**Table 2** Factors associated with cholestatic hepatitis C

| Factors | Cholestatic hepatitis | | *P*-value |
|---|---|---|---|
| | No ($n = 44$) | Yes ($n = 5$) | |
| Recipient age (years) | 57.4 ± 8.0 | 58.2 ± 7.7 | 0.839 |
| Recipient sex, male | 22 (50.0) | 1 (20.0) | 0.203 |
| Hepatocellular carcinoma, yes | 31 (70.5) | 3 (60.0) | 0.631 |
| MELD score | 14.8 ± 7.0 | 14.4 ± 4.3 | 0.908 |
| History of IFN treatment, yes | 34 (80.9) | 3 (60.0) | 0.602 |
| Donor age (years) | 34.5 ± 10.9 | 29.2 ± 10.0 | 0.302 |
| Donor sex, male | 31 (70.5) | 3 (60.0) | 0.631 |
| ABO incompatible, yes | 5 (11.4) | 2 (40.0) | 0.083 |
| Graft type, left lobe | 17 (38.6) | 2 (40.0) | 0.952 |
| GV (g) | 461 ± 91 | 502 ± 61 | 0.341 |
| GV/SLV (%) | 39.2 ± 5.9 | 45.0 ± 7.3 | 0.049 |
| Splenectomy, yes | 42 (95.5) | 5 (100.0) | 0.626 |
| Cold ischemic time (min) | 100 ± 62 | 83 ± 43 | 0.551 |
| Warm ischemic time (min) | 39 ± 10 | 37 ± 9 | 0.631 |
| Operative time (min) | 793 ± 136 | 740 ± 107 | 0.404 |
| Blood loss (L) | 4.5 ± 6.5 | 4.9 ± 3.2 | 0.894 |
| Recipient IL-28B genotype, T/T | 23 (60.5) | 4 (80.0) | 0.393 |
| Donor IL-28B genotype, T/T | 27 (64.3) | 4 (80.0) | 0.483 |
| HCV genotype 1, yes | 34 (80.9) | 3 (60.0) | 0.279 |
| HCV RNA titer ($log_{10}$IU/mL) | | | |
| Before LDLT | 5.4 ± 1.2 | 5.2 ± 0.7 | 0.813 |
| At 2 weeks after LDLT | 5.8 ± 1.3 | 7.7 ± 0.4 | 0.002 |
| Peak titer | 6.8 ± 1.3 | 7.9 ± 0.1 | 0.089 |
| Time to peak HCV RNA titer (weeks) | 9.4 ± 5.6 | 3.7 ± 2.3 | 0.031 |
| Viral response (%) | 22 (64.7) | 5 (100.0) | 0.110 |
| Tacrolimus use, yes | 22 (50.0) | 1 (20.0) | 0.202 |
| Acute rejection, yes | 1 (2.3) | 0 (0.0) | 0.733 |
| Bile duct stenosis, yes | 8 (18.2) | 2 (40.0) | 0.251 |
| Cytomegalovirus infection, yes | 12 (27.2) | 4 (80.0) | 0.017 |
| Central perivenulitis on biopsy, yes | 9 (20.5) | 4 (80.0) | 0.004 |

GV, graft volume; HCV, hepatitis C virus; IL, interleukin; LDLT, living-donor liver transplantations; MELD, Model for End-Stage Liver Disease; SLV, standard liver volume; SNP, single nuclear polymorphism; VR viral response.

## DISCUSSION

IN THE CURRENT study, HCV RNA titer of more than 7.2 $log_{10}$IU/mL at 2 weeks after transplantation was the only predictive factor for recurrent cholestatic hepatitis C after LDLT. None of the other donor or recipient factors, including IL-28B (rs8099917) genotypes were associated with this severe disease in multiple regression analysis. Cholestatic hepatitis C was diagnosed in all five patients based on early extensive viremia and histological findings (e.g. pan-lobular hepatocyte ballooning). VR was achieved in all of the cases following immediate treatment with PEG IFN with ribavirin.

Although cholestatic hepatitis C is an uncommon (2–5%) form of HCV recurrence, it is usually associated with rapid progression of cholestasis with fibrosis, and often results in graft failure within 1 year after transplantation.[3–6] Early and accurate diagnosis of cholestatic hepatitis C and immediate treatment is essential to save the transplanted grafts, although diagnosis is often difficult.[14–16] The difficulties in diagnosis are mainly due to the differential diagnoses, including acute rejection, biliary stenosis or primary graft dysfunction, for which the treatments are opposite or are very different from those used for cholestatic hepatitis C.[3] We think that the combination of HCV RNA titer of more than 7.2 $log_{10}$IU/mL at 2 weeks after LDLT and pan-lobular ballooning of the hepatocytes are key factors for identifying cholestatic hepatitis C.

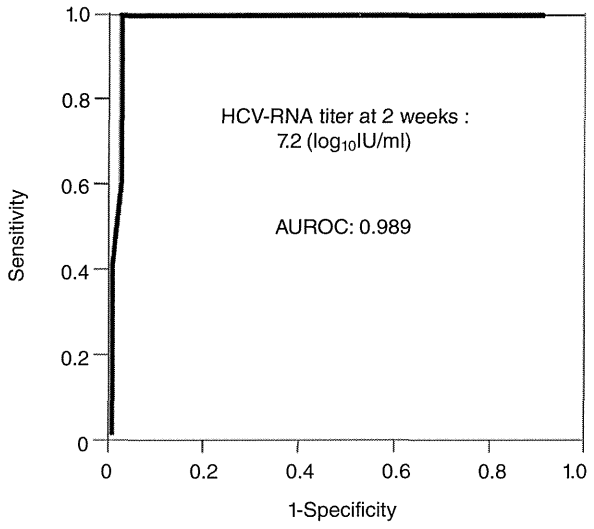


**Figure 1** Receiver–operator curve analysis showed that HCV RNA titer of more than 7.2 $\log_{10}$IU/mL at 2 weeks after LDLT was the optimal cut-off for discriminating cholestatic hepatitis C. AUROC, area under the receiver–operator curve; HCV, hepatitis C virus; LDLT, living-donor liver transplantations.

Extensive HCV infection in hepatocytes and the direct cytopathological effects of HCV, together with a relative absence of inflammation, are thought to be the major mechanisms involved in the development of cholestatic hepatitis C.[17] Therefore, a very high HCV RNA titer was proposed as one of the diagnostic criteria for cholestatic hepatitis after LT in a consensus statement published in 2003.[13] However, the cut-off level for a very high HCV RNA titer was not reported in that consensus statement. More recently, Shackel *et al.*[18] reported that a peak HCV RNA titer of more than 7.0 $\log_{10}$IU/mL within 1 year of LT was a predictor of HCV-associated graft failure. Moreover, Granziadei *et al.*[5] showed that HCV RNA titer of more than 6.0 $\log_{10}$IU/mL 2 weeks after transplantation is the most significant risk factor for the development of cholestatic hepatitis. However, they did not report how they selected this value. We used ROC analysis and found that a HCV RNA titer of more than 7.2 $\log_{10}$IU/mL at 2 weeks after LDLT was the optimal cut-off for predicting cholestatic hepatitis C after transplantation.

Histological features are also important for the diagnosis of cholestatic hepatitis C.[3,14] Hepatocyte ballooning with limited inflammation is considered to be a typical finding, and it was observed in all of our cases with pan-lobular distribution. However, the international consensus criteria stated that ballooning predominantly occurred in the perivenular zone.[14] In LDLT, perivenular hepatocyte ballooning with cholestasis is often observed in dysfunctional grafts associated with small graft size, older donor or systemic inflammation.[19] Hepatocyte cholestasis was apparent in just one case (20%) in our series, and it might be attributed to the early biopsy before becoming fully established and irreversible.

Perivenulitis with centrilobular hepatocyte dropouts is a distinct histopathological process that could occur after LT, and is associated with post-transplant processes, including cytotoxic drugs, acute or chronic rejection, recurrent or de novo autoimmune hepatitis, and viral hepatitis.[20] Recent research focused on its immunological significance with significant graft injuries.[21] In hepatitis C after LT, Khettry *et al.*[22] reported that perivenulitis was significantly recognized in cases with severe recurrent hepatitis C associated with other pathological features with autoimmune hepatitis. Antonini *et al.*[23] reported that this phenomenon was more common in cholestatic patients than in non-cholestatic patients (36% vs 4%). Taking into account that cholestatic type recurrent hepatitis C causes significant hepatocyte injuries with vigorous cytokine production with unspecified immune reactions,[20–23] perivenulitis could be a significant pathological marker in cholestatic hepatitis C.

