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SMALL-FOR-SIZE GRAFT IN LIVER TRANSPLANTATION

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ABSTRACT

Controversies on small-for-size (SFS) graft in liver transplantation have evolved in parallel with the history of living donor liver transplantation for adults. It is true that the liver regenerates rapidly within a limited threshold. But 'normal' liver weight itself is variable and the influences of variable liver graft and extrahepatic factors are not negligible in pathological condition. Clinical features of 'SFS syndrome' are neither specific nor inevitable in low-weight liver and many other factors than actual graft weight contribute to their occurrence. Among them, early elevation of portal venous pressure highly probably plays a key role. In the clinical trials of surgical modification and local pharmacological manipulation targeting portal hemodynamics and tissue congestion, it may be the time to discard an excessive fear for SFS grafts and to minimize unnecessary withdrawal from the opportunity of transplantation.

Key Words: Living donor liver transplantation, Small-for-size graft, Portal venous pressure, Portal venous compliance

Discussion on graft-size mismatching in liver transplantation already existed in the era of whole or split liver transplantation that mostly uses right trisegments for adults. However, it has flourished in the middle of 1990's when living donor liver transplantation (LDLT) was extended to adult patients. The controversies include pathophysiology, clinical features, and strategies for SFS liver grafts. On the other hand, the concept of small-for-size graft is often abused as a convenient 'excuse' for negative sequelae in adult LDLT. This article summarizes current concept and controversies on SFS graft in adult LDLT, which hopefully leads to the evolution of clinical strategies in the near future.

Liver Weight in Non-Transplant Settings

Although liver weight increases with growth from infant to adult, its ratio to body weight gradually decreases and becomes a plateau in the late teen-agers. Furthermore liver weight decreases slightly with aging[1]. Generally male has rather larger liver than female. However, these values may be influenced by other factors such as nutritional status, race, and era[2]. Also habitual intake of alcohol or drugs and mild fatty infiltration increases liver weight even in

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healthy population[3,4]. These facts have important implications in the consideration of donor liver weight, who is postulated to be 'healthy'.

In partial resection of the normal liver, safe regeneration is expected until the remnant liver around 30% and regeneration is correlated with the volume of resection within the safety limit[5]. However, regeneration is delayed or incomplete in diseased liver, potentially including steatotic liver, that may threaten the life after resection[5,6]. In addition, extrahepatic complications can be metabolic load that delays liver regeneration[7]. These findings obtained in liver resection would have very important implications when we discuss minimal weight of tolerable liver graft.

Concept of SFS Graft in Liver Transplantation and Its Evaluation

It is confirmed in a canine model that grafted liver of 50% original weight rapidly restores its size[8]. On the other hand, another canine model claims 25–30% of original liver weight as a prerequisite for posttransplant survival, a similar safety limit to that in liver resection[9]. Furthermore, it is reported in a rodent model that survival of SFS graft is not such a phenomenon as defined by a definite threshold, but that it shows a stepwise reduction in proportion to the reduction of liver weight[10]. Although rodents are potentially more sensitive than humans, this phenomenon is quite similar to that observed later in the latter. However, it is questionable whether these results can be applied directly to clinical settings considering heterogeneity of donor and recipient factors and preservation period of the graft as well as species difference.

Early clinical experience in whole liver transplantation in 1980's has already confirmed that SFS grafts implanted into the recipients 30–60% larger than the donors regenerate to the size defined by body size, gender, and age of the recipients[2]. Similarly it has been confirmed in the early era of LDLT that both SFS and large-for-size grafts (46–192% of estimated liver weight) regenerates to the estimated weight after transplantation[11]. At this stage the varieties in recipients and grafts have been scarcely discussed and the view for safety limit of SFS graft has been rather optimistic.

As indication of LDLT has been extended to large children and adults, however, concerns about SFS graft has increased and many programs have proposed safety limits based on their own experiences. The 'safety limits' varies from 30–50% of 'standard liver volume', the calculation of which is also variable, to 0.8–1.0% of recipient body weight[12-16]. Furthermore, criteria divided by the presence of cirrhosis, fulminant hepatic failure, or life-support care have been proposed[16-20]. On the other hand, not a few successful reports in extreme SFS grafts far below these criteria have been made.

