Obstructing Spontaneous Major Shunt Vessels Might Not Be Mandatory to Maintain Adequate Portal Inflow in Living Donor Liver Transplantation

We read with great interest the article by Ikegami et al. (*1*), who reported on the necessity of obstructing spontaneous major shunt vessels in living donor liver transplantation (LDLT). Since 2000, all identified major (≥10 mm) portosystemic shunt vessels have been ligated during LDLT to maintain an adequate portal inflow. Good outcomes in managing portal vein (PV) hemodynamics in LDLT support this concept. However, regardless of the size of the portosystemic shunt, we do not always obliterate them during LDLT if there is sufficient portal flow into the graft after reperfusion.

Since 1997, we have performed 187 LDLTs in our hospital. Because we have digital data of imaging studies on computed medical chart, which made it possible for us to measure the diameter of the vessels accurately beginning in 2005, 137 LDLT cases were available for retrospective analysis. Of these, 45 patients had major spontaneous shunt vessels (diameter, ≥10 mm on computed tomography). Of these 45 patients, 8 underwent intraoperative ligation of spontaneous shunt vessels, and 1 was excluded from the analysis because the patient underwent anastomosis between the collateral shunt vessel and the PV. Of the 36 unligated patients, 8 were postoperatively complicated: 2 with portosystemic encephalopathy, 1 with decreased PV flow and increased ammonia, 2 with PV thrombosis, 2 with stenosis of PV anastomosis, and 1 with decreased PV flow. Unfortunately, 1 patient died at postoperative day 67 because of decreased PV flow with subsequent graft dysfunction. Another 7 patients were treated as follows: 1 relaparotomy due to PV thrombosis; 3 effective balloon-occluded retrograde transvenous obliterations (BRTOs) for 2 patients with hepatic encephalopathy and 1 with decreased PV flow and increased ammonia; 2 angiographies with stent placement for patients with stenosis of the PV anastomosis; and 1 retrans plantation due to PV thrombosis with subsequent liver failure.

Of our 36 unligated patients, 27 experienced no complications because of major shunt vessels after LDLT. Therefore, we believe that it is not always necessary to expose the patient to additional risk because of the ligation of major shunt vessels during LDLT, if there is sufficient portal flow into the graft after reperfusion. Despite new technical approaches, ligation is not always easy and sometimes even still dangerous, especially for patients who have previously undergone the several abdominal surgeries that have likely led to the formation of severe intra-abdominal adhesions. It should also be noted that even after shunt vessel ligation during LDLT, there is still a chance of recurrence after surgery, and this procedure might be ineffective (*2*).

It remains controversial whether a portosystemic shunt detected before liver transplantation should be occluded during liver transplantation. A portosystemic shunt could decrease PV flow after liver transplantation, leading to the subsequent formation of PV thrombosis, graft dysfunction, and/or other serious consequences (*3, 4*). On the other hand, the presence of a shunt can have a positive effect on liver perfusion in cases with relative portal hypertension in the early postoperative period, especially after LDLT (*3, 5*).

As Ikegami et al. also described in their study, BRTO has recently been reported to be a less invasive treatment for portosystemic shunt complications after LDLT (*6, 7*). The effectiveness of BRTO treatment for patients after LDLT with gastric varices and liver dysfunction, including hyperbilirubinemia and/or hyperammonemia, and without hepatic encephalopathy caused by prolonged portosystemic shunts has also been reported (*7*). One patient analyzed in the present study was complicated with decreased PV flow and high ammonia, and underwent BRTO for a splenorenal shunt at day 6 after LDLT. BRTO therefore seems to be effective, regardless of the interval between the development of complications due to the portosystemic shunt and LDLT. Even if the complication occurs because of a major shunt vessel after LDLT, it can be managed with a less invasive treatment strategy.

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Obstructing Spontaneous Major Shunt Vessels Is or Might Not Be Mandatory in Living Donor Liver Transplantation: The Authors' Reply

We much appreciate Dr. Takashuki and colleagues' comments on our study. As we have reported, our strategy in the management of portal hemodynamics in LDLT is normalizing portal hemodynamics by ligation of major shunts to treat portal stealing combined with splenectomy to treat portal over inflow (*1*). On the other hand, Nagasaki group commented that major shunt vessels should not necessarily been obstructed because shunt ligation is not always easy and might be a chance to cause over portal inflow resulting in graft dysfunction. Although indication of ligation of major shunt vessels was not described in the letter, the Nagasaki group performed shunt ligation for 8 (17.8%) cases among 45 LDLTs with major shunt vessels. Among the cases without shunt ligation (n=37), 8 (21.6%) patients had portal complications including retransplantation (n=1) and graft loss due to decreased portal flow (n=1).

