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## Original Article

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# The Application of Splenectomy to Decompress Portal Pressure in Left Lobe Living Donor Liver Transplantation

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**Abstract** This study was conducted to evaluate the impact of splenectomy in living donor liver transplantation (LDLT) using left lobe grafts. The two hundred and fifty LDLT cases were divided into two groups : Group-S (n = 98, simultaneous splenectomy) and Group-NS (n = 152). Group-S had significantly increased recipient age ( $54.5 \pm 10.9$  years vs.  $46.3 \pm 17.0$  years,  $p < 0.01$ ), advanced liver diseases including Child class C (64.8% vs. 51.5%,  $p < 0.01$ ), higher model for end-stage liver score ( $17.8 \pm 8.1$  vs.  $15.4 \pm 5.8$ ,  $p < 0.01$ ) and more patients with hospitalized status (67.4% vs. 48.0%,  $p < 0.01$ ), and smaller graft volume/standard liver volume ratio ( $36.5 \pm 6.1\%$  vs.  $40.2 \pm 8.2\%$ ,  $p < 0.01$ ). In Group-S, splenectomy decreased portal venous (PV) pressure decreased from  $23.5 \pm 5.2$  mmHg to  $19.2 \pm 4.8$  mmHg ( $p < 0.01$ ). Group-S had significantly increased PV pressure at laparotomy ( $24.9 \pm 5.3$  mmHg vs.  $22.5 \pm 6.3$  mmHg,  $p < 0.01$ ) and decreased PV pressure at closure ( $16.4 \pm 3.5$  mmHg vs.  $18.0 \pm 4.7$  mmHg,  $p < 0.01$ ), compared with Group-NS. On the 14<sup>th</sup> day after LDLT, Group-S had lower total bilirubin ( $5.7 \pm 6.5$  mg/dl vs.  $8.7 \pm 8.9$  mg/dl,  $p < 0.01$ ) and smaller ascites output ( $0.4 \pm 0.7$  L/day vs.  $0.7 \pm 0.4$  L/day,  $p = 0.01$ ) than Group-NS. The cumulative 5-year graft survival rate was 86.8% in Group-S and 76.2% in Group-NS ( $p = 0.03$ ). In conclusion, splenectomy had beneficial impacts on graft outcomes in left-lobe LDLT.

**Key words** : Living donor liver transplantation · Splenectomy · Left lobe · Portal hypertension

## Introduction

Living donor liver transplantation (LDLT) in adults has become recognized as one of the most powerful treatment of choices for end-stage liver disease, especially in eastern countries<sup>1</sup>. Its wider

application, however, has been hampered due to two issues : graft size mismatching and donor safety<sup>2-5</sup>. The graft size mismatching has been called as small-for-size graft syndrome, and the significant negative impacts of the pathological situation have been numerous reported<sup>2</sup>. It is

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### Abbreviations

GRWR, Graft recipient weight ratio ; GV, graft volume ; HA, hepatic artery ; MELD, model for end-stage liver disease ; LDLT, living donor liver transplantation ; OPSS, overwhelming post-splenectomy sepsis ; PV, portal vein ; SLV, standard liver volume.

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sure that right lobe graft will confer acceptable graft volume (GV) on recipients, but it confers more risks on donors<sup>2)–5)</sup>.

Portal hypertension has been postulated as the critically important predictor of graft dysfunction, although it has been recognized that graft dysfunction was attributed to multiple factors including not only GV, but also other factors including donor age, and recipient conditions<sup>6)</sup>. In order to control portal venous (PV) pressure, creation of porto-systemic shunts has been practiced and reported in the literature with acceptable outcomes<sup>7)–9)</sup>. On the other hand, its negative impact represented by portal steal phenomenon was also reported<sup>10)11)</sup>. Instead of creation of shunts, we have performed splenectomy for normalizing or optimizing portal hemodynamics<sup>12)</sup>.

Thus, the aim of study was to evaluate the feasibility and usefulness of splenectomy in LDLT for chronic hepatic disorders in adults.

