移植待機中の肝不全患者のうち，長期に高ビリルビン血症であったり，腹水のコントロールのために利尿剤を長期服用している症例は高率に腎障害を合併しており，抗真菌薬の投与に際しては，投与量，投与間隔の考慮が必要である。

移植後の診断

前記のような術前からの予防策に引き続き，術中には固有肝，胆汁，腸管（胆管・空腸吻合の場合）の培養検査を行いコロニーのチェックをしている。術後においては，週2回の各種培養検査とともにβ-D glucan，アスペルギルス抗原，クリプトコッカス抗原，カンジダ抗原などの生化学検査や38°C以上の熱が2日以上続く場合はCT検査をして感染源が存在するかどうか検索している。

真菌感染症，特に深在性真菌症の診断は肝移植においても非常に難しい問題の一つである。肝移植患者では術前からの監視培養により真菌のコロニーを把握しておくことは重要である。しかし，監視培養は真菌感染の有用な情報ではあるがコロナイゼーションと感染症発症との鑑別が難しいこともあり確定診断には，血液培養，組織診，眼底所見，気管支肺胞洗浄などと画像診断，臨床所見を加味した総合的な診断となることが多い。

本邦ではβ-D glucanの有用性が唱えられているが[4]，特異度の問題があり欧米ではまだ一般的な検査法とはなっていない。肝移植におけるβ-D glucan測定の有用性については現在日本移植外科真菌症研究会で調査中であるが，血液製剤，透析膜による偽陽性，移植直後（2週間ほど）の一過性の上昇などの特徴を理解した上で利用すると有用であると思われる。2003年2月に発表された臓器移植領域のガイドラインには，β-D glucan測定が補助診断として盛り込まれているが，確定診断となる基準にはなっていない[5]。しかし，β-D glucanが高値である肝移植症例に対しては，有熱症状などがなくとも抗真菌薬の投与を開始すべきと考える。また，PCR法による遺伝子診断はもう暫く臨床成績の集積が必要であると思われる[5]。ただ，アスペルギルス属については，PCR法によるスクリーニングを行い成果があったとする報告もある[6]。

移植後の治療

術中には，予防的投与としてFLCZまたはミカファンギン（ファンガード；MCFG）の点滴静注を行っている。カンジダ属に対する肝移植後の抗真菌薬予防投与は，術前の長期ステロイド，術前真菌感染の既往，抗菌薬の長期使用，長時間の移植手術，大量出血，血管合併症，糖尿病などがあるものについては積極的に行うべきと考えるが，危険因子がなく真菌感染を疑わせるものがない症例については，10日から2週間で中止している。FLCZ[7,8]やアムホテリシンB（ファンギゾン；AMPH-B)[9]の予防投与についての大規模試験の報告はあるが，危険因子の少ない肝移植患者に予防投与がどれほど有効であるかについては今後検討の余地がある。

アスペルギルス属による感染症は，肺移植に比べると肝移植では頻度が減少するが，カンジダ属の感染症に比べ致死率が非常に高いのが特徴である。施設によって差はあるが，数%から20%の頻度である[1]。アスペルギルス属に対する肝移植後の有効な抗真菌薬の予防投与の効果は報告されていないが，原疾患が劇症肝炎の患者にAMPH-BやITCZを予防的に投与する試みはされている。

クリプトコッカス属による感染症は，肝移植においてはアスペルギルス感染症に比べやや多い。カンジダ属と同じ酵母菌属であるた

めFLCZなどの予防投与は有効であると考えられるが，感染症としての頻度が低いためevidenceはない。

前記のような予防的抗真菌薬の投与にもかかわらず真菌感染症となった，または，疑われた症例に対しては，先制攻撃的治療，経験的治療，標的治療が必要となる。真菌感染症の発症は免疫抑制剤の量が多く，手術侵襲の影響が残っているため，術後1～2週間が要注意である。重症例では免疫抑制剤の減量を考慮しなくてはならない症例もある。感染部位と起炎菌が明らかになっている場合は，抗真菌薬による治療効果を厳重に監視しながら，効果の上がらない抗真菌薬は速やかに変更することも重要である。

2003年2月に出たガイドラインによると，先制攻撃的治療にはFLCZ 200～400mg/日，AMPH-B 0.2～0.5mg/kg/日，ミコナゾール（フロリード；MCZ）10mg/kg/日，経験的治療にはFLCZ 200～400mg/日，AMPH-B 0.2～0.5mg/kg/日，MCZ 10～15mg/kg/日などとなっており，標的治療にはMCFG 100～150mg/日も加わる[5]（**表2**）。当科においてもおおむねこのガイドラインと同様の治療を行ってきたが，AMPH-Bを投与することはまれである。

注意すべき点は，カンジダ属に比べアスペルギルス属に対しては，抗真菌薬の量が多く必要であることと，クリプトコッカス属に対してMCFGは無効であることである。また，ITCZは経口薬のみであるため，移植後早期の腸管運動が減弱している時期には使用しにくいということが挙げられる。ニューモシスティス・カリニ肺炎に対しては，スルファメトキサゾール・トリメトプリム（バクタ，バクトラミン；ST合剤）12錠／日，イセチオン酸ペンタミジン（ペナンバックス；Benambax）3～4mg/kgを投与している。当科では術後3ヵ月後に外来通院患者でカリニ肺炎を発症し，治癒した症例があった。また，アゾール系の抗真菌薬は肝臓でP-450により代謝されるため，免疫抑制剤のうちタクロリムス（プログラフ；FK506）やサイクロスポリンA（ネオーラル，サンディミュン；CsA）の血中濃度急上昇，腎毒性の増強などがあるため注意が必要である。

表2　真菌感染症に対する抗真菌薬の使い方

カンジダ症	
経験的治療：	フルコナゾール　200～400mg/日
（先制攻撃的治療）	ミコナゾール　10～15mg/kg/日
	アムホテリシンB　0.2～0.5mg/kg/日
標的治療：	フルコナゾール　200～400(800)mg/日
	ミコナゾール　15～20mg/kg/日
	ミカファンギン　100～150mg/日
	アムホテリシンB　0.5～1.0mg/kg/日
アスペルギルス症	
経験的治療：	アムホテリシンB　0.2～0.5mg/kg/日
（先制攻撃的治療）	イトラコナゾール　200～400mg/日
標的治療：	ミコナゾール　15～20mg/kg/日
	アムホテリシンB　1.0～1.5mg/kg/日＋
	フルシトシン　100mg/kg/日
	ミカファンギン　150～300mg/日
	イトラコナゾール　400～600mg/日

おわりに

臓器移植においては，全身状態の悪い患者が対象であることと免疫抑制剤を使用するということで深在性真菌症のリスクが高く，予後を左右する因子の一つになっている。10年，20年前を振り返ってみると，真菌症に対する診断，治療は進歩したが，さらなる移植後生存率の向上のためには，克服されるべき問題は多い。

文献

1）Emmanouilides C, Holt CD, Winston DJ：Infections after liver transplantation. In；Busttil RW and Klintmalm GB, eds. Transplantation of the liver. Philadelphia：WB Saunders Company, 1996, p633-647

2）川岸直樹，大河内信弘，藤盛啓成ほか：肝移植手術のコツと術後管理，術後感染症．外科 63：1341-1344，2001

3）川岸直樹，藤盛啓成，里見　進：生体肝移植における真菌感染症対策．日本腹部救急医学会雑誌 24：57-65，2004

4）Obayashi T, Yoshida M, Mori T et al：Plasma (1-->3)-beta-D-glucan measurement in diagnosis of invasive deep mycosis and fungal febrile episodes. Lancet 345：17-20, 1995

5）深在性真菌症のガイドライン作成委員会：臓器移植領域．深在性真菌症の診断・治療ガイドライン，医歯薬出版，東京，2003，p34-35

6）Kami M, Fukui T, Ogawa S et al：Use of real-time PCR on blood samples for diagnosis of invasive aspergillosis. Clinical Infectious Disease 33：1504-1512, 2001

7）Winston DJ, Pakrasi A, Busuttil RW：Prophylactic fluconazole in liver transplant recipients. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 131：729-737, 1999

