Table 2. Anatomical factors related to intraoperative portal vein thrombosis

	No. of cases	Mean ± SD	Intraoperative portal vein thrombosis (n)	No intraoperative portal vein thrombosis (n)	p-Values (Fisher's exact test)
Velocity of portal vein (cm/s)					
≤ 7	21	1.03 ± 6.27	6	20	0.021
>7	52	11.34 ± 2.13	2	45	
Size of portal vein (mm)					
≤ 4	16	3.35 ± 0.13	6	10	0.001
>4	57	6.09 ± 0.19	2	55	
Portosystemic shunt (mm)					NS
Shunt > 5	29		5	24	
No shunt	43		3	40	

Well-documented risk factors for portal vein thrombosis included small, hypoplastic or sclerotic portal veins, usually associated with extremely young age or low recipient body weight, commonly seen in biliary atresia with other coexisting vascular anomalies (13, 14). The significant predictive factors in our series including age younger than 1 yr, body weight lower than 10 kg, portal vein caliber smaller than 4 mm, were comparable with these documented risk factors.

Low portal flow, implying reduced flow volume due to collaterals and shunting vessels as severity of liver cirrhosis progress, would promote portal vein thrombosis (15). We proposed that portal venous velocity below 7 cm/s at pre-transplant evaluation to be predictive of intraoperative portal vein thrombosis as evident in our series.

Small-for-size graft (< 1% of recipient body weight) has been documented to have lower graft survival rate, as shown in rat model of irreversible endothelial injury during the transient changes after reperfusion (16, 17). Creation of portosystemic shunt for portal flow diversion would avoid venous congestion and over-perfusion (18). However, in our series, due to low probability of the availability of other suitable donors, relatively big and heavy grafts had been used. The exerted mass effects on the vascular structure may have increased the risk of vascular complication such as intraoperative portal venous thrombosis.

There was no statistically significant difference between the surgical techniques used for portal vein anastomosis in our series. The eight cases with intraoperative portal vein thrombosis had sustainable adequate portal flow after transplant without recurrent portal vein thrombosis using the same re-anastomosis method of branch patch anastomosis.

The presence of portosystemic shunt was not associated with intraoperative portal vein thrombosis in our series. However, early closure of the shunts would result in increased portal vein flow that might influence the transient hemodynamic changes of the portal venous system at the reperfusion period. In addition to the surgical closure of the shunt, repositioning of the liver graft in a proper site, and eliminating factors that increase resistance of the graft or portal vein such as hepatic venous outflow obstruction, kinking or stretching of the portal vein allowed adequate blood flow to the graft. Doppler US provided accurate guidance when monitoring portal flow and inflow to the graft during these manipulations.

Our study showed that Doppler US for preoperation evaluation, intraoperative monitoring of the portal flow for early detection of portal vein thrombosis, follow-up evaluation after re-anastomosis was indispensable. We have also established significant predictive factors based on the large group of liver allograft recipients studied. We advocated the identification of high-risk group at pre-transplantation evaluation so that interpositional vein grafts could be considered for patients with the pathological portal vein. Doppler US-guided proper positioning of the portal vein, which takes only a few minutes during the process of artery anastomosis should become a regular practice in high-risk cases.

It is concluded that preoperative identification of high-risk patients for intraoperative portal vein thrombosis would decrease the need for intraoperative re-anastomosis and further maintain long-term graft survival.

Acknowledgements

This work was supported by project grant NRHI-GT-EX92-9228SP from the National Health Research Institutes and NSC 91-231-182A-101 from the National Science Council, Taiwan.

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Hilar Bile Duct Cancer Associated with Preoperatively Undetectable von Meyenburg Complex - Report of a Case

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SUMMARY

A 56-year-old man was admitted to our hospital with a diagnosis of hilar bile duct cancer. Abdominal ultrasonography, computed tomography and endoscopic retrograde cholangiopancreatography showed no other concomitant disease. Biochemical data showed 0.6mg/dL of total bilirubin, 104 IU/L of alanine aminotransferase and 469mg/dL of alkaline phosphatase. Carbohydrate antigen 19-9 was elevated as 112.1 U/mL. Operative findings included a resectable left hilar bile duct cancer and grayish-white nodules 0.3-0.5cm in diameter on the surface of segments 6 and 4 of the liver. Although intrahepatic metastasis of the bile duct cancer was highly suspected under intraoperative US, frozen section was reported to show the small nodules containing multiple biliary hamartomas, so-called von Meyenburg complex. Therefore, a left hepatic lobectomy together with resection of the extrahepatic bile duct followed by a Roux-en-Y hepaticojejunostomy was the procedure of choice. His postoperative course was uneventful. The intraoperative findings could have been misdiagnosed due to their similarity to intrahepatic metastasis and intraoperative histology is indispensable to differentiate von Meyenburg complex in this case. The possibility of a preoperative imaging diagnosis for von Meyenburg complex seems to depend on the size of the bile duct structure in each hamartoma. To the best of our knowledge, this is the fourteenth case of bile duct cancer associated with von Meyenburg complex reported in the literature. The following case is being reported because of the rarity of the disease and to stress the importance of intraoperative histology to avoid misdiagnosis as the disseminated disease, particularly when malignant neoplasia is surgically treated.

KEY WORDS:
von Meyenburg complex (VMC); Bile duct cancer; Intraoperative diagnosis

ABBREVIATIONS:
von Meyenburg Complex (VMC); Computed Tomography (CT); Ultrasound (US); Magnetic Resonance Imaging (MRI); Middle Hepatic Vein (MHV)

INTRODUCTION

Although multiple biliary hamartomas, so-called von Meyenburg complex (VMC), has been a rare asymptomatic disease, reports of VMC are increasing as the quality of imaging modalities improves (1). Ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) are all frequently used as diagnostic methods for the disease with accuracy. Histologically, irregular-shaped bile ducts in the liver surrounded by a dense collagenous stroma were first described by Moschcowitz (2) as an aberrant bile duct, followed by establishment of the concept of multiple bile duct hamartomas by Von Meyenburg (3) in 1918.

When small nodules are encountered intraoperatively in the liver that were not diagnosed preoperatively, especially with a malignant tumor such as bile duct cancer, it embarrasses surgeons to determine the best operative procedure.

Herein, we report a case of hilar bile duct cancer associated with VMC, which was detectable only intraoperatively. We analyzed the problems with pre- and postoperative imaging diagnosis for the disease in comparison with a preoperatively detectable case.

CASE REPORT

A 56-year-old Japanese male was admitted to our hospital with a diagnosis of hilar bile duct cancer because of an abnormal liver function test. His past medical and family histories including liver disease were unremarkable. On admission, the patient's physical examination revealed no particular abnormal findings. Complete blood counts were within normal limits. Biochemical data showed total bilirubin of 0.6mg/dL, alanine aminotransferase of 104 IU/L and alkaline phosphatase of 469mg/dL. Tumor marker, carbohydrate antigen 19-9, was elevated to 112.1 U/mL. Hepatitis B surface antigen and antibody to hepatitis C were negative. Abdominal US, CT and endoscopic retrograde cholangiopancreatography showed no concomitant disease other than hilar bile duct cancer (**Figure 1 A, B**).

Hepato-Gastroenterology 2004; 51:1301-1303

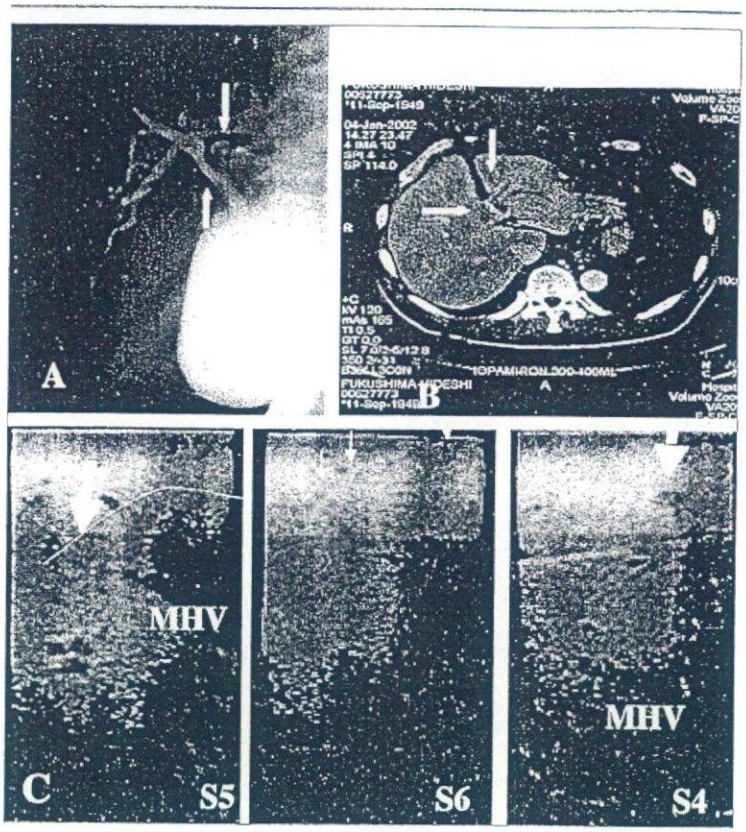

FIGURE 1 (A) Endoscopic retrograde cholangiopancreatography shows defect of left bile duct. (B) Computed tomography scan shows hilar mass with dilatation of intrahepatic bile ducts in the left lobe. (C) Intraoperative ultrasound shows multiple hypoechoic lesions in the bilateral liver lobes (arrows). MHV: middle hepatic vein.

