Received: 5 June 2020 | Revised: 16 July 2020 | Accepted: 17 July 2020

DOI: 10.1111/ajt.16222

CASE REPORT

AJT

Heterotopic segmental liver transplantation on splenic vessels after splenectomy with delayed native hepatectomy after graft regeneration: A new technique to enhance liver transplantation

Matteo Ravaioli[1] | Giovanni Brandi[2] | Antonio Siniscalchi[1] | Matteo Renzulli[2] | Chiara Bonatti[1] | Guido Fallani[1] | Enrico Prosperi[1] | Matteo Serenari[1] | Giuliana Germinario[1] | Massimo Del Gaudio[1] | Chiara Zanfi[1] | Federica Odaldi[1] | Valentina Rosa Bertuzzo[1] | Eddi Pasqualini[1] | Lorenzo Maroni[1] | Giacomo Frascaroli[1] | Anna Rossetto[1] | Maria Cristina Morelli[1] | Luca Vizioli[1] | Carla Serra[1] | Gabriela Sangiorgi[3] | Antonia D'Errico[4] | Federico Contedini[5] | Matteo Cescon[1]

[1]Department of General Surgery and Transplantation, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

[2]Department of Experimental, Diagnostic and Specialty Medicine, S.Orsola-Malpighi University Hospital, Bologna, Italy

[3]Emilia-Romagna Transplant Reference Centre, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

[4]Department of Pathology, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

[5]Department of Medical and Surgical Sciences, Plastic Surgery Unit, S.Orsola-Malpighi Hospital, University of Bologna, Italy

Correspondence
Matteo Ravaioli
Email: mrava1@hotmail.com; matteo.ravaioli@aosp.bo.it; matteo.ravaioli6@unibo.it

Funding information
National Health System Research

We describe a patient with liver metastases from colorectal cancer treated with chemotherapy and hepatic resection, who developed unresectable multifocal liver recurrence and who received liver transplantation using a novel planned technique: heterotopic transplantation of segment 2-3 in the splenic fossa with splenectomy and delayed hepatectomy after regeneration of the transplanted graft. We transplanted a segmental liver graft after in-situ splitting without any impact on the waiting list, as it was previously rejected for pediatric and adult transplantation. The volume of the graft was insufficient to provide liver function to the recipient, so we performed this novel operation. The graft was anastomosed to the splenic vessels after splenectomy, and the native liver portal flow was modulated to enhance graft regeneration, leaving the native recipient liver intact. The volume of the graft doubled during the next 2 weeks and the native liver was removed. After 8 months, the patient lives with a functioning liver in the splenic fossa and without abdominal tumor recurrence. This is the first case reported of a segmental graft transplanted replacing the spleen and modulating the portal flow to favor graft growth, with delayed native hepatectomy.

KEYWORDS
clinical research/practice, liver disease, liver transplantation/hepatology, liver transplantation: auxiliary

1 | INTRODUCTION

Liver transplantation (LT) for the treatment of unresectable colorectal liver metastases has shown promising results in selected patients,[1,2] and auxiliary segment 2-3 LT with left lobe resection and delayed total hepatectomy has been proposed as a strategy to transplant oncological patients with minimal impact on the waiting list. Some procedures of Resection and partial liver segment 2/3 transplantation with delayed total hepatectomy (RAPID) are reported.[3,4] The limitation of this strategy is related to the complex surgery, the possible tumor recurrence due to the surgical manipulation, and

systemic dissemination of the disease favored by the immunosuppression therapy.

Considering a previous experience of heterotopic LT in the splenic fossa,[5-7] we planned a novel procedure: heterotopic transplantation of segment 2-3 in the splenic fossa, removing the spleen and modulating the native portal flow with delayed hepatectomy after regeneration of the transplanted graft.[8] The procedure of Heterotopic transplantation of segments 2 and 3 using the splenic vein and artery after splenectomy and with delayed total hepatectomy (RAVAS) was never reported.

The possibility to transplant a small graft replacing the spleen and waiting for its growth before native hepatectomy may provide new opportunities for LT in the future besides extended criteria donors, as segmental grafts may be retrieved by living donation with low donor risk or by splitting procedure.[9,10] The safety and the efficacy of this procedure need to be confirmed by other cases and center experiences.

