ORIGINAL ARTICLE

Anatomical variations of donor portal vein in right lobe living donor liver transplantation: the safe use of variant portal veins

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Introduction

Living donor liver transplantation (LDLT) has gained worldwide acceptance for the treatment of end-stage liver disease. The experience and the technical advances achieved in the last decade in this field made it possible to steadily improve the post-transplant results [1]. In adult LDLT, right lobe (RL) is generally preferred with the purpose of providing a larger size liver graft; however, a higher incidence of vascular and biliary variations has been reported with the RL grafts as compared with the left lobes [2-6].

Abstract

In right lobe (RL) living donor liver transplantation (LDLT), portal vein (PV) variations are of immense clinical significance. In this study, we describe in detail our PV reconstruction techniques in RL grafts with variant PV anatomy and evaluate the impact of accompanying biliary variations on the recipient outcomes. In a total of 386 RL LDLTs performed between July 2004 and July 2012, the clinical data on 52 (13%) transplants using RL grafts with variant PV anatomy were retrospectively analyzed. Portal vein anatomy was classified as type 2 in 20 patients, type 3 in 24 patients, and type 4 in eight patients. The PV reconstruction techniques utilized included back-wall plasty (n = 21), back-wall plasty with saphenous vein graft interposition (n = 6), saphenous vein graft interposition (n = 5), cryopreserved iliac vein Y-graft interposition (n = 6), and quiltplasty (n = 3). There was no donor mortality. In a median follow-up of 29 months, none of the recipients had vascular complications. Anomalous PV anatomy was associated with a high (54%) incidence of biliary variations; however, these variations did not result in increased biliary complication rate. Overall, the 1- and 3-year patient survival rates of recipients were 91% and 81%, respectively. Vascular and biliary variations in RL grafts render LDLT technically more challenging. By employing appropriate reconstruction techniques, it is possible to successfully use RL grafts with PV variations without endangering recipient and donor safety.

> Portal vein (PV) variations constitute a significant proportion of vascular variations in RL grafts, and their incidence has been reported as high as 22% in previous publications [2,6-10]. Anatomical variations of the PV are also associated with higher rates of biliary variations [2,8]. The clinical implications of PV variations include technically challenging operations with complex reconstructions, as well as the rejection of potential donors. In addition, PV variations can jeopardize donor safety. Inadvertent narrowing during the closure of the PV orifices in the remnant liver has been reported to cause PV thrombosis in the donor [6].

Currently, clinical data on the use of RL grafts with PV variation, as well as the outcome of both the donors and the recipients of such grafts are limited. In this paper, in a large series of LDLTs in which RL grafts with variant PV anatomy were used, we report our experience in PV reconstruction techniques in LDLT. We retrospectively evaluated the different reconstruction techniques, the impact of accompanying biliary variations on the recipient outcomes, and the results of right hepatectomy in donors with PV variations.

Patients and methods

From July 2004 to July 2012, 418 LDLTs were performed at Florence Nightingale Hospital, Istanbul. Donor evaluation started with the assessment of the voluntary intent of the donor and blood group compatibility. Only donors within the fourth degree of consanguinity were accepted. After the serological and thrombophilia testing, a thorough clinical evaluation was performed. Donor candidates who had diabetes, hypertension, or any other significant medical diseases were excluded. Assessment of the vascular anatomy and the liver parenchyma and liver volumetry was performed by computed tomography (CT; 16-detector, Sensation 16-Siemens, Erlangen, Germany), and the evaluation of biliary anatomy was performed by magnetic resonance cholangiography (MRC; 1,5-T scanner, Magnetom Sonata, Siemens, Erlangen, Germany). Donors whose future liver remnant volume was <30% of the whole liver volume were excluded from RL donation in principle. Potential donors with moderate steatosis were managed with short-term combination therapy of diet, exercise, and drugs. Donor candidates with a high (>28) body mass index, those with mild steatosis on the precontrast CT scan, and those who test positive for anti-HBc underwent liver biopsy selectively. The anatomical variations of the PV and the bile ducts were described according to Cheng [9] (Fig. 1) and Huang [11] classifications, respectively.