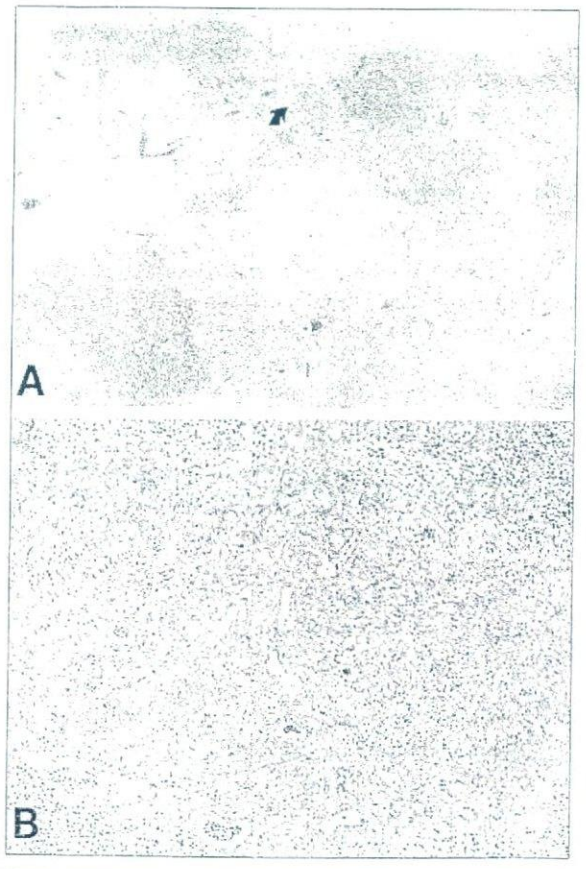

FIGURE 2 Histological findings of the small nodule show multiple biliary hamartomas. Representative lesion has retraction in the surface (A x5, Arrow). Each bile duct-like structure is markedly subtle (B x25).

Under the preoperative diagnosis of hilar bile duct cancer, we scheduled a left lobectomy of the liver with resection of the extrahepatic bile duct and lymph node dissection. Operative findings included resectable left hilar bile duct cancer and a grayish-white nodule 0.3-0.5cm in diameter on the segment 6 and 4 liver surface, which were located within the right liver lobe.

Since intrahepatic metastasis of the bile duct cancer was highly suspected under intraoperative US (**Figure 1C**), intraoperative histology was submitted. Histopathologically, the small nodule was composed of small ducts covered by a single layer of cuboidal epithelial cells, embedded in fibrous stroma, so-called von Meyenburg complex (VMC) (**Figure 2 A, B**). Therefore, a left hepatic lobectomy was performed with resection of the extrahepatic bile duct plus lymph node dissection in the hepatoduodenal ligament with Roux-en-Y hepaticojejunostomy. The pathological finding was cystic space lined by a single layer of cuboidal to flat epithelium and surrounding fibrous tissue with scattered glands. Some of the glands showed mild dilatation. In addition, multiple bile duct hamartomas were found in the hepatic parenchyma around the bile duct cancer.

The patient's postoperative course was unremarkable, and he was discharged on the 14th postoperative day. There has been no evidence of recurrence of the disease, and the patient has been symptom-free for 10 months at this writing. VMC in the liver was undetectable by postoperative imaging studies including US, CT and MRI.

On the other hand, a detectable case of VMC preoperatively (68-year-old female with gastric cancer) showed a bile duct-like tubular structure a few millimeters in diameter, which should have been detectable by US, CT or MRI (**Figure 3 A-C**).

DISCUSSION

VMCs are typically 0.1-0.3cm in diameter and are well-circumscribed, unencapsulated lesions that are recognized most easily when in a subcapsular location. They are frequently mistaken grossly as metastatic tumors preoperatively. Generally, ultrasonographic findings of VMC are masses with a subtle multinodular appearance with alternating hyperechoic and hypoechoic areas (4,5). On CT scans, multiple low-density lesions are 5-10mm in diameter with or without contrast media enhancement. In MRI, T1 hyper and T2 hypointensity was reported (1).

In our case, however, VMCs in the liver were completely undetectable before and after surgery. The presumed reason was that each bile duct-like tubular structure in our case was relatively small so that detection using US, CT or MRI might have been impossible. On the other hand, a detectable case of VMC preoperatively showed a bile duct-like tubular structure a few millimeters in diameter. Thus, it should be noted that VMC sometimes could not be detected in the modern preoperative imaging modality. Therefore, as in our case, if multiple mass lesions are encountered during surgery for bile duct cancer and any kind of malignancies, intraoperative histolog-

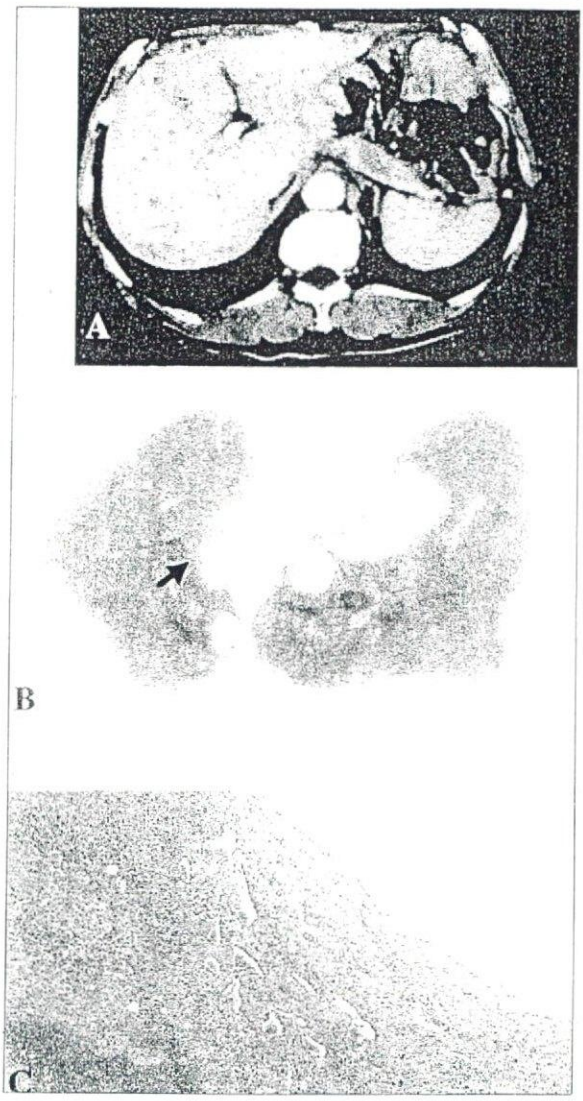

FIGURE 3 Computed tomography (A) and histological findings in the biopsy specimen of the preoperatively detectable case (B loupe view, C x25). CT scan shows multiple hypodense nodules scattered in the liver. Histologically, dilatation and irregular hyperplasia of the relatively large bile duct surrounded by fibrous tissue are observed.

ical examination is indispensable for making a definite diagnosis.

The subject of malignant transformation of VMC to bile duct cancer is still controversial (6-8). Burns *et al.* reported that long-standing cholestasis, dilatation and hepatotoxin might play a role in the bile duct carcinogenesis in patients with VMCs (6), followed by Jain *et al.* showing evidence of the neoplastic transformation of VMC (7). Since this was only the fourteenth case of bile duct cancer associated with VMC reported in the literature, further examination is needed to assert bile duct carcinogenesis in VMC bearing liver.

In summary, we experienced a rare case of hilar bile duct cancer associated with VMCs. Intraoperative histology is indispensable for differentiation in these cases. In addition, the possibility of preoperative imaging diagnosis for VMC seems to depend on the size of the bile duct structure in each hamartoma.

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Original Paper

Primary and Recurrent Retroperitoneal Sarcoma: Factors Affecting Survival and Long-term Outcome

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KEY WORDS: Retroperitoneal sarcoma; Surgery; Chemotherapy; Radiotherapy; Survival

ABBREVIATIONS: Retroperitoneal Sarcoma (RPS); Soft Tissue Sarcoma (STS); International Code for Disease (ICD); Disease-Free Survival (DFS); Computerized Tomography (CT); Magnetic Resonance (MR); External Beam Radiotherapy (EBRT); Brachytherapy (BT)

ABSTRACT

Background/Aims: To analyze treatment and survival in a series of 39 patients with primary or recurrent retroperitoneal sarcoma treated and prospectively followed at a single institution.

Methodology: Between July 1994 and January 2002, 39 patients (20M, 19F; mean age: 56 years, range: 25-77) were evaluated.

Results: Thirty-two out of 39 patients (82%) (18 were affected by primary retroperitoneal sarcoma, and 14 by recurrent retroperitoneal sarcoma), were submitted for resection. Twenty-four out of 32 patients (75%) underwent removal of contiguous intra-abdominal organs. Peroperative mortality was nil and significant peroperative complications occurred in 6 cases only (19%). High tumor grade results were a significant variable for a worse survival in all 32 patients (100% 5 years survival for low grade *vs.* 0% for high grade; $P=0.0004$). Among 27 radically resected patients, only histology grade and peroperative blood transfusions affected survival (100% 5-year survival for low grade *vs.* 24% for high grade; $P=0.003$); (100% 5-year survival for non-transfused patients *vs.* 43% for transfused patients; $P=0.03$). Similar effects were noted for disease-free survival.

