C. 研究結果

HCV 抗体陽性疾患 に対する生体肝移植では、移植後ごく早期（1-2 日目）に血中 HCV-RNA が検出限界付近まで低下するが、その後急速に増加し、多くの症例で移植後約１週で移植前の値付近に、移植後１か月には 10 倍から 100 倍付近まで増加した（一部の症例で、移植時に HCV-RNA が測定限界以下であった場合には、移植後も陰性化が持続した）。移植後１か月～数か月頃より ALT 有意の肝酵素上昇を示す例が多く、組織学的には肝小葉内の壊死炎症反応を示す急性肝炎の時期を経て、門脈域の線維化へと進行した（70%の症例で移植後平均５ヶ月）。HCV-RNA の増加速度、さらに線維化の進行に関与する因子が検討され、前者には拒絶治療としてのステロイド、後者では高年齢患者（55 歳以上）・男性ドナー・女性患者といった因子が有意に関係していた。一部に、移植後早期から著しい HCV-RNA の増加と胆汁鬱滞を示す‘胆汁鬱滞型再発’を示すものがあり、予後不良であった。移植後慢性肝炎再発に対し IFN/ribavirin 治療が行われたが、白血球/血小板の減少、貧血、腎障害などが非移植症例よりも出現しやすく、約 20% の症例が脱落あるいは減量を余儀なくされた。治療継続例ではウイルス学的改善と肝機能、さらに緩徐ながら組織学的進行の抑制がみられ、一部では sustained viral response (SVR)も得られた。ウイルス学的反応は、genotype 1b で有意に不良であった。

D. 考察

HCV-RNA 陽性肝疾患においては、移植後のウイルス増殖における genotype の影響が重要であるが、逆に宿主側の病態や免疫抑制療法の選択と強度の影響が無視できない。Genotype ばかりでなく、ISDR などの特定領域の変異に伴う viral kinetics や免疫抑制剤の個別的影響を解析することは極めて重要である。肝炎再発の組織学的変化や生化学的変化の動態を、これらのステロイド剤の不使用とウイルス学的差異から解析した情報はこれまで極めて限られており、臨床的意義は極めて大きい。特に、生体肝移植の占有率の高い本邦において頻度が高いことが示唆されている‘胆汁鬱滞型再発’についても、HCV ゲノム解析とステロイド剤の影響の解析によって病態解明の鍵が得られることが期待される。これらの情報を、IFN/ribavirin 治療への反応の点から解析していく環境も揃っている。

E. 結論

生体肝移植を中心とした本邦の肝移植医療は、成人症例の急速な増加（現在約 2/3 が成人）に伴って、多くの HCV 由来肝不全や肝細胞癌症例を抱えている。これまでの経験から、臨床的な解析情報は抱負に得られており、ウイルスゲノムの解析とステロイド剤の影響の解析によって、臨床における戦略に迅速に応用可能

な貴重な情報が得られる可能性が高いと思われる。

F. 健康危険情報

なし

G. 研究発表

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H. 知的財産権の出願・登録状況

なし

研究成果の刊行に関する一覧表

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著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
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肝細胞癌に対する生体肝移植

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はじめに

近年，肝細胞癌に対する治療は肝切除術，エタノール注入やラジオ波焼灼術などの穿刺治療，TAE，肝動注などと多様化がみられ，それぞれの治療成績が着実な進歩を遂げている。しかし，併存する慢性肝障害のために治療法の選択は制限を受け，特に進行肝細胞癌の場合は治療による侵襲を考えて根治的治療が行えないことが少なくない。更に肝炎ウイルスに関連した多中心性発癌による再発が予後に大きな影響を与える。一方，肝移植は癌病変の除去と同時にその背景にある慢性肝疾患を根本的に治療できるという利点があり，肝予備能が低下している症例に対しても適応となり得る。最近本邦でも成人に対する生体肝移植が広く行われるようになり，肝細胞癌に対しても生体肝移植が導入されている。このような現況で実際に肝細胞癌患者を前にした場合，治療の選択肢の一つとして生体肝移植の役割をどのように考えるかについて，これまでの経験をもとに筆者らの考えを述べる。

肝細胞癌に対する肝移植の経緯

欧米での脳死肝移植では，初期の頃は切除不能進行肝細胞癌に対して積極的に肝移植が行われたが，術後再発が多くその成績は不良であった。一方，肝移植実施数の増加に伴い移植臓器不足や医療経済などの問題が深刻化し，適応の見直しがはかられた。その結果，肝細胞癌が単発ならば直径5cm以下，多発ならば3個以下で最大径が3cm以下という，いわゆる「ミラノ基準」が移植適応として一般的に用いられるようになった。

京大移植外科での生体肝移植

生体肝移植では，特定の患者（レシピエント）に対する特定のドナーから肝臓が提供されるため，移植臓器の有効な配分という脳死移植の場合の前提にとらわれることがない。また，「ミラノ基準」は術後再発予防という観点から厳しく設定されたものであり適応拡大できる可能性がある。このような考えから京大移植外科では独自の適応基準を設けて1999年2月より肝細胞癌に対する生体肝移植を開始した（図1）。すなわち移植適応として，肝外病変がなく，肝静脈，門脈主要枝への浸潤・腫瘍栓がないこととし，腫瘍の数や大きさは考慮していない。2002年12月までに，68例の肝細胞癌症例に生体肝移植を行った。背景疾患ではHCVまたはHBV関連肝硬変が60例にみられ，肝機能はChild-Pugh分類Cが30例（44％）であった。癌の進行度は27例（40％）がミラノ基準を超えており，50例（74％）が移植前に他の治療を受けていた。その結果，感染症などが原因の術後死亡が18例，癌の再発後死亡が5例であり，術後3年累積粗生存率は全体で56％であった。癌の再発は生存例も含めて8例に認めた。ミラノ基準内および基準逸脱群の3年無再発生存率は91％ vs. 67％で，逸脱群に低い傾向はあるが有意差は認めなかった（図2）。

適応基準

1. 他の治療法では制御不能、または肝機能低下のため治療不可能な腫瘍
2. 腫瘍が肝内に限局して脈管侵襲をもたない
   (腫瘍径・数は問わない)

・移植まで可能な限り ablation 治療を継続
・告知を含めたインフォームドコンセント
・私費治療

図1 肝細胞癌に対する生体肝移植
(京大移植外科)