The difficulties in managing portal hemodynamics after LDLT include changing portal pressure caused by graft regeneration, available approaches for delayed shunt occlusion, and possible graft dysfunction associated with excessive portal inflow by shunt occlusion. Portal pressure after LDLT is primarily determined by graft regeneration but also influenced by other multiple factors including graft quality, graft size, and surgical and nonsurgical complications (*2*). A patient with large shunts always has risk of deterioration, especially if a transplanted graft has unfavorable factors for compliance including older donor age, smaller graft size, and jeopardized venous outflow. On the other hand, if a transplanted graft has favorable factors for better compliance including larger graft size, it could be away from portal stealing even under the presence of shunt vessels. However, even in such cases, nonsurgical complications including acute rejection could cause portal stealing with graft dysfunction. Thus, obstruction of major shunts is a great insurance for secure portal inflow.

The possible approaches for various types of shunts are important issue. For gastroesophageal shunts, no interventional approach is possible, and the only available approach is surgical approach including our stapling division technique (*3*). For splenorenal shunts, BRTO is applicable, but renal dysfunction caused by the use of iodine contrast medium is issue, especially in early posttransplant periods (*4*). For mesocaval shunts, transvenous approach including BRTO is a good option because such shunts usually has very short communication between portal system and vena cava and BRTO possibly causes portal or pulmonary embolization. Thus, we think that BRTO is an available option only for delayed occlusion of splenorenal shunts.

Graft dysfunction caused by excessive portal inflow is another issue caused by shunt ligation. To overcome the issue, we exclusively perform simultaneous splenectomy while shunt ligation is performed. The combination of removing huge spleen and obstructing major shunts, supply, and drainage of portal flow, respectively, is just the trial for normalizing portal hemodynamics (*1*). Application of these strategies has significantly improved graft functions and survivals after LDLT over time at Kyushu University (*5*). Although we have applied our strategies with mandatory shunt ligation for years with acceptable outcomes, further multicenter studies for identifying indication of mandatory shunt ligation is necessary.

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Clinical Transplantation

Post-operative complications requiring hospitalization more than one yr after living donor liver transplantation

Takatsuki M, Soyama A, Muraoka I, Hara T, Kinoshita A, Yamaguchi I, Tanaka T, Kuroki T, Eguchi S. Post-operative complications requiring hospitalization more than one yr after living donor liver transplantation.

Abstract: Background/Purpose: The long-term outcomes after living donor liver transplantation (LDLT) have not been clearly established. This retrospective study assessed long-term outcomes after LDLT through reviewing complications requiring hospitalization more than one yr after engraftment.
Methods: Sixty-five LDLT recipients alive more than one yr post-transplantation were enrolled, 37 males and 28 females, with a median age at transplantation of 53 yr (range, 0–68 yr). We reviewed all post-operative complications requiring hospitalization more than one yr after LDLT.
Results: There were 61 post-operative complications requiring hospitalization in 43 of the 65 patients (66%), and the majority of these complications were transplantation related (59/61; 97%). Despite this, 43 (78%) of 55 surviving patients had normal liver function at their last follow-up, and 50 patients (91%) achieved normal activity (Karnofsky score 100%).
Conclusions: More than one-half of our LDLT recipients required hospitalization more than one yr post-LDLT to treat a complication. Most were able to maintain their quality of life and liver function with appropriate treatment.

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Living donor liver transplantation (LDLT) was developed as an alternative to deceased donor liver transplantation (DDLT), particularly in Eastern countries including Japan, where the number of DDLTs is fairly low and the short-term results of LDLT are comparable to those of DDLT. However, although several studies have examined long-term recipient LDLT technical complication and allograft original disease recurrence rates (1–4), long-term LDLT efficacy remains unclear. Complication severity determines the requirement for hospital treatment. Our study aim was to determine LDLT long-term patient outcomes through analyzing complications requiring in-hospital treatment more than one yr after LDLT.

Patients and methods

Patients

Ninety-three LDLTs were performed at Nagasaki University between August, 1997 and January, 2009. Of the 93 patients, 65 survived more than one yr after LDLT and were enrolled in this study, 37 males and 28 females, with a median age at transplantation of 53 yr (range, 5 months–68 yr). Seven (11%) of these cases were pediatric patients (less than 15 yr old). The original diagnoses were hepatitis C virus (HCV) cirrhosis - 21 patients (15 with hepatocellular carcinoma; HCC), hepatitis B virus (HBV) cirrhosis - 12 (10 with HCC), biliary atresia - 8, fulminant hepatic failure - 8, primary

biliary cirrhosis - 4, alcoholic cirrhosis - 3, and other diagnoses - 9 patients.

