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Liver transplantation using the otherwise-discarded partial liver resection graft with hepatic benign tumor

Analysis of a preliminary experience on 15 consecutive cases

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Abstract

Rationale: The shortage of available donor organs limits the development of liver transplantation. This case-serial study presents a novel way to expand the donor pool by using the other-wise discarded partial liver resection graft with hepatic benign tumor.

Patient concerns: From 2012 to 2016, 15 patients with hepatic lesions were admitted to our hospital. 12 patients suffered from right epigastric discomfort and 3 patients worried about uncertain diagnosis.

Interventions: Regular hepatic lobectomy was performed for all patients and after back-table management the resected partial liver grafts were used for patients with end-stage liver disease for liver transplantation.

Outcomes: All patients had improved liver function within 1 week of transplantation. Patients had no serious small-for-size syndrome despite graft-to-recipient weight ratio less than 0.8%. Back-table hepatic venous reconstruction with prosthetic vascular grafts was performed without serious early complications, and late thrombosis in vessel graft did not affect liver function. Postoperative computed tomography scans demonstrated a remarkable growth in graft volume and a continuous decrease in hemangioma in recipients using the grafts with hemangioma. One patient died from pulmonary embolism on day 7 after transplant, and the rest of 14 recipients had been surviving well, especially recipient 1 for more than 4 years, although 3 recipients had tumor recurrence and had been treated with sorafenib.

Diagnoses: The postoperative pathological diagnosis reported cavernous hemangioma (n = 11), perivascular epithelioid cell tumor (n = 2), inflammatory pseudotumor for (n = 1), and focal nodular hyperplasia (n = 1).

Lessons: The partial liver grafts with hepatic benign tumors are safe for liver transplantation. In addition, prosthetic vascular grafts can be used for hepatic venous outflow reconstruction, especially in right lobe liver transplantation.

Abbreviations: CT = computed tomography, FNH = focal nodular hyperplasia, GRWR = graft-recipient weight ratio, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, IPT = inflammatory pseudotumor, IVC = inferior vena cava, LPRWR = liver parenchyma-recipient weight ratio, MELD = Model for End-Stage Liver Disease, MHV = middle hepatic vein, PEComa = perivascular epithelioid cell tumor, PELD = Pediatric End-Stage Liver Disease Model, SFSS = small-for-size syndrome.

Keywords: hepatic benign tumor, liver transplantation, marginal donor graft, prosthetic vascular graft

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1. Introduction

As improvements of surgical techniques and innovations on medicine, liver transplantation has nowadays been accepted as an optimum treatment for more end-stage liver diseases.[1,2] Today, liver transplantation is still limited by a scarcity of available donor organs, although the development of surgical techniques such as split and living-related donation is helpful but insufficient. Thereafter, the emergence of donation after cardiac death (DCD), subsequent donation after brain death (DBD), and marginal donors further palliates the shortage with the improved graft quality and are potential for liver grafts.[3–5] Liver transplantation using liver allografts from marginal donors has been accepted owing to a severe mismatch between a scarce source of donors and the huge demand of livers. Furthermore, the use of marginal or expanded pool donors is increasingly common, as liver donor acceptance criteria are relaxed, which was shown to have outcome similar to ideal graft.[6]

Hepatic benign tumor including hemangioma, focal nodular hyperplasia (FNH), perivascular epithelioid cell tumor (PEComa), and inflammatory pseudotumor (IPT) necessitates surgical resection in cases of diagnostic uncertainty and development of symptoms.[7] Some sporadic cases of liver transplantations using deceased or living liver grafts with cavernous hemangioma have been described previously, including 1 case performed in our center.[8–12] The main concerns about the transplantations by using the marginal donor grafts with hemangioma are the evolution of hemangioma, the influence of hemangioma on donor graft, and the need to assess the functional donor liver graft volume (GV) to avoid the small-for-size syndrome (SFSS). The partial liver resection grafts with hepatic benign tumor are potential for liver transplant, but few data are currently available. We report here promising data on preoperative assessment, surgical procedure, and clinical prognosis of liver transplantations using the otherwise-discarded partial liver resection grafts with hepatic benign tumor from donors who underwent regular hepatic lobectomy. In addition, prevention of SFSS by hepatic venous outflow congestion was achieved by hepatic venous reconstruction, especially in right lobe donor grafts with prosthetic vessels.