In a total of 386 RL donors, 52 (12.6%) donors were identified to have portal vein variations. The clinical data for these 52 donors and their recipients were retrospectively analyzed in this study. All postoperative complications in donors and recipients were graded according to Clavien classification [12]. All numerical data are reported as median and interquartile range. Incidence rates were compared with the chi-square test. A *P*-value <0.05 was considered statistically significant.

Donor operation

The donors with variant PV and biliary anatomy and their respective recipients were informed about these



Figure 1 Portal vein variations according to Cheng classification. (a) Type 1 variation: Single left and right lobe division of the PV. (b) Type 2 variation: Trifurcation of the anterior–posterior segments of the right PV with the left PV. (c) Type 3 variation: Early segmentation of the right posterior branch of the PV. (d) Type 4 variation: Anterior sectoral branching from the umbilical portion of the left PV.

variations preoperatively and their informed consents were obtained. Donor operation was performed as described elsewhere [13]. In donors with biliary variations or with suboptimal MRC evaluations, cystic cholangiography was performed after cholecystectomy. Hilar dissection was started with the identification and dissection of the right hepatic artery (RHA). Next, the right anterior and the right posterior PV branches were isolated at the hilum by the posterior intrahepatic Glissonian approach. The RHA and the right PV branches were then clamped temporarily to produce a demarcation line between the right and left liver. Before division of the parenchyma and all through the transection process, portal and hepatic venous anatomy was reevaluated with intraoperative ultrasonography. Liver transection was performed with the ultrasonic dissector (CUSA) by either including or excluding the middle hepatic vein (MHV). Type of PV anomaly did not require any modification in the transection plane. When parenchymal transection reached at the hilar plate, biliary anatomy was re-evaluated with a second intraoperative cholangiography, and the most appropriate point for the division of the bile duct was marked with surgical clips. When dividing the bile duct, care was taken to avoid injury to right anterior PV branch, particularly in donors with types 3 and 4 PV anomaly. There were no aborted procedures and all donor right hepatectomies were completed successfully.

Back table procedure

The removed RL grafts were weighed and perfused with histidine–tryptophan–ketoglutarate solution through PV. Based on the previously planned reconstruction technique, cryopreserved iliac and/or saphenous vein grafts were used for reconstruction of PV orifices.

Type 2 portal vein anomaly

In 16 grafts with type 2 (trifurcation) anomaly, there was a single common orifice with a narrow bridge of tissue on the posterior wall. In 11 of these grafts, the PV was anastomosed in an end-to-end fashion (Fig. 2a); in five other grafts with a single orifice, saphenous vein graft interposition was performed to lengthen the PV and to reinforce its walls (Fig. 2b). In the remaining four grafts, posterior walls were separately divided; therefore, a common orifice was created with simple back-wall plasty in three patients (Fig. 2c), and in one other patient, back-wall plasty with saphenous vein reinforcement was performed (Fig. 2d).

Type 3 portal vein anomaly

In 18 grafts with type 3 anomaly, a common orifice was created with back-wall plasty (Fig. 2c). Additional saphenous vein reinforcement was performed in six other grafts, because of the weakness of the PV wall or intraparenchymal retraction after back-wall plasty (Fig. 2d).



Figure 2 Portal vein reconstruction techniques in right lobe grafts with type 2 and type 3 portal vein anomaly. (a) End-to-end anastomosis without reconstruction. (b) Saphenous vein graft interposition. (c) Back-wall plasty. (d) Back-wall plasty with saphenous vein graft interposition.