Two major indices of liver graft size relative to the body is presently used: percentage of 'standard liver volume' of the recipient determined by height and weight (or body surface area) and simply percentage of recipient body weight. The determination of 'standard liver volume' is also variable including data from autopsy cases whose liver weight is regarded as 'normal'[19] and data from volumetry on computed tomography in patients whose liver weight is 'normal'[17,21]. Several different formulas are proposed for the latter and not standardized. To begin with, the hypothesis that necessary liver weight in end-stage liver disease patients can be speculated based only on body size is quite a rough assumption. Both indices are essentially similar ones and the difference would be easily overridden by the variety of original diseases, clinical status, and quality of liver graft[16,22].

SFS Syndrome – Definition and Clinical Features

The phrase 'SFS syndrome' has become popular in the beginning of 2000's. This phrase, however, tends to be abused as a convenient excuse for negative sequelae in adult LDLT. The definition would be 'symptoms attributed to relative shortage of functional liver graft volume including parenchymal and non-parenchymal structure'. Liver grafts in adult LDLT are almost always 'SFS grafts' smaller than the native 'healthy' liver, except for those for low body weight patients. Therefore, technical problems attributable to the anatomy of partial liver or those attributable to perioperative management should be excluded. The authors have reported in 1999 in 176 LDLT patients that graft survival is reduced stepwise within 3–6 months of transplantation in proportion to the reduction of relative graft size[16]. Although this population included only 7% of adult patients, the following analysis in one hundred adult LDLTs has shown a similar trend[23].

Occurrence of primary non-function is quite rare, if any, and does not contribute to the reduction of survival. Suggested clinical features of SFS syndrome include massive ascites, meteolisms, gastrointestinal bleeding, increased infection, and renal dysfunction, as well as those initially reported such as hepatocyte ischemia and degeneration, enhanced cholestasis, delayed protein synthesis, and increased surgical complications[12,16,23]. However, these symptoms are neither specific nor inevitable in SFS graft and have causative relationship each other. Although various factors including infection, rejection, biliary complications, vascular problems, and preoperative factors should be carefully excluded, it is often not an easy task. In addition, no specific histological feature is proven in SFS syndrome. Impact of rapid liver regeneration on vascular and biliary system or on immune system remains to be clarified.

Factors Affecting the Impact of SFS Graft

Surgical, medical, and immunological variations are not small even in adult LDLT. Actually recent preliminary analysis in approximately 300 adult LDLT cases in Kyoto University failed to show a significant impact of SFS graft on early graft survival. This population includes a high variation of recipient and donor factors, as well as graft surgical factors. However, decrease of serum bilirubin in this population is significantly delayed in SFS grafts, especially in those less than 0.8% body weight. Similar trend is observed also in prothrombin time and serum creatinine. It may be attributed in part to the improvement in surgical technique and perioperative management. It is, on the other hand, suggesting that graft survival is affected by many recipient and donor factors not defined only by actual liver weight in a limited range encountered in adult LDLT. Another preliminary analysis suggests that graft survival be not affected by graft size even when stratified by Model for End-stage Liver Disease (MELD) score. However, when cases are stratified by donor age or graft steatosis, impact of SFS graft is enhanced in old donors or steatotic grafts and reaches statistical significance (data not shown).

Table shows factors potentially affecting the impact of SFS graft in adult LDLT. It is very difficult to quantitate and evaluate all of these factors and some of them are still not clear even in their vector of action. It is, however, often experienced that liver graft demand is smaller in acute liver failure with a short history than in deteriorated chronic liver failure. On the other hand, fulminant hepatic failure with a long history of medical treatment is often regarded as similar metabolic status as in chronic diseases. Extrahepatic conditions such as latent infections and hepatorenal syndrome would be important factors that increase liver graft demand. Further-

Table. Factors potentially affecting impact of SFS graft

Recipient factors
Age, Original disease, Extrahepatic complications,
Clinical status (performance status), Cirrhosis, Ascites,
Collateral circulation, Early rejection/extrahepatic complications
Donor/graft factors
Age, Alcohol intake, Whole liver volume relative to body size,
Graft type, Vascular anatomy, Steatosis, Fibrosis
Surgical factors
Preservation/reperfusion injury, Surgical technique

more, early posttransplant severe rejection would reduce functional volume of the graft.