The principal theoretical advantage of the RAVAS technique compared to the RAPID procedure is the absence of manipulation of the native liver with the consequent lower risk of bleeding and biliary complications and the possible application even in case of previous hepatectomies on the native liver (see Supplemental Material).

2 | CASE REPORT

2.1 | Patient description

The patient to be treated was a 40-year-old white male with adenocarcinoma of the sigmoid colon (endoscopic biopsy report: G2 KRAS, NRAS, BRAF wild-type) and unresectable liver metastases, CEA level 202 ng/mL. Neoadjuvant chemotherapy with FOLFOXIRI and cetuximab (6 cycles) was given before left colectomy (histological report: pT3 N2 M1), which was followed by chemotherapy (6 cycles), also with FOLFOXIRI and cetuximab.

The radiological restaging after 6 months of therapy from the first evaluation showed no extrahepatic disease, with normalization of CEA level and partial response on the liver metastases, which were reevaluated as resectable. A 2-stage hepatectomy was planned and the patient underwent a first operation with 4 wedge resections and 3 radiofrequency ablation treatments in the left liver, followed by radiological portal vein embolization 10 days after the procedure and—after 4 weeks—a second operation of right hepatectomy.

The postoperative course was complicated by a severe biliary fistula originating from an ischemic injury of the biliary tract unresponsive to endoscopic treatment, finally managed with external percutaneous transhepatic biliary drainage.

Subsequent tumor restaging 6 months after the right hepatectomy showed multifocal recurrence in the liver remnant.

Further chemotherapy with FOLFIRI and panitumumab was started, which obtained stabilization of the liver disease for 6 months, although frequent suspensions occurred due to episodes of cholangitis related to the percutaneous biliary drainage. Throughout chemotherapy, an enlarged lymph node was evidenced at the hepatic hilum, close to the vessels.

Before consideration for LT, the patient presented with recurrent cholangitis with initial liver function impairment, stable liver disease, and with a suspect lymph node recurrence not suitable for safe biopsy, although a fluorodeoxyglucose positron emission tomography scan was negative (Supporting Information).

2.2 | Implantation of the graft (Video S1)

The liver segment 2-3 graft was procured after an in-situ splitting procedure of a 55-year-old donation after brain death woman whose liver was rejected for pediatric LT due to alcohol use of the donor and liver macrosteatosis of 10%.

The graft presented with left portal vein and hepatic artery, a single left suprahepatic vein, and a single biliary duct.

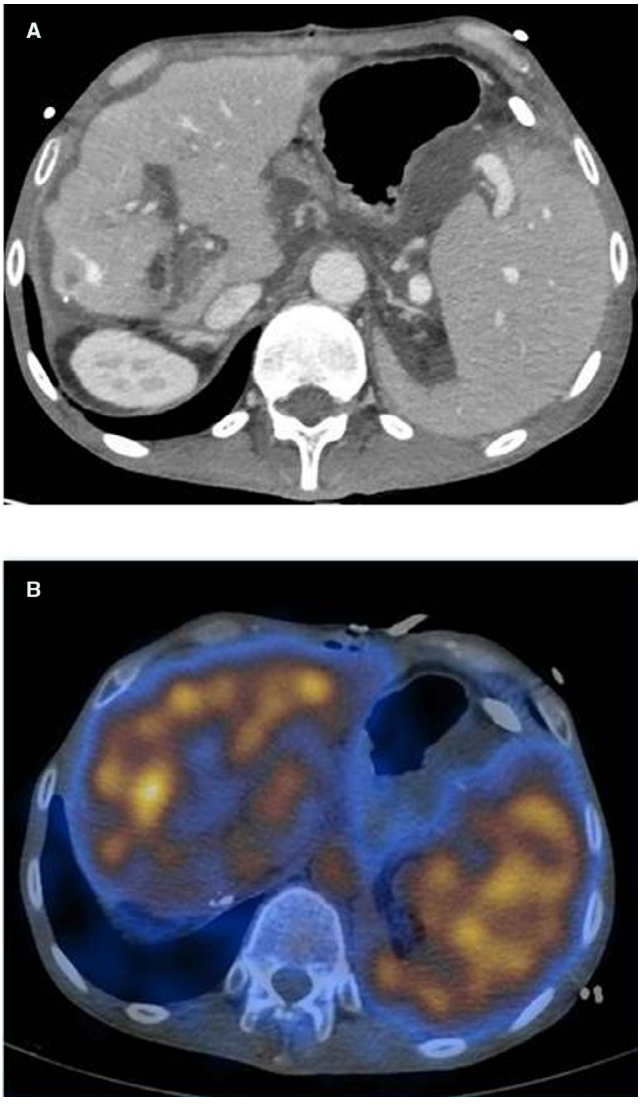

FIGURE 1 Computed tomography scan of the heterotopic auxiliary segment 2-3 liver transplantation and native liver (A) and scintigraphy (B) showing a function of 50% for each liver [Colour figure can be viewed at wileyonlinelibrary.com]

