraoperative stage 2.

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**Fig. 5:** In the case of hilar cholangiocarcinoma (Klatskin tumor) first stage hepatectomy is followed by biliary resection along the main left hepatic duct (free margins from the tumor are preserved). Affected bile ducts will be then removed en bloc with the diseased hemiliver (DH) during stage 2. In that stage, biliodigestive anastomosis between left hepatic duct and jejunum is performed. The asterisk indicates the gallbladder fossa after cholecystectomy.

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Findings and procedure details

Imaging before stage 1

Goals

The main goal of imaging is to contribute to the judgment of feasibility of the procedure by assessing tumor burden, liver status and presence of ancillary findings with potential surgical significance. Thus, imaging is expected to provide:

1. Identification and characterization of FLLs, with careful reporting of the number, size, and location of individual lesions, as well as their relationship with the hepatic artery, main portal pedicles, hepatic veins, first- and second-order biliary branches (Fig. 6-7). This will help the surgeon to establish: i) lesions resectability; ii) the risk for intraoperative complications (e.g., lesions close to the retrohepatic course of inferior vena cava, a region at higher risk of intraoperative bleeding).

2. Evaluation of liver parenchyma, looking for signs of cirrhosis, cholestasis, steatosis or any other pathologic change attributable to the effects of the tumor or chemotherapy. Liver status might influence the judgment of operability, regardless of the FLR volume.

3. Preoperative evaluation of vascular and biliary anatomy, in order to identify variants of potential surgical significance (e.g., aberrant and/or accessory branches).

4. Liver volumetry (LV) of the FLR (Fig. 8). FLR volume should be calculated by excluding FLLs affecting it, in order to obtain a reasonable estimate of viable liver tissue that will be spared by surgery. In our Institution, the radiologist performs LV in the presence of liver surgeon, in order to match as more reliably as possible the intended lines of resection. The majority of commercially available imaging workstations implement LV.

5. Identification of any extrahepatic finding potentially affecting the feasibility of ALPPS, including large, inoperable primary cancer on other sites, as well as portal hypertension (including splenomegaly and venous collaterals).

Imaging technique

Because of panoramicity and lower acquisition time, CT should be preferred as first-line modality to image patients candidate to ALPPS. Our institutional protocol is summarized on Tab. 1.

Though rarely needed, magnetic resonance cholangiopancreatography (MRCP) can be used to evaluate the biliary tree anatomy or the extent of cholangiocarcinoma
involvement. Contrast-enhanced MRI with hepatospecific contrast agent (gadoxetic acid or gadobenate dimeglumine) has the potential to identify small lesions (< 1 cm) undetected on CT, which in turn may contraindicate ALPPS of affecting FLR.

**Imaging between stages 1 and 2**

**Goals of imaging**

Post-operative cross-sectional imaging is always required to assess stage 1 surgery:

1. To calculate the increase in volume of the FLR using LV (Fig. 9, Table 2). Hypertrophy of FLR expected within 6 - 9 days is between 40 % and 80 % compared to baseline (1).

2. To evaluate whether the decrease in size of DH and related lesions occurred.

3. To confirm tumor-free status of the FLR.

4. To assess the patency and caliber of portal vein and non-ligated left main branch, common, right and left hepatic artery, hepatic veins and inferior vena cava.

5. To exclude complications.

**Imaging technique**

Similar to that of imaging before stage 1 (Table 1-3). MRI can be used to evaluate suspicious biliary leakage using gadoxetic acid-based MRCP.

Complementary imaging is often obtained with ultrasonography (US) with ColorDoppler examination, which is a tool for a quick-and-dirty evaluation at patient's bedside for excluding gross complications (e.g., collections) and assessing the patency of portal vein and hepatic artery branches.