8）Lumbreras C, Cuervas-Mons V, Jara P et al：Randomized trial of fluconazole versus nystatin for the prophylaxis of Candida infection following liver transplantation. J Infect Dis 174：583-588, 1996

9）Tollemar J, Hockerstedt K, Ericzon BG et al：Liposomal amphotericin B prevents invasive fungal infections in liver transplant recipients. A randomized, placebo-controlled study. Transplantation 59：45-50, 1995

肝移植の現況と展望

Current Status and Prospect of Liver Transplantation

里　見　　進

東北大学大学院医学系研究科　外科病態学先進外科学

1. はじめに

臓器移植法が成立し脳死肝移植の増加が期待されたがその数は伸び悩んでいる．一方，1989年にスタートした生体肝移植は年々増加し，末期肝不全患者を救命する手段として定着した感がある．適応も小児患者から成人例へと拡大され，年間の実施数では小児例を上回るようになっている．本講演では，これまでに術式や術後管理の面で改善してきたことや現時点での問題点,さらには今後の展望について自験例を中心に述べる．

2. 術　　式

A. ドナー

ドナーの手術は採取するグラフトの種類によって外側区域，左葉，右葉摘出の手術に大別できる．小児への移植では通常ドナーの外側区域や左葉をグラフトとして用いる．近年増加している成人への移植では尾状葉を付けた左葉や右葉をグラフトとして用いることが多い．グラフトの種類関わらずレシピエント手術の進行にあわせて調整するので手術時間はほぼ一定になっている．また出血量も1,000 mlを越えることはほとんど無く術前に準備した自己血を使用しない例も多い(表1)．ドナーからグラフトを採取した後の残肝容積は約35%以上あればよいと考える施設が多いが,先日わが国でもドナーの死亡例がでておりドナーの安全については今後さらに詳細に解析する必要がある．

B. レシピエント

患者さんの固有肝を摘出した後でグラフトの脈管再建を行う．肝静脈，門脈の順に再建し門脈血流を再開した後，肝動脈吻合，胆管の再建を行う．

肝静脈の吻合は血流再開後にoutflow-blockがこないように吻合口を大きくすることが肝要で，そのために通常小児症例ではレシピエントの中，左肝静脈を一本に形成しグラフトの左肝静脈と端々吻合する．レシピエントの右，中，左肝静脈を一本にしてグラフト肝静脈と吻合する場合もある．

門脈はレシピエントの左右の門脈分岐部を開きパッチ状に形成してグラフトの門脈と端々吻合する．連続縫合を基本とするがレシピエントの門脈が細いときには半分を連続,残りを結節縫合とし狭窄を防いでいる．レシピエントの門脈が消失している例や狭窄で充分な流量がえられないと判断した例では，上腸間膜静脈と脾静脈との合流部にドナーから採取した静脈（大伏在静脈や卵巣静脈，下腸間膜静脈等）を間置してから門脈再建を行う．

動脈吻合は顕微鏡を用い，レシピエントの左右いずれかの肝動脈とグラフトの動脈を端々吻合する.通常，1～2 mmの動脈を10針ほどで結節縫合する．グラフトの動脈が二本ある場合でも，口径の大きい動脈の再

表1．当科におけるドナー手術（74例）

術式(症例数)	手術時間 (時:分)	出血量 (ml)	他家血輸血 (症例)	移植肝重量 (g)	術後最高 T-Bil/AST	術後入院 期間（日）
S23 (30)	7:8	595	1	259	1.9/294	11
S234 (18)	8:59	769	0	278	2.3/306	12
S234MHV (12)	8:58	963	0	354	2.1/317	15
S5678 (14)	8:40	814	0	539	2.8/349	13

表2. 生体肝移植後に起こりやすい合併症

1. 出血
2. 血栓症
3. 急性拒絶反応
4. 感染症（細菌，ウイルス，真菌，原虫）
5. 胆道感染症（胆汁漏，吻合部狭窄）
6. 腹水貯留

建だけですむ事が多い．

胆道の再建は肝管空腸吻合が一般的である．成人例では総胆管と肝管を吻合する場合もある．いずれも8針程度で結節縫合し，内ステントや外ステントを留置する．術後に吻合部狭窄や閉塞を起こす例が約15～30%あるので何らかの改善が必要である．

3. 術後合併症と対策

表2に主たる合併症を列記する．

血栓症は肝動脈，門脈，肝静脈いずれの吻合部でも起こり，対処が遅れると致命的であるので早期発見が必要である．ドップラーエコーでの血流の変化は，肝機能の悪化に先行して起こるので早期発見に有用である．術後2週間は一日に3ないし4回の血流チェックを行い早期発見に努めている．血栓症が疑われた場合は血栓溶解療法や観血的な血栓除去術，再吻合，再移植を行う．

一般に肝臓は拒絶反応の起こりにくい臓器といわれている．また，近年の免疫抑制剤の発達は拒絶反応の制御を容易なものとしているが，それでも一般的な拒絶反応療法であるステロイドのパルス療法に抵抗性の拒絶反応がある頻度で起こっている．特に血液型が不適合である組み合わせ間の移植ではその頻度が高い．当科では7例のABO不適合移植中1例を抗体価の上昇に伴う超急性拒絶反応で亡くしている．最近，B細胞に対する抗CD20モノクローナル抗体を使用し，液性拒絶反応の予防や超急性拒絶反応からの回復例を2例経験した．血液型不適合移植での有効な治療法となるか，今後の検討が必要である．

術後は大半の症例で何らかの感染症を発症する．術前からの感染症が顕在化することも多いし耐性菌の出現率も高い．特に胆道閉鎖症の子供は，数回の手術で多くの耐性菌を内在していることが多いので注意が必要になる．適切な治療薬を選択することで細菌，真菌，ウイルス感染症のいずれも以前に比べて対処しやすくなってきている．ウイルス感染症の中では，CMVに対する特効薬が出現したので治療が容易になり，変わってEBウイルスが問題となっている．特に死亡率の高いPTLDが注目されている．

術後数ヶ月から数年を経てから起きる胆道系の狭窄や閉塞は，現時点で最も移植医を悩ませている合併症である．拡張やステントの留置が可能であれば対処は容易であるが，再吻合が必要な場合，難渋することが多い．最初の吻合部に到達が不可能な場合は肝内の拡張した胆管を探し，その胆管と空腸の再吻合を試みることがある．胆管狭窄は患者にとっても主治医にとっても悩みの種であり，狭窄を起こさない吻合法の開発が危急の問題となっている．

4. 成人肝移植と適応の拡大

当初小児患者を対象に始まった生体肝移植は，近年成人例へと適応を広げ，一年間の実施数では小児例を上回るようになっている（図1）．成人肝移植ではレシピエントに必要なグラフト量を得るために尾状葉付き左葉グラフトや右葉グラフトが用いられる．いずれの場合も肝静脈の再建に工夫が必要となる．特に，ドナーの安全を考慮して中肝静脈をドナー側に残したグラフトでは，中肝静脈に注いでいるV5，V8の静脈断端が離断面に露出することになるので再建が必要になってくる．レシピエントから予め採取しておいた浅大腿静脈や大伏在静脈，卵巣静脈などを利用して再建する（表3）．

成人肝移植の普及と共に，ウイルス肝炎後の肝硬変やHCC合併例に対する移植が年々増加している．HCC患者への移植は，欧米ではミラノクライテリアに則って移植をすることが多い．わが国では生体肝移植

表3. 右葉グラフトにおけるV5V8の再建（11/14例）

症例	V5V8の再建方法	再建に用いた静脈
52	V8—レシピエントMHV	
61	V8—再建したMHV	卵巣静脈
62	V8—再建したMHV	浅大腿静脈
64	V8—再建したMHV	大伏在静脈
65	V5, 8—再建したMHV	浅大腿静脈
66	V5, 8—再建したMHV	浅大腿静脈
68	V5, 8—再建したMHV	浅大腿静脈
69	V5, 8—再建したMHV	浅大腿静脈
71	V5, 8—再建したMHV	浅大腿静脈
72	V5—再建したMHV	浅大腿静脈
74	V5, 8—再建したMHV	浅大腿静脈

