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Letter to the Editor

Insights in living-donor liver transplantation associated with two-stage total hepatectomy: First case in neuroendocrine tumor metastases and functional assessment techniques

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To the Editor:

While organ shortage commonly dooms patients on waiting list, alternative options as living-donor liver transplantation (LDLT) are assiduously sought. The principles of liver surgery rule LDLT: there must be sufficient residual volume in the donor and sufficient implanted volume for the recipient. However, the liver left-to-right segmentation confronts us with a respective volume distribution of 1/3–2/3 or even 1/4–3/4. The volume of the left lobe is then too small to ensure the "hepatostat" in the recipient [1], whereas the procurement of a right graft would jeopardize liver residual function in the donor. A Norwegian team combined partial liver transplantation with the procedure associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). This technique was labelled as RAPID (resection and partial liver transplantation with delayed total hepatectomy) and involved deceased-donor left lobes collected by splitting [2]. The first step includes left hepatectomy (segments II, III and IV) and left-graft orthotopic implantation (segments II and III). The native right liver is deportalized by ligation of the right portal pedicle. The ALPPS principles are respected: the reorientation of the complete portal flow towards the graft stimulates regeneration and the physical separation between the remnant and the graft embodies the concept of parenchymal transsection. The rapid volumetric increase of the graft allows right hepatectomy, i.e. the second step, within 15 days. The living-donor RAPID (LD-RAPID), based on left lateral lobe from living donation, has been more recently described [3]. A technical limitation to RAPID seemed to be portal hypertension restricting the technique to non-parenchymal liver diseases, but it has been shown that with good modulation of the portal flow the RAPID technique is applicable to the cirrhotic patient compensated with portal hypertension for hepatocellular carcinoma [4]. RAPID has been mainly described for colorectal cancer liver metastasis but has also been used for other diseases. Patients with neuroendocrine tumor (NET) liver metastases are also candidates with a less controversial oncological indication.

Both donor and recipient were included in our institutional protocol labelled associating living-donor auxiliary partial orthotopic liver transplantation and right portal vein ligation for total staged hepatectomy (ALDAPT). The procedure was approved by the local ethical committee (CEHF 2020/19FEV105), and considered for patients with colorectal cancer liver metastasis, NET liver metastasis, and hepatocellular carcinoma in well-compensated cirrhosis. The recipient, a 46-year-old male had a primary NET of the ileum with bilobar synchronous liver metastases. Ileocolic resection was performed three years prior to transplantation confirming an intermediate grade NET with Ki67 index at 3.3%. Liver disease remained stable during this period under synthetic somatostatin analogues (SSAs). However, a single cardiac septal metastasis was discovered during the pre-transplant evaluation by somatostatin receptor SPECT/CT. This lesion was removed one year before transplantation by minimally invasive robotic excision. The local multidisciplinary oncology board validated, then, the indication for transplantation. The donor was his 42-year-old brother. Liver morphology and vascularization did not allow either a full left or a right donation (Table S1). The first surgical step involved recipient left hepatectomy, donor left hepatectomy (segment II-to-IV including middle hepatic vein), and recipient orthotopic transplantation. We chose a full left liver as the graft, because the procedure is standardized in our center and limits segment IV ischemia in the donor [5]. The graft weighed 365 g and the recipient native left liver was (segments I-to-IV) 282 g. The anatomy was modal in both patients. The graft-to-recipient body weight ratio (GRWR) was 0.42%. We performed per-protocol intraoperative hemodynamic measurements, before and after hepatectomy (Table S1). The truncal portal flow amounted to 500 mL/min, in the native liver, and to 480 mL/min, in the graft. The relative flow rate was therefore 131 mL/min/100 g. Native portal pressure was

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Table 1
The evolution of scientigraphic graft uptake and volumetric variations in this case.