The liver graft weighed 400 g and the recipient weighed 64 kg, so the graft/recipient body weight (GRWR) was 0.6%, which is considered at risk for small-for-size syndrome.[11-15]

The recipient had no portal hypertension but considering the low GRWR and the very complex surgery for 1-stage transplantation, we proceeded with the planned intervention. As described in the previous article,[8] we would have performed a standard partial LT only if the GRWR was higher than 1%. Cryopreserved vascular grafts were anastomosed to the portal vein and the hepatic artery to lengthen the vessels. The left suprahepatic ostium was enlarged through anastomosis with a cryopreserved vein graft, which was further anastomosed to an aortic cryopreserved graft.

The recipient operation started with bilateral subcostal incision and isolation of the spleen. The splenic vessels were dissected and clamped, and the spleen was removed.

The left renal vein was dissected, ligating the adrenal and gonadal veins; the left kidney had 2 arteries, which were also isolated.

The graft was placed in the splenic fossa preserving the anatomical orientation of the left lobe, which lay by gravity in contact with the left diaphragm.

The implantation of the graft started with the anastomosis between the splenic vein and the cryopreserved graft already connected to the left portal vein. Anastomotic leakage was checked by moving the clamp on the left portal vein at the end of the venous anastomosis. Then, the arterial anastomosis was performed between the splenic artery and the cryopreserved graft, already attached to the left hepatic artery. Similarly, hemostasis was checked moving the clamp on the left hepatic artery.

The aortic cryopreserved graft was anastomosed in a termino-lateral fashion to the left renal vein, upon clamping of the renal arteries to prevent congestion of the kidney.

The graft was perfused with the recipient blood, removing the clamps from the left portal vein and left hepatic artery. First-pass blood was flushed through a collateral branch of the aortic graft, which was then sutured before removing the clamp from the left renal vein, obtaining complete reperfusion of the vascular system. To direct the portal flow to the transplanted graft, a tourniquet was placed around the native hilum and clamped, maintaining the hepatic artery flow intact (Figure S1). The flow was checked with intraoperative ultrasound, but portal pressure was not directly assessed.