Type 4 portal vein anomaly

In type 4 anomaly with intraparenchymal partition of the anterior PV branch, the orifices were far away from each other, not allowing for direct back-wall plasty. In five of these grafts, reconstruction was performed by using Y-shaped cryopreserved iliac vein grafts (Fig. 3a). In three others, the distance between the PV orifices was too long and there was the risk of blood flow being hindered due to inappropriate angulations of the Y-graft. In two of these grafts, both orifices were connected with quilt-plasty by using an iliac vein graft, and a second iliac vein graft was placed to contain both orifices within and interposed to form a tube as has been described previously [5]. (Fig. 3b). In one graft, because there was not enough number of cryopreserved iliac vein grafts available, common orifice reconstruction was performed by using saphenous vein grafts and then, the only iliac vein graft at hand was interposed as explained above (Fig. 3c). Postoperative CT images of the portal vein reconstructions in Fig. 3b and c are shown in Fig. 4a and b, respectively.

Recipient operation

The recipient hepatectomy was performed with piggy-back technique as described previously [13]. None of the recipients had PV thrombosis. Hepatic vein anastomosis was usually performed by placing a side-clamp on inferior vena cava (IVC); in cases where complex hepatic venous reconstructions were needed, IVC was clamped totally. Anterior sector drainage was performed selectively in 18 (34.6%) cases, by either including the MHV (n = 16), or reconstructing the segment 5 and 8 veins separately (n = 2). Following portal reperfusion, arterial anastomosis was performed under operating microscope. Before the biliary anastomosis, vascular anastomoses were routinely evaluated with intraoperative ultrasonography. In 45 recipients, duct-to-duct technique was used for biliary anastomoses; in five recipients, Roux-en-Y hepaticojejunostomy was performed. During the early postoperative follow-up, graft vasculature was routinely evaluated with Doppler ultrasonography; for three recipients with type 4 variations



Figure 3 Portal vein reconstruction techniques in right lobe grafts with type 4 portal vein anomaly. (a) Iliac vein Y-graft interposition. (b) Quilt-plasty by using an iliac vein graft with interposition of a second iliac vein graft. (c) Quilt-plasty by using saphenous vein graft with iliac vein graft interposition.



Figure 4 Postoperative computed tomography images of quiltplasty technique performed for type 4 portal vein anomaly. (a) Quilt-plasty by using double iliac vein grafts. (b) Quilt-plasty by using a combination of saphenous and iliac vein grafts.

necessitating complex reconstructions, CT angiography was used for evaluation (Fig. 3). The recipients were not given any anticoagulation therapy.

Results

The clinical profiles of 52 RL donors with PV anomalies and their corresponding recipients are summarized in Table 1. The parenchymal transection was completed in a median of 72.0 (55.0–97.2) min, with a median blood loss of 500 (300–637) ml, and the median cold ischemia time was 81.5 (68.5–106.2) min.

Based on Cheng classification, 20 donors had type 2, 24 had type 3, and 8 had type 4 PV variations. CT angiography images of PV variations are presented in Fig. 1. Table 2 demonstrated the distribution of the RL grafts based on the

 Table 1. Demographic data in 52 RL donors with PV variation and their recipients.

Donor	
Age	36.5 (29.0–45.0)
Gender (Female/Male)	21/31
Parenchymal transection time (min)	72.0 (55.0–97.2)
Blood loss (ml)	500 (300–650)
Hospital stay (days)	9.0 (7.0–11.0)
Recipient	
Age	54.5 (46.2–60.0)
Gender (Female/Male)	8/44
MELD score	15.0 (12.0–21.0)
The graft-to-recipient weight ratio	1.2 (1.0–1.3)
Graft ischemia time (min)	81.5 (68.5–106.2)
Hospital stay (days)	19.0 (15.0–27.0)
Post-transplant follow-up (months)	29.0 (12.0–46.0)

 Table 2. The distribution of 52 right lobe grafts based on the type of portal vein variation and the reconstruction technique used during back table procedure.