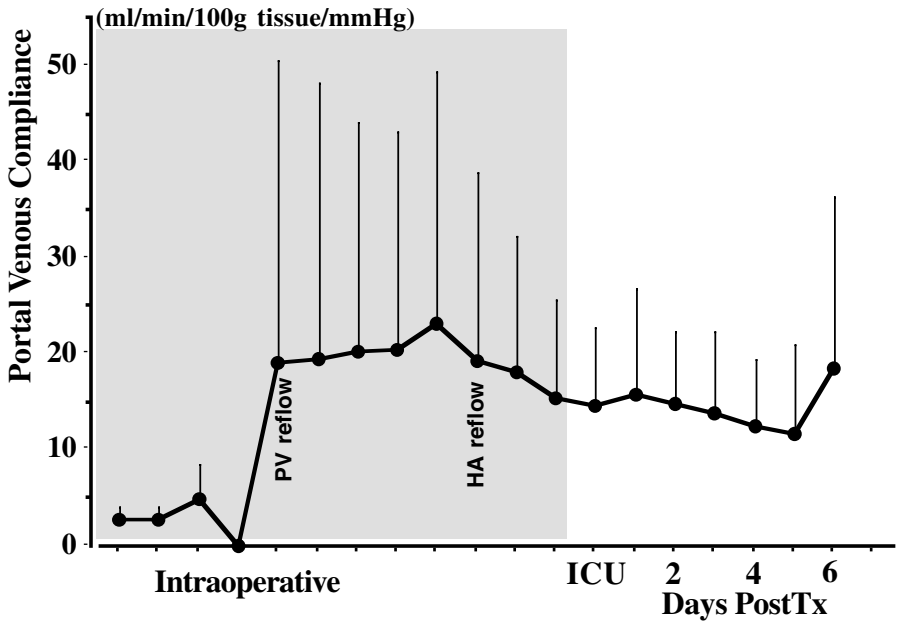
Steatosis or minimal fibrosis is important graft factor that reduces functional volume. Also partial ischemia or congestion created by vascular anatomy or surgical mode not only reduces functional capacity but also can be a metabolic load caused by non-functioning tissue. Although several compensatory mechanisms are proposed for tissue congestion caused by interruption of hepatic venous branches[24], many questions remain to be answered on the development of compensatory pathway and its timing in partial liver graft as well as their impact on functional volume. Considering these variable factors, it is difficult to believe that impact of SFS graft is determined only by absolute weight of the liver graft.

Pathogenesis of SFS Syndrome

The first possibility of the pathogenesis of poor prognosis in SFS graft is relative shortage of hepatic parenchymal cells. For the regeneration of SFS graft to the sufficient level for the recipient, a serial cascade should take place: expression of genes necessary for regeneration, release of growth factors, cytokines and endocrine factors (HGF, EGF, TGFα, Il-6, TNFα, insulin, noradrenalin, etc), protein synthesis, and tissue construction[25]. However, once extrahepatic metabolic demand or metabolic load caused by infection, complication, or non-functioning tissue is too large, disturbance in energy metabolism may stop or delay this signal transduction. On the other hand, it is often experienced that volume restoration is not bad in SFS grafts suffering from prolonged cholestasis or ascites. The possibility should be taken into consideration that the dissociation between graft regeneration and function and that between parenchymal and non-parenchymal regeneration may exist.

A hypothesis is proposed that portal venous 'overperfusion' into small graft may injure the graft tissue especially non-parenchymal tissue. It is known in whole liver transplantation for cirrhotics that portal venous flow is increased early after transplantation and this increase of portal flow, as well as pressure, persists for several months[26]. In partial liver transplants, early portal flow increases in inverse proportion to graft size per body weight and hepatic arterial flow decreases by so-called 'buffer response'[27]. Some group reported that increased portal flow early after reperfusion leads to delayed recovery from cholestasis[28]. But other groups reported that increased portal flow has no causative relationship with graft function or rather promotes the recovery of synthetic function and graft volume[27,29]. The authors have also confirmed using direct monitoring by flow wire probe that increased portal flow volume early after reperfusion contributes to the reduction of serum bilirubin.

On the other hand, from the view point of pressure in the portal system, recent analysis



Changes in portal venous compliance early after adult LDLT (mean+SD, n=17). Portal venous compliance = portal flow volume (ml/min/100g tissue)/portal pressure (mmHg).

showed that portal venous pressure early after adult LDLT is inversely correlated with liver graft size, except around one week after transplantation when acute rejection is rather common. It is also shown that continuous elevation of portal pressure gives a stronger impact on prognosis than graft size itself as well as its impact on cholestasis, coagulopathy, ascites and infection immunity[30]. In parallel, Hong-Kong group reported that portal venous pressure within 30 minutes after reperfusion is higher in SGS grafts, which is accompanied by sinusoidal endothelial injury, the increase of endothelin-1 in graft tissue, and the decrease of hemeoxygenase-1, heat shock protein 70, and nitrogen oxide[31]. This report clearly showed that persistent elevation of portal pressure may injure non-parenchymal tissue of the liver graft.