## Materials and Methods

### *Patients*

Between May 1997 and May 2012, 250 consecutive left-lobe LDLTs including 17 pediatric cases, were performed at Kyushu University Hospital, under approval of from the Ethics and Indications Committee of Kyushu University. The cases were divided into two groups : Group-S (splenectomy during LDLT, n = 98) and Group-NS (no splenectomy during LDLT, n = 152). The mean follow-up time was  $4.5 \pm 3.3$  years.

### *Graft selection process*

Grafts were selected as previously described<sup>13)</sup>. Left lobe grafts were considered to be the primary graft type if the desired graft volume (GV)/standard liver volume (SLV) was  $\geq 35\%$ . Right lobe grafts were considered if the simulated GV/SLV of the left lobe graft was  $< 35\%$  and the donor's remnant liver volume was  $\geq 35\%$ . Major middle hepatic vein tributaries  $\geq 5\text{mm}$  were maximally reconstructed to maintain uncon-

gested GV/SLV  $\geq 40\%$  in right lobe grafts.

### *Surgical procedures*

The donor parenchymal transection was performed using the Cavitron Ultrasonic Surgical Aspirator (CUSA™, Valleylab Inc., Boulder, CO) and a saline-linked radio-frequency dissecting sealer (Tissuelink™, Tissuelink Medical Inc., Dover, DE) with the hanging maneuver<sup>14)</sup>. After donor hepatectomy, the graft was perfused, weighted, and stored in University of Wisconsin solution (Viaspan™, DuPont Inc., Wilmington, DE). After recipient hepatectomy, the grafts were transplanted in a piggyback fashion<sup>13)</sup>. The orifice of the recipient hepatic vein was enlarged with an incision on the vena cava for the venous anastomosis to provide sufficient outflow. Arterial reconstruction was performed under microscope. Biliary reconstruction was performed by duct-to-duct biliary anastomosis primarily if possible.

### *Splenectomy*

The indications for splenectomy during LDLT include hypersplenism, portal venous pressure after reperfusion  $\geq 20\text{mmHg}$  or hepatitis C cases receiving interferon treatment after LDLT<sup>12)</sup>. Pneumococcal Vaccine (Pneumovax® , Banyu Pharmaceutical co., ltd, Tokyo, Japan) is administered before splenectomy since 2007.

Splenectomy was usually performed after reperfusion of the graft. The surgical procedures were previously described<sup>12)</sup>. Briefly, the peri-splenic ligaments including gastrocolic, gastrosplenic, splenocolic, splenophrenic and splenorenal ligaments were all divided using vessel-sealing system. During the division of the splenophrenic or splenorenal ligament, special care is taken to divide only the ligaments to avoid injuries to retroperitoneal collateral vessels. The splenic hilum is divided en bloc using endo-stapling devices. Minor woozing from the divided stump was reinforced using 6-0 Prolene™ (Ethicon Inc., Somerville, NJ) if necessary.

### **Measurement of portal hemodynamics properties**

Portal vein (PV) pressure was continuously monitored during surgery using a cannula (Medicut LCV-UK catheter 14G™, Nippon Sherwood Inc., Tokyo, Japan) placed in the superior mesenteric vein via a terminal jejunal vein by direct cut-down. Intraoperative PV flow (L/min) was measured in the recipients after the establishment of hepatic artery (HA) flow using an ultrasonic transit time flow meter (Transonic System™, Ithaca, NY) in the recipients after reperfusion.

### **Post-transplant medical care**

The basic immunosuppression protocol was described before<sup>12</sup>. Prolonged ascites drainage over 14 days is commonly seen after left lobe LDLT. The amount of ascites drained via the indwelling abdominal drains was recorded. The fluid loss due to drainage of the ascites was corrected using intravenous sodium containing 5% albumin solution to maintain serum albumin level  $\geq 3.5$ mg/dl.