	Type 2		Typo 3	Tupo 4
	Single orifice (n = 16)	Double orifice $(n = 4)$	Double orifice $(n = 24)$	Double orifice $(n = 8)$
Portal vein variations				
No reconstruction	11	_	_	_
Back-wall plasty	_	3	18	_
Back-wall plasty with saphenous vein graft	_	1	6	_
Saphenous vein graft	5	_	_	_
lliac vein Y-graft	_	_	_	5
Quiltplasty	_	_	_	3
Autologous portal vein graft	_	_	_	-

type of PV variation, and the reconstruction technique utilized during back table procedure. In 28 (54%) donors, PV variations were accompanied by biliary variations. When compared with our previously published operative data on biliary variation rate among RL grafts, this rate was significantly higher (54% vs. 37%) [2]. Type 4 PV anomalies were particularly associated with a posterior right hepatic duct draining in the left hepatic duct, such that 88% of these grafts had multiple biliary orifices. Concurrent biliary anatomy according to PV anatomy is shown in Table 3.

Two recipients died in the perioperative period because of septic complications. In the remaining 50 recipients, PV patency was confirmed with Doppler ultrasound (n = 8), CT (n = 29), or magnetic resonance imaging (n = 13) at 3-6 months post-transplant. In a median follow-up of 29.0 (12.0-46.0) months after LDLT, none of the recipients developed PV complication. A total of 19 patients (36%) developed 20 biliary complications: 10 bile leaks and 10 biliary stenoses. Biliary complication rate in recipients with biliary variation was lower than that of those without biliary variation; however, this difference was not of statistical significance (32% vs. 42%, respectively, P = 0.5). There was only one recipient mortality related to biliary complication. In Kaplan-Meier analysis, both patient and graft survival rates at 1 and 3 years were 91% and 81%, respectively.

None of the donors had mortality. There were 12 grade 2, 2 grade 3, and 1 grade 4 complications, with an overall donor complication rate of 29%. Five donors had pleural effusion, two had pneumonia, four had superficial surgical site infection, and one had urinary tract infection. A donor was reoperated 6 h postoperatively due to hemorrhage from the transected liver surface. A donor with type A biliary anatomy underwent reoperation on postoperative day 6 for bile leakage. This donor was found with a bile leak from

 Table 3. Concurrent biliary anatomy according to portal vein anatomy in right lobe grafts with portal vein variation.

	Type 2 (<i>n</i> = 20)	Type 3 (n = 24)	Type 4 (n = 8)
Portal vein variation			
Anatomical variations of th	ne graft bile duc	ts according to	
Huang classification [11]			
A1 (normal anatomy)	7	14	3
A2 (trifurcation)	3	6	-
A3 (PRHD draining in	6	4	4
the left duct)			
A4 (PRHD draining in	4	-	1
the CBD)			
A5 (PRHD draining in	_	_	_
the cystic duct)			

PRHD, posterior right hepatic duct; CBD, common bile duct.

the right main biliary duct stump, which was treated with primary repair and T-tube drainage. In the long-term follow-up, no other biliary complications were identified. A donor with type C biliary and type 3 PV variations developed PV thrombosis on postoperative day 1. The donor was reoperated immediately after the diagnosis with Doppler ultrasonography, which was performed because of prolonged INR and abnormally elevated liver enzymes. During the reoperation, the orifices in the remnant PV were reopened and thrombectomy was performed. Although we realized that this was an issue of inadvertent narrowing during the closure of PV orifices, further work-up showed that the donor has had prothrombin gene mutation, which might have contributed to the occurrence of PV thrombosis. Low molecular weight heparin was started immediately after PV thrombectomy, and the donor was warfarinized for 6 months. In the radiological follow-up of the donor, there was adequate regeneration in the remnant liver and the PV flow was hepatopedal.

Discussion

This paper describes a variety of PV reconstruction techniques utilized in a series of 52 RL grafts with PV variations. The RL grafts with PV variations showed a significantly higher rate of accompanying biliary variations, making the use of these grafts technically more challenging. Yet, with the use of appropriate reconstruction techniques, none of the recipients developed post-transplant PV complications.

In LDLT, donor safety is of utmost importance. However, it should be noted that, unless it threatens donor safety, the presence of PV variations rarely necessitates donor rejection [14]. Furthermore, rejecting a potential donor only because of variant PV anatomy, especially when the donor is the only living donor candidate may jeopardize the recipient outcome. Considering the scarcity of deceased donor livers in Turkey, where organ donation rate is <3 per million population, this further restricts the donor pool for the patients with no living donors. During the selection of living donors, it is our practice to pay special attention to anatomical variations. When recipients with multiple donor candidates are entertained, we look for the graft with the least anatomical variations, provided that the donor and the recipient safety are assured. However, for the patients with a single donor candidate with anatomical variations, we discuss the surgical options and plan the technical modifications preoperatively.