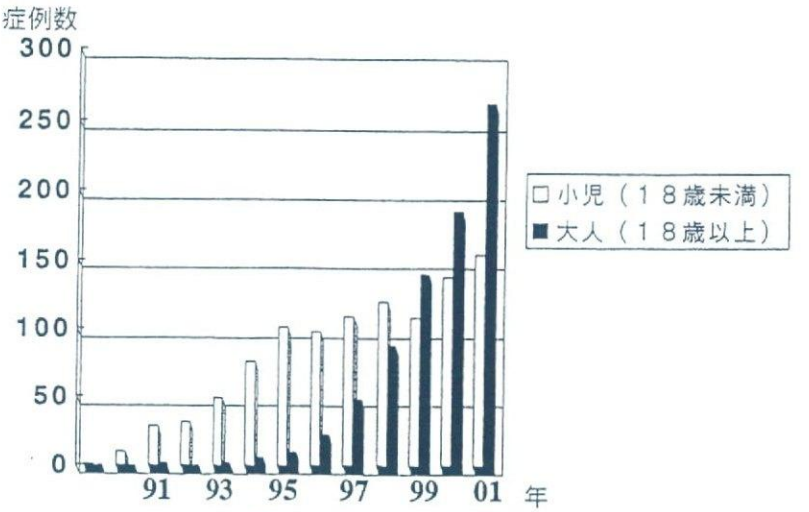

図1. 本邦における生体肝移植

が主流である特殊性もあり進行した例に対する移植が行われている．これまでの集計では，ミラノクライテリアに合致した症例の3年生存率は約80%で，ミラノクライテリアを越えて進行した症例の成績は3年生存が50%程度となっている．

5. おわりに

肝移植の普及で大きな障害になっているのは費用の問題である．特に，成人の生体肝移植は胆汁鬱滞性の疾患だけが保険適応で，わが国に多いB型肝炎，C型肝炎後の肝硬変やHCCに対する移植は適応外となっている．費用の面から移植を断念せざるを得ない患者さんも少なからずあり，医療の公平性の面からも早急な対応が求められている．(2004年から保険適応が拡大され，成人の劇症肝炎，肝硬変，HCCについても保険での移植が可能となった)．

生体肝移植がますます普及していく我が国ではあるが，ドナートなられた方々の中には何らかの合併症に悩む方もおられる．脳死からの臓器提供を増やす努力がこれまで以上に求められている．

International Symposium

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

Mureo Kasahara[2], Yasuhiro Ogura[3], Koichi Kozaki[3], Yasuhiro Fujimoto[3], Kenji Uryuhara[3], Atsushi Yoshizawa[3], Kohei Ogawa[3], Yasutsugu Takada[3] and Koichi Tanaka[2,3]

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].

1. This work was supported in part by grants from the Scientific Research Fund of the Ministry of Education and by a Research Grant for Immunology, Allergy and Organ Transplant from the Ministry of Health, Labour and Welfare, Japan.

2. Organ Transplant Unit, Kyoto University Hospital, Kyoto 606-8507, Japan.
3. Department of Transplant Surgery, Kyoto University Hospital, Kyoto 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.

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

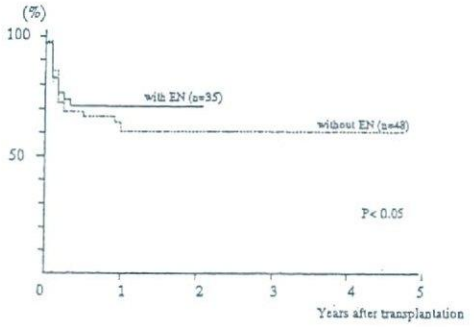

Figure 2. Patient survival in adult-to-adult living donor liver transplantation (MELD* score > 18) with or without enteral nutrition. Better patient survival was found in the patients receiving EN (71.0%) compared those who were not (60.4%) ($p < 0.05$).

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

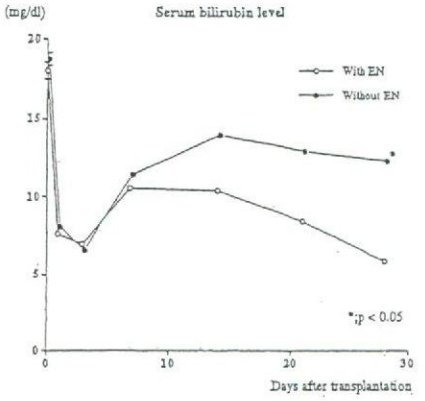

Figure 3A. Changes in serum bilirubin level

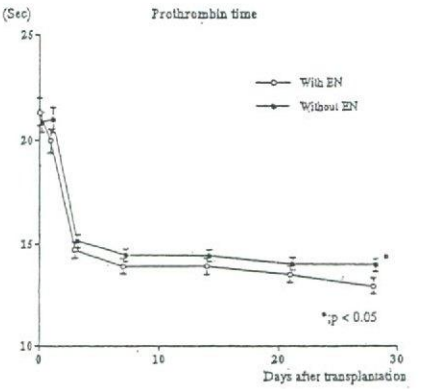

Figure 3B. Changes in Prothrombin time

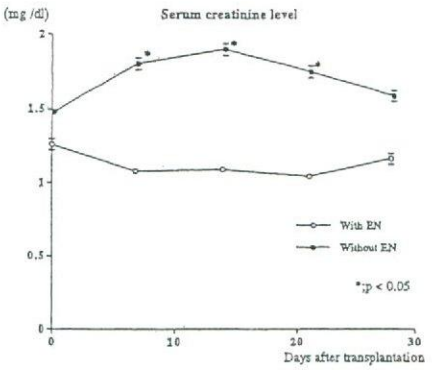

Figure 3C. Changes in serum creatinine level

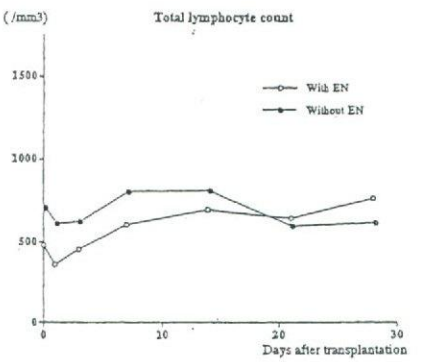

Figure 3D. Changes in total lymphocyte count

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.

Based on the initial experience of 100 adult-to-adult LDLT cases in Kyoto University hospital, 17% of the patients had perioperative infectious complications. It was reported that EN was well tolerated and decreased the rate of postoperative infections in liver transplant recipients[12]. In the present study, we investigated the impact of EN in more deteriorated patients whose MELD score was over 18 points, because of their delayed oral intake.

With this study, however, EN did not provide the same benefit as previously reported in cadaveric liver transplantation, such as bacterial and viral infections and surgical complications[4,5,12]. With regard to adult-to-adult LDLT, the patients had a potential risk of small-for-size graft which sometimes induces poor outcomes[3]. Our recent study demonstrated that infectious complications after LDLT are associated with decreased reticuloendothelial function and gut oxygen extraction, and consequent overgrowth of intestinal bacteria because of the potentially small-for-size graft, and the pathogenesis of infection in small-for-size grafts is related to a functional factor of the graft rather than pretransplant factors[13]. Further study is now going on whether EN can support the graft regeneration in partial liver transplantation using CT volumetry and cytokine expression (eg. TNF-α, INF, TGF-β).

Interesting results from among the biochemical findings were the better bilirubin clearance and serum creatinine level in the EN group. Bile duct epithelium is exposed to ischemia-reperfusion injury in liver transplantation, and bile stasis easily destroys the bile duct epithelium[14]. It was reported that EN could reduce bile stasis[15]. An increase in renal plasma flow and glomerular filtration rate have also been reported using EN, and the protection of renal function was partly related to maintenance of renal blood flow[16]. To prevent bile stasis and support renal insufficiency, the application of EN might be effective in LDLT patients.

The incidence of ACR was lower in the EN group in the present study. There have been several report about mucosal immunity related to nutrition. EN activates mucosal immunity, which induces Th2 cytokine production such as IL4 and IL10[17]. The Th2 cytokine expression of intraendothelial lymphocyte was suppressed, and Th1 cytokines were activated under the use of total parental nutrition[18-20]. As we did not measure immune and inflammatory responses in this study group, further study is necessary to make a definite conclusion about EN and ACR. Postoperative EN was accomplished successfully in LDLT. EN was well tolerated and resulted in better patient survival in patients whose condition had deteriorated further. With our study, EN did not provide the same benefit as previously reported in cadaveric liver transplantatation, such as Bacterial/Viral infections and surgical complications.