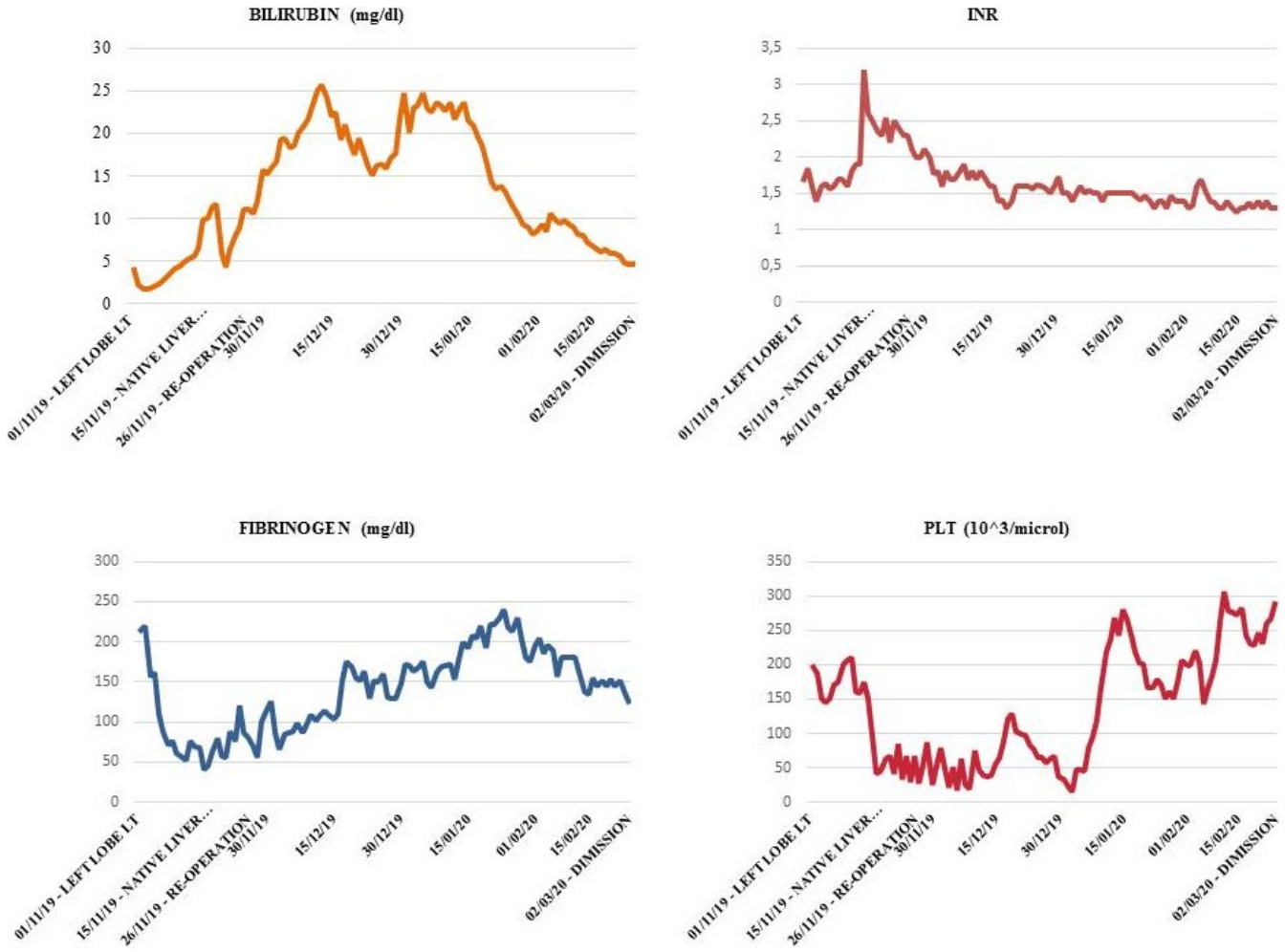

FIGURE 2 Liver function test during the first and second operation. INR, international normalized ratio; LT, liver transplant; PLT, platelet count