**Normal findings**

Both DH and FLR are often surrounded by a thin rim of free fluid, which is usually more prominent around the DH because of the incapsulation within the endobag (that should not be visible per se). Air bubbles are frequently associated, sometimes a large extent (Fig. 10). A similar aspect (free fluid and air bubbles) is found along the line of hepatectomy: it is crucial not to misdiagnose it with an infected collection. Mild periportal edema is commonly presented. On CT, clips and hyperdense linear images can be detected at sites of surgical outcomes.
Except for the main portal branch directed to DH, vascular supply to the liver is preserved (Fig. 11), with the hepatic artery for the DH appearing slightly hypertrophic compared to the baseline examination. No biliary dilation should be observed, both in DH and FLR.

Normal key issue after stage 1 is represented by enlargement of the FLR, that can be easily appreciated both on 2D images and LV compared to the baseline examination. Its of paramount importance to distinguish between true parenchymal hypertrophy and postoperative liver edema, that absolutely must not be confused. Measurements of UH values and or MRI can help in the distinction.

Complications

Postoperative complications of ALPPS include bleeding, bile leak, fluid or bile collections, biliary fistula, cholangitis, persistent postoperative ascites, pleural effusion, prolonged ileus, hepatic dysfunction, liver failure, coagulation disorders, portal vein thrombosis, hepatic vein and hepatic arterial thrombosis, cardiovascular, respiratory, and renal system dysfunction, and infection (7,8). Regardless of the complication, patients’ signs and symptoms tend to be non-specific, including fever, abdominal pain, jaundice, ascites, pleural effusion, abnormal liver tests and suspicious bleeding.

The most common problems encountered on imaging are liver function failure, collections, hematomas and vascular thrombosis. CT and MRI are indicated in case of ambiguous clinical picture and/or inconclusive preliminary US. Bilomas are usually suspected in the case of presence of bile into the drains.

1. Since there are no specific imaging clues to diagnose liver failure, imaging should be performed to exclude any other complication as a co-cause.

2. Collections are represented by fluid accumulation, bilomas and hematomas. Bilomas and hematomas tend to form along the hepatectomy line or within the endobag, depending on the origin from the resection surface of the FLR or DH, respectively (Fig 12). Small bilomas and/or hematomas are almost physiological during the first post-operative days, and usually tend to remain stable or being reabsorbed; large collections or collections increasing over a few days should be regarded as pathological (Fig. 13). Bilomas can be indistinguishable from serous collections, since they present homogeneous fluid content (around 10-15 HU on CT) without contrast-enhancement. Active biliary leakage can be shown on gadoxetic acid-enhanced MRCP because of contrast extravasation from bile ducts or liver surface into the collection. Timely diagnosis of bile leak is essential to avoid the development of biliary sepsis, which may need to anticipate the completion of stage 2 before the FLR is sufficiently hypertrophied, thus increasing the risk of death.Biloma occurs in about 3% of patients after major liver resection; Treatment options include pigtail drainage (under USG/CT guidance) or surgical drainage.
3. Hematomas show more heterogeneous content, with mixed internal areas of low and high attenuation (> 30 HU) on CT images, reflecting the presence of fibrin septa and clots. If needed, MRI may contribute to differential diagnosis with bilomas showing typical hyperintensity on T1-weighted fat suppressed images.

4. Postoperative hemorrhage generally arise within 48 hours from intervention, commonly as an effect of bleeding from the margins of the residual liver (which may be a consequence of arterial branch truncation or congestion of the hepatic vein due to stenosis or ligation), incomplete intraoperative hemostasis or dehiscence of vascular sutures. CT-angiography should be promptly performed to identify the site of bleeding.

5. Vascular thrombosis is a serious complication, that may affect the portal vein trunk and/or FLR portal branches, thus limiting the compensatory effect leading to parenchymal hypertrophy. Hence, patients showing extensive portal vein thrombosis (PVT) are at high risk of liver failure and death. CT and/or MRI provide a panoramic representation of PVT, showing the whole extent and the degree of vascular occlusion, which appears as vessel enlargement with complete or partial absence of internal contrast flow. Contrast enhancement of vessel walls can occur, possibly representing dilated vasa vasorum.