These reports suggest that the essence of pathogenesis in SFS graft is not the increase of portal flow, but the elevation of portal pressure. In other words, absence of pressure elevation even under 'overperfusion' is a benign phenomenon. Direct measurement of 'portal venous compliance (flow volume/pressure)', an index of 'softness' of the portal system, revealed that portal compliance after reperfusion is highly variable and its variability is gradually reduced with time (**Figure**). Preliminary analysis shows that portal compliance itself has no causative relationship with graft size, but is reduced by high age of the donor and by prolonged warm ischemia of the graft.

Current Clinical Strategies

Considering above-mentioned background of SFS syndrome, strategies currently being tried in clinical settings are briefly discussed below.

1. Increase of absolute volume of the graft.

Auxiliary liver transplantation, that preserves a part of the native liver for SFS graft and has

been put into practice before active use of right lobe graft, has advantage in its ability for cholestasis and has been helpful in not a few cases to avoid SFS syndrome[32]. However, its use is now reduced due to its complexity and limited indication in transmissible diseases such as malignancy and viral disease. On the other hand, its indication is still viable when obtained graft is extremely small in selected diseases. Dual graft is proposed when two donors are available[33]. Surgical technique is simpler in right and left dual graft than double left-sided graft[34].

2. Elevation of qualitative volume of the graft

The magnitude of impact of tissue congestion caused by interrupted venous drainage is highly variable among grafts. It is reported that severe congestion in the anterior segment occurs in the right lobe graft without middle hepatic vein, which leads to massive ascites and graft dysfunction[35]. On the other hand, other reports claim that tissue congestion improves with time being accompanied by atrophy of the segment and compensatory regeneration of the posterior segment, thus gives scarce impact on graft function or prognosis[36,37]. It is known that intraparenchymal collateral pathway develops in the early stage in many cases[38]. However, the prediction of this collateral formation is difficult at transplantation. The authors' analysis failed to show a significant impact of the size of interrupted venous branch on portal venous pressure early after transplantation. Indication of *additional venous reconstruction* (V5 and V8) should be decided based on venous anatomy, *i.e.* balance between the right and middle hepatic veins, quality, and size of the graft and recipient condition. Furthermore, complete resolution of tissue congestion is not accomplished by additional reconstruction of venous branches. When graft and/or recipient indication is clear and the safety of residual liver in the donor, *i.e.* size, quality, and V4 drainage, is confirmed, the use of *right lobe graft with the middle hepatic vein* should be considered.

3. Modification of portal hemodynamics

Several technical modifications are proposed in order to reduce excessive portal venous inflow into SFS graft or to decrease elevated portal pressure. *Shunt operation* includes mesocaval shunt[39], partial portocaval shunt, and splenorenal shunt. However, attention should be paid to the possibility of low portal perfusion and thrombus formation. Although *splenectomy* is done with an aim of portal pressure reduction[40], it has a potential risk of portal hypoperfusion in some cases and combined interruption of collaterals can lead to the opposite risk. Also it is known even in adult population that splenectomy in liver transplantation leads to the increased risk of bacterial infection[41]. In contrast, *splenic artery ligation* is effective in reduction of portal pressure, but its influence to portal flow volume is small. Early trial showed that it improves graft prognosis in SFS grafts or grafts with elevated portal pressure[30].

4. Local pharmacological manipulation

Several programs in Japan have started clinical trials to reduce sinusoidal injury in SFS grafts by direct infusion of drugs into the portal flow. Their aim is to reduce local injury with prostaglandin E1 or proteolytic enzyme inhibitors. However, precise mechanisms of action, selection of drugs, and necessary period of local treatment remain to be clarified.

Conclusion – What should our attitude be to SFS grafts?