2. Patients and methods

2.1. Donor and patient selection

Liver transplantations were performed between November 2012 and September 2016 at Liver Transplantation Center of the First Affiliated Hospital of Nanjing Medical University. Like patients who had hepatocellular carcinoma (HCC) out of the Milan criteria or who were in serious condition of end-stage liver disease, these 15 patients were admitted for liver transplantation in the Marginal Donor Liver Study. This study defined extended criteria for liver grafts with benign tumors, including hemangioma, FNH, PEComa, IPT, etc. We considered all the patients with hemangioma or other benign tumors, which necessitated regular hepatectomy, to be the candidate donors, with an exclusion criterion of those who have positive hepatitis serology or any underlying diseases. In addition, 4 cases of marginal donor grafts with cavernous hemangioma were excluded due to intraoperative bleeding of hemangioma (Supplemental Figure 1A, B and D, http://links.lww.com/MD/B812) or performance of conservative local excision of hemangioma (Supplemental Figure 1 C, http://links.lww.com/MD/B812) on the basis of intraoperative exploration. This study was approved by our institutional ethics committee. Written informed consent to donation and acceptance of the extended-criteria donor liver grafts was obtained from all the potential transplant donors and recipients, respectively.

2.2. Organ donation protocol

All potential donors were also admitted for the Marginal Donor Liver Study with the approval of our hospital ethics committee. Donors had medical history recorded and routine investigations done, including blood tests, electrocardiogram, chest radiography, and abdominal thin-layer computed tomography (CT) scans. All CT images were analyzed by using a quantitative imaging system (IQQA-Liver; EDDA Technology Inc., Princeton, NJ) to evaluate liver volume, tumor volume, to-be-resected GV, and remnant liver volume. According to blood type and graft weight/volume, 15 suitable transplant recipients including 3 children were included.

To procure the graft, regular hepatic lobectomy was performed by using cavitron ultrasonic surgical aspirator (CUSA) instead of the pringle maneuver. Intraoperative rapid biopsy confirmed the tumor to be benign tumor, including 11 cases of hemangioma, 2 PEComa, 1 IPT, and 1 FNH. These tumors were reevaluated by ultrasonography for its location and relation with hepatic vein and portal vein during the operation. Meanwhile, intraoperative cholangiography was performed to determine the anatomy of hepatic biliary tree.

2.3. Ex vivo graft preparation

As soon as taken out from the donors, the partial liver grafts were infused with enough cold University of Wisconsin (UW) solution through the portal vein until clear UW solution flowed out. Hepatic artery was also infused using cold normal saline with heparin. The grafts were preserved in cold UW solution. Warm ischemic time was only 1 to 2 minutes in all grafts. After careful investigation on hepatic venous outflow, hepatic venoplasty was performed at the back table.

2.4. Transplantation procedure

The donor grafts were infused with cold compound sodium chloride solution before implantation. A modified piggyback orthotopic liver transplantation procedure was performed in 5 patients with preservation of the recipient side inferior vena cava (IVC), while classic orthotopic liver transplantation was performed in the other 10 patients with removal of the recipient side IVC. For 3 cases of pediatric liver transplant and 1 adult liver transplant, reconstruction of hepatic biliary duct was performed by Roux-en-Y biliary-jejunal anastomosis.

3. Results

3.1. Demographic characteristics of patients and donors

Of the 15 transplantations, 12 were adult-to-adult liver transplantation and 3 were adult-to-child. Thirteen of 15 patients were male and 2 were women, and 6 of 15 donors were female and 9 were male. The median age of the patients was 46.4 years (range: 27–68) at the time of transplantation, and 3 children aged 20, 7, and 7.5 months, respectively. The age of the donors ranged from 24 to 60 years with a median age of 45.9 years at the time of the operation. Patient and donor demographics are summarized in Table 1. Blood types in 12 pairs of recipients and donors were identical except 3 in whom they were compatible. Nine patients

Table 1

Demographic characteristics of patients and donors and information of surgery.