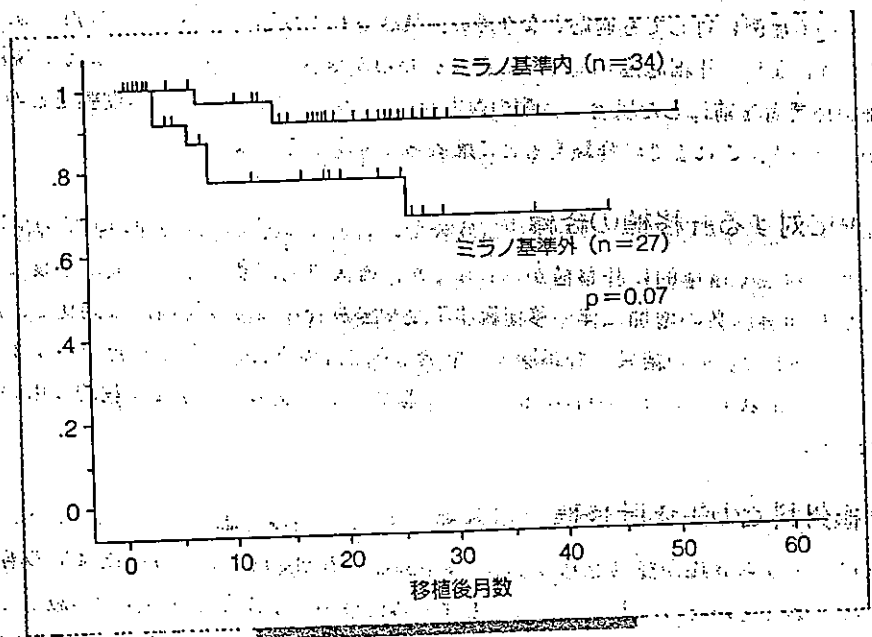

図2 ミラノ基準と累積無再発生存率

今後の展望

術後再発をみると，非腫瘍死を除いた場合ミラノ基準逸脱症例の60％以上が現在も無再発生存中であることは注目に値する。このことから，腫瘍因子からみた適応の拡大は安全かつ可能であると考えられる。合併症による術後死亡率の高さは重要な問題点であり，手術手技や術後管理の更なる改善をはかると同時に，術前におけるリスクファクターの同定が急務である。またドナーのリスク，私費診療という経済面での負担など負の側面とのバランスも考慮しなければならない。しかし，肝機能悪化のため，または繰り返す再発のために他の外科切除や内科治療の適応外と判断された進行肝細胞癌患者にとって，根治性が望める残された治療法として生体肝移植の役割は今後大きくなるものと考えられる。

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Auxiliary Partial Orthotopic Living Donor Liver Transplantation: Kyoto University Experience

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Auxiliary partial orthotopic liver transplantation (APOLT) was initially indicated as a potentially reversible fulminant hepatic failure and non-cirrhotic metabolic liver disease to compensate for enzyme deficiency without complete removal of the native liver. We expand our indication of APOLT for small-for-size grafts to support the function of implanted grafts during the early post-operative period, and for ABO-incompatibility to sustain a patient's life if the patient has a graft failure.

We retrospectively reviewed 31 patients undergoing APOLT from living donor. The indication of APOLT was fulminant hepatic failure in 6, non-cirrhotic metabolic liver disease in 6, small-for-size grafts in 13 and ABO-incompatible cases in 6.

The cumulative survival rate for APOLT at 1 and 5 years was 57.9% and 50.6%, and 78.8% and 73.8% for standard LDLT. None of the patients who underwent transplantation with APOLT for fulminant hepatic failure had long-term patient survival. The incidence of acute cellular rejection was higher in APOLT (58.1%) than standard LDLT (35.0%). Biliary complication was higher and the need for retransplantation was greater in APOLT than standard LDLT ($p < 0.01$).

The results suggest that the indications of APOLT should be reconsidered in view of the risk for complications and retransplantation.

Key words: Auxiliary liver transplantation, living donor liver transplantation

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Introduction

Liver transplantation from a living donor is increasingly accepted with excellent results, usually in coordination with a cadaveric organ transplant program (1). In countries where cadaveric donors are limited, however, living donor liver transplantation (LDLT) is often the only treatment of choice for patients with end-stage liver disease (ESLD). The LDLT program in Kyoto University began in June 1990, and under this program 970 transplants in 920 patients have been carried out in the period up to November 2003. Because of the growing waiting list and the establishment of acceptable results of pediatric LDLT, we have been compelled to expand our indication of LDLT from small children to older children, and even to adults.

Analysis of our studies revealed poor graft survival in older patients receiving small-for-size grafts (2). To treat patients with a graft-to-recipient weight ratio (GRWR) of less than 0.8%, auxiliary partial orthotopic liver transplantation (APOLT) was indicated from 1996 (3). The rationale of APOLT for a small-for-size graft is that the remnant native liver is expected to support the function of the implanted graft during the early post-operative period. The graft liver expands its function in proportion to volume growth. After the graft liver has grown sufficiently, it can be expected to meet the hepatic functional demands of the recipient.

APOLT was initially indicated for potentially reversible fulminant hepatic failure and non-cirrhotic metabolic liver disease (4,5). The double aim of APOLT for fulminant hepatic failure is full native liver regeneration and discontinuation of immunosuppressive therapy (6). The auxiliary graft should support the remnant native liver during regeneration.

The advantage claimed for APOLT in non-cirrhotic metabolic liver disease is that it can compensate for enzyme deficiencies without complete removal of the native liver, which may have to aid the recipient in case of potential graft failure. The remaining native liver could benefit in the future from potential success in gene treatment (7,8).

The other potential indication for APOLT is ABO-incompatible transplantation. Transplants of ABO-incompatible grafts are often unavoidable due to the

limited number of potential donor candidates in the LDLT program. In our LDLT program, 12% of patients had to have an ABO-incompatible graft. A high incidence of early graft failure with a high rate of biliary and vascular complications in ABO-incompatible liver transplantation was reported (9). The remnant native liver could sustain a patient's life if the anticipated graft failure occurred in an ABO-incompatible case.

APOLT from living donors was performed in 31 cases for the following indications: (i) fulminant hepatic failure; (ii) non-cirrhotic metabolic liver disease; (iii) small-for-size graft and (iv) ABO-incompatibility. However, the safety of using this technique in ESLD patients remains open to question. The objective of the present study was to investigate the long-term clinical outcome of the APOLT studies in the Kyoto University LDLT program.

Patients and Methods

Study population

Since APOLT was first indicated in March 1995 for a patient with ornithine transcarbamylase deficiency (OTCD), 31 cases of APOLT have been performed at Kyoto University Hospital. There were 13 male and 18 female patients with a median age of 23 years (range: 1.4–53.7 years) and a median weight of 53.4 kg (range: 11.3–108 kg). The indication for transplantation was fulminant hepatic failure in 6 patients (hepatitis B virus [HBV]-related in 1 and of unknown origin in 5); non-cirrhotic metabolic liver disease in 6 (citrullinemia in 3, OTCD in 2 and Crigler-Najjar syndrome type I in 1); biliary atresia in 7; primary biliary cirrhosis in 3; primary sclerosing cholangitis [PSC] in 2; Wilson's disease in 2; chronic hepatitis B in 2; autoimmune hepatitis in 1; Budd-Chiari syndrome in 1 and cryptogenic cirrhosis in 1. The follow-up period median was 83 months (range: 31–100 months).