Negative impact of SFS graft has been discussed since the extension of LDLT to adult population and the existence of SFS syndrome is an undeniable fact in clinical settings. However, when the discussion is limited to adult population, the variation of graft size relative to the recipient is often smaller than the variation of many factors including the quality, vascular anatomy, surgical mode or technique, and disease status of the recipient. In other words,

although contributing factors are highly variable, SFS graft up to the equivalent in normal liver resection is expected to function safely enough if conditions are met. We can conclude that SFS syndrome exists, but its occurrence is not determined only by graft weight. In areas where transplant medicine is largely dependent on living donors, it would be very important to discuss the pathogenesis of SFS syndrome in individualized multifactorial consideration and to make efforts not to discard the opportunity of possible life-saving transplantation.

REFERENCES

1) Aimi S, Yasoshima S, Sugai M, Sato B, Sakai T, Nakajima Y. Studies on the weight and size of internal organs of normal Japanese. Acta Pathol Jap 2: 173–200, 1952.
2) Van Thiel DH, Gavaler JS, Kam I, *et al.* Rapid growth of an intact human liver transplanted into a recipient larger than the donor. Gastroenterology 93: 1414–9, 1987.
3) Reichel C, Block W, Skodra T, *et al.* Relationship between cytochrome P-450 induction by rifampicin, hepatic volume and portal flow in man. Eur J Gastroenterol Hepatol 9: 975–9, 1997.
4) Blomquist L, Wang Y, Kimiaei S, Jacobsson H. Change in size, shape and radiocolloid uptake of the alcoholic liver during alcohol withdrawal, as demonstrated by single photon emission computed tomography. J Hepatol 21: 417–23, 1994.
5) Yamanaka N, Okamoto E, Kawamura E, *et al.* Dynamics of normal and injured human liver regeneration after hepatectomy as assessed on the basis of computed tomography and liver function. Hepatology 18: 79–85, 1993.
6) Chen MF, Hwang TL, Hung CF. Human liver regeneration after major hepatectomy: a study of liver volume by computed tomography. Ann Surg 213: 227–9, 1991.
7) Szawlowski AW, Faurous P, Saint-Aubert B, *et al.* Single photon emission computerized tomography (SPECT) for monitoring regeneration of the human liver after partial hepatectomy for secondary tumours. Eur J Surg Oncol 12: 389–92, 1986.
8) Kam I, lynch S, Svanas G, *et al.* Evidence that host size determines liver size: studies in dogs receiving orthotopic liver transplants. Hepatology 7: 362–6, 1987.
9) Shirakata Y, Terajima H, Mashima S, *et al.* The minimum graft size for successful orthotopic partial liver transplantation in the canine model. Transplant Proc 27: 545–6, 1995.
10) Xu HS, Pruett TL, Jones RS. Study of donor-recipient liver size match for transplantation. Ann Surg 219: 46–50, 1994.
11) Kawasaki S, Makuuchi M, Ishizone S, Matsunami H, Terada M, Kawarazaki H. Liver regeneration in recipients and donors after transplantation. Lancet 339: 580–1, 1992.
12) Emond JC, Renz JF, Ferrell LD, *et al.* Functional analysis of grafts from living donors: implications for the treatment of older recipients. Ann Surg 244: 544–52, 1996.
13) Furukawa H, Kishida A, Omura T, *et al.* Indication and strategy for adult living related liver transplantation. Transplant Proc 31: 1952, 1999.
14) Park KM, Lee SG, Lee YJ, *et al.* Adult-to-adult living donor liver transplantation at Asan Medical Center, Seoul, Korea. Transplant Proc 31: 456–8, 1999.
15) Harihara Y, Makuuchi M, Kawasaki H, *et al.* Initial experience with 40 cases of living-related donor liver transplantation at the University of Tokyo. Transplant Proc 31: 2893–4, 1999.
16) Kiuchi T, Kasahara M, Uryuhara K, *et al.* Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. Transplantation 67: 321–7, 1999.
17) Kawasaki S, Makuuchi M, Matsunami H, *et al.* Living related liver transplantation in adults. Ann Surg 227: 269–74, 1998.
18) Miwa S, Hashikura Y, Mita A, *et al.* Living-related liver transplantation for patients with fulminant and subfulminant hepatic failure. Hepatology 30: 1521–6, 1999.
19) Lo CM, Fan ST, Chan JK, *et al.* Minimum graft volume for successful adult-to-adult living donor liver transplantation for fulminant hepatic failure. Transplantation 62: 696–8, 1996.
20) Lo CM, Fan ST, Liu CL, *et al.* Minimum graft size for successful living donor liver transplantation. Transplantation 68: 1112–6, 1999.
21) Heinemann A, Wischhusen F, Puschel K, Rogiers X. Standard liver volume in the Caucasian population. Liver Transpl Surg 5: 366–8, 1999.
22) Marcos A. Right lobe living donor liver transplantation: a review. Liver Transplant 6: 3–20, 2000.