Conclusions: Histology grade and peroperative blood transfusions were the only factors which affected overall and disease-free survival. An aggressive surgical approach in both primary and recurrent retroperitoneal sarcoma is associated with long-term survival.

INTRODUCTION

Retroperitoneal soft-tissue sarcomas (RPS) are rare mesenchymal tumors, their incidence being about 10% of all soft tissue sarcomas, which together constitute less than 1% of all malignant neoplasms (1). The lack of early symptoms leads to a delay in diagnosis, and the difficulty of management to a poor prognosis. Surgery is the principal mode of therapy and offers the most favorable prognosis after complete resection (2-4). Complete resection is, however, often problematic to perform because of the large size of the tumor at the time of diagnosis, the difficult, deep-seated central location and common infiltration to adjacent organs. All these factors add to the rate of recurrences even after radical resection.

Adjuvant chemotherapy has been often advised for treatment of soft-tissue sarcomas of the extremities to improve local control (5,6), but the efficacy of radiation treatment is not so clear in retroperitoneal tumors. Frequently, however, it is not possible to deliver therapeutic doses of radiation into the tumor bed in the retroperitoneum, because of the proximity of dose-limiting normal structures, such as the small intestine, spleen and bone marrow, and so the survival advantage remains poor (7,8). The role of adjuvant chemotherapy remains controversial, with no significant benefit in overall survival so far (9-12). Many different reports have combined results of treatment of primary with recurrent RPS cases, where primary resection rates in dedicated units approach 90% (13) and where repeat resection of locally recurrent disease is possible in up to 60% of patients (3). The reported long-term survival and local relapse rates following primary resection are variously quoted as being between 50-66% (13,14) and 39-86% respectively (15), with 5-year survival and further local recurrence following the first recurrence resection reported to be around 60% (12) and 40% respectively (16,17). In primary disease, long-term survival appears to be dependent upon clear gross (18) and microscopic (19) resection margins and low histologic grade (20) although the factors controlling prognosis after resection of recurrent disease are less well characterized. Many studies have failed to show a survival advantage for adjuvant postoperative multimodality therapy (21-23).

We report our experience of 39 patients presenting

Hepato-Gastroenterology 2004; 51:1304-1309

Clin Transplant 2004: 18: 694–699 DOI: 10.1111/j.1399-0012.2004.00279.x

Clinical Transplantation

Impact of late conversion from C0 to C2 monitoring of microemulsified cyclosporine in pediatric living donor liver transplant recipients

Takatsuki M, Chen C-L, Chen Y-S, Wang C-C, Lin C-C, Yang C-H, Yong C-C, Liu Y-W. Impact of late conversion from C0 to C2 monitoring of microemulsified cyclosporine in pediatic living donor liver transplant recipients.
Clin Transplant 2004: 18: 694–699. © Blackwell Munksgaard, 2004

Abstract: The efficacy and feasibility of 2-h post-dose level (C2) monitoring of cyclosporine in long-term living donor liver transplantation (LDLT) is not clear. The aim of this study was to investigate the impact of late conversion from conventional trough-level (C0) monitoring to C2 monitoring of a microemulsion form of cyclosporine (Neoral) in pediatric LDLT recipients. From June 1994 to August 2002, we performed 116 LDLTs in 115 patients. Initially, we adapted conventional C0 monitoring of Neoral, which was converted to C2 monitoring starting in January 2002. The 60 patients who were enrolled in the study had the following characteristics: they were younger than or equal to 15 yr at transplantation, and they had survived LDLT, and they had received a Neoral-based immunosuppression regimen, and they underwent conversion to C2 more than 1 month after transplantation. We evaluated the impact of conversion on doses, blood levels, rejection, adverse effects, and patient/graft outcome. In the long-term patients, the mean C2 levels immediately after conversion were higher than the target levels at any time point selected after transplantation; thus, 34 patients (57%) finally required a dose reduction of Neoral. The current mean C2 level was significantly lower than that observed immediately after conversion (584.6 ± 262.8 ng/ml vs. 893.1 ± 260.2 ng/ml, mean ± SD, $p < 0.0001$) with a mean follow-up period of 7.4 ± 0.6 months (range: 5–8 months) after conversion. Only one patient encountered rejection after conversion (1.7%), and no *de novo* infection or adverse effects were observed. Traditional C0 monitoring of Neoral was safely replaced by C2 monitoring without an increase in the rejection rate or any adverse effects in pediatric LDLT patients. C2 monitoring contributed to the dose reduction of Neoral, which may lead to the avoidance of long-term complications due to immunosuppression.

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Key words: C2 – liver transplantation – living donor – Neoral

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Accepted for publication 9 July 2004

Since it was introduced in the late 1970s, cyclosporine (CsA) has contributed to the field of organ transplantation and has been identified as an effective therapeutic modality (1). Although it has been associated with significant improvements in clinical results, the absorption of the original form of CsA, Sandimmune (Novartis, East Hanover, NJ, USA), was dependent on bile salts, so that it occasionally led to poor bioavailability, especially in cases of liver transplantation (2). After the modification of the absorptive profile by microemulsion (Neoral; Novartis), the inter- and intrapatient variability in blood concentrations were corrected and the results were significantly improved in the prevention of rejection and adverse effects (3–5). Another innovation in the

management of CsA was initiated in the area of monitoring the blood concentration, that is, by 2-h post-dose level monitoring (C2) (6). As regards liver transplantation, several studies have suggested the advantage of this new method over conventional trough level monitoring (C0), both in *de novo* and long-term patients with maintenance immunosuppression (7–9). However, no reports to date have specified the efficacy and feasibility of the new method in living donor liver transplantation (LDLT) patients, who have different immune and pharmacokinetic profiles from cadaveric transplantation cases (10, 11). In this study, we described the impact of late conversion from C0 to C2 on the doses and blood concentration of Neoral, as well as in terms of rejection, adverse effects, and patient/graft outcome in pediatric LDLT recipients.

Patients and methods

Patients

From June 1994 to August 2002, we performed 116 LDLTs in 115 patients. Of them, 80 patients were younger than or equal to 15 yr at transplantation, and were enrolled in this study. At the time of this writing, 78 patients (97.5%) were alive, with a mean post-transplant follow-up period of 31.1 ± 24.6 months (range 0.3–94 months). All patients underwent Neoral-based immunosuppression regimen except one patient, who received primary tacrolimus-based therapy. Two patients with primary Neoral required conversion to tacrolimus during follow-up due to the poor bioavailability of Neoral. One patient achieved complete withdrawal of immunosuppression after treatment for post-transplant lymphoproliferative disorder (PTLD), with a drug-free period of 45 months. Finally, 60 surviving patients were enrolled in the analysis who underwent conversion later than 1 month after transplantation (Fig. 1). These patients consisted of 28 males and 32 females, with a mean age at transplantation of 2.8 ± 2.5 yr (range 0.5–14 yr). The original diagnoses included biliary atresia in 49 patients, glycogen storage disease in five patients, neonatal hepatitis in five patients, Alagille syndrome in one patient. The types of the graft and the number of patients who received each type were as follows: left lateral segment (segments 2, 3) in 33, extended left lateral segment (segments 2, 3 + partial 4) in 24, left lobe including middle hepatic vein in 3. The ratio of graft weight to recipient body weight ranged from 1.3 to 5.1%, with a mean of 2.6 ± 1.0%. The donors were the mother in 41, the father in 17, and a grandmother in two patients.

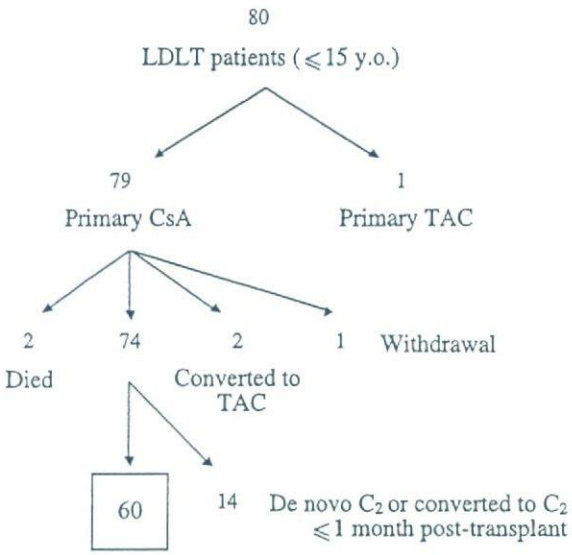

Fig. 1. Patient profiles. Sixty surviving pediatric patients with the following characteristics were enrolled in this study: received a CsA-based immunosuppression regimen, and underwent conversion from C0 to C2 later than 1 month after transplantation. One patient has been immunosuppression-free after treatment for post-transplant lymphoproliferative disorder. TAC, tacrolimus.