Interleukin-28B genotyping is an important predictor for the viral response to IFN. We previously reported that the T/T genotype of rs8099917 in donors and recipients is a positive predictor of the response to IFN after LDLT for hepatitis C.[12] In the current series, however, the T/T genotype was not associated with the recurrence of cholestatic hepatitis C. By contrast, Graziadei *et al.*[5] reported that rs12979860 genotypes, other than the favorable C/C genotype, in the recipients were significantly associated with cholestatic hepatitis C after LT, although the relevance of rs12979860 in donors has not been exclusively investigated. Hanouneh *et al.*[6] reported that the favorable T/T genotype of rs8099917 in the donor was associated with cholestatic recurrence. Based on these results, no consensus can be reached regarding the impact of IL-28B genotype on recurrence of cholestatic recurrent hepatitis C. Additionally, because there is a discrepancy between the IL-28B genotype, IL-28B transcription and the expression of IFN-stimulated genes,[24] further studies are needed to clarify the role of IL-28B in anti-HCV therapy.

It is still unclear why HCV can infect and replicate so vigorously, and cause cholestatic recurrence in a small number of patients after LT. We consider that

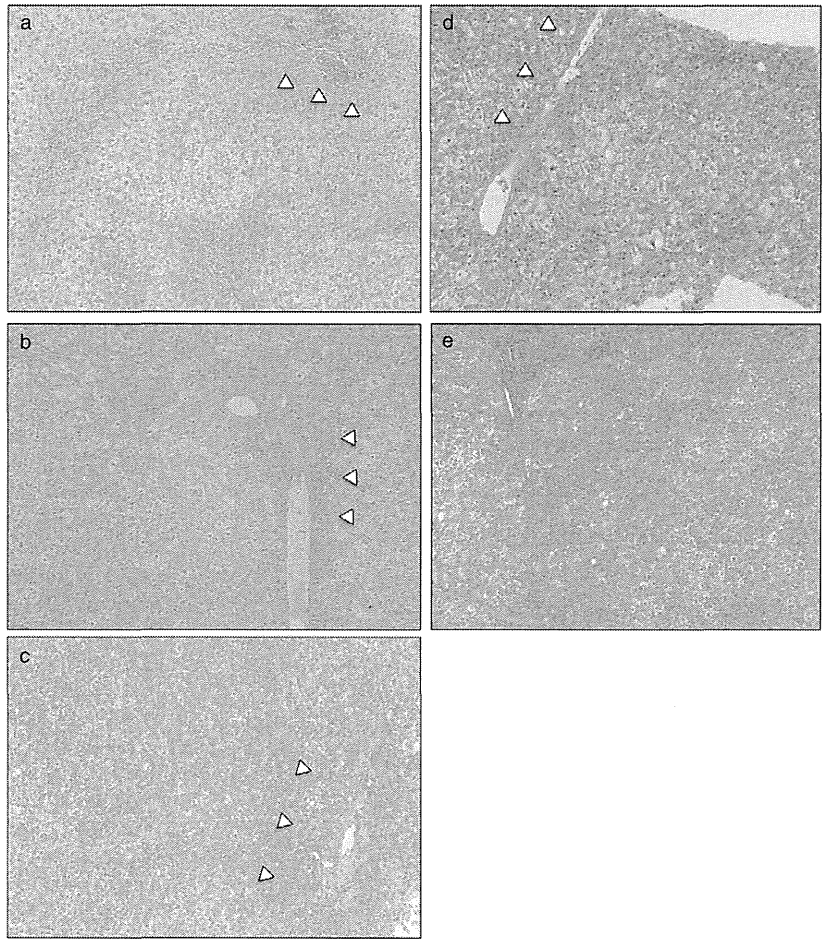


**Figure 2** Histological findings of cases 1–5 (a–e, respectively) with recurrent cholestatic hepatitis C. Pan-lobular hepatocyte ballooning was prominent in all of the five patients. Perivenulitis was observed in cases 1–4 (a–d, white arrowheads) (hematoxylin–eosin, original magnification ×100).

quasispecies of HCV may play some role in this process. Previous studies showed that the number of quasispecies increased following transplantation and onset of mild recurrence, but the species distribution was more homogenous in patients with severe recurrence.[25,26] It was also reported that HCV infection becomes more severe in patients infected with HIV type 1 with decreased or homogenous quasispecies.[23,27] Because an increased number of quasispecies is thought to represent the response of HCV to a strong immune pressure, induction of the local non-specific histocompatibility independent immune system may also mediate the disease process. Although viral mutations with increased capability of antiviral drug resistance as observed in cholestatic hepatitis B may have roles,[28] we regard it as doing little in cholestatic recurrent hepatitis C after LT because it becomes evident very early after transplantation before antiviral treatment is initiated. Therefore, we regard mechanisms in higher replication property against natural immune pressure including quasispecies as playing an important role.[23–27]

In terms of treatment, we think that PEG IFN with ribavirin should be the first choice of regimen for cholestatic hepatitis C, considering its clinically relevant outcomes. Nevertheless, the important point is that antiviral treatment should only be initiated once clinical cholestasis is evident, and histological cholestasis and fibrosis are established.[4–6,14] If started too late, the tolerability of IFN may become a major problem for decompensated liver grafts. Satapathy *et al.*[4] reported that seven out of eight patients (88%) with cholestatic hepatitis discontinued IFN because of decompensation or complications. The important key step to initiate early antiviral treatment for cholestatic hepatitis C is the accurate

pathological diagnosis differentiating acute rejection, although it is not an easy task. Bolus steroids for severe hepatitis C could terminate a transplanted graft.[29] Therefore, we maintain an appropriate immunosuppression level for the first 3 months after LT for HCV-associated liver diseases and never perform rapid tapering, making pathological interpretation easier. If treatment is started early, routine splenectomy of HCV patients during LDLT is reported to increase their tolerability of intense antiviral therapies.[9]

In conclusion, HCV viremia of more than 7.2 $\log_{10}$IU/mL at 2 weeks after transplantation was the predictor of recurrent cholestatic hepatitis C after LDLT in this study. IL-28B (rs8099917) genotype and other donor and recipient factors were not associated with its recurrence. Early diagnosis followed by antiviral treatment using PEG IFN with ribavirin is important to achieve VR and graft survival.

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***Original Article***

# Clinical usefulness of $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography for patients with primary liver cancer with special reference to rare histological types, hepatocellular carcinoma with sarcomatous change and combined hepatocellular and cholangiocarcinoma

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*Aim:* The role of $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET) in the diagnosis and staging of primary liver cancer has been demonstrated in several reports. However, no preoperative evaluations of sarcomatous hepatocellular carcinoma (HCC) and combined hepatocellular and cholangiocarcinoma (cHCC-CC) with FDG-PET have been reported so far.

*Methods:* Fifty-three HCC patients and three cHCC-CC patients who received liver resection or living-donor liver transplantation were enrolled in this study. All 56 patients had undergone preoperative FDG-PET, and a total of 67 HCC and three cHCC-CC were analyzed histologically. The relationship between clinicopathological features and the maximum standardized uptake value (SUVmax) of tumors were evaluated.

*Results:* The detection rate of HCC by FDG-PET was 43.3 %, and the sensitivity of FDG-PET for the detection of HCC was significantly associated with tumor differentiation, tumor size and microvascular invasion. All three cHCC-CC were detected by FDG-PET. The SUVmax values of the three sarcomatous HCC (SUVmax 14.1, 18.6 and 25.0) and the three cHCC-CC (SUVmax 9.9, 12.0 and 13.0) were higher than that of the poorly differentiated HCC (mean SUVmax 5.7 ± 2.3).

*Conclusion:* SUVmax may be a useful diagnostic tool for the preoperative evaluation of the aggressiveness of primary liver cancers such as sarcomatous HCC and cHCC-CC.