Perioperative management

The indication for transplantation in HCC cases was based on the Milan criteria. Splenectomy was performed in HCV cirrhosis recipients and pre-emptive HCV treatment with pegylated interferon and ribavirin was administered for several months post-transplantation. For HBV cirrhosis cases, lamivudine or entecavir was administered pre-transplantation and intravenous anti-HBV immunoglobulin was administered while the recipient was an-hepatic, and thereafter, with intermittent re-treatment to maintain HBV surface antibody levels post-transplantation. The target blood levels of antibody were; more than 200 IU/mL during the first month post-transplantation, 100–200 IU/mL for months one through 3 and 50–100 IU/mL thereafter.

Lamivudine or entecavir was continued post-LDLT. Base immunosuppression was with tacrolimus and steroids. Oral tacrolimus 0.05 mg/kg twice daily was begun on the first post-operative day. The target trough levels were: 10–15 ng/mL for the first month post-transplantation and less than 10 ng/mL, thereafter. Methylprednisolone was administered intravenously – 10 mg/kg for pediatric cases and 1 g for adult cases – during surgery, just after allograft reperfusion. Post-operative methylprednisolone tapering was from 0.5 mg/kg i.v. four times daily for the first three post-operative d to 0.5 mg/kg twice daily for the next three d to prednisolone 0.5 mg/kg once daily at day seven post-transplantation. Steroids were discontinued, after tapering, at six months if the liver function was stable. In selected cases, mycophenolate mofetil or azathioprine was added. Post-transplant antibiotic prophylaxis consisted of cefazolin and ampicillin, 1 g each, four times a day, for three d. When anti-cytomegalovirus immunoglobulin G was positive in the donor and negative in the recipient, prophylactic gancyclovir, 5 mg/kg/d twice daily for 14 d post-transplantation was administered. Trimethoprim-sulfamethoxazole 1 g daily was administered for three months post-transplantation for *Pneumocystis jirovecii* pneumonia prophylaxis.

Biliary reconstruction was through duct-to-duct anastomosis, when possible, except in patients with biliary atresia or primary sclerosing cholangitis. A chloride vinyl tube (2 mm diameter) biliary splint was placed at the anastomotic site to prevent stricture and this was externalized through the upper edge of the duodenum with a Witzel-type fistula. This tube was removed three to four months after the LDLT in a two-step protocol (5): the tube was withdrawn under X-ray control to the most peripheral part of the tract established by the Witzel's canalization. On the next day, after confirming the absence of bile leakage and peritonitis, the tube was completely removed.

Follow-up at the outpatient clinic

After discharge, patients were followed at an outpatient clinic every two wk to three months, the frequency being case determined. The patient's complete blood count, prothrombin time, serological studies, and standard liver function tests were checked routinely. Multi-detector computed tomography (MDCT) and/or a magnetic resonance imaging studies were performed routinely to determine liver regeneration, the blood vessel patency, and HCC recurrence every 6–12 months. Cytomegalovirus antigen and/or beta-D glucan levels were checked occasionally. HCV-RNA was checked monthly in HCV patients and HBV-DNA was checked in HBV cases.

When a study disclosed a significant abnormality, hospitalization was determined by the disease severity, the requirement for additional tests (e.g., liver biopsy) and the anticipated treatment. Usually, the decision to hospitalize was made by the attending physician at the outpatient clinic. When a patient developed liver failure, the indication for re-transplantation considered the patient's general condition including the existence of infections. The model for end-stage liver disease (MELD) score was considered, but not applied strictly.

Assessment of the daily activity

Karnofsky scoring was used to assess a patient's daily activity as follows:

1. 100% = normal, no complaints, no signs of disease
2. 90% = capable of normal activity, few symptoms or signs of disease
3. 80% = normal activity with some difficulty, some symptoms or signs
4. 70% = caring for self, not capable of normal activity or work
5. 60% = requiring some help, can take care of most personal requirements
6. 50% = requires help often, requires frequent medical care
7. 40% = disabled, requires special care and help
8. 30% = severely disabled, hospital admission indicated but no risk of death

9. 20% = very ill, urgently requiring admission, requires supportive measures or treatment
10. 10% = moribund, rapidly progressive fatal disease processes
11. 0% = death

This evaluation was done for each patient at the last follow-up by the same clinician (M.T.).

The incidence and types of complications, and their treatment and outcome, for all 65 patients were retrospectively reviewed.