Characteristics	
Patients	
Number	15
Adults/Children	12/3
Age, y/mo (median, range)	47 (27–68)/12 (7–20)
Gender (male/female)	13/2
Body weight, kg (median, range)	64 (53–77)
Original liver disease (HCC/BA /cirrhosis/ALF)	9/3/2/1
Hepatitis B virus infection	9
MELD score (median, range)	10 (6–30)
Child–Pugh score (median, range)	7 (5–10)
PELD score (median, range)	18 (17–19)
Donors	
Number	15
Age, y (median, range)	46 (24–60)
Gender (male/female)	6/9
Body weight, kg (median, range)	65 (54–80)
Original liver disease (hemangioma/PEComa/IPT/FNH)	11/2/1/1
Range of lesion volume, cm^3	5.2–770.8
Location of hepatic benign tumor (left/right lobe)	4/11
Surgery	
Graft type (left/right lobe)	4/11
Graft weight, g	200–1150
Involvement of MHV (yes/no)	1/14
GRWR, % (median, range)	1.37 (0.78–3.24)
LPRWR, % (median, range)	1.12 (0.50–3.24)
Removal of hepatic lesion (yes/no)	5/10

ALF = acute liver failure; BA = biliary atresia; FNH = focal nodular hyperplasia; GRWR = graft-to-recipient weight ratio; HCC = hepatocellular carcinoma; IPT = inflammatory pseudotumor; LPRWR = liver parenchyma-to-recipient weight ratio; MELD = Model for End-Stage Liver Disease; MHV = middle hepatic vein; PEComa = perivascular epithelioid cell tumor; PELD = Pediatric End-Stage Liver Disease Model.

presented with HCC beyond the Milan criteria, secondary to hepatitis B virus (HBV)-induced or alcoholic cirrhosis. Three children were admitted for cholestatic cirrhosis due to congenital biliary atresia, with progressing jaundice irrespective of portoenterostomy. One patient presented with acute drug-induced liver failure. Two patients presented with HBV-induced cirrhosis.

All donors tolerated the operation well without significant intraoperative or immediately postoperative complications and recovered well. All patients made a quick recovery of the graft after transplantation, but patient 2 died from pulmonary embolism on day 7 after transplantation. The graft type was right lobe donor graft in 10 patients, and left lobe in 4 patients, with the inclusion of the middle hepatic vein (MHV) in only 1 patient. Graft-recipient weight ratio (GRWR) ranged from 0.78% to 3.24% with a median value of 1.37%, whereas the minimum of liver parenchyma-recipient weight ratio (LPRWR) that represents graft weight by subtracting weight of hepatic tumors fell to 0.50% with a median value of 1.12%. Ten patients had a LPRWR less than 0.8%. Ten donor grafts were implanted without resection of hepatic hemangioma and FNH, and 5 grafts were prepared by removal of hepatic tumors (2 hemangiomas, 2 PEComas, and 1 IPT) at the back table. All the 14 recipients had been surviving well, especially recipient 1 for more than 4 years, as shown in Supplemental Figure 2,http://links.lww.com/MD/B812 , although 3 recipients had HCC recurrence.

3.2. Evolution of the grafts and hemangiomas

Nine patients were transplanted of the partial liver resection grafts with inclusion of cavernous hemangioma and followed up. However, no hemangioma-associated complications were observed within the postoperative duration in all these patients. Volumetric CT scans showed that the graft made an obvious growth in volume with no observation of change of hemangioma volume in patient 1 as described previously.[11] Long-term follow-up for 50 months after transplantation using CT scans revealed the growing volume of liver graft and a continuous decrease in hemangioma volume in patient 1 (Fig. 1A, B). For patient 3, volumetric CT on day 21 and 2 months after surgery also revealed a