**Key words:** $^{18}$F-fluorodeoxyglucose positron emission tomography, combined hepatocellular and cholangiocarcinoma, hepatocellular carcinoma, sarcomatous hepatocellular carcinoma

## INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) using $^{18}$F-fluorodeoxyglucose (FDG) has become standard procedure for the detection of a variety of malignant tumors.[1] It is considered a useful diagnostic tool for tumor characterization and assessing therapy response.[2] For hepatocellular carcinoma (HCC), however, several reports suggest that the sensitivity of FDG-PET (50–55%) is insufficient.[3,4] Because the enzymatic activity of well-differentiated HCC cells is similar to that of the surrounding normal liver, the accumulation of FDG in these tumors is low, and the role of FDG-PET imaging in the early detection of HCC is limited.[5] On the other hand, previous studies have demonstrated that FDG accumulation is increased in undifferentiated HCC, and recently, preoperative FDG-PET has been shown to be closely associated with tumor differentiation and prognosis in HCC patients.[6,7]

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The histological differentiation grade is an important prognostic factor for HCC.[8] Once cancer is established, HCC dedifferentiates to a more malignant histology in a multistep fashion, from well- and moderately to poorly differentiated tumors.[9] Although the prognosis of well-differentiated HCC is good following resection, poorly differentiated HCC have a poor prognosis due to a high rate of vascular invasion and metastasis.[10,11] The basic histological pattern of HCC is trabecular; however, a sarcomatous appearance has been sporadically reported as one of the histological features of HCC.[12] Approximately 1.8% of all resected HCC have a sarcomatous feature, usually associated with a very poor prognosis because of its rapid growth, low resectability and frequent recurrence after resection.[13,14]

Combined hepatocellular and cholangiocarcinoma (cHCC-CC) is a rare primary liver cancer that contains the histological features of both HCC and CC.[15] cHCC-CC has been reported to show frequent vascular invasion and lymph nodes metastasis, and has a poorer prognosis than HCC.[16,17] It is difficult for patients with cHCC-CC to get a correct preoperative diagnosis because of the lack of a sensitive diagnosis procedure.[18]

Although previous studies have shown that FDG-PET is useful for evaluating various liver tumors, there have been no reports regarding preoperative FDG uptake in resectable sarcomatous HCC and cHCC-CC. In the present study, we retrospectively investigated the feasibility of FDG-PET for the detection of different types of primary liver cancer including sarcomatous HCC and cHCC-CC.

## METHODS

### Patients

IN THIS STUDY, we retrospectively reviewed 53 HCC patients and three cHCC-CC patients who received liver resection (LR) or living-donor liver transplantation (LDLT) at Kyushu University Hospital between April 2010 and August 2011. There were 35 male and 21 female patients, and the mean age (± standard deviation [SD]) of the patients was 65 ± 12 years (range, 36–87). All 56 patients were diagnosed as having HCC or cHCC-CC by conventional radiologic imaging and FDG PET/computed tomography (CT). Thirteen patients with HCC in cirrhosis underwent LDLT, and the other 43 patients with HCC or cHCC-CC underwent LR. Among the HCC patients, 29 had a single lesion, and the other 24 had multiple lesions. Among the cHCC-CC patients, one had a single lesion and the other two had multiple lesions.

### Patient follow up

After discharge, all patients were examined for recurrence by ultrasound and by tumor markers every 1–3 months. Dynamic CT was performed every 6 months. Patients with any sign of recurrence and/or inconclusive imaging studies underwent additional FDG PET/CT. All of the patients were followed up while they were alive.

### FDG PET/CT

$^{18}$F-Fluorodeoxyglucose positron emission tomography studies were performed with Discovery ST Elite (GE Healthcare, Milwaukee, WI, USA) and Biograph mCT (Siemens AG, Erlangen, Germany) PET/CT scanners. All patients fasted for at least 4 h before FDG administration, and 185 MBq of FDG was i.v. administrated to each patient. Approximately 60 min after the FDG injection, whole-body PET images were acquired from thigh to head with 7–10 bed positions. The Discovery ST Elite scanner consists of a 16-slice multidetector CT and bismuth germanium oxide crystal. The unenhanced CT was performed first with the following parameters: 5-mm slice thickness, 120 kV, 30–250 mAs with auto mode (Smart mA). Then, PET images were obtained in 3-D mode for 3 min per bed position with a 3.27-mm slice thickness, at 70 cm field of view (FOV) in a 128 × 128 matrix. Based on the CT data, transmission maps were created and used for the attenuation correction of the PET images. The PET data were reconstructed using a 3-D ordered subset expectation maximization (3D-OSEM) algorithm (VUE Point Plus) with two iterations and 28 ordered subsets. A 6-mm post-filter of full-width at half maximum (FWHM) was applied. The Biograph mCT scanner is equipped with a 128-slice multidetector CT and lutetium crystal. The unenhanced CT was performed at 120 kV with automatic mAs adjustment (Care Dose 4D) and the slice thickness was 3 mm. The PET emission time was 2 min per bed position. The PET images were acquired with a 2-mm slice thickness, at 70 cm FOV in a 256 × 256 matrix. The concomitant CT data were used for attenuation correction. The PET data were reconstructed using a 3D-OSEM algorithm with two iterations and 21 subsets. Time of flight and point spread function techniques were also used for the image reconstruction (ultra-HD-PET). A 3-D Gaussian filter of 6-mm FWHM was applied. The PET images were qualitatively evaluated to assess whether the FDG uptake in the tumor was (PET positive status) or was not

(PET negative status) significantly higher than in the surrounding non-cancerous hepatic parenchyma.

### Histopathological study

A total of 67 HCC and three cHCC-CC were evaluated histologically. Formalin-fixed specimens were embedded in paraffin. Deparaffinized 4-μm sections were stained with hematoxylin–eosin for microscopic evaluation. The histopathological definition of HCC and the criteria for cHCC-CC were based on the classification proposed by the World Health Organization. The cHCC-CC contain unequivocal hepatocellular and cholangiocellular components that are intimately admixed. The HCC displayed a trabecular pattern with little stroma, a pseudoglandular pattern with or without bile production, abundant eosinophilic cytoplasm, and immunoreactivity for Hep par 1. The CC was defined by a definite glandular pattern with fibrous stroma, low columnar cells with round vesicular nuclei, mucin production confirmed by Alcian blue, and immunoreactivity for cytokeratin 19 but not Hep par 1.

### Statistical analysis

All statistical analyses were performed using the StatView ver. 5.0 software package. Continuous variables were compared using the Mann–Whitney *U*-test or Student's *t*-test. The $\chi^2$-test was used for categorical variables. The differences were considered to be significant if $P < 0.05$.

## RESULTS

### Patients with HCC

PATIENT CHARACTERISTICS ARE summarized in Table 1(a). The mean age (± SD) was 66 ± 12 years (range, 36–87), and the sex ratio (M : F) was 32:21. Thirty-two patients (60.4%) were seropositive for hepatitis C virus, 11 for hepatitis B surface antigen (20.8%) and 10 (18.8%) had non-B/non-C etiologies. Twelve of the 53 patients had a serum α-fetoprotein (AFP) level of more than 100 ng/mL (median, 11.8; range, 1.6–994 600) and 24 patients had a serum des-γ-carboxy prothrombin (DCP) level above 100 mAU/mL (median, 81; range, 10–109 730). Twenty-nine patients with solitary tumors were divided into two groups: PET positive ($n = 16$) and PET negative ($n = 13$). Although there was no significant difference in serum AFP levels between the PET positive and negative groups (110.2 ± 196.9 and 132.9 ± 372.7 ng/mL, respectively), the PET positive group had higher serum