However, EN can reduce hospital stay.

We conclude that after introduction of EN in adult-to-adult LDLT, the patient survival was improved. It could be recommended that EN should be indicated for the patients with MELD score greater than 18. The incidence of infections was not significantly reduced according to our conventional EN. Recently, the effectiveness of a fiber diet containing immunonutrition was reported[12]. To clarify the efficacy of EN in the LDLT program, further study is now going on as to whether EN can support small-for-size graft function.

References

1) Kiuchi T, Uemoto S, Egawa H et al. Living donor liver transplantation in Kyoto, 2001. Clin Transpl. 2001 ; 195.
2) Inomata Y, Uemoto S, Asonuma K et al. Right lobe graft

in living donor liver transplantation. Transplantation 2000；69：258.

3）Kiuchi T, Kasahara M, Uryuhara K et al. Impact of graft-size mismatching on graft prognosis in liver transplantation from living donors. Transplantation 1999；67：634

4）Wicks C, Somasundaram S, Bjarnason I et al. Comaparison of enteral feeding and total parenteral nutrition after liver transplantation. Lancet 1994；344：837

5）Hasse JM, Blue LS, Liepa GU et al. Early enteral nutrition support in patients undergoing liver transplantation. JPEN 1995；19：437

6）Mehta PL, Alaka KJ, Filo RS, Leapman SB, Migrom ML, Pescoviz MD. Nutrition support following liver transplantation：comparison of jejunal versus parenteral routes. Clin Transplantation 1995；9：364

7）Wlesner R, Edwards E, Freeman R et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroentelogy 2003；124：91

8）Inomata Y, Tanaka K, Egawa H, Uemoto S, Ozaki N, Okajima H. The evolution of immunosupression with FK506 in pediatric living related liver transplantation. Transplantation 1996；61：247

9）Tanabe M, Shimazu M, Wakabayashi G et al. Intraportal infusion therapy as a novel approach to adult ABO-incompatible liver transplantation. Transplantation 2002；73：1959

10）Lowell JA. Liver transplant recipients and enteral feeding. Surgery 1996；119：357

11）Pescovits MD, Mehta PL, Leapman SB, Milgrom ML, Jindal RM, Filo RS. Tube jejunostomy in liver trasplant recipients. Surgery 1995；117：642

12）Rayes N, Seehofer D, Hansen S et al. Early enteral supply of lactobacillus and fiber versus selective bowel decontamination：a controlled trial in liver transplant recipients. Transplantation 2002；74：123

13）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 2003；75：1313

Noninvasive Evaluation of Graft Steatosis in Living Donor Liver Transplantation

Minoru Iwasaki,[1,6] Yasutsugu Takada,[1] Michihiro Hayashi,[2] Sachiko Minamiguchi,[3] Hironori Haga,[3] Yoji Maetani,[4] Kazuhiro Fujii,[1] Tetsuya Kiuchi,[5] and Koichi Tanaka[1]

Background. Hepatic steatosis affects graft function as well as postoperative recovery of donors in living donor liver transplantation. Liver macrovesicular steatosis in living donors was assessed using quantitative X-ray computed tomography (CT) analysis and histological examination of intraoperative liver biopsy.

Methods. A total of 266 living donors with complete pretransplant CT data and intraoperative "time 0" biopsy were included in the study. Liver biopsy specimen obtained during donor operation was examined for macrovesicular steatosis and was classified as none; mild (<30%); moderate (30%–60%); or severe (>60%). Liver-to-spleen CT attenuation values ratio (L/S ratio) on noncontrast-CT was evaluated for its usefulness as an index of hepatic steatosis in comparison with other parameters including body mass index (BMI) and serum liver function tests (gamma-glutamyl transpeptidase, alanine aminotransferase, aspartate aminotransferase, cholinesterase, and total cholesterol) using receiver operating characteristic (ROC) analysis.

Results. Histological grade of macrovesicular steatosis was none in 198 patients (74.4%), mild in 50 (18.8%), moderate in 15 (5.7%), and severe in 3 (1.1%). The median L/S ratios for the respective histological grades were 1.20 (range: 1.00–1.46), 1.12 (0.83–1.37), 1.01 (0.74–1.21), and 0.90 (0.70–0.99) ($P<0.0001$). The ROC curve for L/S ratio was located closest to the upper left corner, and the area under the curve of L/S ratio was significantly larger than that of any other preoperative variables.

Conclusion. L/S ratio calculated from preoperative CT can be a useful tool to discriminate hepatic macrovesicular steatosis. Based on the present results, the optimal cut-off value for L/S ratio to exclude more than moderate steatosis would be 1.1.

Keywords: Liver-to-spleen CT attenuation values ratio, Receiver operating characteristic analysis, Macrovesicular steatosis, Living donor liver transplantation.

(*Transplantation* 2004;78: 1501–1505)

In cadaveric liver transplantation (CLT), fatty infiltration of the liver is common among the brain-dead donor population. Most centers will use cadaveric grafts with up to 30% macrosteatosis (*1*), and there are reports of successful CLT with extensive hepatic microsteatosis (*2*). However, the presence of significant macrosteatosis (>60%) has been associated with primary nonfunction (PNF) of the graft liver, a condition that is catastrophic to liver transplant recipients (*3–5*). In living donor liver transplantation (LDLT), graft steatosis is one of the risk factors for graft dysfunction, and it is thought that the presence of severe macrovesicular steatosis is an absolute contraindication for the use of that organ for transplantation (*6*). In addition, hepatic steatosis affects postoperative recovery of the living donor (*7*). It is therefore very important to accurately diagnose the grade of donor hepatic steatosis in preoperative donor evaluation.

Several methods, including abdominal ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), body mass index (BMI) [kilograms/(height in meters)], waist/hip ratio, and liver function tests, have been used for evaluating hepatic steatosis (*8–10*). While these modalities are useful for investigating liver diseases, liver biopsy is still essential for diagnosis of hepatic steatosis and is the gold standard for the majority of patients (*11, 12*). Although liver needle biopsy is considered a relatively safe procedure, it has been reported that up to 5% of patients require hospitalization after the procedure and the incidence of significant bleeding is 1% with a fatal outcome in 1 of 10,000 patients (*13, 14*). To minimize such complications of needle biopsy, a noninvasive method would be required to evaluate hepatic steatosis in living donors before donor surgery.

Noncontrast-CT is currently one of the best radiological techniques for diagnosing of hepatic steatosis. The purpose of this study was to evaluate the accuracy of liver-to-spleen CT attenuation values ratio (L/S ratio) on noncontrast-CT in comparison with BMI or serum liver function tests for predicting hepatic steatosis.

PATIENTS AND METHODS

Donor Selection

Selection criteria for living donors in our institute were in principal based on age (20 to 60 years), ABO-blood type

This work was supported in part by a grant-in-aid for Scientific Research from the Ministry of Education, and by a Grant for Immunology, Allergy and Organ Transplantation from the Ministry of Health and Welfare, Japan.

[1] Department of Transplantation and Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan.
[2] Department of Gastroenterological Surgery, Osaka Medical College, Osaka, Japan.
[3] Laboratory of Anatomic Pathology, Kyoto University Hospital, Kyoto, Japan.
[4] Department of Radiology, Kyoto University Hospital, Kyoto, Japan.
[5] Department of Endocrine and Transplantation, Nagoya University Graduate School of Medicine, Nagoya, Japan.
[6] Address correspondence to: Minoru Iwasaki, M.D., Department of Transplantation and Immunology, Kyoto University Graduate School of Medicine, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto, 606–8507, Japan. E-mail: iwasaki@kuhp.kyoto-u.ac.jp.

Received 17 March 2004. Accepted 7 June 2004.

ISSN 0041-1337/04/7810-1501
DOI: 10.1097/01.TP.0000140499.23683.0D

compatibility, estimated graft size (greater than 1.0% of recipient body weight), and estimated residual liver volume (greater than 30% of the whole liver). Donor candidates with suspicion of hepatic steatosis were put on a diet and exercise program and later reevaluated.