Baseline protocol of Neoral-based immunosuppression

The basic immunosuppression protocol consisted of a triple-drug regimen, which included Neoral, azathioprine [or mycophenolate mofetil (MMF)], and steroids. After confirming that there was adequate urine output, Neoral was started orally on the day after transplantation via the naso-gastric tube at a dose of 600 mg/m^2/d. Steroids were intravenously administered at an initial dose of 20 mg/kg intraoperatively, followed by 2 mg/kg/d the day after transplantation, and gradually the dose was tapered to a maintenance oral dose of 3–5 mg/d. During the follow-up period, this maintenance dose was gradually decreased until it was discontinued at a time point exceeding 6 months after transplantation. Azathioprine was started at 2 mg/kg/d intraoperatively, and was reduced to 1 mg/kg/d after 2 wk, and was discontinued by 6 months after transplantation. After the introduction of MMF, several patients received MMF as a substitution of azathioprine. MMF was started with initial doses of 600 mg/m^2/d, which also was discontinued after gradual reduction during the follow-up period. At the time of conversion, 24 patients were given Neoral only, 25 patients were given Neoral and steroids, and 11 patients received the triple-drug treatment; the mean period was 29.5 ± 21.9 months from transplantation to conversion (range 1–78 months).

Monitoring of Neoral blood levels

From the start of our program in 1994, we had adapted conventional trough level (C0) monitoring until January 2002, when we converted the entire system to a method of 2-h post-dose level (C2) monitoring. The blood levels were periodically monitored after transplantation, and target C0 levels were 300–400 ng/ml during the first post-operative month, 100–200 ng/ml for up to 1 yr, and approximately 100 ng/ml or less thereafter. As regards C2 monitoring, the target levels were 800–1200 ng/ml in the first 6 months, 640–960 ng/ml for 1 yr, and 480–720 ng/ml thereafter, based on the recommended levels by Levy (12). The blood concentration in both monitoring systems was determined by whole blood monoclonal specific radioimmunoassay (INCSTAR, Stillwater, MN, USA).

Data analyses

Values are presented as the mean ± SD. Statistical analyses were performed by the Mann–Whitney *U*-test. Throughout this study, a p-value of less than 0.05 was regarded as significant.

Results

Doses and blood levels

Just before conversion, the mean doses of Neoral were 10.9 ± 2.7 (7.5–15.9), 7.3 ± 2.0 (4.1–10.9), 5.9 ± 1.3 (3.8–8.6), and 4.3 ± 1.1 (1.7–7.1) in the following groups: 1–6, 6–12, 12–24, and more than 24 months after transplantation, respectively (mg/kg (range); $p < 0.0001$ between the following groups: 1–6 and more than 24 months). Regarding the blood concentration of C0, the values were 215.8 ± 49.2 (151–316), 212.1 ± 104.7 (108–449), 138.0 ± 54.1 (64.9–281), and 100.0 ± 33.0 (28.4–178), in each group [ng/ml(range); $p < 0.0001$ between the following groups: 1–6 months and more than 24 months]. At any time point of conversion after transplantation, the blood concentration of C2 monitoring just after conversion was higher than the expected target levels in a majority of the patients, with mean levels of 1125.0 ± 196.6 (825–1424), 825.0 ± 216.9 (479–1103), 925.9 ± 299.1 (552–1784), and 830.8 ± 222.7 (405–1334), respectively [ng/ml (range); $p = 0.0031$ between the following groups: 1–6 months and more than 24 months] (Fig. 2). There was a significant, but weak correlation between the blood levels before (C0) and just after conversion (C2) (Fig. 3). The ratio of C2 levels just after conversion to C0 levels just before conversion

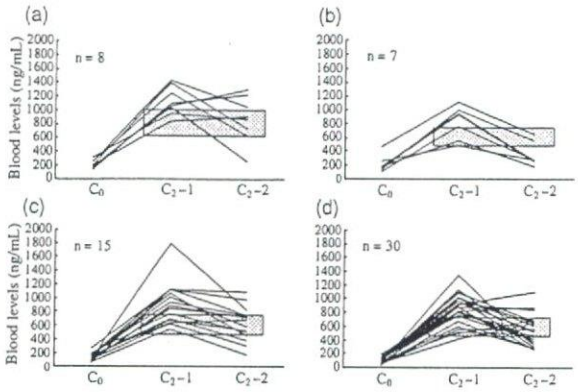

Fig. 2. Changes in blood levels of Neoral before and after conversion according to the time period after transplantation, 1–6 months (a), 6–12 months (b), 12–24 months (c), and more than 24 months (d). The shaded area indicates target C2 levels at each period. C0, trough levels before conversion to C2; C2-1, C2 levels just after conversion; C2-2, C2 levels at the last follow-up.

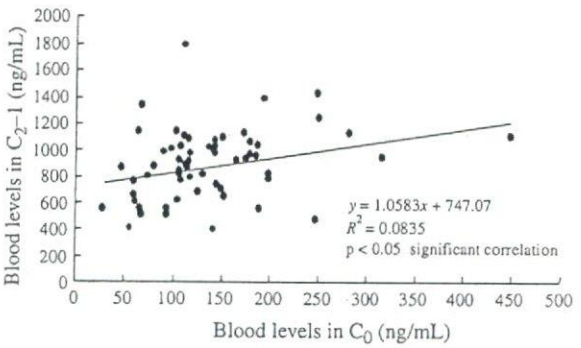

Fig. 3. Relationship between blood levels before (C0) and just after conversion (C2-1).

was significantly greater in the patients with a follow-up period of more than 12 months than in those of less than or equal to 12 months (8.7 ± 4.0 vs 5.1 ± 1.7, $p < 0.0001$) (Fig. 4). As a result of the high blood concentration of Neoral, 34 patients (57%) required a dose reduction of Neoral, with a mean reduction ratio of 21.3 ± 11.3% (range 6.2–52.9%), whereas only four patients (7%) underwent a dose increase. In general, the blood levels in the last follow-up were significantly lower than they had been just after conversion (584.6 ± 262.8 ng/ml vs. 893.1 ± 260.2 ng/ml, $p < 0.0001$) with a mean follow-up period after conversion of 7.4 ± 0.6 months (range 5–8 months).

Rejection

Fourteen acute rejections were identified in 11 patients (18.3%) before conversion. There was no

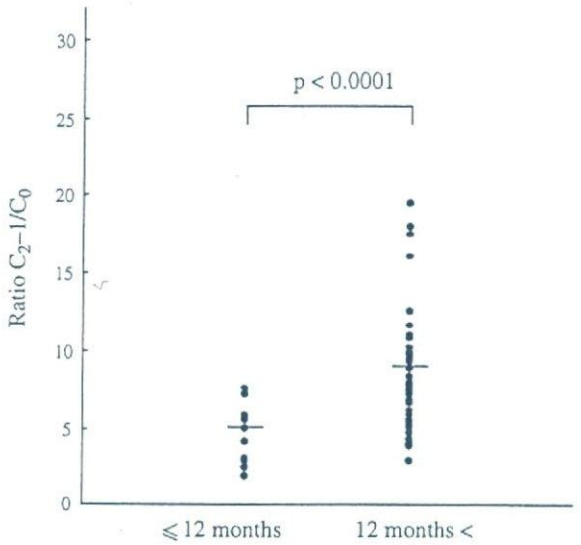

Fig. 4. Comparison of disparity between C0 levels and C2 levels by the timing of conversion. C2-1, C2 levels just after conversion.

case of steroid-resistant rejection or chronic rejection among any of the patients. During the follow-up after conversion, five patients underwent six liver biopsies due to several degrees of liver enzyme abnormality. One acute cellular rejection was identified (1.7%), which was easily reversed by steroid bolus therapy. Other pathological diagnosis included the following: no definite abnormalities in four patients, and hepatitis in one patients with no evidence of viral infection.

Infection/adverse effects

At conversion, no symptomatic infections were identified in any of the patients. Eight patients (13.3%) had encountered cytomegalovirus disease before conversion, the diagnosis of which was based on positive IgM antibody or a more than fourfold increase of IgG antibody, or identification of the viral antigen by polymerase chain reaction in the blood. There were two patients (2.9%) who had *de novo* HBV hepatitis, transmitted from the HB core antibody-positive donors, and these cases were well controlled with lamivudine monotherapy until conversion (65 and 42 IU/L in aspartate aminotransferase; 49 and 35 IU/L in alanine aminotransferase, and 1.0 and 1.3 mg/dl in total bilirubin at conversion for each patient, respectively). No reactivation or flare-up of these viruses was observed in any of the patients after conversion. As regards other adverse effects, one gingival hyperplasia, three hirsutisms, and one alopecia had been seen in four patients (6.7%); all of these other

Table 1. Changes in liver/kindly function

	Before conversion	Current
AST (IU/L)	35.9 ± 13.8 (18–90)	39.7 ± 20.5 (14–106)
ALT (IU/L)	27.7 ± 21.8 (10–150)	28.1 ± 33.8 (7–259)
Total bilirubin (mg/dl)	0.8 ± 0.3 (0.4–2.0)	0.9 ± 0.3 (0.1–2.0)
Creatinine (mg/dl)	0.6 ± 0.3 (0.3–1.4)	0.6 ± 0.3 (0.2–1.7)

Data expressed as mean ± SD (range).
AST, aspartate aminotransferase; ALT, alanine aminotransferase.

adverse effects were already resolved at conversion, and no recurrence or deterioration occurred thereafter. No *de novo* side effects, including nephrotoxicity, diabetes, hyperlipidemia, or neurotoxicity developed after conversion, not even among the four patients who required a dose increase.

Liver/kidney functions

The liver/kidney functions before conversion and in the current follow-up values are listed in Table 1. There was no significant deterioration in any of the tests after conversion.