Potential donors were evaluated by liver function tests, blood group, anatomical variation and graft size with computed tomography (CT) volumetry. All patients received grafts from family members. There were 14 male and 17 female donors with a median age of 43 years (range: 20–62 years) and a median weight of 57.3 kg (range: 39–81 kg). The indications for APOLT were: (i) fulminant hepatic failure in 6 patients; (ii) non-cirrhotic metabolic liver disease in 6 patients; (iii) small-for-size graft in 13 patients and (iv) ABO-incompatibility in 6 patients.

Surgical procedures

The operative procedure has been previously described (3,10). Native hepatectomy that varied in graft segment and volume, was performed prior to graft implantation. Graft types were left lateral segment in 8 cases, left lobe in 20 and right lobe in 3. The GRWR range was 0.45–2.08% (median 0.67%). The range of the operation time was 513–1379 min (median: 861 min), the range of the cold and warm ischemic time was 36–460 min (median: 157 min) and 32–77 min (median 48 min), respectively. Blood loss ranged 260–37650 g (median: 2645 g).

In one patient with biliary atresia, the left lateral segment of the native liver was prominently atrophic, and native hepatectomy was not necessary for graft implantation. The patient needed hepatic vein anastomosis with a new orifice of the inferior vena cava (11).

Part of the caudate lobe was resected in an initial 3 patients to shorten distance and to prevent kinking of the portal venous anastomosis. The stump of the native hepatic vein and hepatic artery was used for anastomosis. Twenty-five cases (80.6%) had diversion of the native portal vein to prevent functional portal vein competition between the native and graft liver, meaning that interruption of portal flow to the native liver with all portal flow going through the graft (3,12). Hepatic artery reconstruction was performed using the microvascular technique in all cases without using vascular grafts. Biliary reconstruction was achieved using Roux-en-Y hepaticojejunostomy.

Immunosuppression

The immunosuppression protocol consisted of tacrolimus and low-dose steroids (13). Tacrolimus was begun 1 day prior to transplantation at a dose of 0.15 mg/kg/day divided into two doses, except for cases of hepatic encephalopathy and severe infection. The target for the post-transplantation whole blood trough concentration of tacrolimus was 10-12 ng/mL during the first 2 weeks and around 10 ng/mL thereafter. Steroids were started at graft reperfusion at a dose of 10 mg/kg, and then gradually reduced from 2 mg/kg/day to 0.3 mg/kg/day until the end of the first month. For patients receiving ABO-incompatible grafts, plasma exchange or double filtration plasmapheresis was performed to reduce anti-ABH antibody titers before transplantation. Post-operatively, prostaglandin E1, azathioprine and additional steroids were administered (14).

Rejection

Acute cellular rejection was diagnosed with liver biopsy. Histological diagnosis and grading of acute rejection were performed according to the criteria proposed by Demetris et al. (15). All the rejection episodes were treated with a steroid bolus injection. Diagnosis of chronic rejection was based on internationally accepted histological criteria (16). Graft failure was defined as patient death or allograft removal regardless of the reason.

Statistical analysis

Values are presented as mean ± standard deviation. Statistical analysis was performed with the generalized Wilcoxon test. Actuarial 1- and 5-year graft survival curves were calculated with the non-parametric Kaplan–Meier method and compared among groups with the Wilcoxon test. p-values of less than 0.01 were regarded as significant throughout the study.

The institutional review board approved the study and informed consent was obtained in all cases.

Results

APOLT was initiated between March 1995 and September 2001. In the same period we carried out 536 LDLTs. Thirty-one of 536 patients (5.8%) received APOLT (Table 5). None of the patients were lost to follow-up.

APOLT for fulminant hepatic failure (Table 1)

Six patients underwent APOLT for fulminant hepatic failure. Etiology of fulminant hepatic failure was HBV in 1 patient and of unknown origin in 5. The median interval between onset of jaundice and encephalopathy was 42 days (range: 9–140 days). Coma grade at transplantation was grade III in 2 patients and grade IV in 4 patients. All patients necessitated pre-operative plasma exchange and continuous veno-venous hemodiafiltration therapy for progressive encephalopathy, coagulopathy and combined kidney/pulmonary dysfunction.

Table 1: Characteristics of APOLT for fulminant hepatic failure

Case	Age (year)	Sex	Blood type	Graft type	GRWR	PVD	Outcome
1	1.8	M	Identical	Left lateral	2.08	–	Died* (POD55, sepsis)
2	1.5	M	Identical	Left lateral	2.00	–	Died† (POD141, sepsis)
3	19.5	M	Identical	Left lobe	0.62	+	Died (POD32, necrotizing enteritis)
4‡	43.3	F	Identical	Left lobe	0.51	+	Died (POD9, graft failure)
5	53.6	M	Compatible	Left lobe	0.61	+	Died (POD25, sepsis)
6	38.6	F	Identical	Right lobe	0.90	+	Died (POD43, sepsis)

GRWR = graft-to-recipient weight ratio (%); PVD = portal vein diversion; POD = post-operative day.
*Portal flow steal phenomenon.
†Retransplantation on day 34 from living donor for recurrent hepatitis.
‡HBV-related fulminant hepatic failure.
Retransplantation on day 29 from living donor for hepatic artery and portal vein thrombosis.

Patient 1, in whom portal blood flow to the native liver was preserved, showed a portal flow steal phenomenon resulting in continuously poor portal blood flow to the graft. Native portal vein diversion at the time of transplantation was indicated in the latter four cases to prevent functional portal flow competition between the graft and remnant native liver (17). Acute cellular rejection that was confirmed by liver biopsy, was observed in 3 patients (patients 2, 4 and 5). Three technical complications occurred in 6 patients, biliary stricture in patient 1 and intra-abdominal bleeding in patients 5 and 6. Retransplantation was indicated in 2 patients: for recurrent hepatitis in patient 2 and for arterial/portal thrombosis in patient 6. All patients died within 5 months of APOLT, due to sepsis in four cases, necrotizing enteritis in one case and graft failure in one case. None of the patients showed sufficient native liver recovery, and none of them were able to withdraw from immunosuppressive therapy.

In the same period, 53 patients had a transplant with standard LDLT for fulminant hepatic failure. Etiology of fulminant hepatic failure was drug-induced in 1, HBV in 15 and of unknown origin in 37. The median age of recipients was 23.3 years (range: 0.1–68.9 years). Recipient and donor characteristics of APOLT or standard LDLT were comparable at the time of transplant. The cumulative 5-year graft and patient survival rates were 58.4% and 60.2% in the standard LDLT group, respectively. The graft survival was significantly lower after APOLT ($p < 0.01$).