### Imaging after the step 2

**Normal findings**

Common CT findings after surgical stage 2 are: i) intraabdominal air or small fluid collections, that can persist from early postoperative period up to two months; ii) a thin hypoattenuating linear band adjacent to liver resection margin (seen in 30-50% of cases), that has been related to bile or blood accumulation, focal steatosis or effects of parenchymal devascularization.

Vascular pedicle of liver remnant is patent. No biliary dilatation should be observed (Fig. 14).

**Complications**

Complications can be classified into early and late ones, respectively. Early complications occur within a few weeks from stage 2, and are similar to that occurring after stage 1 surgery, i.e. collections/bilomas (Fig. 15-16), hematoma, bleeding and portal vein thrombosis.

Late complications occurs from 3 months to about six months after stage 2, and are mainly represented by:

1. Tumor recurrence (Fig. 17).
2. Biliary stricture and fistula (Fig. 18). Biliary benign stricture is a possible complication caused in part by the hypertrophy with subsequent rotation and displacement of FLR and in parte by bile duct surgical injury (inaccurately placed clips, erroneous cutting of bile ducts, periductal bile leakage and ischemia due to injury to the left hepatic artery). Endoscopy, with stent placement, is widely used approach for treatment. Generally in patients with postoperative biliary fistulae endoscopic sphincterotomy or endoprosthesis placement is performed to aide fistula closure.
Fig. 6: Massive involvement from colorectal metastases of the right hepatic lobe (red arrow) in a 64 male years-old patient (A). One small satellite lesion was found on the left side of the middle hepatic vein (arrowhead in B), indicating the need for FLR (segments II+III+IV) clean-up during stage 1. No vascular involvement was shown, as exemplified by patent main portal trunk and intrahepatic branches (asterisk in C), except for infiltration of the middle hepatic vein (double asterisk in C). Based on this finding, a wide free margin between the line of resection and the middle hepatic vein was obtained.

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Fig. 7: Hilar colangiocarcinoma in a 59 years old male patient. Large periductal infiltrating lesion was found on venous phase (asterisk on A), with mild contrast enhancement on delayed phase (double asterisk on B). Biliary dilatation upstream was associated, as shown on oblique coronal minIP image in C, delineating a Bismuth IV lesion. Lesion was found operable because of early bifurcation of right and left hepatic arteries seen on MIP reconstruction (arrow in D): both vessels encircled hilar lesion, with no encasement.

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**Fig. 8:** During liver volumetry (LV), the radiologist and surgeon in consensus perform slice-by-slice liver segmentation using manually-drawn ROIs (A-C). The software then calculates on a 3D map the volume of the segmented regions, which are usually represented, in our Institution, by the FLR (D) and the whole liver (E). During segmentation, vessels and focal lesions in the FLR should be not included.

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<td>Delayed (if needed)</td>
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**Table 1:** CT protocol for ALPPS in our Institution. Venous phase can be extended to the thorax if indicated (e.g., for pulmonary staging or exclusion of pulmonary contraindication to proceed). Contrast dose is 500-600 mgI/Kg, whereas injection rate is between 3-4 ml/sec.

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**Fig. 9:** A. Evolution of the FLR (liver segments II + III) before (A-B) and after stage 1 surgery (C-D). FLR remnant almost doubled in volume, showing clear enlargement on 2D images.

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<table>
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<td>(postoperative FLR-preoperative FLR)/ preoperative FLR</td>
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Table 2: LV measurements before and after stage 1. Baseline FLR volume calculation is essential to predict whether liver function will be preserved after the ALPPS procedure. Hypertrophy of the FLR and kynetic estimate whether sufficient hypertrophization of the FLR has been achieved before stage 2 on an absolute basis and on per-day normalized velocity of volume increase, respectively.