Patient/graft outcome

No patient/graft losses were identified after conversion, and all the patients are currently doing well without any impairment in their quality of life.

Discussion

Our work with pediatric LDLT patients suggests that although all of our subjects were apparently doing well after LDLT, these long-term patients might be subclinically over-immunosuppressed after transplantation, based on conventional trough level monitoring of Neoral. In this study, we were able to achieve a dose reduction with minimal rejection by C2 monitoring. Although the optimal blood levels of calcineurin inhibitors immediately after transplantation seemed to be well established (13, 14), the optimal target levels remain controversial in long-term LDLT patients. It is difficult to determine what the optimal blood level should be in long-term liver transplant recipients, especially in those patients who are apparently doing well, i.e. in patients without any symptoms or signs of rejection. In principle, these levels might be maintained as low as possible, under consideration of the balance between the prevention of rejection and adverse effects. In a reported series, target trough levels beyond 1 yr after transplantation varied from around 100 to 600 ng/ml, depending on the method of

measurement (15–18). Jain *et al.* reported a significantly higher incidence of rejection and a lower achievement of steroid-free statement with CsA than with tacrolimus; this result was obtained in spite of their intensive immunosuppression with CsA, targeting trough levels between 400 and 600 ng/ml beyond 3 months after transplantation in pediatric patients (the actual mean trough level at 1 yr after transplantation was 473 ± 319 ng/ml) (18). We believe that our long-term target levels (approximately 100 ng/ml or less) were reasonable, although our levels were among the lowest reported; in our study, we observed a low incidence of rejection, no steroid-resistant rejection, and minimal adverse effects (19). However, we did find that the levels could be further reduced, when the patients were followed by C2 monitoring based on the recommended levels by Levy who demonstrated the possibility of minimizing both acute rejection and Neoral-related toxicity in cases involving cadaveric transplantation (12). Additionally, Cantarovich *et al.* reported in their randomized study that they were able to achieve significantly better clinical results (no rejection and no increase in serum creatinine over the baseline value) with low target C2 levels (300–600 ng/ml) than with high target C2 levels (700–1000 ng/ml), or with target levels of 100–200 ng/ml of C0 in long-term stable liver transplant recipients (9). Accordingly, when their results are combined with the present results demonstrating minimal rejection after conversion, it may be possible to further decrease these target doses during the follow-up period. It is preferable to administer patients a minimal-dose regimen that is also supportive of only minimal rejection, as studies of long-term follow-up protocols have indicated that the majority of late morbidity and mortality cases can be related to the adverse effects of immunosuppression, including infection, recurrence of original viral hepatitis, renal dysfunction, diabetes, and various kinds of malignancies (20–22).

Interestingly, the intrapatient disparity between C0 and C2 blood levels was greater among long-term patients than among relatively short-term patients. One possible explanation for this phenomenon is that drug absorption and metabolism, which should reflect these blood levels, may function better in long-term patients than in short-term patients after they achieve stable bowel absorption and graft function following completion of the regeneration of the partial graft. In addition, the trough level of tacrolimus was shown to be higher in adult LDLT patients than in cadaveric recipients in spite of the administration of the same dose of tacrolimus; this result was probably due to poor drug metabolism of the partial graft, which should be observed early after transplantation (11, 23). However, it may be unreasonable account for our results using this hypothesis, because the majority of our recipients were small children who received a sufficient graft volume. We do believe that the insufficient volume of a partial graft, combined with other mechanisms, can contribute to impaired drug metabolism and absorption during the early period before the establishment of stable graft function in long-term patients; however, the impact of C2 on the pharmacokinetics of Neoral in long-term LDLT patients has not yet been unequivocally determined, and therefore, an appropriate pharmacokinetic study will still be needed to identify the reasons for this phenomenon. Also, further study should be necessary whether our results can be extrapolated to adults, who should have different pharmacokintetics and smaller GRWR than that of children. In any case, it is important to consider that even with a low dose of Neoral, the peak level can be high in long-term patients, despite reasonably low trough levels. C2 monitoring may significantly contribute to dose adjustments in the future, especially in long-term patients. In the present study, although 57% of the patients achieved dose reduction, some of them are not in adequate target levels yet at the last follow-up, as shown in Fig. 2. Further dose adjustment should be necessary in these patients.

In conclusion, traditional trough level monitoring of Neoral was safely replaced by 2-HR post-dose level monitoring, and this new type of monitoring contributed to successful dose reduction with minimal rejection in long-term pediatric LDLT patients. Further study will still be required in order to determine the adequate target levels of C2 in these patients.

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Selective Suppression of Initial Cytokine Response Facilitates Liver Regeneration after Extensive Hepatectomy in Rats

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ABSTRACT

Background/Aims: After extensive hepatectomy, the cytokine network plays an important role in injury to the remnant liver and subsequent impairment of liver regeneration. Tumor necrosis factor α (TNF α) and interleukin 1β (IL-1β) are thought to be the initial cytokines associated with liver injury as well as with regeneration. We investigated the effect of the suppression of these cytokines on liver function and on liver regeneration after subtotal hepatectomy in rats.

Methodology: Following 90% hepatectomy, rats were divided into two groups. Animals in the FR group received intraperitoneal FR167653, a selective inhibitor of TNF α and IL 1β, while those in the Control group received vehicle only. Liver chemistry and serum levels of TNF α and IL-6 were measured serially. Liver specimens were obtained 48 hr after surgery and regenerative activity assessed by proliferating cell nuclear antigen (PCNA) expression and remnant liver weight.

Results: The survival rate was significantly better in the FR group (76.4±11.7 hrs) than in the Control group (26.8±4.3 hrs, $p=0.0014$). Liver enzyme and blood sugar levels after surgery were higher in the FR group compared to the Control group ($p=0.03$ or less). Changes in serum levels of both TNF α and IL-6 were suppressed in FR group rats after surgery. Microscopically, hepatocellular damage and steatosis was less prominent in FR group livers. PCNA labeling index and residual liver weights were higher in the FR group ($p<0.001$).

Conclusions: Following extensive hepatectomy in rats, suppression of early cytokine induction improved liver function and facilitated liver regeneration. Suppression of selective cytokine responses could allow extended liver resection and reduced risk of liver failure.

KEY WORDS: FR167653; Extensive hepatectomy; TNF α; IL-6; Liver regeneration

ABBREVIATIONS: Tumor Necrosis Factor α (TNF α); Interleukin 1β (IL-1β); Proliferating Cell Nuclear Antigen (PCNA); Ischemia/Reperfusion (I/R); Intracellular Adhesion Molecule-1 (ICAM-1); Nuclear Factor κB (NFκB); Aspartate Transaminase (AST); Alanine Transaminase (ALT); Lactate Dehydrogenate (LDH)

INTRODUCTION

Extensive resection of the liver, especially the cirrhotic liver, is frequently associated with postoperative liver failure with sustained portal hypertension and hepatic congestion by microcirculatory disturbance (1). Cytokines have been reported to play key roles in mechanisms of liver damage (2).

Tumor necrosis factor α (TNF α) and interleukin-1 (IL-1) are recognized as initial-phase cytokines in the inflammatory response following systemic infection or injury (3). They also appear to play pivotal roles in liver disease following hepatectomy or ischemia/reperfusion (I/R) injury. TNF α released from Kupffer cells and/or hepatic sinusoidal endothelial cells stimulates the expression of chemo-attractants (4,5) such as intracellular adhesion molecule-1 (ICAM-1) (6) and induces neutrophil accumulation in hepatic sinusoids. Adherence of these neutrophils to endothelial cells causes microcirculatory disturbances (6), with subsequent neutrophil elastase release and accelerated I/R injury. In addition, several cytokines are induced by TNF α through nuclear factor κB (NFκB) activation (7). Recent evidence suggests that TNF α affects IL-6 expression downstream in the cytokine cascade through NFκB activation. While IL-6 is a strong promoter of liver regeneration in rats treated with 70% hepatectomy (8), other investigators including ourselves (9) have demonstrated excessive IL-6 production in extensively (90%) hepatectomized rats, which was associated with adverse effects on hepatic microcirculation and liver regeneration.

FR157653 is a selective inhibitor of IL-1β and TNF α production in monocytes and macrophages (10-12). Using 90% hepatectomized rats, we investigated whether the blockade of the initial cytokine response by FR167653 could modulate the cytokine cascade, resulting in improved hepatocyte protection and proliferation.

METHODOLOGY

Animal studies were performed in compliance with the Nagasaki University guidelines for humane care of experimental animals.

Animals

Adult male Wistar rats weighing 200-250g were obtained from Ohtsubo Co. Ltd. Nagasaki, Japan, and

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acclimatized to our laboratory conditions for 1 week prior to use in experiments. Animals were housed in climate-controlled (21°C) conditions under a 12-hr light/dark cycle and given tap water and commercial rat chow *ad libitum*. Surgical procedures were performed under ether inhalation anesthesia in sterile conditions between 9 am and 12 am. After surgery, the animals were warmed externally and given a single bolus of 15mL of 10% glucose in normal saline subcutaneously to avoid dehydration.

Surgical Procedures

Under ether inhalation anesthesia, the abdomen was entered by median laparotomy. Nearly 90% hepatectomy was archived using Gaub's technique (13). Prior to resection, vascular pedicles of the right and median lobes were ligated and resected. Remnant livers consisted of two omental lobes that represented approximately 10% of the whole liver mass.