### **Statistical analysis.**

Values are expressed as the mean  $\pm$  standard

deviation. Variables were analyzed using the  $\chi^2$  tests for categorical values or the Mann-Whitney's test for continuous variables. Cumulative survival analyses were determined using the Kaplan-Meier method with the log-rank test. Values of  $p$ -value  $< 0.05$  were considered statistically significant.

## **Results**

### **Comparison of recipient and donor factors.**

Group-S had significantly increased recipient age ( $54.5 \pm 10.9$  years vs.  $46.3 \pm 17.0$  years,  $p < 0.01$ ), advanced liver diseases including Child class C (64.8% vs. 51.5%,  $p < 0.01$ ), higher MELD score ( $17.8 \pm 8.1$  vs.  $15.4 \pm 5.8$ ,  $p < 0.01$ ) and more patients with hospitalized status (67.4% vs. 48.0%,  $p < 0.01$ ), and smaller graft volume/standard liver volume ratio ( $36.5 \pm 6.1\%$  vs.  $40.2 \pm 8.2\%$ ,  $p < 0.01$ , Table 1). Group-S also had increased rate of having hepatitis C (48.9% vs. 31.3%,  $p < 0.01$ ) and hepatocellular carcinoma (50.0% vs. 32.9%,  $p < 0.01$ ). There were no differences in donor age, donor gender, and blood type incompatibility. Group-S had significantly smaller GV ( $402 \pm 67$ g vs.  $442 \pm 86$ g,  $p < 0.01$ ), GV/SLV ( $36.5 \pm 6.1$  vs.  $40.2 \pm 8.2$ ,  $p < 0.01$ ) and graft recipient weight

**Table 1** Recipient and donor demographics

Variables	Splnectomy		$p$ -value
	No (n=152)	Yes (n=98)	
Recipient age (years)	$46.3 \pm 17.0$	$54.5 \pm 10.9$	$< 0.01$
Recipient gender, male	63 (41.4)	31 (31.6)	0.12
Child class C	50/97 (51.5)	59/91 (64.8)	$< 0.01$
MELD score	$15.4 \pm 5.8$	$17.8 \pm 8.1$	$< 0.01$
Hepatocellular carcinoma	49 (32.9)	49 (50.0)	$< 0.01$
Hepatitis C	47 (31.3)	48 (48.9)	$< 0.01$
Major shunts	24 (15.8)	46 (46.9)	$< 0.01$
Hospitalized status	73 (48.0)	66 (67.4)	$< 0.01$
Donor age (years)	$35.2 \pm 10.6$	$35.1 \pm 10.8$	0.97
Donor gender, male	119 (71.2)	68 (69.4)	0.11
Blood type incompatible donor	0 (0.0)	10 (10.2)	0.12
GRWR	$0.81 \pm 0.23$	$0.72 \pm 0.15$	$< 0.01$
GV (g)	$442 \pm 86$	$402 \pm 67$	$< 0.01$
GV/SLV ratio (%)	$40.2 \pm 8.2$	$36.5 \pm 6.1$	$< 0.01$

GRWR, graft recipient weight ratio ; GV, graft volume ; MELD, model for end-stage liver disease ; SLV, standard liver volume.

ratio (GRWR,  $0.72 \pm 0.15$  vs.  $0.81 \pm 0.23$ ,  $p < 0.01$ ).

**The changes of PV pressure by splenectomy.**

In Group-S, splenectomy decreased portal venous (PV) pressure decreased from  $23.5 \pm 5.2$  mmHg to  $19.2 \pm 4.8$  mmHg ( $p < 0.01$ , Fig. 1).