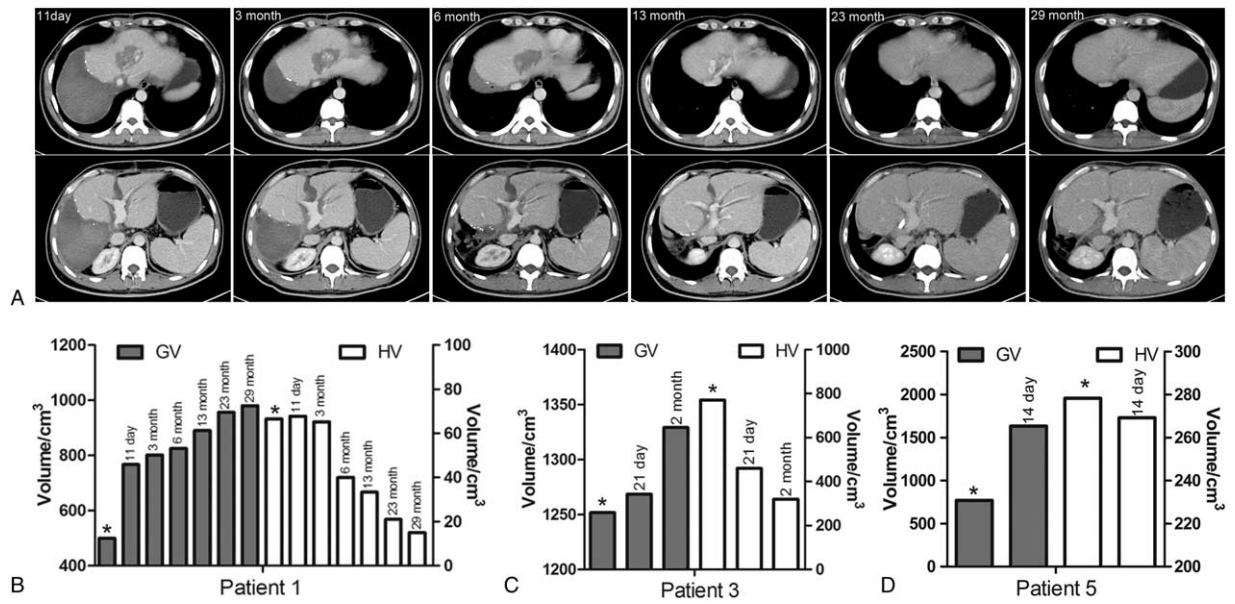

Figure 1. Postoperative changes of graft and hemangioma volume (GV and HV) in patient 1 (A and B), patient 3 (C), and patient 5 (D). *The original graft volume.