**Table 1** Characteristics of patients with HCC and clinicopathological data of HCC

a. Characteristics of patients with HCC

| Characteristic | No. of patients (%) |
|---|---|
| Total number of patients | 53 |
| Age (years) | |
| Mean (range) | 66 (36–87) |
| Sex | |
| Male : female | 32 (60.4):21 (39.6) |
| Etiology of liver disease | |
| Hepatitis B | 11 (20.8) |
| Hepatitis C | 32 (60.4) |
| Other | 10 (18.8) |
| Child–Pugh classification | |
| A | 40 (75.5) |
| B | 6 (11.3) |
| C | 7 (13.2) |
| Tumor stage (UICC) | |
| I | 21 (39.6) |
| II | 25 (47.2) |
| III | 5 (9.4) |
| IV | 2 (3.8) |
| Type of hepatic surgery | |
| Resection | 40 (75.5) |
| Liver transplantation | 13 (24.5) |
| Tumor number | |
| Solitary | 29 (54.7) |
| Multiple | 24 (45.3) |
| Preoperative serum AFP (ng/mL) | |
| Median (range) | 11.8 (1.6–99 4600) |
| Preoperative serum DCP (mAU/mL) | |
| Median (range) | 81 (10–109 730) |

b. Clinicopathological data of HCC

| Characteristic | No. of HCC (%) |
|---|---|
| Total number of nodules | 67 |
| Tumor differentiation | |
| Well | 7 (10.4) |
| Moderately | 47 (70.1) |
| Poorly | 9 (13.4) |
| Undifferentiated | 1 (1.5) |
| Moderately with sarcomatous change | 1 (1.5) |
| Poorly with sarcomatous change | 2 (3.0) |
| Tumor size (cm) | |
| Mean ± SD | 3.4 ± 3.4 |
| Microvascular invasion | 16 (23.9) |

AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HCC, hepatocellular carcinoma; SD, standard deviation; UICC, Union for International Cancer Control.

**Table 2** Association between PET status and clinicopathological data of HCC

| Characteristic | PET negative ($n = 38$) | PET positive ($n = 29$) | *P*-value |
|---|---|---|---|
| Tumor differentiation (%) | | | <0.05 |
| Well | 7 (100) | 0 (0) | |
| Moderately | 31 (66) | 16 (34) | |
| Poorly | 0 (0) | 9 (100) | |
| Undifferentiated | 0 (0) | 1 (100) | |
| Moderately with sarcomatous change | 0 (0) | 1 (100) | |
| Poorly with sarcomatous change | 0 (0) | 2 (100) | |
| Tumor size (cm) | | | |
| Mean ± SD | 2.1 ± 1.5 | 5.1 ± 4.3 | <0.05 |
| Microvascular invasion (%) | 4 (11) | 12 (41) | <0.05 |

HCC, hepatocellular carcinoma; PET, positron emission tomography; SD, standard deviation; UICC, Union for International Cancer Control.

DCP levels than the PET negative group (529.6 ± 748.3 and 54.2 ± 50.7 mAU/mL, respectively; $P < 0.05$) (± SD). Using the modified Union for International Cancer Control staging system, we enrolled 21 (39.6%) stage I patients, 25 (47.2%) stage II patients, five (9.4%) stage III patients and two (3.8%) stage IV patients.

The characteristics of HCC are summarized in Table 1(b). The histological grades were well differentiated in seven HCC (10.4%), moderately differentiated in 47 (70.1%), poorly differentiated in nine (13.4%), undifferentiated in one (1.5%), moderately differentiated with sarcomatous change in one (1.5%) and poorly differentiated with sarcomatous change in two (3.0%). Mean tumor size (± SD) was 3.4 ± 3.4 cm, and microvascular invasion was observed in 16 HCC (23.9%). The detection rate of HCC by PET was 43.3%. The sensitivity of PET for the detection of HCC was significantly associated with tumor differentiation, tumor size and microvascular invasion (Table 2). None of the seven well-differentiated HCC were detected by PET. The mean maximum standardized uptake value (SUVmax) (± SD) was 4.7 ± 1.3 in moderately differentiated HCC with positive PET findings, 5.7 ± 2.3 in poorly differentiated HCC and 26.2 in undifferentiated HCC. One poorly differentiated HCC with a maximum diameter of 17.0 cm, direct invasion to the stomach, and lymph node and pulmonary metastases, had a high SUVmax of 11.3. Moderately differentiated HCC with sarcomatous change had a high SUVmax of 18.6, and poorly differentiated HCC with sarcomatous change also showed high FDG uptake (SUVmax 14.1 and 25.0) (Fig. 1). One poorly differentiated HCC with sarcomatous change had a high SUVmax of 14.1 despite the small size of the tumor (1.6 cm) and absence of microvascular invasion (Fig. 2). The patients with poorly differentiated HCC with sarcomatous change developed recurrences soon after surgery. One patient with an SUVmax of 14.1 had metastasis to the mediastinal lymph nodes 9 months after surgery, and another with an SUVmax of 25.0 developed intrahepatic metastasis 44 days after surgery.

## Patients with cHCC-CC

Patient characteristics are summarized in Table 3. All three cHCC-CC were detected by PET and the SUVmax

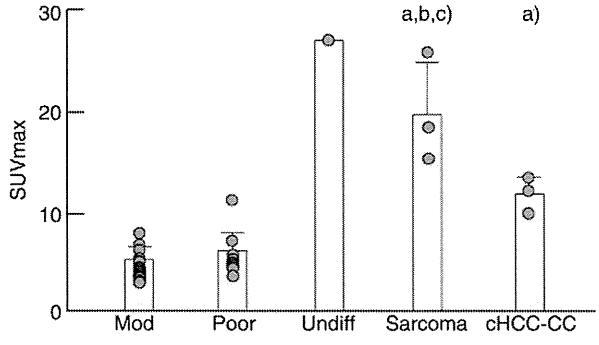


**Figure 1** Maximum standardized uptake value (SUVmax) values of hepatocellular carcinoma (HCC) and combined hepatocellular and cholangiocarcinoma (cHCC-CC) with positive positron emission tomography (PET) findings. Undifferentiated HCC, moderately or poorly differentiated HCC with sarcomatous change, and cHCC-CC have high SUVmax values (>9.9), respectively. Data are expressed as mean ± standard deviation. (a) $P < 0.05$ vs mod; (b) $P < 0.05$ vs poor; (c) $P < 0.05$ vs cHCC-CC. Mod, moderately differentiated HCC; poor, poorly differentiated HCC; undiff, undifferentiated HCC; sarcoma, moderately or poorly differentiated HCC with sarcomatous change.

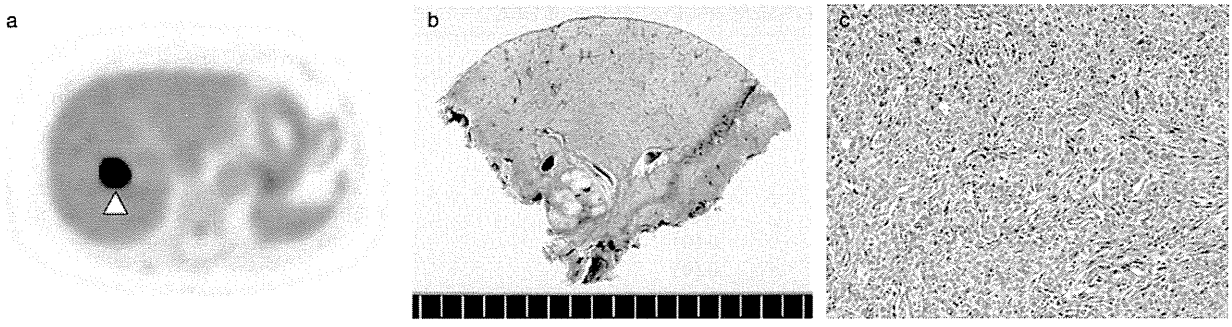


**Figure 2** A 74-year-old female patient with poorly differentiated hepatocellular carcinoma (HCC) with sarcomatous change. (a) $^{18}$F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) image shows a liver mass with a maximum standardized uptake value (SUVmax) of 14.1 (arrow head). (b) Macroscopic image of the liver mass. (c) The liver tumor demonstrates histological features of poorly differentiated HCC with sarcomatous change (hematoxylin–eosin, original magnification ×100).

of cHCC-CC was 9.9, 12.0 and 13.0 (Fig. 1). One cHCC-CC had a high FDG uptake (SUVmax 12.0) despite the small size of the tumor (2.2 cm) and low levels of tumor markers (patient no. 1) (Fig. 3).