**Comparison of recipient and donor factors.**

Group-S had significantly increased PV pressure at laparotomy ( $24.9 \pm 5.3$  mmHg vs.  $22.5 \pm 6.3$  mmHg,  $p < 0.01$ ) and decreased PV pressure at closure ( $16.4 \pm 3.5$  mmHg vs.  $18.0 \pm 4.7$  mmHg,  $p$

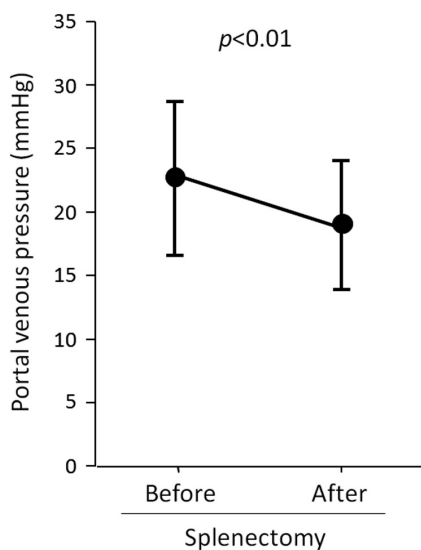
$< 0.01$ ), compared with Group-NS (Table 2). Although there was no difference in PV flow, Group-S had significantly increased PV flow/GV ratio ( $373 \pm 132$  ml/min/100g vs.  $326 \pm 143$  ml/min/100g,  $p = 0.01$ ). The addition of splenectomy did not increase operative time or operative blood loss.

Group-S had significantly decreased acute cellular rejection rate (10.1% vs. 20.4%,  $p = 0.03$ ) but did not increased the incidence of bacterial sepsis. On the 14<sup>th</sup> day after LDLT, Group-S had lower total bilirubin ( $5.7 \pm 6.5$  mg/dl vs.  $8.7 \pm 8.9$  mg/dl,  $p < 0.01$ ) and smaller ascites output ( $0.4 \pm$

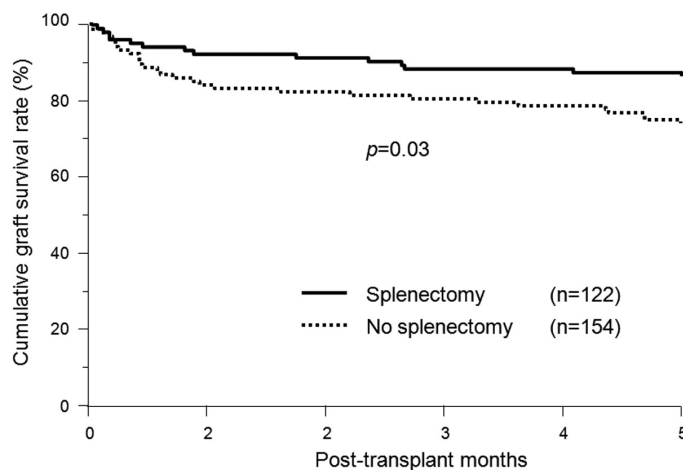
**Table 2** Operative and post-operative outcomes.

Variables	Splenectomy		p-value
	No (n=152)	Yes (n=98)	
PV pressure at laparotomy (mmHg)	$22.5 \pm 6.3$	$24.9 \pm 5.3$	$< 0.01$
PV pressure at the closure (mmHg)	$18.0 \pm 4.7$	$16.4 \pm 3.5$	$< 0.01$
PV flow (L/min/graft)	$1.58 \pm 0.40$	$1.58 \pm 0.65$	0.99
PV flow/GV (ml/min/100g)	$326 \pm 143$	$373 \pm 132$	0.01
HA flow (ml/min)	$113 \pm 70$	$97 \pm 52$	0.1
Operation time (min)	$759 \pm 165$	$749 \pm 132$	0.63
Operative blood loss (L)	$8.3 \pm 21.6$	$4.5 \pm 5.6$	0.08
Acute cellular rejection	31 (20.4)	10 (10.1)	0.03
Hepatic artery thrombosis	3 (1.9)	3 (3.1)	0.58
Portal vein thrombosis	3 (1.9)	0 (0.0)	0.16
Bacterial sepsis	23 (15.2)	10 (10.2)	0.26
Total bilirubin on day 14 (mg/dl)	$8.7 \pm 8.9$	$5.7 \pm 6.5$	$< 0.01$
Ascites output on day 14 (L)	$0.7 \pm 1.2$	$0.4 \pm 0.7$	0.02

HA, hepatic artery ; PV, portal vein



**Fig. 1** The changes in portal venous pressure by splenectomy.



**Fig. 2** The cumulative graft survival curves.

0.7 L/day vs.  $0.7 \pm 0.4$  L/day,  $p = 0.01$ ) than Group-NS.

### **Graft survivals.**

The 1- and 5-year cumulative graft survival rate was 90.7% and 86.8% in Group-S and 83.5% and 76.2% in Group-NS ( $p = 0.03$ ) respectively (Fig. 2).