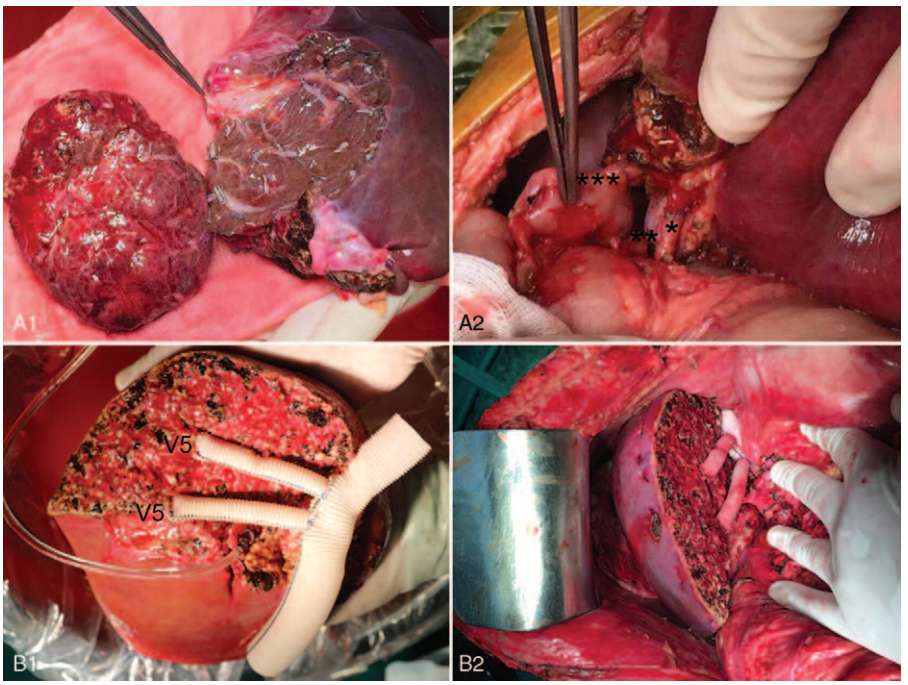

Figure 2. Marginal donor left lobe (A1 and A2) and right lobe (B1 and B2) liver graft liver transplantation. Anastomosis of hepatic artery (*), portal vein (†), and bile duct (‡). V5 = segment V hepatic vein orifice.

significant increase in total GV (from 1251.7 to 1268.6, and to 1329.1 cm^3) and a reduction by 40% of hemangioma volume (from 770.8 to 460.1, and to 320.6 cm^3). In other words, liver parenchyma of the graft actually grew from 481.0 to 1008.5 cm^3 by 110% within 2 months (Fig. 1C). For patient 5, volumetric CT on day 14 after operation showed a remarkable increase in GV (from 769.8 to 1633.2 cm^3) with a mild decrease in hemangioma volume (from 278.3 to 269.2 cm^3) (Fig. 1 D).

3.3. Hepatic venous outflow reconstruction and safe use of artificial blood vessel

To ensure good outflow without congestion, a venoplasty technique was performed in left lobe liver transplantation in 4 patients as described previously.[11]

In right lobe liver transplantation, hepatic vein from segment V5/V8 was often encountered on the transection plane of the graft, especially in the right lobe graft without inclusion of the MHV. In 1 right lobe graft, hepatic venous construction was performed using cryopreserved iliac artery (pictures not shown). For the rest of right lobe liver grafts, the IVC was replaced with prosthetic vessel grafts (Terumo, Vascutek Limited, UK), and right hepatic vein and the inferior right hepatic vein were anastomosed to the artificial IVC by end-to-side or bridged to the artificial IVC using prosthetic vessel grafts. Hepatic vein from segment V5/V8 was bridged to the IVC by using prosthetic vessel grafts (Fig. 2B1, B2). Low-molecular-weight heparin sodium was also administered to prevent thrombosis if there was no risk of bleeding, and anticoagulant was changed into aspirin and warfarin for 1 year. International normalized ratio (INR) was monitored and controlled in the range of 2.0 to 3.0 for patients using warfarin. From follow-up CT scans after transplant, prosthetic vascular grafts were observed in position and without any serious thrombosis-related complications.

3.4. Precise assessment of graft size/weight helps preventing from small-for-size syndrome

The graft size (volume/weight) is the main limitation for partial graft liver transplantation. In order to keep donor safety foremost and supply a sufficient graft for the recipient, the size of graft should be assessed preoperatively and intraoperatively. It is generally accepted that it is safe for the patient to avoid SFSS that a liver graft that provides more than 35% of the patient's GV/standard liver volume (GV/SLV) or graft-to-recipient weight ratio (GRWR) >0.8%. Measurement of donor liver by volumetric CT was performed in all patients to calculate the graft size and design donor hepatectomy procedure (Fig. 3). Although LPRWR < 0.8%, which should be small-for-size grafts, no sign of SFSS was observed in patients who underwent liver transplantation using the grafts containing cavernous hemangioma. So, we have a hypothesis that cavernous hemangioma in the grafts could be a "buffer pool," which to some extent reduced the hepatic inflow and alleviated the portal hypertension so as to avoid SFSS. In addition, hepatic venous outflow reconstruction at the back table further helps preventing outflow occlusion and congestion. Furthermore, postoperative volumetric CT scans demonstrated a powerful regeneration ability of donor liver graft around 2 weeks, which also reduced the risk of SFSS. In view of those above, LPRWR could be lowered to 0.5% for liver transplantation using the partial liver graft with cavernous hemangioma.