Time after transplant	0 d	7 d	14 d	21 d	90 d	180 d
GRWR (%)	0.42	0.81	1.03	1.14	1.63	1.54
Graft volume (mL) [a]	403	766	946	1046	1321	1281
Graft weight (g) [b]	365	404	519	941	1188	1152
Graft/total capitatio ^{99m}Tc- labeled mebrofenin (%)	NA	47	44	55	NA	NA
Graft captation function (%/min/m^2)	NA	2.00	1.69	2.17	NA	NA
Graft + right liver capitation function (%/min/m^2)	NA	4.29	3.80	3.94	NA	NA
Ki67 labellng (%) [c]	2.2/2.1	NA	NA	9.5	NA	4.9

[a] Volume estimation based on MRI and CT scan imaging, obtained through the software Vitrea® (Vital Images Inc., Minnetonka, US-MN)
[b] Weight estimation based on Vitrea® calculation -10%
[c] Ki67 calculated in one thousand hepatocytes. GRWR: graft-to-recipient body weight ratio; NA: non-available.

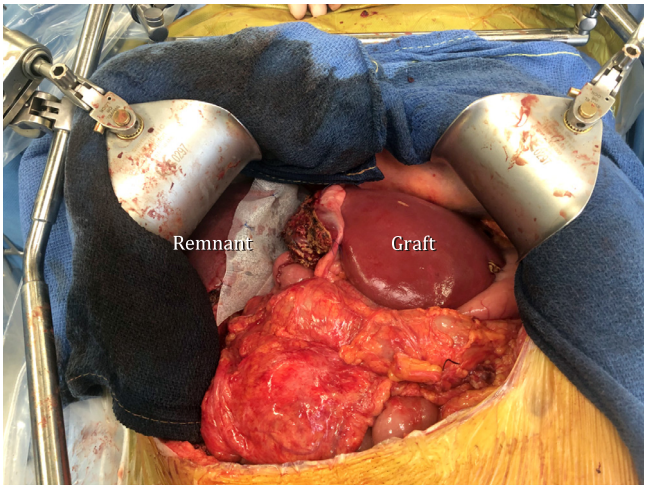


Fig. 1. Final aspect at the end of the first surgical step. Graft: Segment II-to-IV including middle hepatic vein. Remnant: Deportalized right liver, segment V-to-VIII.

10 and 12 mmHg in graft portal vein after implantation. The remaining right liver was deportalized with the suture and resection of the main portal convergence. The graft was arterialized in standard fashion, and its left hepatic biliary duct connected to a Roux-en-Y loop. Fig. 1 shows the final appearance at the end of the first surgical step. Our original aim was to perform the second step, i.e. the right hepatectomy, by laparoscopy, and, accordingly, the pedicles of the right liver were marked with vessel loops and the remnant liver wrapped in a silicone sheet. During the postoperative evolution, the recipient developed an incomplete left portal thrombosis, suspected with ultrasonography on postoperative day (POD) 12 and confirmed at POD 14 at CT scan. This was treated with therapeutic low-molecular-weight heparin at 200 U/kg per day. Functional imaging using ^{99m}Tc-labelled mebrofenin hepatobiliary scintigraphy (HBS) with SPECT was also performed on PODs 7 and 14 (Fig. 2A). The latter confirmed an overall decrease in liver uptake function. Considering the portal partial thrombosis in the transplant, right hepatectomy was delayed until the third week after transplant. Table 1 shows the evolution of the scintigraphic graft uptake and volumetric variations, both suggesting short-term liver function and volume recovery. We noticed a discrepancy between volume gain and global liver function on POD 14 (Fig. 2B). The patient did not present with postoperative ascites or signs of liver dysfunction. On POD 21, we performed a Doppler, a CT scan and a third HBS, which showed, respectively, disappearance of portal vein thrombosis, an additional increase in graft volume, and a significant improvement in graft function. Right hepatectomy was carried on the next day. The planned laparoscopy was converted to laparotomy, because of peri-hepatic dense adhesions. The immunosuppressive treatment entailed low-dose tacrolimus mono-therapy, as per our center practice.