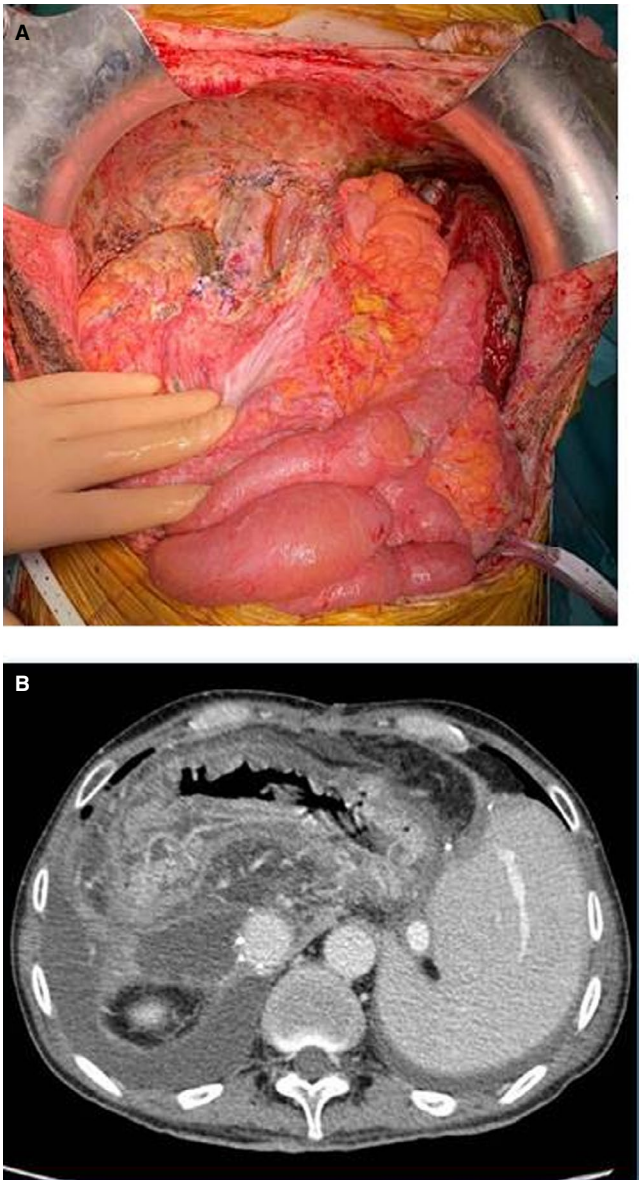

FIGURE 3 Intraoperative abdomen after native hepatectomy and with graft transplanted in the left side (A); computed tomography scan of the heterotopic auxiliary segment 2-3 liver transplantation 3 months after the procedure (B) [Colour figure can be viewed at wileyonlinelibrary.com]

We completed the operation performing a hepaticojejunostomy on Roux-en-Y limb with 6-0 Prolene. The duration of the operation was 10 hours, without any intraoperative surgical or anesthesiological complication (Supporting Information).

2.3 | Native liver hepatectomy

After 2 weeks the computed tomography (CT) scan showed a doubled volume of the graft, and hepatobiliary scintigraphy confirmed that the function was equally distributed between the 2 livers (Figure 1). Also, the native liver developed a portal vein thrombosis due to the tourniquet; as laboratory tests showed a fibrinogen concentration drop (Figure 2), we suspected a sequestration due to the portal vein thrombosis, even if the platelet count was >100 000/L.

The arterial phase of the CT scan and magnetic resonance scan showed a steal syndrome from the hepatic artery of the native liver to the transplanted graft, similar to buffer syndrome[16]: We correlated this event with a progressive increase in the bilirubin blood level (Figure 2).

Even if daily ultrasound examination of the graft inflow perfusion did not evidence any pathological issues, we were concerned about the risk of arterial hypoperfusion of the biliary tree. For this reason, considering also the oncological risk of tumor spread to the transplanted graft, we planned the native hepatectomy after 2 weeks, even if scintigraphy results were unclear about the function of the graft compared to the native liver and the bilirubin serum concentration was increasing (see Supplemental Material).

Native hepatectomy was complex due to the previous surgeries and to the presence of an enlarged lymph node, which was adherent to the portal vein and hepatic artery. We managed to remove the native liver while preserving the vena cava, removing the thrombus in the portal vein and removing the enlarged lymph node.

Upon completion of the native hepatectomy, portal pressure was assessed showing a value of 16 mm Hg. We performed a liver biopsy on the graft, which showed a moderate cholestasis without any signs of rejection. The histology of the native liver showed a multifocal area of adenocarcinoma metastasis with different rates of tumor necrosis; the enlarged lymph node had a 70% necrotic area, but the remaining part showed active tumor.

2.4 | Postoperative course

At the time of the second intervention, the graft had a volume of 650 cm^3, reaching a GRWR close to 1%, which is considered a safe limit to avoid small-for-graft syndrome. Despite those values, the patient developed encephalopathy and reversible liver failure, with intact renal function. Therefore, he was managed with hemofiltration to reduce the ammonia levels and to protect the nervous system. The postoperative course was also complicated with small-bowel perforation, which required relaparotomy and a small ileal resection and anastomosis. Liver function progressively improved (Figure 2), and a second liver biopsy showed decreasing cholestasis, associated with mitoses and regeneration of hepatocytes.

Due to the development of tacrolimus-related neurotoxicity, the immunosuppressive regimen was switched to cyclosporine with resolution of the neurological symptoms.

After 8 months, the patient is in good clinical condition, with a functioning liver on the left side (last CT scan volume 830 cm^3) of the abdomen and without any tumor recurrence (Figure 3). A longer follow-up will permit evaluation of the oncological efficacy of the transplant procedure for this patient, but in terms of liver function impairment related to cholangitis, cure was achieved.

3 | DISCUSSION

This is the first reported case of a segmental graft transplanted replacing the spleen and modulating the portal flow to favor graft growth, with delayed native hepatectomy.

This technique may encourage other clinical strategies for LT in addition to living donation or extended criteria donors,[10] because the procurement of a left lobe may be obtained safely through a split procedure; furthermore, the opportunity to wait for the growth of the graft may permit using split grafts even from suboptimal donors.