## DISCUSSION

THE ROLE OF FDG PET/CT in the diagnosis and staging of HCC and other forms of liver cancer has been demonstrated in several reports.[6,7,19] However, preoperative evaluation of sarcomatous HCC and cHCC-CC with FDG PET/CT has not been reported so far. In the present study, we showed that sarcomatous HCC and cHCC-CC could be detected by PET/CT with high FDG uptake, and positive preoperative FDG uptake in HCC was significantly associated with tumor differentiation, tumor size and microvascular invasion.

Recently, several studies have shown that FDG-PET is useful for predicting tumor characterization, clinical outcome and prognosis in patients with HCC. Well-differentiated HCC regions were reported to show a tendency toward negativity by PET, whereas poorly differentiated types show increased FDG accumulation.[6,7] Our data also demonstrate that well-differentiated and some moderately differentiated HCC do not show FDG uptake exceeding that of the surrounding normal liver, whereas poorly differentiated and undifferentiated HCC have positive PET findings. There was no significant difference between the mean SUVmax of poorly differentiated HCC and that of moderately differentiated HCC with positive PET findings. On the other hand, the SUVmax of sarcomatous HCC were 18.6, 14.1 and 25.0, much higher than that of poorly differentiated HCC.

**Table 3** Characteristics of patients with cHCC-CC

| Characteristic | Patient no. 1 | Patient no. 2 | Patient no. 3 |
|---|---|---|---|
| Age (years)/sex | 78/M | 54/M | 47/M |
| Viral infection | HBsAg positive | Negative | HCVAb positive |
| Maximal tumor size (cm) | 2.2 | 12.3 | 4.0 |
| Microvascular invasion | Positive | Positive | Positive |
| Tumor stage (UICC) | II | IV | III |
| AFP (ng/mL) | 4.3 | 16.4 | 18 286 |
| DCP (mAU/mL) | 20 | 45 | 231 |
| CEA (ng/mL) | 1.7 | 0.5 | 2.8 |
| CA19-9 (U/mL) | 7.4 | 76.6 | 31.9 |
| Maximum SUV | 12.0 | 9.9 | 13.0 |

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; DCP, des-γ-carboxy prothrombin; HBsAg, hepatitis B surface antigen; HCVAb, anti-hepatitis C virus antibody; SUV, standardized uptake value; UICC, Union for International Cancer Control.

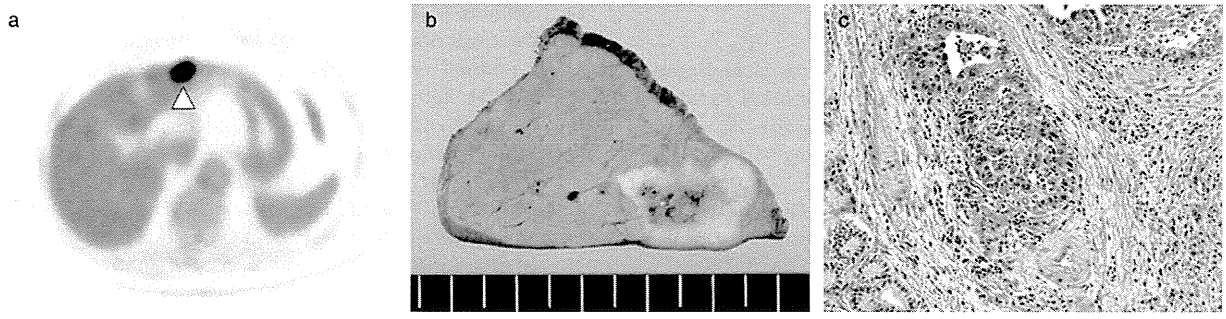


**Figure 3** A 78-year-old male patient with combined hepatocellular and cholangiocarcinoma (cHCC-CC). (a) $^{8}$F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) image shows a liver mass with a maximum standardized uptake value (SUVmax) of 12.0 (arrow head). (b) Macroscopic image of the liver mass. (c) The liver tumor demonstrates histological features of cHCC-CC with microvascular invasion (hematoxylin–eosin, original magnification ×100).

Sarcomatous HCC is a rare histological variant of HCC.[13] Although the pathogenesis of sarcomatous HCC has not been clarified, the sarcomatous components are thought to be derived from a dedifferentiation or anaplasia, rather than from a combination of HCC and sarcoma.[13,20] Previous reports have suggested that anticancer therapy has an influence on the development of sarcomatous features in HCC, and the prognosis of patients with sarcomatous HCC is very poor due to frequent widespread metastases.[13,14,21] Although we performed curative resection for primary sarcomatous HCC, two of the three patients developed recurrences soon after surgery. Honda *et al.* reported that sarcomatous HCC appears as an irregularly demarcated intrahepatic mass with delayed or prolonged peripheral enhancement on CT.[22] However, it seemed to be difficult to make a correct preoperative diagnosis of sarcomatous changes by imaging or serological tumor markers. Our results show that FDG-PET may be a useful diagnostic tool for sarcomatous changes of HCC because the high FDG uptake of sarcomatous HCC seems to be related to its progression or aggressiveness.

In the present study, the SUVmax values of three cHCC-CC were higher than those of the poorly differentiated HCC. cHCC-CC is an uncommon subtype of primary liver cancer that contains elements of both HCC and CC.[15] Several studies have reported that the prognosis of patients with cHCC-CC was worse than that of patients with HCC because of frequent portal venous invasion and metastasis to lymph nodes and other organs.[16,17] Vascular invasion, tumor size and tumor stage were found to be prognostic factors for poor outcome in patients with cHCC-CC.[16,23] Moreover, recent studies have demonstrated that a large CC component in cHCC-CC and a high serum carbohydrate antigen 19-9 (CA19-9) level were also associated with poorer survival rates.[24,25] We demonstrated that one cHCC-CC showed high FDG uptake (SUVmax 12.0) despite the low CA19-9 level (7.4 U/mL) and small size of the tumor (2.2 cm) (patient no. 1). In addition, another cHCC-CC showed high FDG uptake (SUVmax 13.0) despite the small CC component in the tumor (1%) (patient no. 3) (data not shown). If the degree of FDG uptake in cHCC-CC also reflects the aggressiveness of the tumor like other malignant tumors, FDG-PET may become a useful diagnostic tool for the preoperative evaluation of cHCC-CC.

Our data show that the SUVmax of sarcomatous HCC and cHCC-CC are much higher than those of liver cancers reported to be associated with poor prognosis in previous studies. Seo *et al.* have demonstrated that high FDG uptake (SUVmax ≥5.0) was a predictive factor of postoperative early recurrence and poor survival in patients with HCC.[7] Riedl *et al.* have also reported that an SUVmax of 5.0 or greater was correlated with worse long-term prognosis after liver resection for colorectal metastases.[26]

In summary, our studies demonstrate that FDG-PET shows high FDG uptake in sarcomatous HCC and cHCC-CC that have been reported to be associated with poor prognosis after surgery. Therefore, FDG-PET may be an effective diagnostic tool for the non-invasive evaluation of the aggressiveness of primary liver cancer before surgical resection and liver transplantation. Further clinical studies are warranted.

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CASE REPORT

# Renoportal anastomosis in right lobe living donor liver transplantation: report of a case

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**Abstract** End-stage liver disease is often accompanied by thrombosis of the portal vein and the formation of splanchnic collateral vessels. Successful liver transplantation in such situations is more likely if the surgeon uses a strategy to establish a graft inflow. A 59-year-old male with a decompensated liver secondary to idiopathic portal hypertension underwent living donor liver transplantation (LDLT) using a right lobe liver graft donated from his son. His portal venous trunk was atrophied and a splenorenal shunt drained the mesenteric venous flow into the systemic circulation. LDLT was performed with renoportal anastomosis (RPA) using his right internal jugular vein as an interposed venous graft, without dissecting the collateral vessels. Although he developed temporary functional hyperbilirubinemia, he was discharged from the hospital 23 days after LDLT. This case suggests that RPA is a useful technique to manage patients with an obstructed portal vein and a splenorenal shunt.