As published previously, the techniques used for obtaining a single PV orifice with the aim of easing recipient anastomosis may cause tissue loss, stricture, and thrombosis in the remnant PV of the donor [6]. With the use of cryopreserved vein grafts, it is possible to perform PV lengthening and create single orifice for all double PV branches. In this series, especially in the presence of type 4 PV variations, the branches of the right PV were transected intraparenchymally, thereby preventing tissue loss in the remnant liver PV. However, despite these technical modifications, one donor with type 3 PV variation still developed postoperative PV thrombosis, which was the only vascular complication in our RL donor series of 386 patients.

In the past, a number of techniques have been described for the reconstruction of multiple PV orifices in RL grafts [5,6,15]. Among these, the most frequently used techniques are back-wall plasty and graft interposition using either the recipient's own portal vein or cryopreserved iliac vein [3,8]. The presence of chronic thrombosis, ascites, or changes stemming from previous interventions on the wall of the recipient PV and the presence of hepatocellular carcinoma, which was the case in one-third of the recipients, can exclude the use of autologous PV grafts [5]. In this context, autologous as well as cryopreserved saphenous vein grafts, which can be remodeled into a cylinderic configuration, play a versatile role. Because of their high availability and better thickness match, we always prefer saphenous vein grafts to autologous PV grafts. On the other hand, given the scarcity of deceased donors, the supply of cryopreserved iliac vein grafts is limited. Therefore, we have a propensity to keep these grafts for more complex reconstructions.

In PV reconstruction, saphenous vein grafts can be used in several ways. As the PV branches are transected intraparenchymally, graft PVs are shortened and their walls get thinner. Regardless of the need for back-wall plasty, the use of saphenous vein graft both lengthens the PV and strengthens the PV wall. Furthermore, saphenous vein grafts can be of benefit in instances where recipient PV is short (due to wall thickening, previous operations, partial PV thrombosis) or when there are PV incompatibilities between the donor and the recipient (diameter and wall thickness) [16]. In our center, as of 2011, we started using saphenous vein interposition technique in all the grafts with types 2 and 3 PV variations with the aim of obtaining a longer PV and making reconstruction in the recipient easier.

Cheng type 4 PV variation with intraparenchymal partition of the anterior branch poses significant difficulty, which is not preferred even in the most experienced centers because of the difficulty of reconstruction [10]. In this variation, as the distance between the portal vein orifices is long, back-wall plasty would not be possible. On the other hand, problems in angulations or diameter mismatch might not allow for the use of cryopreserved iliac Y-grafts either. In such instances, complex reconstructions such as quilt-plasty might be necessary. In one of the grafts with type 4 PV variation, as sufficient number of cryopreserved iliac vein grafts could not be found, a saphenous vein graft was used for bridging the neighboring walls of both PV branch orifices, similar to the case in back-wall plasty technique. Then, the only cryopreserved iliac vein graft in hand was used for graft interposition by creating a tube and containing both orifices within (Fig. 3c).

In RL grafts with PV variation, another important issue is the high rate of biliary tract anomalies [2,17]. Accurate assessment of donor biliary anatomy is important for surgical decision-making in the recipient. In the presence of variant biliary anatomy, diagnostic accuracy of preoperative MRC is lower [2,18]. Thus, to better plan hilar dissection during recipient hepatectomy and to decide on the type of biliary anastomosis, it would be wise to confirm biliary anatomy of the donor by using intraoperative cholangiogram before parenchymal transection.

In conclusion, LDLT has become a valuable treatment option in the adult patient population. Yet, high rates of vascular and biliary variations, especially in RL grafts, render LDLT technically more challenging, which may result in donor rejections. By employing appropriate reconstruction techniques, it is possible to successfully use RL grafts with PV variations without endangering recipient and donor safety.