3.5. Clinical indications for liver transplantation using the partial liver resection allografts with hepatic benign tumors

Considering good clinical course in our patients, the partial liver resection allografts with cavernous hemangioma or other hepatic benign tumors could be provided for not only adult but also pediatric liver transplantation according to donor liver GV/weight and volume of hepatic benign tumors. So, the indications

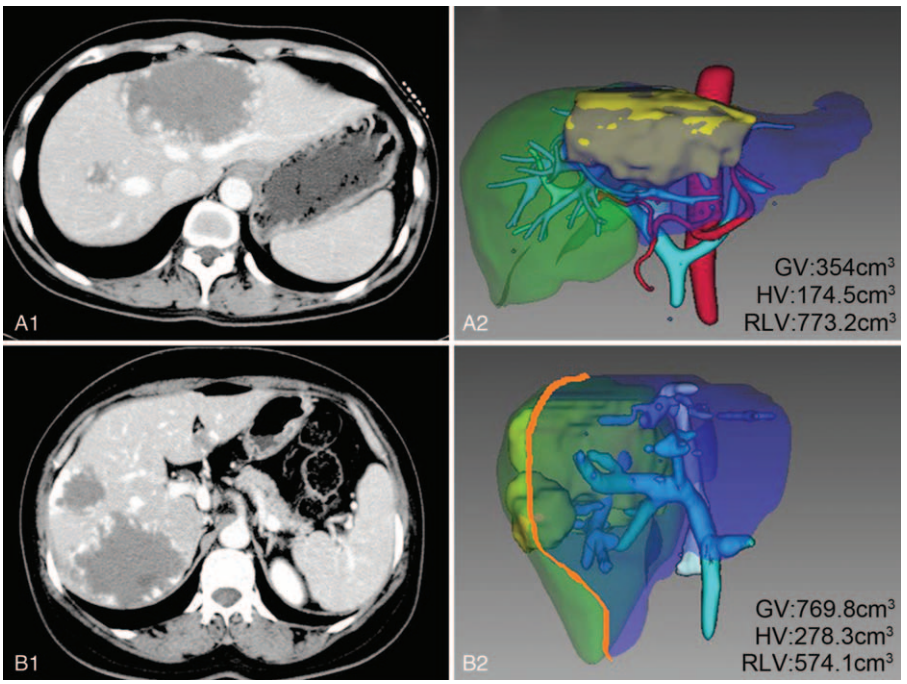

Figure 3. Preoperative volumetric assessment of the graft volume and the designed hepatectomy procedure in 2 cases. (A) Left hepatectomy. (B) Right hepatectomy.

for liver transplantation with such a graft were drafted here. First, systematic and precise assessment of the donor with hepatic benign tumors makes it necessary for hepatectomy. In addition, the assessment and performance of the operation should be supervised by the institutional ethics committee. Second, the graft should be allocated on the basis of sufficient assessment of the recipient. For example, right lobe grafts with cavernous hemangioma could be applied for adult-to-adult liver transplantation on the basis of LPRWR >0.5%. Meanwhile, hepatic vein from segment V5/V8 and the inferior right hepatic vein needed to be reconstructed at the back table in order to ensure perfect hepatic venous outflow and avoid congestion, which also shorten implantation time. And, prosthetic vascular graft has been demonstrated to be safe to be used in hepatic venous reconstruction. Nevertheless, left lobe grafts, if LPRWR >0.5%, could be used for adult liver transplant; if LPRWR <0.5%, then the grafts could be applied for pediatric liver transplant after resection of hepatic tumors. Third, for the grafts with PEComa or IPT that have an uncertain evolution in the future, hepatic tumors should be removed at the back table and then transplanted into adult or children, while hemangioma or FNH with benign prognosis could be reserved.