APOLT for non-cirrhotic metabolic liver disease (Table 2)

Six patients had a transplant with APOLT for non-cirrhotic metabolic liver disease. Primary native portal vein diversion was indicated in the last four cases. We reported the case of patient 1 with OTCD who did not receive primary ligation of the native portal branch at the time of APOLT (18). After a severe rejection episode, the graft became smaller and the native liver showed compensatory hypertrophy. As a result of the delayed native portal vein diversion, at 26 months after APOLT the graft volume increased properly and was revealed to have acceptable metabolic function. In our previous study, the resistance of portal venous inflow in the graft liver was higher than in the native liver after APOLT (17), and the dominant portal venous flow to the native liver could be readily observed in the event of severe rejection. After the experience of the first two cases, we changed the standard procedure for APOLT of non-cirrhotic metabolic liver disease to indicate native portal vein diversion in all subsequent cases so that the graft liver received the entire portal venous flow. The native liver was supplied by arterial blood flow. In case 2, native partial hepatectomy was done to compensate the hypertrophy of the native liver after native portal vein diversion (12). No significant difference was found in pericellular or perivenular fibrosis in the native liver between the specimen at APOLT and at native hepatectomy. Despite the native portal vein diversion, steatosis of the native liver improved from 80% to 30% (19).

Table 2: Characteristics of APOLT for non-cirrhotic metabolic liver disease

Case	Age (year)	Sex	Original disease	Blood type	Graft type	GRWR	PVD	Outcome
1	3.0	F	OTCD*	Compatible	Left lateral	2.08	+†	Alive
2	5.8	F	OTCD*	Identical	Left lateral	1.34	+‡	Alive
3	52.7	F	Citrullinemia	Identical	Left lobe	0.84	+	Alive
4	5.5	M	Crigler-Najjar (type I)	Compatible	Left lateral	1.23	+	Alive
5	23.5	M	Citrullinemia	Identical	Left lobe	0.78	+	Alive
6	20.2	M	Citrullinemia	Compatible	Left lobe	1.21	+	Died (POD29, sepsis)

GRWR = graft-to-recipient weight ratio (%); PVD = portal vein diversion; POD = post-operative day; POM = post-operative month.
*Ornithine transcarbamylase deficiency.
†PVD for portal flow steal phenomenon (POM 26).
‡PVD for portal flow steal phenomenon (POM 14), and native hepatectomy for compensate hypertrophy (POM66).

Five patients had an episode of acute cellular rejection (patients 1, 2, 3, 4, 6). Patient 3 had biliary stricture and underwent rehepaticojejunostomy 3 years after transplant. Patient 5 had minor biliary leakage that was successfully managed with percutaneous aspiration drainage under ultrasound guidance. Patient 6 died from sepsis on post-operative day 29. The overall cumulative 5-year graft and patient survival rates were 83.3% and 83.3%, respectively.

Seventeen patients received standard LDLT for non-cirrhotic metabolic liver disease in the same study period. Etiology of liver disease was tyrosinemia in four cases; OTCD in three; citrullinemia in three; glycogen storage disease in three; Crigler-Najjar type I in one; familial amyloidotic polyneuropathy in one; methylmalonic acidemia in one and propionic acidemia in one (20,21). The overall cumulative 1- and 5-year graft and patient survival rates were 70.6% and 62.7% and 70.6% and 62.7%, respectively. There was no significant difference in graft and patient survival between APOLT and standard LDLT for non-cirrhotic metabolic liver disease.

APOLT for small-for-size graft (Table 3)

Thirteen patients underwent transplant with APOLT for a small-for-size graft. Small-for-size grafts can be defined by a recognizable clinical syndrome that results from the transplantation of too small a functional mass of liver for a designated recipient (22,23). The definition of a small-for-size graft in this study is an actual GRWR of less than 0.8% (2,3). The original liver disease was biliary atresia in 2 patients; liver cirrhosis in 2 (of which 1 was HBV-related); primary biliary cirrhosis in 3; primary sclerosing cholangitis in 2; Wilson's disease in 2; autoimmune hepatitis in 1 and Budd-Chiari syndrome in 1. The median GRWR was 0.62% (range: 0.45–0.75%). The decision was made pre-operatively in this group of patients to use APOLT.

All patients had histologically proven fibrosis in the native liver, and a pre-operative Doppler study revealed that the blood supply depended on the hepatic artery being dominant rather than the portal vein. Native portal vein diversion was indicated in 10 patients. Six patients had an episode of acute cellular rejection (patients 3, 4, 5, 7, 8, 13) and one patient had chronic rejection (patient 13).

Four patients required relaparotomy for complications: intestinal perforation in patient 3; intra-abdominal bleeding in patients 4 and 9. Patient 7 with primary sclerosing cholangitis underwent native hepatectomy on post-operative day 35 after competent graft regeneration confirmed by CT volumetry and ^{99m}Tc-galactosyl serum albumin scintigraphy, which reflected the general function of the hepatocyte in the graft and native liver (24). The delayed native hepatectomy was intended to eliminate the potential risk of carcinogenecity of the remnant native liver. Interestingly, the explanted native liver showed no histological difference between the specimen at APOLT and at delayed native hepatectomy.

Two patients (patients 4 and 6) had hepatic vein stenosis that was treated by intervention. A metallic stent was inserted in patient 4 after several courses of balloon dilatation, but was thrombosed despite adequate anticoagulation therapy. Biliary complications were observed in 6 patients; biliary leakage in 3 (patients 1, 5 and 10) and stricture in 3 (patients 3, 7 and 8). Hypersplenism was observed in 2 patients (patients 3 and 6) who underwent splenectomy 7 years and 1 year after APOLT, respectively. Patient 6 developed *de novo* autoimmune hepatitis 2.5 years after APOLT (25).

Retransplantation was indicated in 2 patients due to hepatic vein thrombosis in patient 4 and chronic rejection in

Table 3: Characteristics of APOLT for small-for-size graft

Case	Age (year)	Sex	Original disease	Blood type	Graft type	GRWR	PVD	Outcome
1	23.2	F	Wilson's	Identical	Left lobe	0.72	–	Alive
2	47.1	M	LC (HBV)	Compatible	Left lobe	0.51	–	Died (POD35, sepsis)
3	22.9	F	Biliary atresia	Identical	Left lobe	0.48	+	Alive
4	24.1	M	Wilson's	Identical	Left lobe	0.62	–	Alive*
5	48.7	F	PBC	Compatible	Left lobe	0.62	+	Alive
6	15.9	F	Biliary atresia	Identical	Left lobe	0.54	+	Alive
7	20.6	F	PSC	Identical	Left lobe	0.49	+	Alive†
8	44.1	F	PBC	Identical	Left lobe	0.45	+	Alive
9	50.6	F	LC	Identical	Left lobe	0.67	+	Alive
10	30.0	F	PBC	Identical	Left lobe	0.59	+	Died (POD59, sepsis)
11	39.0	F	Budd-Chiari	Identical	Left lobe	0.69	+	Died (POD22, sepsis)
12	19.2	F	AIH	Identical	Right lobe	0.75	+	Alive
13	30.9	M	PSC	Identical	Right lobe	0.68	+	Died‡ (POD372, sepsis)

GRWR = graft-to-recipient weight ratio (%); PVD = portal vein diversion; POD = post-operative day; POM = post-operative month; LC = liver cirrhosis; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; AIH = autoimmune hepatitis.