Donor and Recipient Profiles

A total of 266 living donors with complete pretransplant CT data and histological assessment of intraoperative "time 0" liver biopsy was included in this study. There were 137 male and 129 female donors. Donor age, body weight, and BMI were 19–66 (median 38) years, 39–108 (median 61.3) kg, and 17.4–34.3 (median 22.6) kg/m^2, respectively. Selected graft types were left lateral segment in 122 donors, left lobe in 62, and right lobe in 82. Graft-to-recipient weight ratios (GRWR) for each graft types were 2.60 (range: 0.89–6.87), 0.96 (range: 0.61–1.56), and 1.14 (range: 0.66–3.18), respectively. Age and body weight of the recipients were 0.3–68.9 (median 11.1) years and 4.3–108 (median 28) kg. Primary disease of the recipients consisted of cholestatic disease in 138 patients, liver cirrhosis in 42, fulminant hepatic failure in 23, liver tumor in 23, metabolic liver disease in 20, retransplant in 12, and others in 8.

Donor Biopsy and Histological Assessment

During donor surgery, after confirming that there was no abnormal finding in the peritoneal cavity on gross examination, the "time 0" wedge biopsy was taken from the liver. When graft livers were left lateral segment, left lobe, or right lobe, biopsy specimen was taken from segment III, segment IV, or segment V, respectively.

Histological grading of macrovesicular steatosis of "time 0" biopsies was performed by two independent pathologists (S.M., H.H). Macrovesicular steatosis was defined as hepatocytes containing one large vacuole of fat displacing the nucleus peripherally, and graded as none, mild (<30%), moderate (30%–60%), and severe (>60%) based on the percentage of hepatocytes containing cytoplasmic fat droplets, as previously reported (*15*).

Calculation of L/S Ratio

All CT examinations were performed with a CT-W3000 (Hitachi Medical Systems, Tokyo, Japan). Scanning parameters were 120 kV, 200 mA, collimation of 7 mm, and table speed of 10 mL/s with reconstruction increments of 7 mm.

In noncontrast-CT, attenuation of normal liver is greater than the spleen. It has been reported that when this is reversed with a difference in liver-spleen attenuation of greater than −10 Hounsfield units, the liver is suspected to be steatotic (*16*). Hepatic and splenic attenuation values were measured on noncontrast-CT scans by using 16 circular region-of-interest (ROI) cursors in the liver and four in the spleen. In the liver, four ROIs were located in each of the right anterior, right posterior, left medial, and left lateral segments. This method was originally developed by us to raise the validity of the result by means of reducing errors in measurement and disappearance of overlap in each segment. All measurements were manually obtained in regions of uniform parenchymal attenuation, with care being taken to avoid vessels, artifacts, and other areas that might have spuriously increased or decreased measurements. The four measurements in each segment of the liver and spleen were averaged.

In this study, the ratio of attenuation values in the liver to those in the spleen (L/S ratio) was evaluated for its efficacy as a marker for steatosis in the liver (Fig. 1). Calculation of L/S ratio was as follows:

$$\text{L/S ratio} = \frac{\text{Average attenuation value of liver (16 points)}}{\text{Average attenuation value of spleen (4 points)}}$$

Inter-segmental variation of L/S ratio was also analyzed.

Statistical Analysis

Values are shown as median and range. For statistical comparison, chi-squared test or Fisher's exact probability test for categorical data, Kruskal-Wallis test or Mann-Whitney test for continuous data, Friedman test or Wilcoxon signed-ranks test for L/S ratio data of hepatic segments, and Cox-Mantel test for Kaplan-Meier survival curve were used. *P* values of less than 0.05 were regarded as statistically significant. To compare the preoperative diagnostic accuracy of L/S ratio, BMI, gamma-glutamyl transpeptidase (GGTP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholinesterase (ChE), and total cholesterol (T-CHO) receiver operating characteristic (ROC) analysis was used with the "time 0" biopsy taken as the gold standard. The ROC curve can be drawn by plotting sensitivity (or "true-positive rate") on the

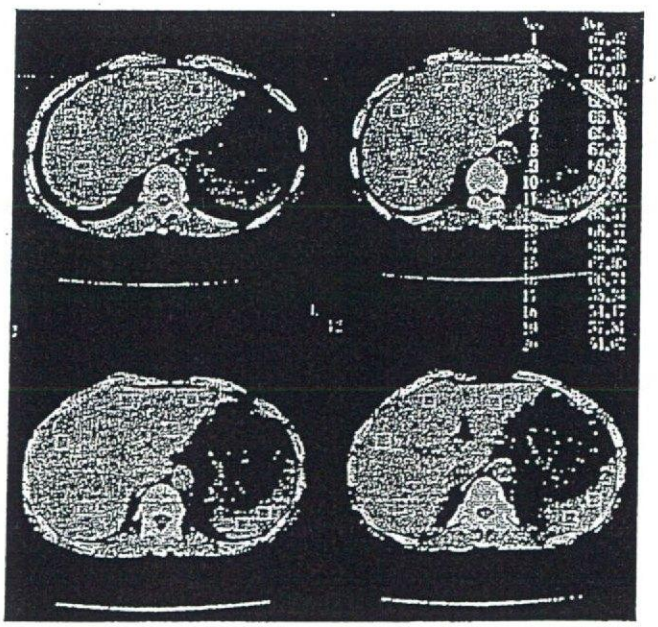

FIGURE 1. Calculation of liver-to-spleen CT attenuation values ratio. Hepatic and splenic attenuation values were measured on noncontrast-CT scans by using 16 circular region-of-interest (ROI) cursors in the liver and four in the spleen. In the liver, each four ROIs were measured at right anterior, right posterior, left medial, and left lateral segments. The size of one picture is 8×9 cm. Four sequential slices used for calculation of L/S ratio are demonstrated.

TABLE 1. Preoperative variables according to histological grades of macrovesicular steatosis

	Grade of macrovesicular steatosis (266)				
	None (198)	Mild (50)	Moderate (15)	Severe (3)	*P* values
Preoperative variables					
Donor age (yr)	37 (19–65)[b]	38 (21–61)[d]	48.5 (36–66)[b,d]	38 (30–47)	0.0127
BMI (kg/m^2)	21.9 (17.4–34.3)[a,b,c]	24.3 (18.0–31.6)[a,d]	26.5 (19.4–33.8)[b,d]	25.6 (24.1–26.8)[c]	<0.0001
AST (IU/L)	17 (9–41)[a,b]	20 (11–87)[a]	23 (12–32)[b]	22 (11–25)	<0.0001
ALT (IU/L)	14 (4–123)[a,b,c]	25 (9–142)[a]	26 (15–55)[b]	33 (20–47)[c]	<0.0001
GGTP (IU/L)	16 (7–113)[a,b,c]	29 (10–90)[a]	27 (11–146)[b,e]	47 (30–87)[c,e]	<0.0001
ChE (IU/L)	296 (168–508)[a,b]	345 (237–482)[a]	362 (277–486)[b]	309 (265–517)	0.0006
T-CHO (mg/dL)	188 (120–314)[a,b,c]	202 (139–441)[a]	214 (166–251)[b]	237 (222–249)[c]	0.0013
L/S ratio	1.20 (1.00–1.46)[a,b,c]	1.12 (0.83–1.37)[a,d,f]	1.01 (0.74–1.21)[b,d]	0.90 (0.70–0.99)[c,f]	<0.0001

BMI, body mass index; AST, aspartate aminotransferas; ALT, alanine aminotransferase; ChE, cholinesterase GGTP, gamma-glutamyl transpeptidase; T-CHO, total cholesterol; L/S ratio, liver-to-spleen CT attenuation values ratio.