**Keywords** Living donor liver transplantation · Portal vein thrombosis · Splenorenal shunt

**Abbreviations**

| | |
|---|---|
| LDLT | Living donor liver transplantation |
| LRV | Left renal vein |
| PV | Portal vein |
| RPA | Renoportal anastomosis |
| SRS | Splenorenal shunt |

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## Introduction

End-stage liver disease is often accompanied by thrombosis or atrophy of the portal vein (PV) or inferior vena cava, thus resulting in the formation of splanchnic collateral vessels [1, 2]. Although such complications are considered to be difficult to overcome, recent improvements in surgical techniques have allowed these conditions to be operable [2, 3]. Recent innovations in the surgical techniques for thrombosis or atrophy of the PV include portal venous thrombectomy, resection and reconstruction of the atrophied PV, or placement of a graft to bridge the mesenteric vein and the graft PV [4]. Renoportal anastomosis (RPA) is a strategy to establish a portal inflow in patients with an occluded portal inflow in patients undergoing liver transplantation and was first described by Kato et al. [3]. Despite the rationale for this technique, anastomosis has been reported in very few cases. This report presents a case in which RPA was performed using the patient's internal jugular vein during right lobe living donor liver transplantation (LDLT). The report also discusses the relevance of this technique to LDLT and examines the feature of each vein graft used in RPA.

## A case report

A 59-year-old male was referred to our hospital for possible LDLT because of a decompensated liver. He was negative for viral hepatitis markers, including hepatitis B

and hepatitis C, or immune-mediated hepatic disorders, and was thought to have cryptogenic cirrhosis of an unknown origin. He had a history of ruptured esophageal varices that were treated by endoscopic sclerotherapy and subsequent partial splenic embolization. His hepatic profiles was: total bilirubin 2.9 mg/dl, albumin 2.0 g/dl, aspirate aminotransferase 44 IU/l, alanine aminotransferase 22 IU/l, creatinine 0.9 mg/dl, international normalized ratio 1.71, ammonia 100 μg/dl, white blood cell count 5,500 cells/μl, hemoglobin 13.4 g/dl, and platelet count 6.8 × $10^4$ cells/μl. His Child-Pugh score was 11 (Grade C), and his model for end-stage liver disease score was 16. Abdominal computed tomography (CT) showed atrophy of the PV, an active splenorenal shunt (SRS) draining from the splenic vein into the left renal vein (LRV) via the left adrenal vein, and a deformed spleen because of the prior partial splenic embolization (Fig. 1). The donor was the 31-year-old son of the patient and had the identical blood type. He had no prior medical problems and his liver function tests were normal.

LDLT was started with the patient placed in a supine position with neck extension. A longitudinal incision was created on the right side of the neck and was deepened at the medial border of the sternocleidomastoid muscle. The right internal jugular vein was identified, taped, isolated from the surrounding tissue, and then removed. The length of the obtained internal jugular vein was 8 cm. The abdomen was opened via a bilateral subcostal incision with a midline extension. Total hepatectomy was performed as described elsewhere [5].

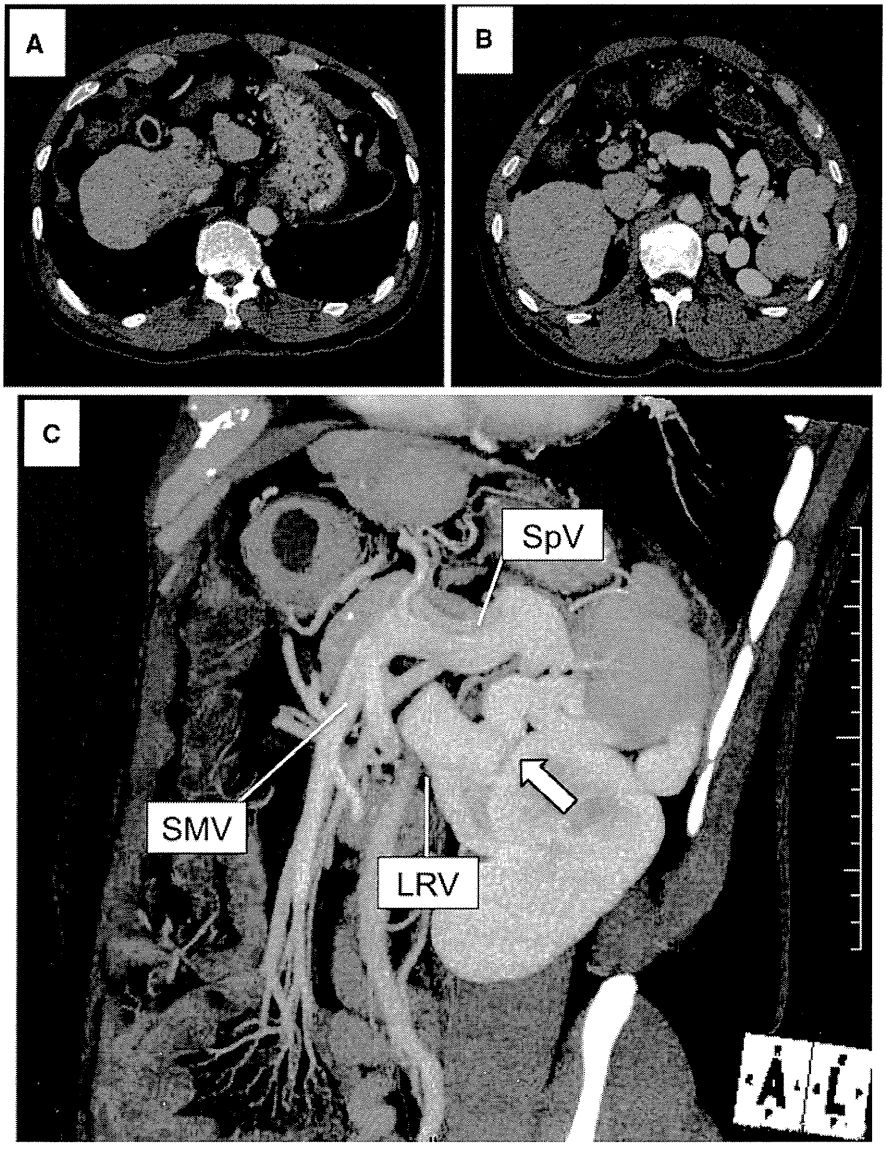


**Fig. 1** Abdominal CT scans showing (**a**) atrophy of the liver with minimum portal flow and (**b**) a highly active splenorenal shunt with a deformed spleen. **c** Maximum intensity projection image. The *white arrow* indicates the junction of the splenorenal shunt into the LRV. *SMV* Superior mesenteric vein, *LRV* left renal vein, *SpV* splenic vein

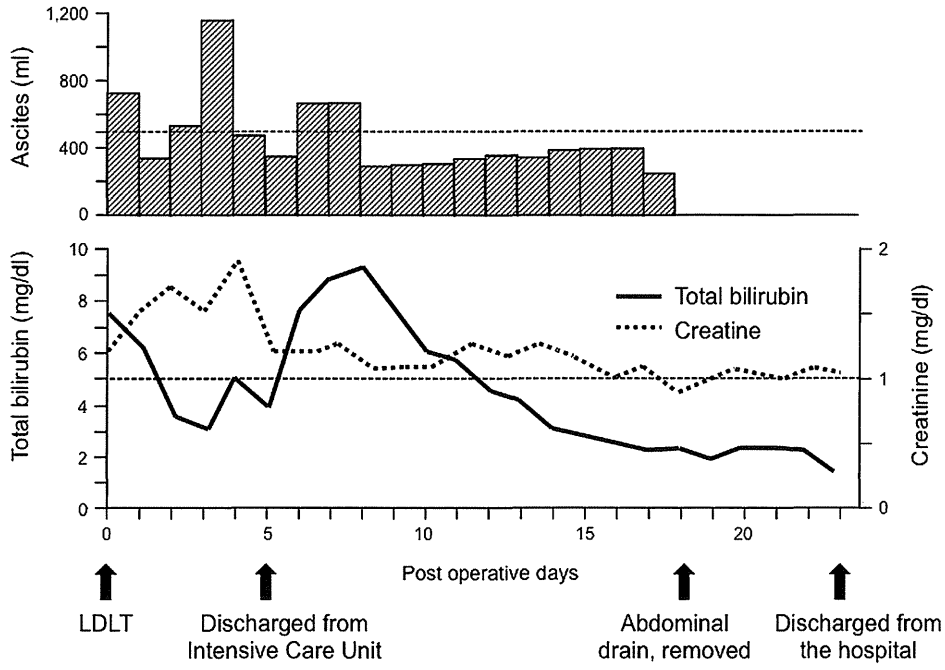


**Fig. 2** Postoperative course. The patient showed a temporary increase in the output of ascites and hyperbilirubinemia

The right lobe LDLT graft donated from his son weighed 580 g, representing 44.1 % of the calculated standard liver volume. The graft had a right hepatic vein and a V5 vein for venous drainage. The opening of the V5 was anastomosed to the manually dilated explanted PV, which was connected to the right hepatic vein in a side-to-side fashion, to enable one-step venous anastomosis. A venovenous bypass was used for circulatory stabilization during the anhepatic phase.