*Retransplantation from living donor for hepatic vein thrombosis (POM 33).

†Native hepatectomy after regeneration of graft (POD 35).

‡Retransplantation from living donor for chronic rejection (POM 6).

Table 4: Characteristics of APOLT for ABO-incompatible case

Case	Age (year)	Sex	Original disease	Graft type	GRWR	PVD	Outcome
1	19.6	M	Biliary atresia	Left lobe	0.55	+	Died (POD59, hepatic necrosis)
2	51.4	M	LC (HBV)	Left lobe	0.55	+	Died (POD32, sepsis)
3	13.8	F	Biliary atresia	Left lobe	0.62	+	Alive
4	4.5	F	Biliary atresia	Left lateral	1.37	+	Alive*
5	14.9	M	Biliary atresia	Left lateral	0.63	+	Alive
6	9.8	F	LC	Left lateral	1.16	+	Alive

GRWR = graft-to-recipient weight ratio (%); PVD = portal vein diversion; POD = post-operative day; POM = post-operative month.
*Retransplantation from cadaveric donor (split liver transplantation) for chronic rejection (POM 22).

patient 13. Patient death occurred in 4 of 13 patients, the main cause of death being sepsis. The overall cumulative 1- and 5-year graft survivals were 69.2% and 69.2%, respectively.

Forty patients received standard LDLT for a small-for-size graft during the same period in conjunction with APOLT. The median GRWR in the standard LDLT group was 0.73% (range: 0.60–0.79%). The GRWR was significantly lower for patients receiving APOLT versus those receiving standard LDLT ($p < 0.01$). The overall cumulative 1- and 5-year graft and patient survivals in the standard LDLT group were 65.0% and 65.0%, respectively. No significant difference was observed between the groups.

APOLT for cases of ABO-incompatibility (Table 4)

Six patients had a transplant with APOLT for ABO-incompatibility. Median recipient age was 14.4 years (range: 4.5–51.4 years). Acute cellular rejection was observed in 4 patients (patients 1, 4, 5 and 6). Patient 4 had chronic rejection.

Relaparotomy was indicated for 2 patients: ligation of the collateral vessel in patient 1 and intra-abdominal bleeding in patient 2. Patient 1 underwent ligation of the collateral vessel on post-operative day 9. After an episode of acute cellular rejection, graft portal venous flow decreased and the steal phenomenon of portal flow to the collateral vessel was confirmed by Doppler ultrasonography even though native portal vein diversion was indicated. The graft function did not recover and the native liver function was not sufficient to support the severe dysfunction of the graft. The patient died from hepatic necrosis on post-operative day 59. Three patients had biliary complications: bile leakage in patients 4 and 5, and biliary stricture in patient 6. Patient 4 underwent retransplantation with a cadaveric split graft in post-operative month 22 for chronic rejection. The overall cumulative 1- and 5-year graft survival rates were 66.7% and 44.4%, and the 1- and 5-year patient survival rates were 66.7% and 66.7%, respectively.

Thirty patients, all over 2 years old, underwent standard LDLT with an ABO-incompatible graft. Median recipient age was 30.1 years (range: 2.0–59.3 years). Acute cellular rejection was observed in 9 of 30 patients (30%). The overall cumulative 1- and 5-year graft and patient survival rates were 53.3% and 42.7%, respectively. There was no significant difference in graft and patient survival between APOLT and standard LDLT for ABO-incompatibility.

Profiles of APOLT and standard LDLT (Table 5)

Profiles of APOLT and standard LDLT performed in the same study period are shown in Table 5. The GRWR was significantly lower for patients receiving APOLT versus those who received standard LDLT.

The duration of the operation was significantly longer in the APOLT group (831.2 ± 222.0 min) than the standard LDLT group (690.8 ± 198.5 min).

Acute cellular rejection was detected in 18 of 31 (58.1%) cases of APOLT versus 177 of 505 (35.0%) cases of standard LDLT ($p = 0.02$). Chronic rejection was diagnosed in 2 of 31 (6.5%) cases of APOLT, versus 2 of 505 (0.4%) cases of standard LDLT ($p < 0.01$). The incidence of rejection was higher in the APOLT group.

There were no significant differences in vascular complications between APOLT and standard LDLT. Biliary leakage was observed in 6 of 31 (19.4%) cases of APOLT, versus 30 of 505 (6.0%) in standard LDLT ($p < 0.01$). Biliary stricture was observed in 7 of 31 (22.6%) cases of APOLT, versus 28 of 505 (5.5%) in standard LDLT ($p < 0.01$). Biliary complication was significantly higher in the APOLT group.

The need for retransplantation was significantly greater in the APOLT group (16.1% vs. 4.2% for standard LDLT group, $p < 0.01$). In-hospital deaths occurred in 13 of 31 patients (41.9%), 10 patient deaths (76.9%) were related to infectious complication. The median delay was 32 days (range: 9–184 days) after APOLT.

The 1- and 5-year cumulative grafts were lower after APOLT versus standard LDLT (57.9 and 50.6% vs. 78.8 and 73.8%, respectively), but the difference did not reach statistical significance ($p = 0.45$ and 0.18, respectively).

Table 5: Profiles of Auxiliary partial orthotopic liver transplantation and standard living donor liver transplantation

Characteristics	APOLT (n = 31)	Standard LDLT (n = 505)	p-values
Male/female	13/18	213/292	0.87
Age (year)	25.8 ± 16.8 (1.5–53.6)	18.9 ± 20.4 (0.1–69.1)	0.06
Donor age (year)	43.5 ± 10.3 (20–62)	37.9 ± 10.8 (19–66)	<0.01
GRWR* (%)	0.87 ± 0.47 (0.45–2.08)	1.96 ± 1.27 (0.60–9.68)	<0.01
Cold ischemic time (min)	177.4 ± 111.2 (36–460)	116.7 ± 89.5 (14–943)	<0.01
Warm ischemic time (min)	49.4 ± 13.6 (32–77)	46.9 ± 13.8 (16–145)	0.32
Duration of operation (min)	831.2 ± 222.0 (513–1379)	690.8 ± 198.5 (329–1800)	<0.01
Blood loss/recipient boy weight (g/kg)	116.4 ± 140.4 (6.3–607.3)	119.7 ± 146.0 (8.3–1414.1)	0.89
Acute cellular rejection (%)	58.1	35	0.02
Chronic rejection (%)	6.5	0.4	<0.01
Surgical complications (%)			
Intestinal perforation	3.2	4.1	0.83
Intra-abdominal bleeding	16.1	9.4	0.62
Hepatic artery thrombosis	3.2	2.0	0.86
Portal vein thrombosis	3.2	1.4	0.95
Hepatic vein stenosis	6.5	1.4	0.16
Biliary leakage	19.4	6.0	<0.01
Biliary stricture	22.6	5.5	<0.01
Retransplantation (%)	16.1	4.2	<0.01
Graft survival (1-, 5-year survival, (%))			
For fulminant hepatic failure	0, 0	58.4, 58.4 (n = 53)	<0.01
For metabolic liver disease	83.3, 83.3	70.6, 62.7 (n = 17)	1.47
For small-for-size graft	69.2, 69.2	65.0, 65.0 (n = 40)	1.59
For ABO incompatible case	66.7, 44.4	53.3, 42.7 (n = 30)	0.53
Overall	57.9, 50.6	78.8, 73.8	0.45

GRWR = graft-to-recipient weight ratio (%).