The patient was discharged eight days after right hepatectomy. The second postoperative course was uneventful. Histological analysis of the two sequential hepatectomy specimens identified more than ten metastases. Ki67 labelling was calculated at 10%. Eight weeks after completion surgery, an angio-CT confirmed the patency of the portal axis, and therapeutic anticoagulation was discontinued. Percutaneous cholangiography at six months showed a normal biliary anastomosis. Graft biopsies were obtained at regular intervals (Fig. 3). The baseline biopsy showed normal parenchyma. At reperfusion, slight ischemia-reperfusion injury was identified. The 22-day liver biopsy displayed acute rejection Banff 6/9 (portal 2, biliary 2, vein 2). The six-month biopsy revealed minor steatosis with the absence of rejection. At baseline and reperfusion, Ki67 labelling was respectively at 2.2% and 2.1% (Fig. 3E). The 22-day biopsy found an increased proliferation rate of 9.5% (Fig. 3F), which, then, dropped to 4.9% at six months (Fig. 3G).

In essence, this report describes the first LD-RAPID performed for NET liver metastasis, whose six-month results are satisfactory for both donor and recipient, despite an extremely low initial GRWR of 0.42%. Our experience emphasises, in a novel indication, the potential of this technique and has taught us some technical concepts. Firstly, LD-RAPID is safe for the recipient. We were confronted with a sub-complete portal thrombosis of the graft, a major complication potentially responsible for acute liver failure and often requiring urgent re-transplantation in standard LDLT. Thanks to the persistence of the residual native liver, this severe adverse event brought about no liver functional consequences, in the absence of liver failure. The native liver functional reserve allowed us to conservatively manage thrombosis with anticoagulation and to safely postpone the second operation. Conversely, the deferment of a required re-transplantation in standard adult-to-adult LDLT is difficult and forewarns dramatic consequences. Secondly, the systematic measurement of flow and pressure is key to understand arterial and portal hemodynamic in this new surgical model and can lead to unforeseen evidence. In this case, our recipient had been on SSAs for a long-time for his NET. The recipient's native total-liver flow was 500 mL/min, much lower than standard portal flow in patients without cirrhosis. We surmised that chronic administration of SSAs had induced portal hypoperfusion. This low splanchnic perfusion might protect the graft from hyper flow and, therefore, from the small-for-size syndrome. Indeed, after graft implantation, the portal flow was spontaneously below the cut-off of 200 mL/mL/100 g. This circumstance avoided further portal flow modulation but exposed the recipient to portal thrombosis. Whether portal thrombosis was a consequence of a low basal portal flow or of the quick hypertrophy, which stretches graft vessels, remains to be ascertained. At any rate, graft growth should be anticipated when performing vascular anastomoses. A wide supra-