4. Discussion

Liver transplantation is limited by a scarcity of donor organs. The use of marginal or expanded pool donors is increasingly common, as liver donor acceptance criteria are relaxed.[2,3] Hepatic benign tumor including hemangioma, FNH, PEComa, and IPT made it necessary to be resected when the diagnosis is uncertain or abdominal symptoms occurred.[7] Hemangioma, the most common benign tumor of the liver, is actually vascular malformations and usually found incidentally on imaging.[13] In giant cavernous hemangiomas (>4 cm), rapidly enlarging tumors cause pain (abdominal, back, or shoulder), fullness, nausea, and vomiting in the patients. Compared with irradiation therapy and hepatic artery embolization, surgical resection of hepatic hemangioma is the only consistently effective method for treatment for those with symptomatic or enlarging tumors, or uncertainty of diagnosis. Anatomic lobectomy and simple enucleation are the most common operative approaches for resection of liver hemangioma. The former is reserved for those tumors occupying most of a lobe or most of segment 2 and 3, or located deeply within the hepatic parenchyma while the latter is preferred when feasible, as it preserves more hepatic parenchyma and minimizes complications. In our cases, as in donor 1, the hemangioma was central, not superficial, and was located in the left hepatic lobe involving the MHV, necessitating performance of left hepatic lobectomy together with the MHV.[11] In the other 8 hemangioma donors, there was a giant hemangioma locating inside the hepatic parenchyma and occupying most of one lobe, which made hepatic lobectomy favorable. For grafts of other hepatic tumors, symptomatic manifestation, the growth of hepatic tumor and its uncertainty of diagnosis necessitated the resection of the tumor.

The concerns on use of partial liver graft with cavernous hemangioma are whether hemangioma would make a rapid growth or result in any severe complications including Kasabach–Merritt that which would need a retransplant.[14] Many growth factors such as vascular endothelial growth factor (VEGF),[15] interleukin-6 (IL-6),[16] and nitric oxide,[17] which are able to initiate liver regeneration, would be secreted in human body after hepatectomy. However, the influence on hemangioma remains unclear. In view of the follow-up, no hemangioma-related complications were observed, but regeneration of liver parenchyma and shrink of hemangioma was observed in 3 recipients.

Inadequate graft venous outflow can result in varying degrees of liver dysfunction including rapid progressive liver failure and even graft loss, which usually occurs in living donor liver transplantation especially with right hepatic lobe.[18] Reconstruction of hepatic venous outflow could reduce its occurrence with effect.[19] The variations of hepatic vein such as hepatic vein from segment V5/V8 and inferior right hepatic vein were often encountered in living donor liver transplantation when using right lobe grafts. In patients using right lobe graft, back-table hepatic venous reconstruction with prosthetic vessels provides more convenience and shortens cold ischemia time for veno-venous anastomosis during operation, which reduces recurrence risk of postoperative complications.[20] In addition, 4 cases of parent living donor right lobe liver transplantation were also performed successfully by using prosthetic vascular grafts (data not shown), which has been applied to hepatic venous reconstruction in living donor liver transplantation.[21] And aspirin and warfarin can be used to prevent from venous thrombosis postoperatively. Given this successful experience, prosthetic vessels could be applied to living donor liver transplantation for vascular reconstruction, especially using right lobe grafts without the MHV or single hepatic segment grafts.

SFSS follows liver transplantation or extended hepatectomy when the donor graft or remnant liver volume is insufficient to maintain normal liver function.[22] After the donor and the recipient were evaluated thoroughly, SFSS was avoided with GRWR below 0.8% in all patients.[23] Expectedly, volumetric CT scans demonstrated the powerful growth potential of the liver. Long-term follow-up demonstrated a reduction in the size of hemangioma because of squeeze from rapid liver regeneration. Excessive portal vein infusion increases portal hypertension so as to make it more likely to happen for SFSS.[24] However, giant cavernous hemangioma within the liver allograft could be considered to be a "buffer pool," which could reduce portal vein pressure to avoid SFSS. Therefore, for liver transplantation using the allograft with cavernous hemangioma, GRWR could be lowered to 0.5% without SFSS. However, the long-term follow-up and well-designed experiments are required to confirm this hypothesis.

Overall, this report describes a case series of successful liver transplantation with the otherwise-discarded partial liver resection allograft including hepatic benign tumors, which offers a novel strategy in expanding the donor pool. In addition, prosthetic vascular graft can be used for hepatic venous outflow reconstruction, especially in right lobe liver transplantation. Nevertheless, more cases are needed to confirm this method. A broader adoption of liver allografts from donors, who underwent lobectomy, would lead to a significant increase in numbers of liver transplantation and, to a certain extent, palliates the organ shortage.

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