Discussion

The most common indication for APOLT in western countries is fulminant hepatic failure (8). The first successful case of APOLT for fulminant hepatic failure, that is, full native liver regeneration and withdrawal of immunosuppressive therapy was reported in 1991 (26). The indication of APOLT for fulminant hepatic failure remains controversial because APOLT does not rule out potential regeneration of the native liver, resulting in unsatisfactory outcomes (6). In our series of APOLT for fulminant hepatic failure, none of the patients achieved long-term survival. The reasons for our poor results might be application of preemptive portal vein diversion and patient selection. The rationale of portal vein diversion is to prevent the portal flow steal phenomenon. We reported that the native liver has less resistant than the graft in fulminant hepatic failure (17), however, sufficient portal blood flow might be essential for native liver recovery and subsequent regeneration. An experimental study reported that the necessity of portal vein diversion in APOLT was dependent on the pathophysiology of the remnant native liver (27). The efficiency of portal vein diversion for fulminant hepatic failure, a paradox between the functional competition and the native liver recovery, remains unclear. Moreover, the optimal APOLT candidate for fulminant hepatic failure has not yet been clearly defined. A previous study suggests that native liver recovery is more likely to occur in those with a short interval between jaundice and encephalopathy (28). The median interval between onset of jaundice and encephalopathy was 42 days in our series. This delay might be one of the reasons for the poor outcome.

Bismuth et al. reported that the main advantage of APOLT for fulminant hepatic failure, that is, the potential for withdrawal of immunosuppressive therapy, was rarely achieved and that the indication of APOLT for fulminant hepatic failure should therefore be reconsidered because of the high degree of technical complications (6,10). We fully agree with this suggestion. While our experience of APOLT for fulminant hepatic failure is limited, based on the poor outcome, we also consider that APOLT should have a limited place in the treatment of fulminant hepatic failure. There might be a possibility, however, that APOLT could be used in toxic injury such as acetaminophen toxicity where recovery of the native liver is more likely than in idiopathic or viral fulminant hepatic failure (29–31).

In the case of non-cirrhotic metabolic liver disease, APOLT had a satisfactory outcome in our series with a 5-year graft survival of 83.3%. After the initial two cases of the portal flow steal phenomenon, we changed the standard procedure for APOLT of non-cirrhotic metabolic liver disease to indicate native portal vein diversion in all subsequent cases whereby the graft liver receives the entire portal venous flow. Concern remains about the dysfunction of the remnant native liver after portal vein diversion, which may

negate the support of a patient's life and the possibility of future gene therapy. However, it has been reported that occluded portal flow induces hepatocyte apoptosis rather than necrosis in the embolized lobe without changing the functional efficiency of the hepatocyte (32,33). Our previous report showed that ligation of the native portal vein had no detrimental effects on the native liver supplied by arterial flow only (17,34). The remnant native liver may sustain the recipient's life if the native portal vein is transected. APOLT with portal vein diversion is an effective technique to induce graft regeneration and to avoid functional portal flow competition in non-cirrhotic metabolic liver disease.

With regard to our experience of APOLT for small-for-size grafts, the patients had high surgical complications and unsatisfactory patient survival. Recent technical improvements in left lobe donation have led to the use of right lobe grafts in adult-to-adult LDLT to overcome problems encountered with small-for-size grafts (35). After a period of APOLT using left lobe grafts, which partially relieved the problems of small-for-size grafts, right lobe LDLT was systematically introduced from February 1998. The cumulative 1-year graft survival rate of right lobe LDLT was 76.8%, which was significantly higher than that of APOLT for small-for-size grafts ($p < 0.01$, $n = 168$). Moreover, in some cases, if the functional volume of the right lobe was not sufficient for recipients, right lobe with middle hepatic vein graft was indicated with special attention to donor safety. The overall cumulative 1-year graft survival rate of right lobe with middle hepatic vein graft was 82.2% ($n = 28$). Our current strategy is to consider the right lobe as the first choice followed by APOLT with a right lobe graft for small-for-size grafts.

The graft survival in children younger than 2 years old receiving an ABO-incompatible graft is similar to those receiving compatible grafts. The survival is gradually affected with age by specific complications associated with blood type mismatching such as focal hepatic necrosis due to microcirculatory disturbance and multiple non-anastomotic biliary strictures attributable to arteriole insufficiency (36). In our LDLT program, an ABO-incompatible graft was unavoidable in 12% of the recipients. Despite the application of pre-operative plasma exchange, splenectomy and enhanced immunosuppression, the 5-year graft survival was less than 50% in an adult population. The application of APOLT to ABO-incompatible cases improved graft survival; however, graft survival was not satisfactory. Recently, an intra-portal infusion protocol was introduced (37), and improved patient survival was observed in ABO-incompatible cases. We modified the protocol from intra-portal to intra-hepatic arterial infusion from December 2001. Although it is still a tentative trial, intra-hepatic arterial infusion protocol dramatically improved survival with 1-year graft survival of 85% (data not shown). After the introduction of a novel immunosuppression protocol, APOLT is not adopted for ABO-incompatible cases. Further study of hepatic artery infusion therapy is now underway in order to transcend the ABO-barrier.

The higher rejection episodes in APOLT series are a consequence that requires further investigation. Immunological differences in the responses to orthotopic and auxiliary allografts were reported in an experimental study, given the increased expression of class II MHC antigen on hepatocytes in auxiliary liver transplantation, and the increase in the rejection response to the auxiliary grafts (38). Auxiliary liver allografts were also demonstrated to be more susceptible to rejection than non-auxiliary allografts (39). Further histopathological studies into the mechanisms of susceptibility to rejection in APOLT cases are currently underway.

Unlike standard LDLT, the incidence of biliary complications and the need for retransplantation were shown to be higher in APOLT cases. According to our present study, we conclude that APOLT should have a restricted indication in the treatment of fulminant hepatic failure, small-for-size grafts and ABO-incompatibility. Conceptual changes were made in the treatment of small-for-size grafts, through the introduction of LDLT using right lobe with or without middle hepatic vein graft, and in the treatment of ABO-incompatible cases, through the use of a novel intra-hepatic arterial immunosuppression protocol. Non-cirrhotic metabolic liver disease may be a suitable indication for APOLT.