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Table 3: MRI protocol used in our Institution. HASTE T2 = half-Fourier acquisition single-shot turbo spin-echo; GRE = gradient echo; EPI = echo-planar imaging; SPAIR = Spectral attenuated inversion recovery; VIBE = volumetric interpolated breath-hold examination; MRCP = magnetic resonance cholangiopancreatography; BH = Breath hold; NAV = navigator gated

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Fig. 10: Normal findings after stage 1 surgery on axial (A) and coronally-reformatted (B) CT images acquired on venous phase. A thin rim of free fluid with air bubbles is visible along the surface of DH (right liver lobe), suggesting its accumulation within the plastic bag (asterisk on A and B). A similar finding is visible along the line of transection (falciform ligament). Mild periportal edema (red arrowhead in A), thin hypodense bands along the edges of surgical resection (arrows on both A and B) and drains (blue arrowheads) are visible.

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Fig. 11: Vascular status after stage 1 surgery on a volume rendering 3D reconstruction. Main right portal branch was ligated and transected (thick arrow). Hepatic artery branches are patent, including right hepatic artery, which shows mild hypertrophy (arrowhead), and left hepatic artery (thin arrow), which follows the course of left intrahepatic portal branch.

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Fig. 12: Biloma in a 49 years-old female patient who underwent ALPPS because of peripheral cholangiocarcinoma of the right liver lobe. CT was performed because of bile flowing from the right drain. The examination confirmed a large fluid collection beneath DH (asterisk), which distended the plastic bag (arrows). Biloma was removed with the DH during stage 2 surgery; the removal of DH also resolved the biliary leakage originating from right transection surface.

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**Fig. 13:** Normal position of the two drains, as visible on the panoramic volume rendering reconstruction in A. Left drain has a vertical course along the line of transection up to the inferior margin of the diaphragm (arrow). Right drain has an horizontal course beneath DH (asterisk in A): his tip (asterisk in B) is placed within the plastic bag, in order to drain collections like the one shown in B (arrows).
Fig. 14: Patient operated for hilar colangiocarcinoma, showing biliodigestive anastomosis between jejunum and biliary branches for hepatic segments II and III. MRI HASTE T2 weighted images acquired on axial (A) and coronal plane (C), as well as thick MPR axial (B) and coronally-reformatted images acquired on the hepatobiliary phase show absence of biliary dilatation and regular passage of bile through the anastomosis.

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**Fig. 15:** Collection after stage 2. Large, encapsulated collection with fluid-air level was shown after DH removal, with mild parietal enhancement (arrow). Part of the collection surrounded liver segment I (thin arrow).

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**Fig. 16:** Intrabdominal collections after stage 2 in the same patient of Figure 11 on MPR coronally- and sagitally-reformatted CT images. Fluid attenuating, encapsulated collections are visible around the spleen (A), in the gastro-hepatic ligament (B and C), as better shown on the sagittal image (D).

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Fig. 17: Multiple recurrences of cholangiocarcinoma, after 16 months from ALPPS, localized on liver segment II and III (arrows).

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Fig. 18: Biliary fistula and biliary stricture 1 month after wedge resection of multiple recurrences of cholangiocarcinoma (the same patient of Fig. 14), 20 months from stage 2. Because of fever and sonographic detection of ascites, the patient was addressed to percutaneous transhepatic cholangiography, showing biliary leakage along the resection margin of liver remnant, where metastsectomy has been performed (A). Bile leakage and a co-existing stricture of the distal common bile duct (B) were treated by placing a biliary stent graft within extrahepatic bile duct and left intrahepatic duct (C). MIP reconstruction (D) and coronally-reformatted image (E) after CT show both the drainage within the biloma and the biliary stent graft. Biloma is shown in (F).

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Conclusion

1) The role for CT is of pivotal importance in planning ALPPS procedure and monitoring different surgical stages. CT also confirm a clinical or sonographical suspicion of complications, mainly including collections, biloma, hematoma, post-surgical bleeding and portal vein thrombosis. MRI should be used as a problem solving tool, especially in biloma characterization.

2) Liver volumetry is of special importance in assessing whether FLR is adequate in supporting liver function after surgery, and can be easily performed on CT images.