Authorship

NG and MD: analyzed the data and wrote the manuscript. OY: performed the statistical analysis. YG, FT, and BT: involved in the data collection. MA and FB: participated in interpretation of data and involved in drafting the manuscript. YY and YT: revised the manuscript and have given final approval. All authors read and approved the final manuscript.

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References

- 1. Chan SC, Fan ST, Lo CM, *et al.* A decade of right liver adult-to-adult living donor liver transplantation: the recipient mid-term outcomes. *Ann Surg* 2008; **248**: 411.
- 2. Yaprak O, Demirbas T, Duran C, Dayangac M, Tokat Y, Yuzer Y. Living donor hiler variations: surgical approaches and implications. *Hepatobiliary Pancreat Dis Int* 2011; **10**: 474.
- Sugawara Y, Makuuchi M, Tamura S, *et al.* Portal vein reconstruction in adult living donor liver transplantation using cryopreserved vein grafts. *Liver Transpl* 2006; 12: 1233.
- 4. Chan AC, Lo CM, Chok KS, Chan SC, Fan ST. Life made easy: simplifying reconstruction for dual portal veins in

adult right lobe live donor liver transplantation. *Hepatobiliary Pancreat Dis Int* 2010; **9**: 547.

- Yaprak O, Guler N, Balci NC, *et al.* A new technique for the reconstruction of complex portal vein anomalies in right lobe living liver donors. *Hepatobiliary Pancreat Dis Int* 2012; 4: 438.
- 6. Lee SG, Hwang S, Kim KH, *et al.* Approach to anatomic variatons of the graft portal vein in right lobe living-donor liver transplantation. *Transplantation* 2003; **75**: 28.
- Marcos A, Orloff M, Mieles L, Olzinski A, Sitzmann J. Reconstruction of double hepatic arterial and portal venous branches for right-lobe living donor liver transplantation. *Liver Transpl* 2001; 7: 673.
- Hwang S, Lee SG, Ahn CS, *et al.* Technique and outcome of autologous portal Y-graft interposition for anomalous right portal veins in living donor liver transplantation. *Liver Transpl* 2009; 15: 427.
- Cheng YF, Huang TL, Lee TY, Chen TY, Chen CL. Variation of the intrahepatic portal vein; angiographic demonstration and application in living-related hepatic transplantation. *Transplant Proc.* 1996; 28: 1667.
- Nakamura T, Tanaka K, Kiuchi T, *et al.* Anatomical variations and surgical strategies in right lobe living donor liver transplantation: lessons from 120 cases. *Transplantation* 2002; **73**: 1896.
- Huang TL, Cheng YF, Chen CL, Chen TY, Lee TY. Variants of the bile duct: clinical application in the potential donor of living-related hepatic transplantation. *Transplant Proc* 1996; 28: 1669.
- 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.
- Taner BC, Dayangac M, Akin B, *et al.* Donor safety and remnant liver volume in living donor liver transplantation. *Liver Transpl* 2008; 14: 1174.
- 14. Duran C, Taner B, Dayangac M, *et al.* Why we did not use this donor. *Liver Transpl* 2007; **13**: 1199.
- Thayer WP, Claridge JA, Pelletier SJ, *et al.* Portal vein reconstruction in right lobe living donor liver transplantation. *J Am Coll Surg* 2002; **194**: 96.
- Chen LC, Concejero MA, Wang CC, *et al.* Remodeled saphenous vein as interposition graft for portal vein reconstruction in living donor liver transplantation. *Liver Transpl* 2007; 13: 1472.
- Macdonald DB, Haider MA, Khalili K, *et al.* Relationship between vascular and biliary anatomy in living liver donors. *AJR Am J Roentgenol* 2005; 185: 247.
- Xu X, Wei X, Ling Q, *et al.* Inaccurate preoperative imaging assessment on biliary anatomy not increases biliary complications after living donor liver transplantation. *Eur J Radiol* 2012; 81: e457.