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Impact of Enteral Nutrition in Adult-to-Adult Living Donor Liver Transplantation : A Preliminary Study

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The Impact of enteral nutrition (EN) in living donor liver transplantation (LDLT) has not been well examined. We analyzed 83 consecutive adult-to-adult LDLT cases who had a preoperative MELD score of over 18points. There was no major complication related to the placement of EN tube. The better patient survival was found in the patients receiving EN (n=35) compared those who were not (n=48). Bilirubin clearance, prothrombin time, serum creatinine level and total lymphocyte count were better in EN group. Incidence of acute cellular rejection was lower in EN group. There was no difference about incidence of infectious and surgical complications. Our results demonstrated in adult-to-adult LDLT that EN was well tolerated and provided the better patient survival in more deteriorated patients.

Living donor liver transplantation, Enteral nutrition

Introduction

The living-donor liver transplant program first started in Japan in 1990, and remains the major form of liver transplantation because of the scarcity of the cadaveric donor pool[1]. Experience of, and technical improvements in pediatric living donor liver transplantation (LDLT) have led to the use of right lobe grafts in adult-to-adult LDLT[2]. Recently, the rapid increase in adult LDLT using right lobe grafts has dramatically changed the age and disease distribution. The overall 5-year survival of adult-to-adult LDLT in our center is 74.1% (n=200), and is comparable with those of cadaveric liver transplantation. However, the postoperative catch-up is not always satisfactory compared with cadaveric liver transplantation because of the 'small-for-size' graft. Major concems remain about the relatively 'small-for-size' syndrome in LDLT, such as the persistent hyperbilirubinemia, massive ascites, coagulopathy, and the possibility of inducing susceptibility to infection and kidney dysfunction associated with 'small-for-size' grafts[3].

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In nutrition care after liver transplantation, the superior status of enteral nutrition (EN) over total parenteral nutrition has been established in cadaveric liver transplantation, meaning that enteral feeding after liver transplantation is effective in maintaining the nutritional status and has potential benefits in terms of reduced complications[4,5,6]. However, all of these reports were based on the experience with cadaveric liver transplantation. It is expected that the positive impact of enteral nutrition might be significant with 'partial liver' more than with 'whole liver' transplantation. To support the nutrition status of patients, the maintenance of the relatively 'small-for-size' graft function and to obtain better patient survival following adult-to-adult LDLT, we initiated EN from October 2000. In the present study we evaluate the impact of EN in the patients who received adult-to-adult LDLT in Kyoto University Hospital.

Patients and Methods

Of 820 patients who underwent liver transplantation between June 1990 and October 2002, 200 patients received adult-to-adult LDLT at Kyoto University Hospital. Among the 200 patients, 83 patients (41.5%) had a preoperative MELD score of over 18 points, which stands as the model for end-stage liver disease[7]. Of these 83 patients, 13% received a blood type incompatible graft and 31% were kept in the ICU preoperatively. Thirty-five patients were managed posttransplantation with EN and 48 without EN. Table 1 shows the profile of the patients and operations involved in this study. There were no significant difference between the with and without EN groups as far as patient age, disease distributions and operation profiles were concerned. The follow-up period was shorter with the EN group ($p < 0.01$). None of the patients in the group without EN received nasogastric tube feeding.

The EN tube was placed after the completion of all transplant anastomoses. A site in the jejunum was selected which could be easily reached from the abdominal wall. The entry site in the proximal jejunum was 20 cm distal to the ligament of Treiz. A Witzel tunnel was created over the tube to avoid leakage.

Selective bowel decontamination including Kanamiycin sulfate, lactulose and polymyxin B by mouth was initiated 3 days before transplantation and enteral nutrition with ELENTALR® (Ajinomoto Pharma Co., LTD, Tokyo, Japan) was started on postoperative day 2. The formula contains nitrogen, carbohydrate and lipid, and is a special formula consisting only elemental components which are chemically well-defined and mostly absorbed in their original form, not being digested in the intestinal tract. It additionally contains free amino acids, carbohydrates, vitamins, mineral and 0.64g /100g fat.

Enteral nutrition was started at 480 kcal/day and increased to a maximum of 30 kcal/kg/day. Once oral intake was established, tapering off of the EN was started.

The operation was performed according to the standard right lobe LDLT procedure 2. A veno-venous bypass was not used as total clamping of the inferior vena cava could be avoided in all cases. Biliary reconstruction was basically achieved with duct-to-duct anastomosis, and 91.6 % of the group with EN and 89.6% of the group without EN received duct-to-duct biliary reconstruction ($p = NS$).

Immunosuppression consisted of tacrolimus and low dose steroids[8]. Tacrolimus administration was started from the day after transplantation. The target whole blood trough level of tacrolimus was 10-12 ng/ml for the first two weeks, approximately

Figure 1. Patients and operation profiles in adult-to-adult living donor liver transplantation (MELD* score >18)

	With EN**	Without EN**
Case number	35	48
Median follow-up (month)	9.0	31.0
Recipient age (years)	47.6±10.5	45.2±9.5
Donor age (years)	39.8±11.9	40.2±11.8
GRWR*** (%)	1.10±0.27	1.10±0.31
Cold ischemic time (min)	127±91.9	116±99.2
Warm ischemic time (min)	45.2±13.4	44.3±8.4
Original liver disease		
Liver cirrhosis (with HCC)	16 (7)	25 (5)
Fulminant hepatic failure	10	15
Cholestatic liver disease	5	4
Metabolic liver disease	1	1
Others	3	1

*; MELD: Model for end-stage liver disease 7)

**; EN: Enteral nutrition

***; GRWR: Graft-to-recipient weight ratio

10 ng/ml for the following two weeks and 5-10 ng/ml thereafter. Steroids treatment was initiated at the time of graft reperfusion at a dose of 10 mg/kg, then tapered from 1 mg/kg/day to 0.3mg /kg/day during the first month. Patients who received ABO-incompatible transplants had preoperative plasma exchange or double filtration plasmapheresis in order to reduce the anti-ABH antibody titer, and prostaglandin E1, cyclophosphamide and additional steroids were administered postoperatively from the portal vein or hepatic artery catheter[9].

Acute rejection was diagnosed on the basis of liver biopsy. All the rejection episodes were treated with a steroid bolus injection.

Values are presented as means±standard deviations. Statistical analysis was performed with the generalized Wilcoxon test. Actuarial 1- and 5-year graft survival curves were calculated with the non-parametric Kaplan-Mejer method and compared among the groups with the Wilcoxon test. P values less than 0.05 were regarded as significant throughout the study.

This study was approved by the institutional review board and informed consent was obtained in all the cases.

Results

There were 3 complications (8.6%) related to placement of the EN tube. Three patients had skin infection around the entry site of EN tube, which was easily managed with drainage.