Experimental Design

FR167653, a potent suppresser of IL-1 and TNF α production, was provided by Fujisawa Pharm. CO. Ltd (Osaka, Japan) (10-12). Animals were divided into two groups, FR and Control. Each animal in the FR group received FR167653 intraperitoneally at 10mg/kg twice, 1 hour prior and immediately after surgery. Each animal in the Control group received the same volume of saline intraperitoneally.

Assessments

Blood samples were obtained postoperatively from the inferior vena cava 2, 6, and 12 hr after surgery. Aspartate transaminase (AST), alanine transaminase (ALT) and lactate dehydrogenate (LDH) levels in the blood samples were then measured using commercially available kits. Blood glucose was also measured to evaluate the severity of liver failure. TNF α and IL-6 levels were measured 2, 6, and 12 hr after surgery using a rat TNF α immunoassay kit (TECHNE corporation, Minneapolis, MN) and an IL-6 ELISA kit (WAKO corporation, Osaka, Japan), respectively.

Fifteen animals from each group that underwent 90% hepatectomy were observed for survival until death, after which the residual omental liver lobes were harvested, weighed and fixed in 10% neutral formalin.

At 48 hr after hepatectomy, animals were killed and the residual livers weighed to assess liver regeneration, and stained with hematoxylin-eosin to evaluate histological liver damage. Hepatocyte proliferation was also assessed by proliferating cell nuclear antigen (PCNA) staining. The PCNA-labeling index was defined as PCNA-positive cells per 1,000 hepatocytes from 10 high power fields (x400).

Statistical Analyses

StatView-J 4.5 software was used for statistical data analysis. Student's *t* and Mann-Whitney's U tests were performed and results expressed as a mean ± standard deviation (SD). Survival rates were compared by the Kaplan-Meier method. *P* values less than 0.05 were considered significant.

RESULTS

FR treatment did not affect systemic hemodynamics, and no obvious side effects were observed in the FR group. All animals tolerated surgery well and recovered uneventfully from anesthesia.

Survival

The survival rate in the FR group was significantly higher compared to the Control group ($p=0.0014$) **(Figure 1)**.

Blood Chemistry

FR group rats exhibited lower serum ALT levels at 2, 6, and 12 hr after surgery compared to Control group rats ($p=0.015$ at 12 hr) **(Figure 2)**. Changes in AST and LDH levels after surgery were similar to that observed for ALT (data not shown). Blood sugar levels decreased gradually after surgery. Control group rats demonstrated severe hypoglycemia (<50mg/dL) 12 hr after surgery, whereas FR group rats exhibited significantly higher serum blood sugar levels, maintained at least 12 hr after surgery ($p=0.03$) **(Figure 2)**.

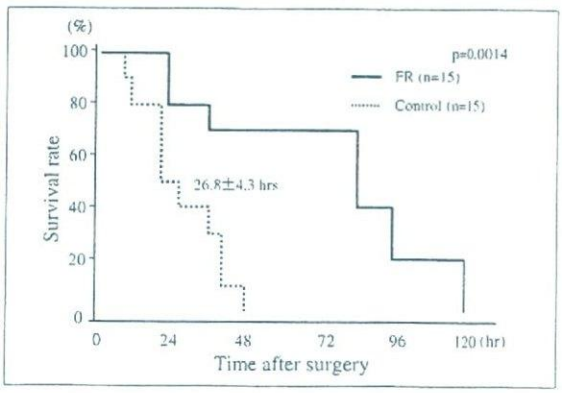

FIGURE 1 All FR group rats survived over 24 hours after surgery, and had significantly better survival compared to Control group rats (76.4±11.7 hrs *vs.* 26.8±4.3 hrs, respectively, $p=0.0014$).

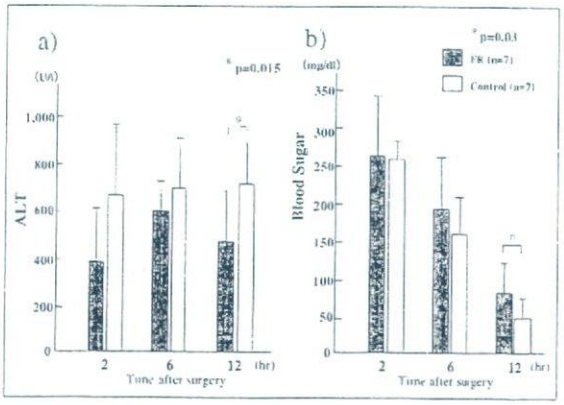

FIGURE 2 (a) FR group rats exhibited lower serum ALT levels at 2, 6, and 12 hr after surgery compared to Control group rats ($p=0.015$ at 12 hr). Changes in serum LDH and AST levels after surgery were similar to ALT. (b) Blood sugar levels decreased gradually after surgery. Control group rats demonstrated severe hypoglycemia (<50mg/dL) 12 hr after surgery, whereas serum blood sugar levels FR group rats 12 hr after surgery remained significantly higher ($p=0.03$).

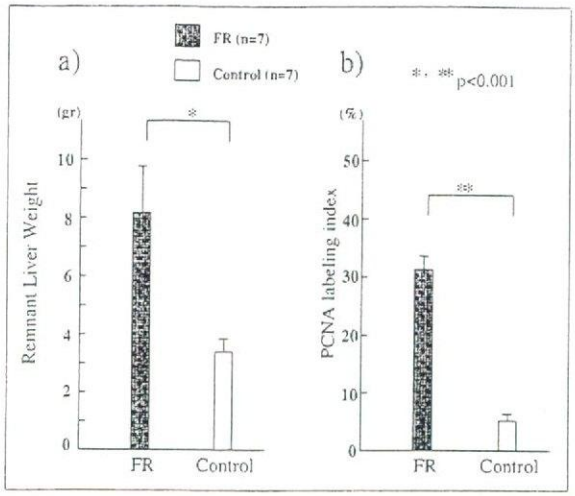

FIGURE 3 (a) Mean remnant liver weight in the FR group was greater than in the Control group (3.2±0.4g *vs.* 8.2±1.6g, respectively, $p<0.001$). (b) The PCNA-labeling index for FR treated rats was significantly higher than for Control group rats ($p<0.001$).

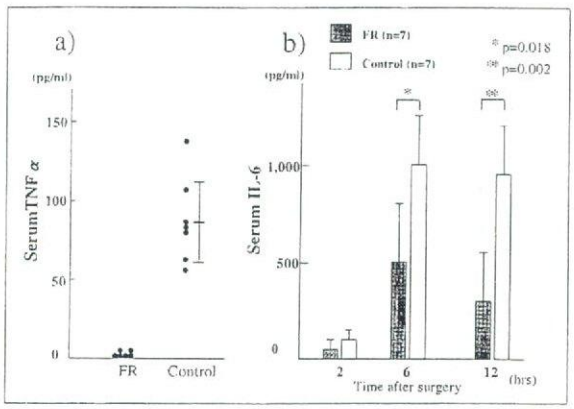

FIGURE 4 (a) Serum TNF α levels in Control group rats 2 hr after surgery were elevated (80±9.2pg/mL), but undetectable in FR group rats. b) Changes in IL-6 serum levels were suppressed in FR group rats at each time point after surgery. At 6 and 12 hr after surgery, serum IL-6 levels in the FR group was significantly lower than in the Control group ($p=0.002$ or less).

Liver Regeneration

Mean remnant liver weights were 3.2±0.4g in Control group rats and 8.2±1.6g in FR group rats ($p<0.001$). The PCNA labeling index of the FR group was significantly higher compared to the Control group ($p<0.001$) **(Figure 3)**.

TNF α and IL-6 Serum Levels

At 2 hr after surgery, serum TNF α levels in Control group rats increased (80±9.2pg/mL), while TNF α remained undetectable in FR group rats. Serum IL-6 values in the FR group were significantly lower than in the Control group at each time point after surgery ($p=0.002$) **(Figure 4)**.

Histological Findings

The degree of histological liver damage was less prominent in the FR group than in the Control group. While Control group liver tissues exhibited hepatocellular damage, steatosis, and marked sinusoidal neutrophil infiltration, FR group livers demonstrated much less hepatocellular damage and sinusoidal neutrophilic infiltration **(Figure 5)**.

DISCUSSION

Following extensive hepatectomy, congestion of the remnant liver leads to portal hypertension followed by hepatic injury due to gut-derived endotoxins (14). This results in severe liver dysfunction, hypoglycemia and poor liver regeneration, and is often fatal (13). Free radicals released following reperfusion stimulate the production of TNF α and IL-1 from non-parenchymal liver cells (15,16). Both TNF α and IL-1 stimulate the production of each other and further amplify the inflammatory response. Our results demonstrated that the inhibition of these initial key cytokines prevented neutrophil accumulation and the inflammatory response in the remnant liver.

Recent reports have suggested that TNF α affects IL-6 expression in the cytokine cascade, and that IL-6 is associated with hepatoprotective effects. IL-6 is an acute reactant cytokine with anti-inflammatory properties (17,18), which has been found to prevent injury in a murine model of acute hepatitis through down-regulation of TNF α (19). Other positive effects of IL-6 have also been reported, including that recombinant IL-6 (rIL-6) was able to reduce acute inflammation in endotoxin-induced tracheal injury and sepsis in rats (20,21). Camargo *et al.* (8) also reported that IL-6 has hepatoprotective effects through the prevention of TNF α expression in rats.