### **Complications of splenectomy**

Complications in splenectomy includes pancreas leakage ( $n = 10$ , 6.5%), splenic vein thrombosis requiring short-term anticoagulation ( $n = 7$ ), post-operative bleeding from the splenic hilum ( $n = 1$ ) and overwhelming post-splenectomy sepsis (OPSS,  $n = 3$ , 1.9%). Among the patients with pancreas leakage, two patients had secondary intra-abdominal bleeding requiring interventional coiling ( $n = 1$ ) or laparotomy ( $n = 1$ ). Other eight patients were treated successfully with percutaneous drainage. Among the three patients with OPSS, two had Streptococcus Pneumonia sepsis (1- and 2-year after LDLT respectively) and one had Klebsiella Pneumonia sepsis 5-year after LDLT. These all patients did not received vaccination before LDLT, and were treated successfully with antibiotics.

## **Discussion**

In the current analyses in LDLT using left lobe grafts, splenectomy rendered sufficient portal decompression, increase in portal compliance and better graft outcomes, despite more deteriorated primary liver disease and smaller graft size compared with the patients without splenectomy.

Because graft size mismatching has been the major issue of concern in LDLT in adults, portocaval shunting gave the most striking impact for the treatment during the last decade for treating or preventing severe graft dysfunction<sup>7-9</sup>. Boillot et al.<sup>7</sup> was the frontiers to control the PV pressure during LDLT using small left lobe grafts. They created mesocaval shunt with ligating superior mesenteric vein, allowing

the small intestinal portal flow drained into the vena cava. Thereafter, numerous centers started to use hemi-portocaval shunting with excellent outcomes<sup>8,9</sup>). However, negative impacts of shunt creation in LDLT have been also reported in the literature<sup>10,11</sup>.

Thus, we propose decompressing portal hypertension in left-lobe LDLT without complexion but with splenectomy, is a rational strategy. The rational of splenectomy is constant decompression of PV pressure in cirrhotic situations and the avoidance of unstable PV hemodynamics including portal steal phenomenon after LDLT. Recently, Kyoto group<sup>15</sup> reported that they perform splenectomy to keep PV pressure  $< 15$  mmHg. They also suggested that portosystemic shunting needs to be newly created if PV pressure is over 15 mmHg. Their strategy is quite different from ours because we ligate all the major shunt vessels as possible with splenectomy even if PV pressure elevated over 20 mmHg, based on our dismal experiences with portal steal phenomenon : severe graft dysfunction due to naturally created shunt vessels with early graft loss<sup>11</sup>.

Regarding splenic artery ligation, we have abandoned the technique due to technical difficulties, insufficient effect of PV pressure control, and insufficient recovery of pancytopenia after transplantation<sup>16</sup>. Technically speaking, splenic artery ligation, in which splenic artery buried in the nests of collateral vessels needs to be excavated, is much more difficult than modern splenectomy<sup>17</sup>.

One of the important aspects of the findings is better graft function in Group-S with more deteriorated hepatic condition and smaller graft size, than Group-NS with the opposite characters. It could be attributed to the improvement of portal flow per graft volume. Regarding the impact of splenectomy on improved portal flow, we have previously showed that splenectomy upregulates hepatic serotonin levels and downregulates endothelin level in a rodent model of cirrhotic<sup>18,19</sup>. Moreover, it was also reported that

hepatic serotonin stimulates endothelial cells to release sinusoidal vascular endothelial growth factor, resulting in endothelial relaxation and openings of the fenestrae, which ultimately improves hepatic perfusion<sup>20)21)</sup>.