[a]$P < 0.05$ none vs. mild; [b]$P < 0.05$ none vs. moderate; [c]$P < 0.05$ none vs. severe; [d]$P < 0.05$ mild vs. moderate; [e]$P < 0.05$ moderate vs. severe; [f]$P < 0.01$ mild vs. severe.

vertical (Y) axis and specificity (or "false-positive rate") on the horizontal (X) axis with a given cut-off point and changing the cut-off points from more stringent to less stringent. Because the accuracy of a test depends on its sensitivity and specificity, ROC curves of tests with higher discriminating ability are closer to the upper left corner than curves of those with lower ability (*17, 18*). Area under the ROC curve (AUC) can be calculated using the trapezoidal method (*17*). AUC represents the probability of correctly ranking a randomly chosen pair of persons with and without the disorder. For comparison of two AUC's, the nonparametric method developed by Hanley and McNeil (*17, 19*) was employed.

RESULTS

Graft Steatosis and L/S Ratio

The grade of macrovesicular steatosis as evaluated in the "time 0" biopsy specimens was none in 198 livers (74.4%), mild in 50 (18.8%), moderate in 15 (5.7%), and severe in 3 (1.1%) (Table 1). The median L/S ratio for livers of each histological grade was 1.20 (range: 1.00–1.46), 1.12 (0.83–1.37), 1.01 (0.74–1.21), and 0.90 (0.70–1.21), respectively. The differences among the four groups were statistically significant (Table 1). There were also significant correlations between steatosis grade in "time 0" biopsy specimens and increases in BMI or other blood chemistry results.

An intersegmental variation of L/S ratio was analyzed in the four segments (left lateral, left medial, right anterior, and right posterior segments) in patients with more than moderate grade steatosis (n=18). The L/S ratios in the left lateral, left medial, right anterior, and right posterior were 0.985, 0.985, 0.89, and 0.945, respectively. Although no statistically significant differences were observed among the four segments, L/S ratio tended to be higher in the left lateral segment than in the right anterior or posterior segments.

ROC Analysis

To compare the abilities of L/S ratio and other preoperative variables to discriminate between none to mild and moderate to severe steatosis, the ROC curves of these tests were determined (Fig. 2). The ROC curve of the L/S ratio was located closer to the upper left corner than that of any other preoperative variables (BMI, GGTP, ALT, AST, ChE, and T-CHO). For statistical comparison, Z statistics for the difference in areas under the ROC curves between L/S ratio and each of the other conventional variables are shown in Table 2. The AUC of L/S ratio was larger than that of any other variables, and the differences were significant, except for comparisons with BMI and ALT (Table 2).

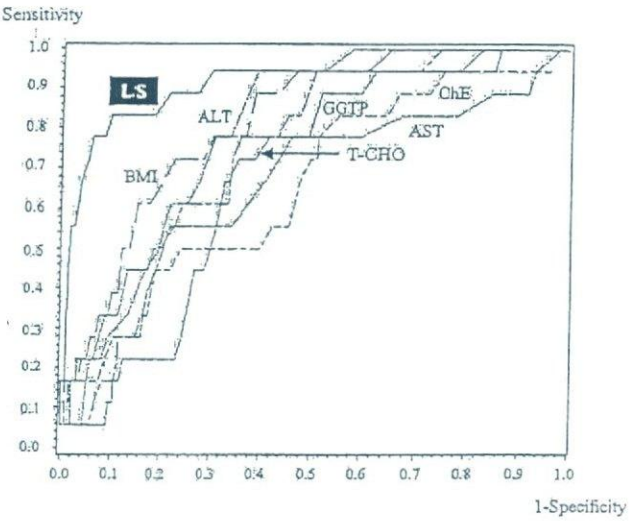

FIGURE 2. ROC curves were determined for L/S ratio, BMI, GGTP, ALT, AST, ChE, and T-CHO, all of which were measured preoperatively in 266 cases of LDLT.

Graft Outcome

Postoperative peak AST and ALT levels in both donors and recipients were higher in patients with moderate to severe macrovesicular steatosis. AST levels in donors with none to mild steatosis and in those with moderate to severe steatosis were 300 IU/L and 362 IU/L ($P<0.05$), respectively. Similarly, ALT levels in the respective donors were 270 IU/L and 388 IU/L ($P<0.05$). Moreover, the respective levels in recipients

TABLE 2. Statistical comparison of areas under the ROC curves between L/S ratio and preoperative variables

	Z statistics vs. L/S ratio	(*P* value)
BMI	1.61206	0.10695
GGTP	3.00589	0.00265
ALT	1.53605	0.12453
AST	2.74714	0.00601
CHE	3.37740	0.00073
T-CHO	2.94694	0.00321

were 295 IU/L and 417 IU/L and 317 IU/L and 418 IU/L, with no statistical differences being observed. However, the 5-year graft survival rates for grafts with none to mild steatosis and those with moderate to severe steatosis were 74.1% vs. 71.8%, but this difference was not significant. PNF was not seen in any of this series.

DISCUSSION

New insights into the mechanisms of failure of fatty livers should result in new prophylactic and therapeutic approaches (*20*). Livers with significant steatosis may increase the severity of ischemia-reperfusion injury and the incidence of graft PNF. Zamboni et al. (*21*) reported that macrovesicular steatosis involving 25% or more of the hepatocytes in the donor liver was significantly associated with shorter post-transplant survival and with a higher number of delayed graft failures. Worldwide, severely steatotic grafts (>60%) are routinely discarded for CLT. On the other hand, use of graft liver with microsteatosis did not influence either short- or medium-term survival (*2, 22*). In the case of LDLT, due to the limited selection of donors, grafts with moderate to severe grade steatosis have been sometimes used with fully informed consent. Probably due to the minimized cold ischemic time in part, PNF has not been observed in our series (cold ischemic time: 2 hr in this series). However, the risk of using grafts with severe steatosis has also been clearly identified in LDLT (*7*)

Although liver needle biopsy may be required for definitive preoperative diagnosis of hepatic steatosis, it is not a universally safe procedure and should not be routinely applied to all living donor candidates. To minimize the risks of liver needle biopsy, noninvasive diagnostic methods using clinical, imaging, and/or biochemical parameters have been investigated (*23, 24*). In a recent study on living liver donors, Mary et al. (*8*) reported that BMI was a reliable predictor of hepatic steatosis with a positive correlation between increasing BMI and steatosis grade on biopsy. It was also suggested that liver biopsy could be avoided in subjects with normal BMI, but that living donors with high BMI should undergo liver biopsy because biochemical and imaging data are not reliable enough to accurately diagnose the degree of steatosis (*8*).

In the present study, ROC analysis was used to compare the diagnostic ability of L/S ratio to predict the grade of hepatic steatosis with that of other preoperative variables. Because the ROC curve of L/S ratio is closer to the upper left corner of the graph than that of other variables, the sensitivity and specificity of L/S ratio can be considered higher when compared with these variables (BMI, GGTP, ALT, AST, ChE, and T-CHO). The ROC curve is a graph of sensitivity versus specificity, both of which are independent of disorder prevalence, and analysis does not depend on the prevalence of disorder in the actual population to which the preoperative variable may be applied (*17*). Moreover, statistical analysis of the differences in AUCs reveals that L/S ratio could predict >30% hepatic steatosis more accurately than any other variable, although the differences were not significant in comparison with BMI or ALT.

If a liver with less than 30% steatosis is thought to be appropriate for a living donor, the mean ± SD of the L/S ratio in donors with none to mild steatosis was 1.184±0.091. With regard to discriminating between none to mild and moderate to severe steatosis by L/S ratio, when the cut-off level was set at 1.1, the sensitivity and specificity were 0.833 and 0.815, respectively (Table 3), and the ROC curve closely approached the upper left corner. With regard to balance between sensitivity and specificity, the optimal level of L/S ratio to predict >30% hepatic steatosis would be 1.1.

From the results of intersegmental variation of L/S ratio, it is likely that fat deposition is heterogeneous throughout the liver. Because a single biopsy specimen shows the grade of hepatic steatosis only at the area where it was taken, multiple needle biopsies would be necessary to accurately evaluate steatotic changes in the whole liver. On the other hand, evaluation of hepatic steatosis using CT attenuation values enables the assessment of fatty changes in each part of the liver. To simultaneously express a representative value of fatty changes of the whole liver as well as to estimate the risks of both the graft and the remnant liver, the averaged value was employed to determine L/S ratio in the present study.