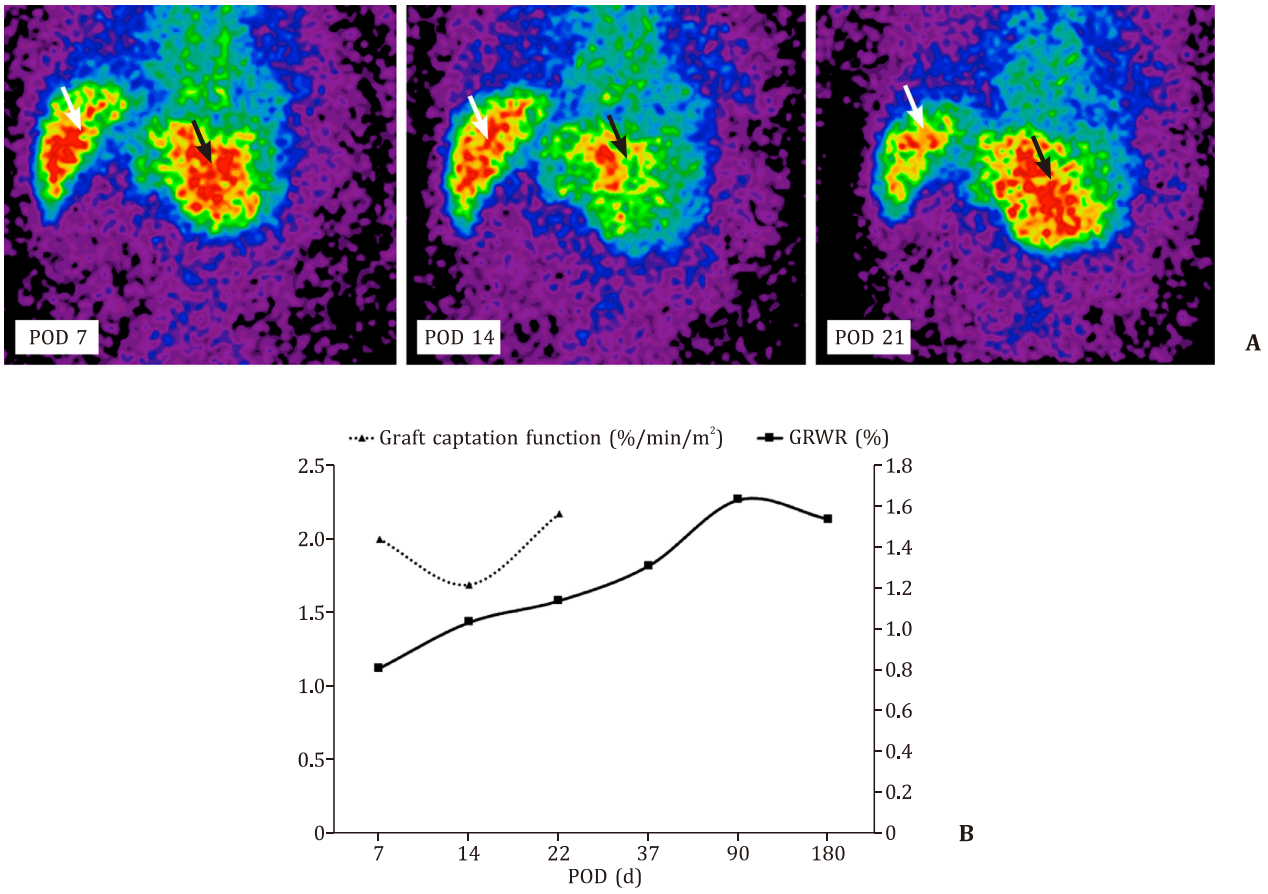


Fig. 2. A: ^{99m}Tc-mebrofenin hepatobiliary scintigraphies (HBS). Dynamic phase-3 min post venous injection. White arrows show the uptake of the native liver and black arrows the uptake in the graft. **B:** Graft-to-recipient body weight ratio (GRWR) and graft HBS function. Discrepancy between liver volume and function highlighted on POD 14 owing to the graft portal vein thrombosis.

hepatic anastomosis, with the triangulation and inferior cleavage technique, and a straight portal anastomosis, performed after systematic resection of the main convergence, are necessary. We also deduced that somatostatin and its analogues, given early (in a sort of preconditioning) or immediately after LDLT, might prevent or contain small-for-size syndrome. Thirdly, we argue for functional imaging to obtain a comparable projection of the function of the left graft and of the deportalized liver. Scintigraphy is valuable to assess the liver function, before major resection [6], and, in our experience, helped increase recipient's safety and helped decide the correct timing of the right hepatectomy. While there are not yet enough defined uptake cut-offs, functional data are more informative than simple volumetry, which is heavily influenced by post-operative congestion. Lastly, we report the first histological data on this type of auxiliary transplantation, collected up to 6 months after the procedure. Histology is the first step in the mechanistic analysis of the machinery behind the success of RAPID techniques. In this regard, a collateral study will comparatively investigate the mechanisms of rapid liver regeneration behind the auxiliary transplant model and the extended hepatectomy model, i.e. ALPPS.