It is also needs to be noted that there have been complications of splenectomy, including pancreas leakage, splenic venous thrombosis and infection. Among them most important complication is pancreas juice leakage. Although effective drainage of the amylase rich fluids is performed, conservative treatment for a few weeks heal up the complication, undrained fluid should bleeding disaster<sup>22)</sup>. For infectious issues, Lüsebrink et al.<sup>23)</sup> reported that splenectomy caused increased frequency of severe infectious episodes 2.5 times in deceased donor liver transplantation. However in our left lobe series, septic complications were decreased by splenectomy although without statistical significance. OPSS is another significant issue after LDLT with a high mortality rate after splenectomy<sup>24)</sup>. Recent reports recommended that all those who receive splenectomy should receive vaccinations regardless of the etiologies even in adult populations, based on evidence that the increased risk of severe sepsis after splenectomy is permanent<sup>24)</sup>.

In conclusion, splenectomy had beneficial impacts not only in portal decompression but also increase in portal compliance, resulting in favorable graft outcomes in left lobe LDLT.

### Disclosure

We have no conflicts of interest to report. The manuscript was not prepared or funded by a commercial organization.

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(和文抄録)

## 肝左葉を用いた生体肝移植における門脈圧低下を目指した 脾臓摘出術の適応に関する検討

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【はじめに】生体肝移植に於いて、左葉グラフトを使用することはドナーの安全性をより高める意味で重要であるが、グラフトサイズが小さいことによりグラフト機能不全そしてグラフト不全に繋がる可能性も秘めている。我々は、摘脾を行うことで左葉グラフト移植をより安全に行う試みを行っている。

【対象および方法】対象は左葉グラフトを用いた生体肝移植 250 例とした。摘脾群 (n=98) および非摘脾群 (n=152) の二群に分類し、背景因子、手術・術後因子、そしてグラフト生存に関する比較検討を行った。

【結果】摘脾群は非摘脾に比し、有意にレシピエント年齢が高齢 (54.5 歳 vs. 46.3 歳,  $p < 0.01$ ), Child C 症例が多く (64.8% vs. 51.5%,  $p < 0.01$ ), model for end-stage liver スコアが高値 ( $17.8 \pm 8.1$  vs.  $15.4 \pm 5.8$ ,  $p < 0.01$ ), そしてグラフト標準肝容積比が小さい ( $36.5 \pm 6.1\%$  vs.  $40.2 \pm 8.2\%$ ,  $p < 0.01$ ) 症例群であった。摘脾群では摘脾により門脈圧が有意に低下 ( $23.5 \pm 5.2$  mmHg to  $19.2 \pm 4.8$  mmHg,  $p < 0.01$ ) した。また、摘脾群は非摘脾群に比し有意に開腹時門脈圧が高値 ( $24.9 \pm 5.3$  mmHg vs.  $22.5 \pm 6.3$  mmHg,  $p < 0.01$ ) であったが、閉腹時門脈圧は低値 ( $16.4 \pm 3.5$  mmHg vs.  $18.0 \pm 4.7$  mmHg,  $p < 0.01$ ) であった。そして術後 14 日目の総ビリルビン値および腹水排出量は摘脾群が非摘脾群に比し、それぞれ有意に低値 ( $5.7 \pm 6.5$  mg/dl vs.  $8.7 \pm 8.9$  mg/dl,  $p < 0.01$ ), 少量 ( $0.4 \pm 0.7$  L/day vs.  $0.7 \pm 0.4$  L/day,  $p = 0.01$ ) であった。そしてグラフトの 5 年生存率は摘脾群 (86.8%) が非摘脾群 (76.2%) に比し有意に良好であった ( $p = 0.03$ )。

【まとめ】左葉を用いた生体肝移植に於いて、摘脾を行うことはグラフト機能を改善するうえで有用な手段であると考えられた。