The present study suggests that L/S ratio on noncontrast-CT can be clinically used as a noninvasive method to correctly evaluate hepatic steatosis. This method is actually feasible because CT examination has been routinely done in donor preoperative evaluation for the assessment of liver anatomy and graft size and the calculation of L/S ratio is not time consuming. By employing this modality, preoperative liver needle biopsy could be omitted for most donors at our institution. However, when hepatic steatosis of more than moderate grade indicated by the L/S ratio does not show any significant improvement regardless of adequate diet and exercise treatment, or is accompanied by other complications including diabetes mellitus and/or hyperlipidemia, liver biopsy is performed to exclude disorders such as nonalcoholic steatohepatitis.

TABLE 3. Assessment for cut-off point of L/S ratio more than 30% steatosis in time zero biopsy according to ROC analysis

Cut-off point of L/S ratio (≥30%)	Sensitivity	Specificity	Diagnostic accuracy
1.2	0.944	0.448	0.481
1.1	0.833	0.815	0.816
1.0	0.556	0.984	0.955
0.9	0.222	0.992	0.940
0.8	0.111	1.000	0.940

ACKNOWLEDGMENTS

We are indebted to Toshimitsu Kobayashi and Shinichi Yamaguchi, Division of PostMarketing Development Research Center, Fujisawa Pharmaceutical Co., Ltd. for their highly appreciated contributions in performing the statistical analysis.

REFERENCES

1. Urena M, Gonzalez EM, Romero CJ, et al. An approach to the rational use of steatotic donor livers in liver transplantation. *Hepato-Gastroenterol* 1999; 46: 1164.
2. Fishbein TM, Fiel MI, Emre S, et al. Use of livers with microvesicular fat expands the donor pool. *Transplantation* 1997; 64: 247.
3. Imber CJ, St Peter SD, Handa A, et al. Hepatic steatosis and its relationship to transplantation. *Liver Transpl* 2002; 8: 415.
4. D'Alessandro AM, Kalayoglu M, Sollinger HW, et al. The predictive value of donor Liver biopsies for the development of primary nonfunction after orthotopic liver transplantation. *Transplantation* 1991; 51: 157.
5. Todo S, Demetris AJ, Makowka L, et al. Primary nonfuction of hepatic allografts with preexisting fatty infiltration. *Transplantation* 1989; 47: 903.
6. Hayashi M, Fujii K, Kiuchi T, et al. Effects of fatty infiltration of the graft on the outcome of living-related liver transplantation. *Transplant Proc* 1999; 31: 403.
7. Ito T, Kiuchi T, Egawa H, et al. Surgery-related morbidity in living donors of right lobe liver graft: lessons from the first 200 cases. *Transplantation* 2003; 76: 158.
8. Rinella ME, Alonso E, Rao S, et al. Body mass index as a predictor of hepatic steatosis in living liver donors. *Liver Transpl* 2001; 7: 409.
9. Angulo P, Keach JC, Batts KP, et al. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology* 1999; 30: 1356.
10. Kral JG, Schaffiner F, Pierson RN, et al. Body fat topography as an independent predictor of fatty liver. *Metabolism* 1993; 42: 548.
11. Chen YS, Cheng YF, Vanessa H, et al. Evaluation of living liver donors. *Transplantation* 2003; 75: 16.
12. Stotland BR, Lichtenstein GR. Liver biopsy complications and routine ultrasound. *Am J Gastroenterol* 1996; 91: 1295.
13. Van Ness MM, Diehl AM. Is liver biopsy useful in the evaluation of patients with chronically elevated enzymes? *Ann Inter Med* 1989; 111: 473.
14. Goddard CJ, Warenes TW. Raised liver enzymes in asymptomatic patients: Investigation and outcome. *Dig Dis* 1992; 10: 218.
15. Ploeg RJ, D'Alessandro AM, Knechtle SJ, et al. Risk factors for primary dysfunction after liver transplantation-A multivariate analysis. *Transplantation* 1993; 55: 807.
16. Siegelman I, Rosen MA. Imaging of hepatic steatosis. *Semin Liv Dis* 2001; 21: 71.
17. Imber CJ, St Peter SD, Handa A, et al. Hepatic steatosis and its relationship to transplantation. *Liver Transpl* 2002; 8: 415.
18. Metz CE. Basic principles of ROC analysis. *Semin Nucl Med* 1978; 8: 283.
19. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating curves derived from the same case. *Radiology* 1983; 148: 839.
20. Selzner M, Clavien PA. Fatty liver in liver transplantation and surgery. *Semi Liv Dis* 2001; 21: 105.
21. Zamboni F, Franchello A, David E, et al. Effect of macrovesicular steatosis and other donor and recipient characteristics on the outcome of liver transplantation. *Clin Transplant* 2001; 15: 53.
22. Urena MAG, Ruiz-Delgado FC, Gonzalez EM, et al. Assessing risk of the use livers with macro and microsteatosis in a liver transplant program. *Transplant Proc* 1998; 30: 3288.
23. Ounwater E, Blasbalg R, Siegelman E, et al. Detection of lipid in abdominal tissue with opposed-phase gradient-echo images at 1.5T: technical and diagnostic importance. *Radiographics* 1998; 18: 1465.
24. Ricci C, Longo R, Gioulis E, et al. Noninvasive in vivo quantitative assessment of fat content in human liver. *J Hepatol* 1997; 27: 108.

Functional Portal Flow Competition After Auxiliary Partial Orthotopic Living Donor Liver Transplantation in Noncirrhotic Metabolic Liver Disease

By Mureo Kasahara, Yasutsugu Takada, Koichi Kozaki, Kenji Uryuhara, Yasuhiro Ogura, Kohei Ogawa, Yasuhiro Fujimoto, and Koichi Tanaka

Kyoto, Japan

Auxilliary partial orthotopic liver transplantation (APOLT) was introduced initially as a tentative or permanent support for patients with potentially reversible fulminant hepatic failure and has extended its indication to congenital metabolic disorder of the liver that has otherwise normal functional integrity. Postoperative management of APOLT is complicated because of functional portal flow competition between the native and graft liver. The native portal vein diversion to the graft is sometimes indicated to prevent functional competition; however, it is still an open question whether this technique can be theoretically indicated for APOLT patients. The authors report a on patient with ornithine transcarbamylase deficiency who received APOLT from a living donor without native portal vein diversion. Because of functional portal vein competition between the native and graft liver, the patient had to have portal vein diversion, portal vein embolization, and finally native hepatectomy to induce the graft regeneration after APOLT. After the experience of the current case, primary portal vein diversion for APOLT with noncirrhotic metabolic liver disease patients to prevent functional portal flow competition is recommended.

J Pediatr Surg 39:1138-1141.

INDEX WORDS: Auxiliary liver transplantation, living donor liver transplantation, noncirrhotic metabolic liver disease, ornithine transcarbamylase deficiency.

Liver transplantation can offer a complete cure for genetic metabolic errors in the liver.[1] The main purpose of liver transplantation for noncirrhotic congenital metabolic disorders is to supply missing enzymes by replacing the native liver, which is a normally functioning entity. Auxiliary partial orthotopic liver transplantation (APOLT) has been introduced as a treatment for noncirrhotic congenital metabolic disorder of the liver.[2-4] The claimed advantage of APOLT for noncirrhotic congenital metabolic disorder of the liver is that APOLT compensates for deficiencies in enzymes without complete removal of the native liver, which may help rescue the patient in case of graft failure and may make future gene treatment possible. One of the controversies surrounding APOLT is functional competition between the native and graft liver. Severe acute rejection induces rapid graft shrinking because of a portal flow steal phenomenon affecting to the remnant native liver.[5,6]

Ornithine transcarbamylase deficiency (OTCD) is an X-chromosome–linked genetic disorder, which results in fulminant hyperammonemia with a poor prognosis.[4] The usual medical treatment consists of protein restriction combined with the administration of sodium benzoate.[7] This treatment, however, is not always sufficient to avoid life-threatening fulminant hyperammonemia and induces serious neurologic sequelae in which APOLT is sometimes indicated.