With regard to the enhanced liver regeneration by FR167653 in our study, the suppression of IL-6 expression by blocking TNF α production may have played a role. While IL-6 has hepatoproliferative effects that stimulate hepatocyte and bile duct cell proliferation *in vitro* and *in vivo* (22,23), perioperative administration of IL-6 lowered hepatocyte prolifera-

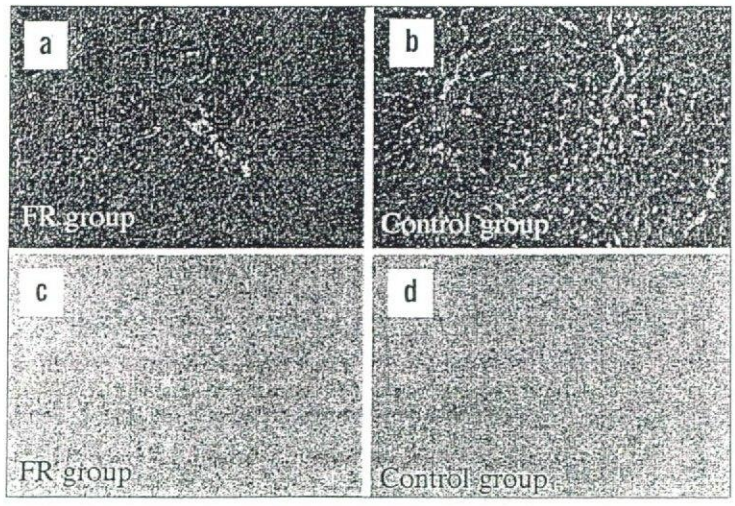

FIGURE 5 (a, b) Control group rat livers showed marked neutrophilic infiltration and parenchymal hemorrhage of the sinusoids as well as severe steatosis of the parenchymal cells. In contrast, FR group rats exhibited neither significant hepatocellular damage nor neutrophilic infiltration of the sinusoids. (c, d) PCNA-positive cells were more prominent in FR group rats than in Control group rats.

tion in rats with 70% hepatectomy. In our previous study, serum IL-6 levels in rats after conventional 70% partial hepatectomy decreased gradually, while in rats that had undergone subtotal hepatectomy, levels were persistently elevated and associated with poor proliferative activity of the liver cells with transcriptional derangement. It is possible that excessive enhancement of cytokine levels may cause intracellular missignaling, such that the hepatocytes are no longer able to proliferate and lose function. Therefore, it appears that control of cytokine levels is vital. To suppress initial key cytokines, we used FR167653, a dual synthetic inhibitor of TNF α and IL-1, probably through suppression of the mitogen-activated protein kinase p38 pathway (12). Beneficial effects of FR167653 have been reported in I/R injury of the lung (24,25), liver (26) and pancreas (27) as well as cardiac transplantation (28) in rats. For the liver, improvement of both proliferation and function has been reported (24,26).

In our study, the production of IL-6, a secondary cytokine, was suppressed compared to controls. Initially activated transcription factors, such as NF-κB, may be involved through TNF α/IL-1β suppression. It is also possible that suppression of initial cytokine stimulation may inhibit the inflammatory response, allowing the proper elevation of IL-6, and contributing to hepatocyte proliferation.

In conclusion, suppression of the initial cytokine response by FR167653, a dual TNF α and IL-1 inhibitor, in rats that had undergone subtotal hepatectomy facilitated liver regeneration and exhibited hepatoprotective effects with improved hepatocyte proliferation. Thus, suppression of the initial cytokine response after massive hepatectomy may improve the outcome of major hepatic resection.

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CHANGES IN SERUM LEVELS OF HEPATOCYTE GROWTH FACTOR IN PATIENTS UNDERGOING ADULT-TO-ADULT LIVING-DONOR LIVER TRANSPLANTATION

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Changes in the serum concentration of hepatocyte growth factor (HGF), a potent mitogen for hepatocytes, were investigated in adult-to-adult living-donor liver transplantation (LDLT) in which liver regeneration is involved. Between August 2000 and November 2002, 15 consecutive adult-to-adult LDLTs were performed using the right lobe graft. The recipients were divided into two groups: acute liver failure (n=6) and chronic liver failure (n=9). In addition, right lobe donors (n=12) were evaluated. Measurement of HGF was performed on preoperative and postoperative days 1, 3, 7, and 14 after LDLT. The pretransplant levels of serum HGF were higher in the acute liver failure group than in the chronic liver failure group ($P<0.05$). After liver replacement, serum HGF levels normalized rapidly in both groups and remained rather low. Despite vigorous liver regeneration in all groups, serum HGF levels did not change significantly after adult-to-adult LDLT with right lobe graft.

Because of a shortage of brain-dead donors, partial liver transplantation from living donors has gained worldwide popularity. In contrast with whole liver transplantation, partial liver allograft allows the graft to regenerate to adapt to the recipient environment. For this reason, partial liver transplantation offers a unique opportunity to investigate the yet unresolved mechanisms of liver regeneration (*1*, *2*). Hepatocyte growth factor (HGF), a potent mitogen for hepatocytes, has been isolated and purified from the plasma of patients with fulminant hepatic failure and from rat platelets. After liver resection and whole liver transplantation, the levels of HGF increase depending on the injury of the remnant or graft liver (*3*, *4*). However, no report has been published on the long-term changes in blood HGF levels in patients who have undergone living-donor liver transplantation (LDLT) or on the especially interesting case in which vigorous liver regeneration took place in adult-to-adult LDLT (*5*).

Between August 2000 and November 2002, 15 adult-to-adult LDLTs using the right liver lobe without the middle hepatic vein were performed at Nagasaki University Hospital, Nagasaki, Japan. The age of the recipients ranged from 16 to 63 years (mean 41.2±15.7 years), and five were female. The recipients were divided into two groups depending on the indication for transplantation: the acute liver failure (ALF) group (n=6, 38.2±17.5 years), consisting of four patients with fulminant hepatic failure and two patients with acute on chronic liver failure, and the chronic liver failure (CLF) group (n=9, 43.2±15 years), consisting of three patients with postnecrotic cirrhosis, three patients with primary biliary cirrhosis, two patients with biliary atresia, and one patient with Budd-Chiari syndrome. Living right-lobe donors (D group: n=13, age 45.1±14.2 years, nine males and four females) were enrolled as the control group. The grafts were perfused with 500 mL of chilled (4°C) University of Wisconsin solution through the portal vein. The right hepatic veins and portal veins were anastomosed end-to-end, and the hepatic arteries were anastomosed using an operative microscope. The recipients uniformly received tacrolimus or cyclosporine and a standard prednisone taper. Interleukin-2 receptor antagonist basiliximab was also used in two patients. One patient in the ALF group demonstrated renal failure and was placed on continuous hemodiafiltration preoperatively, and one patient in the CLF group also required continuous hemodiafiltration postoperatively. These two patients showed portal malcirculation (to-and-fro or hepatofugal portal flow) and died 1 month after LDLT. All other patients recovered without vascular complications in the early posttransplant period.

The levels of HGF in the serum were measured in both the donors and recipients by an enzyme-linked immunosorbent assay. The liver volume of the donors was estimated before and after transplantation by computed tomography using the volumetric software Flexi Trace 1.03 (Tree Star, Inc., San Carlos, CA). Computed tomography was performed on postoperative days 7 and 28, and 3 months after LDLT. Because the calculation of the degree of liver regeneration depends on the standard liver volume (SLV) of the patients, the SLV of the recipients was calculated using the equation presented by Urata et al. (*6*). The proportion of the liver graft to the SLV was expressed as the liver volume ratio (LVR). These studies were planned as a routine part of postoperative surveillance for which informed consent was obtained in each case. All results are expressed as a mean±standard deviation, and statistical significance was determined by analysis of variance with Scheffe's test.

In the ALF group, the serum levels of HGF before transplantation were extremely high, but they decreased rapidly after liver replacement. Preoperative levels of serum HGF were significantly higher in the ALF group than in the CLF group ($P<0.05$). After liver replacement, the serum levels of HGF remained low despite vigorous liver regeneration (Fig. 1). There was no correlation between the serum levels of HGF on posttransplant day 3 or 7 and LVR before or at 1 month postoperatively. Liver regeneration was steady in all patients, particularly in the CLF group (LVR of days 0, 14, and 28: ALF group 50.5%±13.2%, 73.7%±12.2%, and 84.6%±13.6%; CLF group 58.4%±10.5%, 90.4%±15.9%, and 102.5%±24.1%; D group 39.6%±5.4%, 63.7%±6.4%, and 75.2%±15.6%). Even in two patients who demonstrated post-

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Received 24 March 2003; revised 14 April 2003. Accepted 1 July 2003.