The patient had no suitable living donor candidates, and split graft procurement from a suboptimal DBD donor guaranteed that no patient on the waiting list would have disadvantages.

The surgical procedure still needs refinements to be developed through further experience; the timing of native hepatectomy and the technique of portal flow modulation are probably—based on this case—the key issues to be better addressed. Beside those points, many other technical aspects will emerge with more experience (eg, complexity of hepaticojejunostomy in partial grafts, and indications for the procedure). Moreover, the follow-up of the patient needs to be longer.

The liver failure condition that developed in the patient after native hepatectomy may suggest that the timing of the second operation should probably be postponed to at least 4 weeks after transplantation; also, functional assessment processes need to be implemented, to better compare the graft to the native liver in terms of function. Portal pressure may be another important element to consider for native hepatectomy planning; in our case the high values measured during the last stage are probably related to the reversible liver failure.

Some authors may argue that the absence of portal hypertension of the recipient and the GRWR of 0.6% may permit a 1-stage transplantation, with standard modulation of the portal flow through portacaval shunt or splenectomy, but the complex native hepatectomy due to previous right hepatectomy and biliary fistula and the encasement of the hilum with the pathological lymph node were relevant obstacles for a 1-stage operation. Furthermore, the patient developed reversible liver failure even if graft function was significantly increasing. The functional competition among the native liver and the auxiliary graft was investigated in the past[17,18] in cases of metabolic liver disease transplanted with auxiliary partial graft; this amount of knowledge was recently improved through the scientific advancements on liver partition and portal vein ligation during staged hepatectomy.[19,20]

While the present operation has gained many insights from these studies, further experience with this peculiar technique is recommended to encourage its wider use. In our opinion, it is important to present this preliminary experience to the scientific community, because the RAVAS technique may enhance the spread of LT indications; thus, to achieve such purpose, many other transplant centers should perform and gain experience with this procedure.

ACKNOWLEDGMENTS

We would like to thank the following physicians for their clinical and scientific support: AD Pinna; U. Cillo; N. Costa; M. Cardillo; P. Iannone; E. Casadio; S. Spedicato; M. Cimatti; A. Dante; A. Bianchini; C. Laici; E. Bernardi; I. Aprile; A. Baldan; C. Felicani; S. Berardi; V. Vero; A. Vitale; R. Golfieri; A. Cappelli; PL Viale; M. Ranieri; F. Vasuri; and D. Malvi. We would like to thank National Health System Research, which funded this clinical trial for Bologna Transplant Center (RF-2016-02364732, Bando Ricerca Finalizzata 2016, Ministero della Salute – Rome, Italy).

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Matteo Ravaioli https://orcid.org/0000-0001-5862-6151
Giovanni Brandi https://orcid.org/0000-0003-0013-2858
Antonio Siniscalchi https://orcid.org/0000-0002-2014-4680
Matteo Renzulli https://orcid.org/0000-0002-1311-5670
Chiara Bonatti https://orcid.org/0000-0003-4203-7824
Guido Fallani https://orcid.org/0000-0002-5774-7696
Enrico Prosperi https://orcid.org/0000-0002-9389-1812
Matteo Serenari https://orcid.org/0000-0003-1471-8585
Giuliana Germinario https://orcid.org/0000-0002-8019-1956
Massimo Del Gaudio https://orcid.org/0000-0003-2754-1627
Chiara Zanfi https://orcid.org/0000-0002-7141-7386
Federica Odaldi https://orcid.org/0000-0003-2910-2273
Valentina Rosa Bertuzzo https://orcid.org/0000-0002-4339-4877
Lorenzo Maroni https://orcid.org/0000-0003-4195-3580
Giacomo Frascaroli https://orcid.org/0000-0002-9235-9744
Anna Rossetto https://orcid.org/0000-0002-2682-4898
Maria Cristina Morelli https://orcid.org/0000-0002-9742-1981
Luca Vizioli https://orcid.org/0000-0003-2278-2181
Carla Serra https://orcid.org/0000-0001-5555-0745
Gabriela Sangiorgi https://orcid.org/0000-0003-2229-4903
Antonia D'Errico https://orcid.org/0000-0003-2747-3732
Matteo Cescon https://orcid.org/0000-0003-1715-3794

REFERENCES

1. Hagness M, Foss A, Line PD, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg*. 2013;257:800-806.
2. Serenari M, Ravaioli M. Refining selection criteria to further increase survival benefit in liver transplantation for unresectable colorectal liver metastases. *Hepatobiliary Surg Nutr*. 2019;9 (4): 490–492.