The second portion of the duodenum was mobilized from the retroperitoneum and the LRV was identified and controlled with a tape, clamped, and divided. The supra- and infra-hepatic vena cava was clamped and total hepatectomy was performed. The right lobe graft was placed in the body and venous anastomosis between the conduit of the graft venous system and the vena cava was performed using continuous 5-0 PDS sutures. The right internal jugular vein was anastomosed to the LRV using continuous 6-0 PDS sutures coated with growth factor. The interposed jugular vein was then connected to the grafted PV. Reperfusion was initiated and the circulatory system remained stable. The cold, warm and anhepatic times were 150 min, 44 min and 284 min, respectively. Portal venous pressure at the end of surgery was 24 mmHg. The total surgical time and operative blood loss were 819 min and 6.3 L, respectively.

The patient's post-transplant course is shown in Fig. 2. Although the patient temporarily showed an increased output of ascites and hyperbilirubinemia, he was discharged from the hospital on postoperative day 23 with normal liver function tests. CT showed a patent smooth portal venous flow from the persistent large SRS scans at 4 months after surgery (Fig. 3).

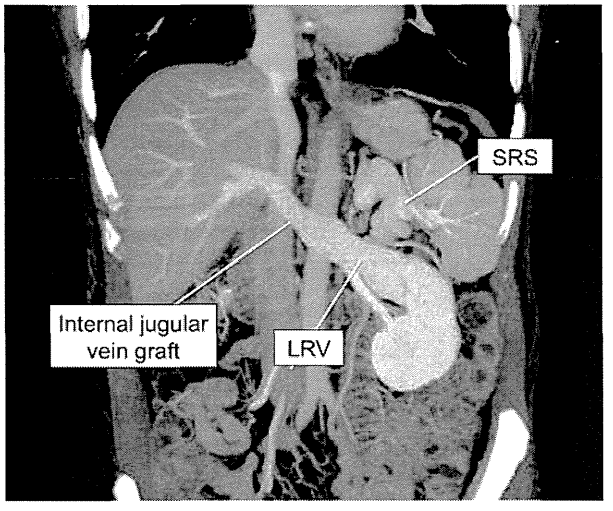


**Fig. 3** Maximum intensity projection image taken 4 months after transplantation. *LRV* Left renal vein, *SRS* splenorenal shunt

## Discussion

Thrombectomy or patch plasty of the PV followed by direct anastomosis between the graft and recipient PV may be possible for most patients with thrombosis or atrophy of the PV [4]. However, establishing an appropriate portal flow capacity is essential to prevent re-thrombosis of the

anastomosed PV or graft dysfunction because of the decreased portal inflow [5]. The obstruction of these vessels is necessary to prevent the occurrence of steal phenomenon in patients with major porto-systemic shunt vessels. However, the ligation of such large and fragile shunt vessels in a deep surgical field is technically difficult and may cause significant bleeding, morbidity or mortality [6].

RPA offers one solution to establish graft inflow in patients with a large SRS and either an occluded or markedly reduced portal inflow, using an anomalous shunt [7]. Marubashi et al. [8] first reported three patients who underwent this technique during LDLT. Moon et al. [9] used a prosthetic graft in an end-to-side fashion to establish a renoportal connection, and thus achieved an excellent graft function. However, a prosthetic graft has the disadvantage of its thickness and rigidity, and the patients must receive aspirin daily to prevent prosthetic graft thrombosis. Furthermore, they have the risk of developing prosthetic infection caused by immunosuppressant. Table 1 is the respective data of the variations in vein grafts. The internal jugular vein is used in this department. The removal of the internal jugular vein does not have any harmful effects on the central nervous system. An external iliac vein is usually 7–8 cm and shorter than the internal jugular vein. The main advantage of creating a RPA is that manipulation or dissection around the large and fragile shunt vessels is unnecessary. Moreover, an adequate blood flow into the graft is guaranteed, which drains from the mesenteric and left renal system. The PV flow/graft volume ratio in this case was 2.90 ml/min, which is considered to be an acceptable score.

However, this technique does have some disadvantages in comparison to direct portal anastomosis. First, an excessive inflow caused by the addition of a left venous return into a graft is possible after LDLT, in which a smaller graft is implanted. Graft dysfunction caused by an excessive portal inflow has been called small-for-size syndrome, and it is characterized by the production of persistent ascites and prolonged hyperbilirubinemia [10]. The present patient's maximum output of ascites was 1 L on postoperative day 4 and his maximum total bilirubin concentration was 9.4 mg/dl on postoperative day 8. Although these values do not necessarily indicate small-for-seize graft syndrome, the post-operative clinical characteristics of the present recipient, including a model for end-stage liver disease score of 16 and a sufficient graft volume/standard liver volume ratio of 44.1 %, are consistent with graft over-perfusion syndrome.

Possible congestion of the left kidney may be another disadvantage of RPA. The serum creatinine levels were elevated for 1 week, in the present patient with levels reaching 2.0 mg/dl. However, Lee et al. [11] reported that manipulation of the outflow of the LRV after the ligation of the proximal LRV in patients with a large SRS causes only a temporary renal impairment. These surgical procedures caused a temporary renal impairment in the present case, and the creatinine levels returned to the normal range within 1 month after LDLT.

Finally, the indications for RPA in patients with hepatitis C are considered to be another topic for debate. In our institute, splenectomy is suggested for patients undergoing LDLT for hepatitis C to treat hypersplenism and facilitate

**Table 1** Primary disease, graft type, venous graft, and prognosis of patients that underwent RPA during LTx renoportal anastomosis in adult-to-adult living donor liver transplantation

| Reference | Primary disease | Liver graft | GV/SLV (%) | GRWR | Vascular graft | Technique | Complications |
|---|---|---|---|---|---|---|---|
| Marubashi et al. [8] | PSC | Right | 56 | N/A | Jugular vein | End-to-end | Ascites |
| | Cryptogenic | Right | 49 | N/A | Jugular vein | End-to-end | – |
| | Wilson | Right | 38 | N/A | Jugular vein | End-to-end | Ascites, pneumonia |
| Moon et al. [15] | Hepatitis B | Right | 46 | N/A | Iliac vein | Side-to-end | Ascites |
| | Hepatitis B, HCC | Right | 73 | N/A | Iliac vein | End-to-end | – |
| | Hepatitis B, HCC | Dual graft (2 left lobe) | 79 | N/A | Iliac vein with IVC | Side-to-end | Cerebral hemorrhage, ascites, decrease of PV flow |
| | Hepatitis B, HCC | Right | 45 | N/A | Aorta | Side-to-end | – |
| | Alcoholic | Right | 52 | N/A | Aorta + GSV | Side-to-end | – |
| Moon et al. [9] | Hepatitis B | Right | N/A | 1.14 | ES-PTFE | Side-to-end | – |
| Present case | IPH | Right | 44.1 | 0.81 | Jugular vein | End-to-end | Ascites, hyperbilirubinemia |

*ES-PTFE* Externally stented polytetrafluoroethylene, *GV* graft volume, *IPH* idiopathic portal hypertension, *N/A* not available, *PSC* primary sclerosing cholangitis, *SLV* standard liver volume, *GRWR* graft-recipient body weight ratio, *IVC* inferior vena cava, *GSV* great saphenous vein

post-transplant interferon treatment for the almost inevitable recurrence of hepatitis C [12]. Persistent hypersplenism in LDLT is a major cause of discounting interferon treatment discontinuation in patients with hepatitis C [12, 13]. Cirrhosis occurs in almost 10–30 % of patients with untreated hepatitis C within 5 years of liver transplantation [14]. Therefore, RPA, in which the spleen stays in place, should not be indicated for patients with hepatitis C. However, RPA may be considered in patients with hepatitis C with severe portal vein stenosis or thrombosis.