DOI: 10.1097/01.TP.0000093466.21749.E3

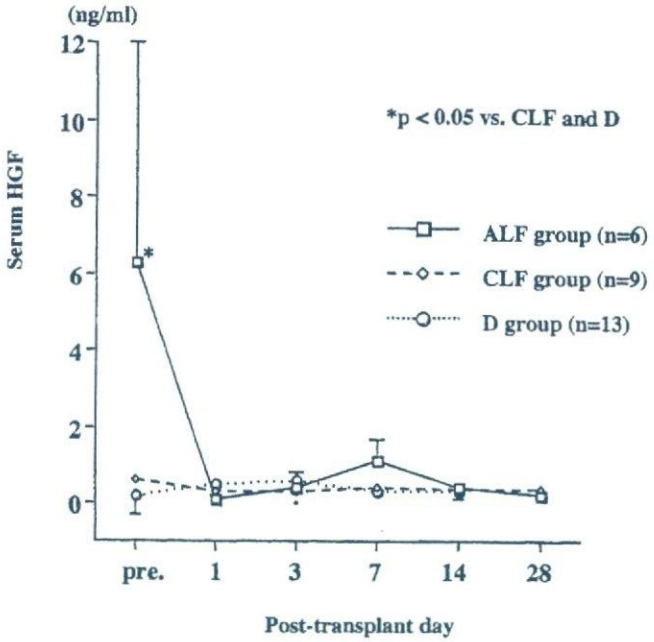

FIGURE 1. Levels of serum hepatocyte growth factor (HGF) in recipients after living-donor liver transplantation (LDLT). The normal range of HGF is less than 0.31 ng/mL. Patients were divided into two groups: acute liver failure (ALF, n=6) and chronic liver failure (CLF, n=9). Living right-lobe donors (D, n=13) were enrolled as the control group.

transplant portal malcirculation, the levels of serum HGF showed no remarkable change except on day 7 when the portal malcirculation was evident (1.61±0.43 ng/mL before LDLT, 0.61±0.02 on day 1, 0.34±0.01 on day 3, 2.79±0.56 on day 7, 0.61±0.14 on day 14, and 0.23±0.18 on day 28).

Changes in serum HGF levels after hepatic resection have been thoroughly investigated, and a correlation has been demonstrated between the serum levels of HGF and the existence of liver cirrhosis (*3*). Furthermore, rather constant and low posttransplant serum HGF levels have been documented in uncomplicated whole liver allografting (*4*). An explanation for this finding could be that liver regeneration would not take place with whole liver allografting. In partial liver allografting that involves liver regeneration, especially in cases of right lobe graft, little was known about the changes in serum HGF levels. In pediatric cases of LDLT with left lateral lobe graft in which liver regeneration does not take place, changes of serum HGF levels were reported to be minimal (*5*). Notably, in the present study, although the number of our patients was limited, no marked increase was observed even after right lobectomy for donor surgery or right lobe engraftment for the recipient in either the ALF or CLF group. In addition, as also reported by Kimura et al. (*7*), HGF level after partial hepatectomy of the normal human liver did not increase dramatically. The reason for the constant serum HGF level could be either of the following: (1) The engrafted livers were healthy with the expression of intact HGF receptors, which is the main site of HGF clearance, as previously reported (*8–11*). (2) HGF may not be involved in healthy human liver regeneration, although it was presumed that production of HGF could be in an ectopic site (e.g., the lung, kidney and spleen) rather than in nonparenchymal cells of the liver (*12*).

Our standard immunosuppressive regimen included tacrolimus and steroid taper. In addition, interleukin-2 receptor antagonist (basiliximab), which acts only on the activated form of interleukin-2 receptor to control rejection, was used in two patients. Because our patients did not develop acute rejection in the early posttransplant periods, we presumed that the effect of basiliximab in our patients, if any, was small. Also, the same degree of liver regeneration was found in patients with renal failure compared with patients with healthy renal function, and no major changes of serum HGF were observed after LDLT.

In summary, after liver replacement with normal partial liver allografts, the serum HGF level remains low despite vigorous liver regeneration.

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2004増刊 / 癌の標準手術アトラス /
IV. 肝癌・胆嚢癌・膵癌の標準手術

肝癌に対する標準手術 - 肝後区域切除術

Hepatic posterior segmentectomy

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Key word 肝後区域／肝細胞癌／開胸アプローチ

肝切除の原則は腫瘍の完全な除去と可及的な肝機能の温存である．そのためには肝予備能に応じた切除範囲の設定が重要である．とくに後区域に存在する腫瘍に対しては，右葉切除は過大な侵襲となる場合も少なくない．後区域切除術は肝細胞癌はもとより，転移性肝癌における残肝機能を考慮した系統的術式である．

本稿ではわれわれの行っている肝細胞癌に対する術式を中心に紹介する．

概　説

■対　象■

手術適応は日本肝癌研究会の障害度A，Bを対象とし，切除範囲はICG(0.5 mg/kg負荷)の停滞率15分値(R 15)と門脈圧によって決定し，最近は肝機能を反映するアシアロシンチを参考としている[1)2)]．門脈圧は，術中にTreitz靭帯から80～100 cm肛側の空腸静脈にカテーテル(カットダウン用のチューブ)を挿入し，マノメータを接続，水柱圧で測定している．とくに右葉で区域以上の切除を計画する場合，脈管遮断後に門脈圧を再度測定し，急激な圧亢進(主として20 cmH_2O 以上)が見られる時には切除範囲を1ランク縮小するようにしている(表1)．また，肝細胞癌では非癌部の炎症が高度である場合，再発頻度が高いという教室での検討結果に基づき，術前の中等度以上の肝細胞障害・γグロブリン高値例では術中非癌部の肝生検を行いHistological Activity Index；HAIを算出し，高値では切除範囲を最小限にとどめるようにしている[3)-5)]．

■術前管理■

超音波，CT，MRIにより腫瘍および周囲脈管構築を検討する．画像診断技術が発達したため，侵襲的検査である術前の血管造影は血管走行の変異を認めない限り行っていない．術前にトランス

表1　術中門脈圧と肝切除範囲

門脈圧(cmH_2O)	ICGR15(%)	切除範囲
20未満	10未満	3区域または2区域切除以上
20以上	10以上20未満	区域切除
	20以上30未満	亜区域切除
	30以上	部分切除，焼灼術

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アミナーゼ高値の場合は，肝庇護療法を行い80 IU/L 以下に維持するようにしている．また，腸管前処置は不要な bacterial translocation を避けるため機械的な下剤投与にとどめ，抗生物質は開腹直前からセフェム２世代の投与を行う．

表２　周術期対策

術前	AST，ALT 80 IU/L 以下 腸管前処置は機械的洗浄のみ
術中	セフェム２世代，蛋白分解酵素阻害薬投与 中心静脈圧を低く保つ
術後	H2拮抗薬投与 早期の経口摂取再開

■術中管理■

術中出血は肝静脈枝からのものが大半であるため，中心静脈圧を低圧(5～7 cmH_2O 程度)に保つよう換気・輸液の調節を麻酔科に依頼している．また，障害肝は凝固線溶系が変動しやすいため，術中からタンパク分解酵素阻害剤を投与している．

■術後管理■

術後は，ドレーンからの出血・排液の性状を経時的に観察する．肝静脈のうっ血を避けるため中心静脈圧を測定し輸液は若干 dry side の管理を行っている．また，ストレス潰瘍の発生予防のためＨ２拮抗薬を投与している．肝切除後は胆汁漏が認められることが少なくないが，多くは離断面からの一過性のものであり，経口摂取とともに胆汁の腸管へのドレナージが促進され胆汁漏は減少することが多い．この点も考慮に入れ，経口摂取は腸管運動が良好に聴取されたら直ちに開始している．ドレーンは排液が清明で減少したら通常５～７日で抜去する．開胸併用の場合は胸腔ドレーンの排液が100 ml 以下となったところで抜去する(表２)．

手術手技

手術は開腹，胆摘，肝門処理，脱転，切離の順で進む．

1　開　　腹

皮膚切開は通常，肋弓下２横指下の右肋骨弓下切開を基本とし前腋窩線からは肋弓に沿って右後方に延長する(図１)．腹筋群の切離には電気メスをスプレーモードで用いると止血が良好である．S７に位置する腫瘍では７-８肋間開胸を併用したＪ型切開を行うと胸腔より横隔膜ごと後区域が持ち上げられるので視野が良好となる．

2　門脈圧測定

肝鎌状間膜を切離しつつ肝円索を同定し，結紮切離する．肝側の糸はそのまま残しておき，肝臓の牽引に用いる．腫瘍の位置を術中超音波で確認し，腫瘍の部位・個数を再度確認する．続いて，Treitz 靭帯から80～100 cm の空腸の静脈よりカテーテルを挿入する．同部からは約10 cm の挿入で門脈内への到達が可能である(図２)．門脈圧測定後，切除範囲を決定する．開腹所見が術前所見と解離する場合，非癌部組織生検を行う．

3　肝門処理

胆嚢を摘出する．胆嚢管と動脈を同定し順向性に行う．胆嚢漿膜を肝床ぎりぎりで切除すると

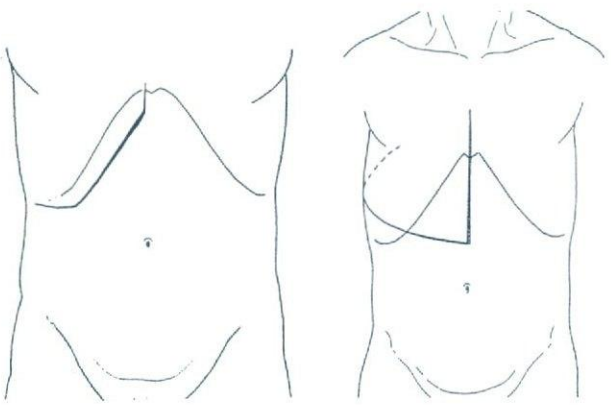

図　1
(幕内雅敏，高山忠利編：肝臓外科の要点と盲点，文光堂より引用)