23) Kiuchi T, Tanaka K. How much liver does the patient need? In: Split liver transplantation: theoretical and practical aspects. (Rogiers X, Bismuth H, Busuttil RW, Broering DC, Azoulay D, eds.) Steinkopff Verlag Darmstadt, Germany, 2002, pp. 105–114.
24) Q-J Ou, Robert E. Hermann. The role of hepatic veins in liver operations. Surgery 95: 381–391, 1984.
25) Michalopoulos GK, DeFrances MC. Liver regeneration. Science 276: 60–66, 1997.
26) Gondolesi GE, Florman S, Matsumoto C, Huang R, Fishbein TM, *et al.* Venous hemodynamics in living donor right lobe liver transplantation. Liver Transpl. 8: 809–813, 2002.
27) Marcos A, Olzinski AT, Ham JM, Fisher RA, Posner MP. The interrelationship between portal and arterial blood flow after adult to adult living donor liver transplantation. Transplantation. 70: 1697–1703, 2000.
28) Miller CM, Masetti M, Cautero N, DiBenedetto F, Lauro A, *et al.* The impact of cardiac index and inflow modification on acceptable graft size in living donor liver transplantation. American Transplant Congress 2003, abstract #204.
29) Garía-Valdecasas JC, Fuster J, Charco R, Bombuy E, Fondevila C, *et al.* Changes in portal vein flow after adult living-donor liver transplantation: does it influence postoperative liver function? Liver Transpl 9: 564–569, 2003.
30) Ito T, Kiuchi T, Yamamoto H, *et al.* Changes in portal venous pressure in the early phase after living donor liver transplantation: pathogenesis and clinical implications. Transplantation 75: 1313–1317, 2003.
31) Man K, Fan ST, Lo CM, Liu CL, Fung PC, *et al.* Graft injury in relation to graft size in right lobe live donor liver transplantation: a study of hepatic sinusoidal injury in correlation with portal hemodynamics and intragraft gene expression. Ann Surg. 237: 256–264, 2003.
32) Inomata Y, Kiuchi T, Kim I-D, *et al.* Auxiliary partial orthotopic living donor liver transplantation as an aid for small-for-size grafts in larger recipients. Transplantation 67: 1314–1319, 1999.
33) Lee SG, Hwang S, Park K, Lee Y, Choi D, *et al.* An adult-to-adult living donor liver transplant using dual left lobe grafts. Surgery. 129: 647–50, 2001.
34) Kaihara S, Ogura Y, Kasahara M, Oike F, You Y, Koichi Tanaka. A case of adult-to-adult living donor liver transplantation using right and left lateral lobe grafts from 2 donors. Surgery 131: 682–684, 2002.
35) Lee S, Park K, Hwang S, Lee Y, Choi D, *et al.* Congestion of right liver graft in living donor liver transplantation. Transplantation 71: 812–4, 2001.
36) Maetani Y, Itoh K, Egawa H, *et al.* Factors influencing liver regeneration following living-donor liver transplantation of the right hepatic lobe. Transplantation 75: 97–102, 2003.
37) Yamamoto H, Maetani Y, Kiuchi T, Ito T, Kaihara S, *et al.* Background and clinical impact of tissue congestion in right-lobe living-donor liver grafts: a magnetic resonance imaging study. Transplantation. 76: 164–9, 2003.
38) Sano K, Makuuchi M, Miki K, Maema A, Sugawara Y, *et al.* Evaluation of hepatic venous congestion: proposed indication criteria for hepatic vein reconstruction. Ann Surg 236: 241–7, 2002.
39) Boillot O, Delafosse B, Mechet I, Boucaud C, Pouyet M. Small-for-size partial liver graft in an adult recipient; a new transplant technique. Lancet 359: 406, 2002.
40) Sato Y, Yamamoto S, Oya H, Nakatsuka H, Tsukahara A, *et al.* Splenectomy for reduction of excessive portal hypertension after adult living-related donor liver transplantation. Hepatogastroenterology 49: 1652–5, 2002.
41) Cescon M, Sugawara Y, Takayama T, *et al.* Role of splenectomy in living-donor liver transplantation for adults. Hepatogastroenterology. 49: 721–3, 2002.