In summary, RPA is therefore thought to be a useful option for patients with portal occlusion and large SRS undergoing LDLT, particularly in cases selected based on appropriate indications by carefully considering the limitations of RPA.

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# Nutrition Support and Infections Associated With Hepatic Resection and Liver Transplantation in Patients With Chronic Liver Disease

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### Abstract

Malnutrition is common in liver cirrhotic patients who will undergo liver resection or liver transplantation. A precise evaluation of their nutrition status is thus difficult because of the presence of ascites and the edema caused by their impaired protein synthesis. Both perioperative enteral and parenteral nutrition have benefits in reducing the morbidity and mortality of liver surgery, and in general, oral nutrition supplements are recommended. Branched-chain amino acids (BCAAs) promote protein and glycogen synthesis and regulate immune system function. Synbiotics, a combination of pro- and prebiotics, is reported to enhance immune responses. Oral nutrition support with BCAAs, synbiotics, and an immune-enhancing diet have a beneficial effect on preventing the perioperative infections associated with hepatic resection or liver transplantation. (*JPEN J Parenter Enteral Nutr.* 2013;37:318-326)

### Keywords

nutrition; infection; bacteremia; liver cirrhosis; liver surgery; hepatic resection; liver transplantation; branched-chain amino acids; synbiotics

## Clinical Relevancy Statement

In liver surgery and transplantation, postoperative infection is one of the most important problems that cause postoperative morbidity and mortality. The nutrition therapy may improve the clinical outcome in cirrhotic patients undergoing hepatic surgery and liver transplantation. This review focused on the role of nutrition supports especially on perioperative infection or sepsis.

## Introduction

Malnutrition is a common complication of chronic liver diseases, and it is an independent risk factor for survival in patients with liver cirrhosis.[1-3] Inadequate dietary protein intake may have a deleterious effect on hepatic encephalopathy, nutrition status, and clinical outcome in patients with end-stage liver failure.[4,5] In patients with an indication for liver surgery and/or transplantation, a decreased liver function with nutrition deficiency is common. This poor nutrition status before hepatic resection or transplantation has been suggested to increase the risk of postoperative complications and/or mortality.[6-12] However, other reports suggest that the nutrition parameters and markers of disease severity do not correlate with the outcomes after liver transplantation.[13]

The branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine—are essential amino acids, especially in patients with liver cirrhosis, and may have an effect on hepatic encephalopathy, immunity, and infections.[14-17]

Postoperative infections are one of the most important problems leading to postoperative morbidity and mortality in patients who undergo liver surgery or transplantation.[18] The recipients' preoperative malnutrition is a risk factor that increases infectious complications after liver transplantation.[12,19-21] In fact, several reports have shown that a decreased liver function before liver transplantation may be related to postoperative bacteremia.[22-25] The use of nutrition therapy may improve the clinical outcome in cirrhotic patients undergoing general surgery and liver transplantation.[8]

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This review focuses on the role of nutrition support, especially on the development of perioperative infection or sepsis after hepatic resection and liver transplantation. The reports mainly published after 1995 were assembled and discussed.

### *Prevalence of Malnutrition in Cirrhotic Patients*

Malnutrition develops in patients with cirrhosis independent of the etiology.[6,26] The prevalence of malnutrition is reported to be 50%–90% in cirrhotic patients.[27] A multicenter Italian study including more than 1400 patients with cirrhosis showed malnutrition to be recognized in 20% of patients with Child-Pugh class A and in 50%–60% of patients with Child-Pugh class C.[8,28] Actually, the prevalence of malnutrition in cirrhotic patients may depend on how the nutrition assessment was performed.[8]

### *Mechanisms Responsible for the High Frequency of Infections in Cirrhosis*

Cirrhotic liver patients show a high frequency of infections such as spontaneous bacterial peritonitis (SBP), bacteremia/sepsis, respiratory tract infections, urinary tract infections, meningitis, endocarditis, phlegmonous colitis, and hepatic abscess.[29] Bacterial translocation is reported to be a key mechanism of SBP.[30] The pathogenetic mechanisms of such a high susceptibility of infections may be associated with polymorphonuclear leucocyte dysfunction, complement deficiency, reticuloendothelial system dysfunction, macrophage dysfunction, increased production of interleukins, and decreased tumor necrosis factor (TNF)–α activity.[29]

## Assessment of Nutrition Status

Assessing the nutrition status of patients with liver dysfunction is often difficult because of the fluid collections caused by the impaired protein synthesis in these patients. Weight is not a reliable indicator of malnutrition because of the presence of ascites and edema, which may lead to an increase in body weight despite a reduction in lean body mass.[6] Body mass index (BMI) may afford a more reliable indicator of malnutrition if different cutoff values are used depending on the presence and severity of ascites.[31]

Anthropometry measurements include the triceps skin-fold thickness, mid-arm circumference (MAC), and mid-arm muscle circumference (MAMC), assessing the skeletal muscle mass.[32-34] Subjective global assessment (SGA) is a technique that combines multiple elements of nutrition assessment to classify the severity of malnutrition (Supplement 1).[32,35-37] These components include weight loss during the previous 6 months, changes in dietary intake, gastrointestinal symptoms, functional capacity, metabolic demands, signs of muscle wasting, and the presence of edema in the lower extremities.[35] The SGA is not affected by fluid retention or the formation of ascites.[38] A modified SGA, named the Royal Free Hospital–SGA, combines a subjective assessment of the nutrition status with BMI, MAMC, and dietary intake.[38,39] Assessment of muscle function, determined by measuring hand-grip strength and respiratory muscle strength, has also been used in nutrition evaluation.[12,31,40] Recently, sarcopenia in the lumbar skeletal muscle, as calculated by computed tomography, has been used to evaluate the nutrition state or degree of liver dysfunction.[41] In patients undergoing liver transplantation, it is reported that sarcopenia correlates with post–liver transplant mortality.[42] Concerning muscular status, the level of 3-methylhistidine is a marker of muscular proteolysis and can be used as a nutrition marker.[43]

Depletion of the body cell mass (BCM) is a useful estimation of nutrition status.[11,44] Bioelectrical impedance is a more readily available tool for estimating the BCM.[45] An evaluation of the status of energy metabolism might be a reasonable component of a nutrition assessment because there seems to be a correlation between hypermetabolism and malnutrition.[6]

The concentrations of rapid turnover proteins, such as serum albumin, prealbumin, retinal-binding protein (RBP),[46] and transferrin,[47] may be low because of low levels of synthesis, rather than because of poor nutrition status.[6] Some reports have suggested that alterations in serum albumin level improve both surgical and postsurgical complications of liver transplantation.[48-50] These proteins, especially serum albumin, correlate with liver function and may not be reliable as a nutrition marker in cirrhotic patients.[51] In patients with relatively stable liver disease, rapid turnover proteins may be simple and useful nutrition markers.

Various other measures can indicate the nutrition status. For example, an imbalance in the plasma levels of aromatic amino acids (AAAs) and BCAA, the so-called Fisher's ratio, or the BCAA/tyrosine ratio (BTR) has been demonstrated to have a causal role in hepatic encephalopathy.[52]

The nonprotein respiratory quotient (npRQ), a unitless number estimated from carbon dioxide production, is used to evaluate the nutrition status of patients with liver cirrhosis.[53]

The homeostasis model assessment (HOMA), a method used to quantify insulin resistance and β-cell function,[54,55] has been reported to accurately reflect nutrition status in patients with nonalcoholic fatty liver disease.[55]

Combinations of some anthropometric measurements, physical examinations, and laboratory data can be more reliable to assess nutrition status in patients with relatively stable liver disease who are scheduled to undergo a liver resection. A marker that is not related to the fluid collection, such as sarcopenia, might reliably determine nutrition status in patients with severe liver dysfunction expecting liver transplantation.

## Parenteral Nutrition

In vitro, liver regeneration can be accelerated by administering a parenteral nutrition (PN) solution tailored to normalize the plasma amino acids associated with compromised liver function.[56] Fan et al[57] reported that perioperative intravenous (IV)