No significant difference in the patient survival was seen between the group with EN (n=92, 75%) and the group without EN (n=108, 74.1%) after the overall adult-to-adult LDLT series (n=200) (p=0.18). However, if we compare those patients in a more advanced state of deterioration, whose preoperative MELD score was over 18 points, better patient survival was

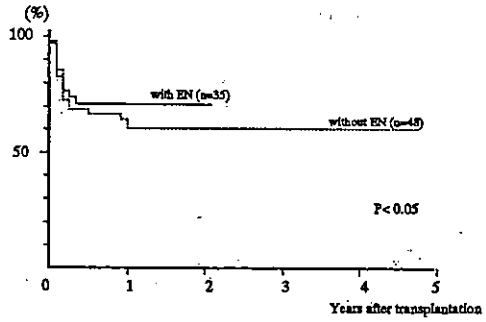

Figure 2. Patient survival in adult-to-adult living donor liver transplantation (MELD* score > 18) with or without enteral nutrition. Better patient survival was found in the patients receiving EN (71.0%) compared those who were not (60.4%) ($p < 0.05$).

found in the patients receiving EN (n = 35) compared those who were not (n = 48) (Figure 2. $p < 0.05$). Among these patients, 42% of the patients were classified as UNOS status 1 or classical 2A. Mean MELD score 28.5 ± 8.8 in the EN group and 28.1 ± 9.0 in the group without EN.

Biochemical findings

Serum asparate aminotransferase (AST), total bilirubin, prothorombin time (PT), serum creatinine, total cholesterol, cholinesterase, serum albumin and total lymphocyte count (TLC) were collected preoperatively and for the first 4 postoperative week.

There was no significant difference in AST levels between the two groups. Serum bilirubin clearance was much delayed and persistent hyperbilirubinemia was observed in the group without EN at POD 10 and later ($p < 0.05$). The difference in prothrombin time was not prominent, but some delayed recovery was observed also in the group without EN. Interestingly, the serum creatinine level was significantly lower in the enteral nutrition group ($p < 0.01$). Whether this was really caused by prevention of a catabolic state cannot be answered by the present study. Twenty-three percent of patients in the EN group, and 15% of those in the no EN group received continuous hemofiltration therapy in perioperative period. Total cholesterol and cholinesterase levels were better in the latter half of the first month in the EN group, although the difference was not statistically significant. The albumin lebel was better in the group without EN, which might reflect frequent use of intravenous albumin for correction of ascites and pleural effusion in the immediate post-transplant period. Regarding the total lymphocyte count (TLC), better TLC recovery was found in the EN group, although without statistical significance (Figure 3).

Infectious complications

Incidence of bacteremia during the first month post-transplant, which is defined as postperative blood culture positive, was higher in the EN group (31.4%) than in the group without EN (18.8%). However, the incidence of Gram negative bacteremia was lower in the EN group (36.4%) than in the group without EN (44.4%). The common Gram negative bacteremia was caused by *Pseudomonas aeruginosa, Serratia, and Xanthorophomonas maltophilia*. Gram positive bacteremia was mainly caused by the Staphylococcus species. The incidence of EBV infection was higher in EN group (8.6% for the EN, and 0% for the group without EN), and CMV infection was also high in the EN group (40.0% for the EN, and 14.6% for the group without EN), but the differences were not statistically significant.

Acute cellular rejection

The incidence of acute cellular rejection (ACR) was lower in the EN group (22.9% vs. 45.8%, $p < 0.05$), however the onset of ACR did not differ with each group. As we did not measure immune

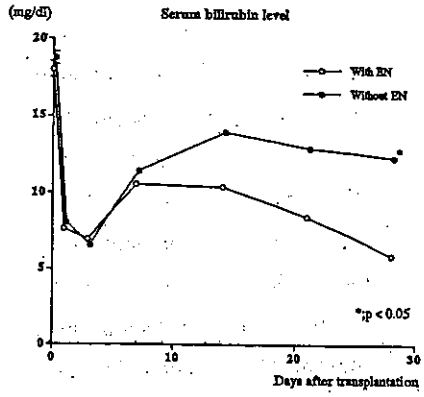

Figure 3A. Changes in serum bilirubin level

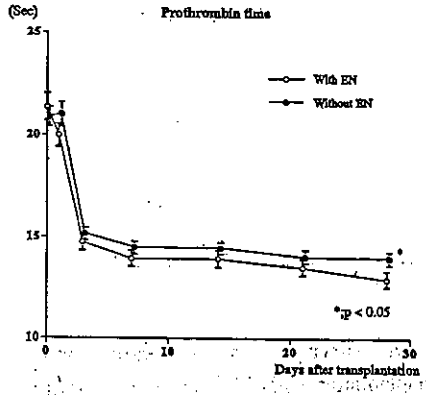

Figure 3B. Changes in Prothrombin time

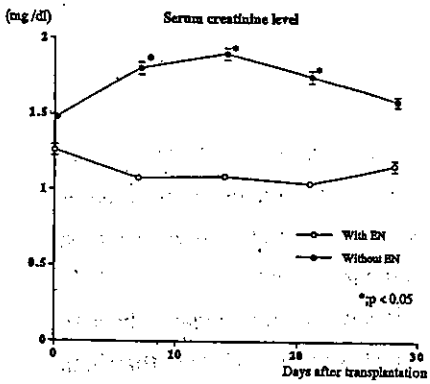

Figure 3C. Changes in serum creatinine level

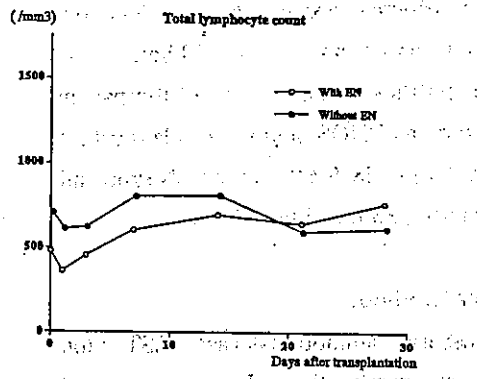

Figure 3D. Changes in total lymphocyte count

and inflammatory responses in this study group, further study is necessary to make a definite conclusion about EN and ACR.

Surgical complications

There was no difference concerning the surgical complications between the two groups, such as bleeding (20.0%, EN ; 18.8%, no EN), perforation (5.7% vs. 4.2%), biliary leakage (8.6% vs. 10.4%), and HAT (5.7% vs. 2.0%) in each group. Shorter hospital stay was seen in the EN group (45.7±26.8 days in the EN, and 56.2±39.3 days in the group without EN), but the difference was not statistically significant.

Discussion

The patients after liver transplantation are at high risk for malnutrition related complications. Most patients who undergo liver transplantation, however, do not need nutrition assistance to meet their metabolic demands, aside from oral dietary supplementation[10]. The actual percentage of liver transplant recipients who might benefit from EN is a difficult number to obtain and will somewhat depend on the referral base[11]. Also the selection criteria for EN are difficult to determine who the most appropriate liver transplantation candidates might be.