3. Line PD, Hagness M, Berstad AE, et al. A novel concept for partial liver transplantation in nonresectable colorectal liver metastases: the RAPID concept. *Ann Surg*. 2015;262(1):e5-e9.
4. Königsrainer A, Templin S, Capobianco I, et al. Paradigm shift in the management of irresectable colorectal liver metastases: living donor auxiliary partial orthotopic liver transplantation in combination with two-stage hepatectomy (LD-RAPID). *Ann Surg*. 2019;270(2):327-332.
5. Azoulay D, Lahat E, Salloum C, et al. Heterotopic liver retransplantation for impossible former graft explantation. *Hepatology*. 2017;66:655-657.
6. Scatton O, Azoulay D, Castaing D, et al. Transplantation auxiliaire pour cirrhose. Une alternative possible pour l'utilisation de greffons de petit poids? [Auxiliary partial orthotopic liver transplantation using small grafts. A way to avoid small-for-size syndrome?] *Gastroenterol Clin Biol*. 2005;29:76-79.
7. Dou K, Wang D, Tao K, et al. A modified heterotopic auxiliary living donor liver transplantation: report of a case. *Ann Hepatol*. 2014;13:399-403.
8. Ravaioli M, Fallani G, Cescon M, et al. Heterotopic auxiliary segment 2–3 liver transplantation with delayed total hepatectomy: New strategies for nonresectable colorectal liver metastases. *Surgery*. 2018;164:601-603.
9. Roll GR, Parekh JR, Parker WF, et al. Left hepatectomy versus right hepatectomy for living donor liver transplantation: shifting the risk from the donor to the recipient. *Liver Transpl*. 2013;19:472-481.
10. Ravaioli M, Grande G, Di Gioia P, et al. Risk avoidance and liver transplantation: a single-center experience in a national network. *Ann Surg*. 2016;264(5):778-786.
11. Ravaioli M, Cescon M, Grazi GL, et al. Liver transplantation with left lateral segments in adults: a risk or a possibility? *Transplantation*. 2009;88:849-850.
12. Kilic M, Seu P, Stribling RJ, et al. In situ splitting of the cadaveric liver for two adult recipients. *Transplantation*. 2001;2:1853-1858.
13. Ikegami T, Yoshizumi T, Sakata K, et al. Left lobe living donor liver transplantation in adults: what is the safety limit? *Liver Transpl*. 2016;22:1666-1675.
14. Hwang S, Lee SG, Lee YJ, et al. Lesson learned from 1,000 living donor liver transplantations in a single center: how to make living donations safe. *Liver Transpl*. 2006;12:920-927.
15. Reichman TW, Sandroussi C, Azouz SM, et al. Living donor hepatectomy: the importance of the residual liver volume. *Liver Transpl*. 2011;17:1404-1411.
16. Liu C, Song JL, Lu WS, et al. Hepatic arterial buffer response maintains the homeostasis of graft hemodynamics in patient receiving living donor liver transplantation. *Dig Dis Sci*. 2016;61:464-473.
17. Serenari M, Ardiles V, Ravaioli M, et al. Comment on "Rapid but not harmful: Functional evaluation with hepatobiliary scintigraphy after accelerated liver regeneration techniques". *Ann Surg*. 2019;270:e61-e62.
18. Kasahara M, Takada Y, Egawa H, et al. Auxiliary partial orthotopic living donor liver transplantation: Kyoto University experience. *Am J Transplant*. 2005;5:558-565.
19. Schadde E, Tsatsaris C, Swiderska-Syn M, et al. Hypoxia of the growing liver accelerates regeneration. *Surgery*. 2017;161(3):666-679.
20. Dili A, Bertrand C, Lebrun V, et al. Hypoxia protects the liver from Small For Size Syndrome: A lesson learned from the associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure in rats. *Am J Transplant*. 2019;19:2979-2990.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Ravaioli M, Brandi G, Siniscalchi A, et al. Heterotopic segmental liver transplantation on splenic vessels after splenectomy with delayed native hepatectomy after graft regeneration: A new technique to enhance liver transplantation. *Am J Transplant*. 2021;21:870–875. https://doi.org/10.1111/ajt.16222