We reported on a patient with OTCD who did not receive primary ligation of the native portal branch at the time of APOLT.[4] After a severe rejection episode, the graft became smaller, and the native liver underwent compensatory hypertrophy. We surgically ligated the native portal branch, then the graft recovered its volume and function. However, it is still controversial as to whether this technique can be indicated to APOLT patients. We report here a complicated case of OTCD, who had several episodes of functional portal flow competition between the native and graft liver after APOLT from a living donor. The management of portal flow competition, which includes native portal vein diversion, portal vein embolization, and native hepatectomy are also discussed.

CASE REPORT

The patient was a girl aged 5 years and 8 months. Vomiting and somnolence developed at the age of 22 months, and OTCD was diagnosed on the basis of low enzyme activity by liver biopsy. Despite

From the Department of Transplant Surgery, Kyoto University Hospital, Kyoto, Japan.

Supported in part by grants from the Scientific Research Fund of the Ministry of Education and by a Research Grant for Organ Transplant from the Ministry of Health and Welfare, Japan.

Address reprint requests to Mureo Kasahara, MD, Department of Transplant Surgery, Kyoto University Hospital, 54, Kawara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.

0022-3468/04/3907-0032$30.00/0

doi:10.1016/j.jpedsurg.2004.03.079

treatment with protein restriction and medication, the patient went into a hyperammonemic coma more than 30 times during 4 years of follow-up and was referred for living donor liver transplantation. APOLT was performed with a left lateral segment from the father in July 1996.[4] The left lateral segment of the native liver was removed followed by auxiliary orthotopic implantation of the left lateral segment.[8] The actual graft weight was 255 g, and the graft-to-recipient weight ratio (GRWR) was 1.34%. The left hepatic vein of the graft was anastomosed in an end-to-end fashion to the recipient's left hepatic vein. The portal venous flow to the graft was shared with the recipient's remnant right lobe, meaning that the left portal vein of the graft was anastomosed with the native left portal vein in an end-to-end fashion. The right portal vein was preserved. Hepatic artery reconstruction was performed end-to-end with the recipient's left hepatic artery using a microvascular technique. Biliary reconstruction was achieved by Roux-en-Y hepatico-jejunostomy. The patient was discharged from the hospital without complication. Postoperative computed tomography (CT) volumetry found the native liver to be 551 mL and the graft liver 255 mL (Native to Graft liver ratio, 2.16). Doppler echography showed the native and graft portal venous flows to 194 and 154 mL/min, respectively.

One year after transplantation, the patient had a severe rejection. Doppler echography showed hepatofugal flow of the graft portal vein and the entire portal blood flow going into the native liver. CT scan showed the decreasing volume of the graft (160 mL) and increasing volume of the native liver (600 mL, native to graft liver ratio, 3.75). A technetium 99 m-GSA scintigraphy study showed tracer uptake in the graft versus native liver to be 49.5: 50.5%. The patient had several episodes of relapsed fulminant hyperammonemia. The rejection episode was treated successfully with steroid bolus injections, and the serum ammonia level was normalized.

However, the native liver volume was not recovered, because the graft liver already lost much of the portal blood flow to the native side.[8] To prevent functional portal flow competition and induce graft regeneration, portal vein diversion (PVD) from the native portal blood flow to the graft was indicated. Before surgery, the indication of initial native hepatectomy was also discussed; however, CT volumetry of the graft liver showed "small-for-size" (GRWR 0.75%), defined as GRWR less than 0.8%,[9] which made us discard the possibility.

The right portal vein was isolated and transected in an operation performed in August 1997. Results of a ^{99m}Tc-GSA scintigraphy study showed the uptake in graft versus native liver to be improved to 72.6: 27.4%. The graft volume and function recovered satisfactorily, and the serum ammonemia level was restored to its normal level.

Four years after portal vein diversion, the patient had an episode of fulminant hyperammonemia again. Doppler echography showed recanalization of the native portal flow through cavernous transformation of connective tissue around the right hepatic hilum. Doppler echography showed the native and graft portal venous flow to be 198 and 176 mL/min (Fig 1A). A CT volumetry study showed the graft liver to be shrunk to 200 mL and the native liver to have grown to 776 mL (native to graft liver ratio, 3.88). A ^{99m}Tc-GSA scintigraphy study revealed the uptake in graft versus native liver to be 32.0: 68.0%. Native hepatectomy was planned; however, the estimated graft volume was 200 mL, which was 0.6% in GRWR. The GRWR showed "small-for-size" to sustain the recipient's metabolic demand.[9]

To induce the graft regeneration, percutaneus transhepatic portal vein embolization (PTPE) to the right native lobe was indicated in October 2001. Three weeks after PTPE, the graft liver volume increased from 200 mL to 270 mL, which showed 0.8% in GRWR, and the native right lobe decreased from 776 mL to 726 mL (native to graft liver ratio, 2.69). A ^{99m}Tc-GSA scintigraphy study showed the uptake in graft versus native liver to be improved to 36.4: 63.5%.

To preserve a sufficient liver volume and retain the possibility of future gene therapy, we performed a right hepatectomy of the native liver preserving the native caudate lobe in December 2001. The estimated GRWR of the native caudate lobe and graft was 1.1%, which might be a sufficient liver volume for the patient. Actual weight of the resected native right lobe was 600 g. Histologic findings of the native liver showed mild portal fibrosis and occlusion owing to PTPE. One month after native right hepatectomy, the estimated CT volumetry showed 416 mL in the graft and 106 mL in the native caudate lobe

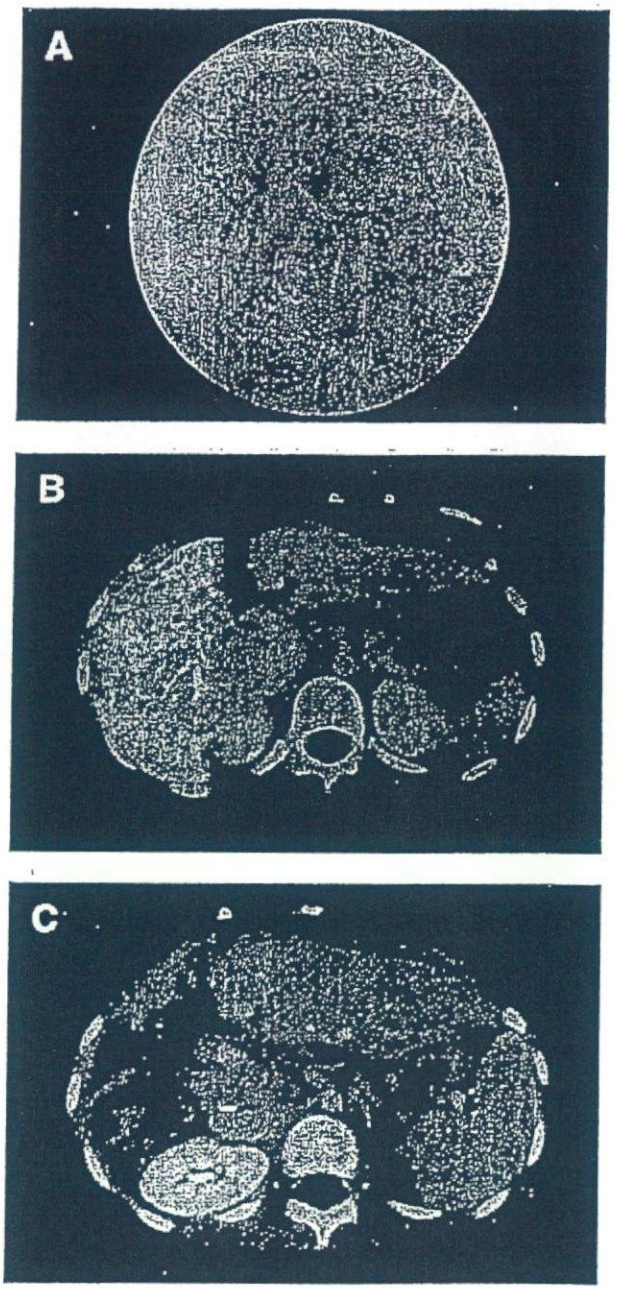

Fig 1. (A) Portal phase of angiography shows caverunous transformation of the native right portal vein after portal vein diversion. (B) After PTPE for native right portal vein. Right portal vein was occluded by Lipiodol. (C) CT after native right hepatectomy. The volumetric analysis showed 416 mL in the graft and 106 mL in the native caudate lobe.