To conclude, we first reported LD-RAPID in NET liver metastases with the goal of underlining its' safety for the donor and also for the recipient, because of the delayed resection of the native right liver. This game-changing strategy helped us conservatively manage a critical portal thrombosis of the left graft which was a complication after the first operation. We recorded as well a remarkable discrepancy between the volumetric increase and the functional gain of the graft, by means of sequential assessment with ^{99m}Tc-labelled mebrofenin HBS.

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None.

CRediT authorship contribution statement

Laurent Coubeau: Conceptualization, Data curation, Methodology, Writing - original draft, Writing - review & editing. **Samuele Iesari:** Formal analysis, Writing - review & editing. **Paulina Henry:** Data curation, Writing - review & editing. **Philippe D'Abadie:** Data curation, Writing - review & editing. **Aude Vanbuggenhout:** Data curation, Writing - review & editing. **Raymond Reding:** Writing - review & editing.

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Ethical approval

This study was approved by the Ethical Committee of Université catholique de Louvain (CEHF 2020/19FEV105). Written informed consent for publication was obtained from the patient.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

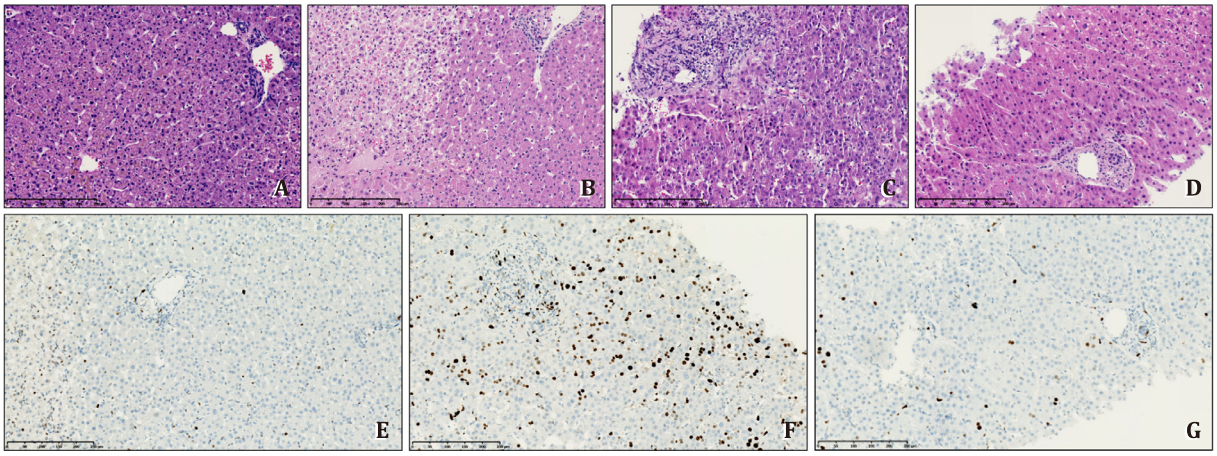


Fig. 3. Graft histopathology (hematoxylin eosin and Ki67 immuno-staining, original magnification × 15). **A:** Baseline liver biopsy showing normal liver parenchyma. Only a few scattered lymphocytes are visible within the portal tract and in the lobules. **B:** Reperfusion biopsy showing eosinophils and neutrophils in the portal tract along with a mild centrolobular necrosis consistent with reperfusion damage. The proliferation rate of hepatocytes is similar to that of the baseline biopsy, with an average of 2.1%. **C:** Moderate acute rejection Banff 6/9 (portal 2, biliary 2, vein 2) on POD 22. **D:** Six-month biopsy showing normal portal tracts with no more sign of rejection. Only mild steatosis was described, probably as a sequela resulting from previously described lesions. **E:** Immunohistochemistry for Ki67 shows an average proliferation rate of 2.2%. **F:** Immunostaining for Ki67 emphasizes an increased hepatocellular proliferation with an average rate of 9.5%. Special attention was given to the count to prevent including any proliferative inflammatory cells. **G:** Hepatocellular proliferation rate slightly decreases to an average of 4.9%.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hbpd.2021.08.007.

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