Results

Complications more than one yr after LDLT

The overall one-, three-, and five-yr patient/graft survivals after LDLT were 90%/88%, 75%/74%, and 70%/69%. Sixty-one complications requiring hospitalization more than one yr after LDLT occurred in 43 patients (66%) with a median follow-up period of 42 months (range, 14–137 months). Most complications were related to transplantation (59/61; 97%). These complications were

1. Surgical complications in 18 patients (15 biliary strictures, two cases portal vein stenosis, one hepatic vein stenosis)
2. Complications of the original disease in 11 patients (with induction of HCV treatment in eight patients, untreated HCC recurrence in two, liver failure due to alcohol abuse in one)
3. Rejection in eight patients (acute cellular rejection in seven and chronic rejection in one)
4. Infectious complications in nine patients (enteritis in three patients, cellulitis in two, and one patient each with herpes zoster, spontaneous bacterial peritonitis, *Aspergillus* sinusitis, and human T lymphocyte virus-1 associated myelopathy [HAM]).
5. Other complications in 13 patients (de novo autoimmune hepatitis in four, non-B non-C hepatitis in one, surgery for cataracts possibly from steroid treatment in three, gastrointestinal bleeding due to portal hypertension in two, one renal failure possibly tacrolimus related, one pancreatitis, and one splenic artery embolization to increase the platelet count for anti-HCV interferon therapy)

Two complications unrelated to transplantation were iron deficiency anemia and gastric cancer. There were no complications from opportunistic infections or malignancy such as cytomegalovirus infection, Epstein–Barr virus infection or skin cancer.

During the study period, four patients underwent repeat LDLT, three of which were done within one yr after the primary LDLT. One patient underwent repeat LDLT 25 months after a primary LDLT for liver failure, due to a biliary stricture (described below).

Outcomes of treatment

Biliary stricture. Of the 15 episodes of biliary stricture, 14 were after duct-to-duct biliary reconstruction and the other was after hepaticojejunostomy. Eleven strictures were treated by endoscopic placement of a biliary stent and four by percutaneous transhepatic biliary drainage (PTBD). At their last follow-up, eight patients had normal liver function, two had slightly diminished liver function, and one patient developed liver failure, subsequently successfully undergoing repeat LDLT. Of the four remaining patients, three died from liver failure and two of these cases had associated biliary stricture. One patient died of HCV recurrence and another died of Langerhans histiocytosis (Table 1).

Vascular complications. Two cases of portal vein stenosis were successfully treated with balloon dilatation 38 and 16 months after LDLT. Each patient currently has reasonable portal flow and normal liver function. One patient with hepatic vein stenosis, which was treated with stent placement 14 months after LDLT, currently has good blood flow and normal liver function.

HCV recurrence. Eight of 21 patients (38%) undergoing LDLT for HCV cirrhosis required hospitalization more than one yr post-LDLT to treat HCV recurrence with interferon therapy. Most patients undergoing LDLT for HCV cirrhosis received interferon and ribavirin within one yr after LDLT as preemptive therapy and prior to the development of biopsy-proven hepatitis. Therefore, all treatments performed more than one yr post-LDLT involved re-induction with interferon and so the incidence of HCV clearance (HCV-RNA negative at the last follow-up) was significantly less than patients not requiring additional interferon therapy (1/12 vs. 7/9, $p < 0.05$ [Fisher's test]).

HCC recurrence. Two patients developed HCC recurrence and died 27 months and 40 months after LDLT, respectively. The former patient, a 62-yr-old male meeting the Milan criteria, developed pelvic dissemination of HCC, possibly related to a percutaneous ethanol injection prior to transplantation. During the preoperative surveillance there were no definitive extra-hepatic lesions so we

Table 1. Patients who died beyond one yr after LDLT

Case no.	Original diseases	Gender	Age at Tx	Graft	Blood type	Biliary stricture	Cause of death	Months after Tx
1	BA	F	1	LLS	Identical	(−)	GI bleeding	66
2	B-LC/HCC	M	56	RL	Identical	(+)	Liver failure	41
3	BA	F	1	LLS	Identical	(−)	GI bleeding	29
4	Alcoholic LC	M	47	RL	Identical	(−)	Liver failure (alcohol abuse)	46
5	FHF	F	0	LLS	Identical	(+)	Langerhans histiocytosis	35
6	C-LC	M	51	RL	Identical	(+)	Liver failure (HCV)	30
7	C-LC/HCC	F	54	ELL	Incompatible	(+)	Liver failure	23
8	C-LC/HCC	M	62	LL	Compatible	(−)	HCC recurrence	27
9	C-LC/HCC	M	50	RL	Identical	(−)	HCC recurrence	40
10	C-LC/HCC	M	67	RLS	Identical	(−)	Liver failure	18

BA, biliary atresia; B-LC, HBV cirrhosis; FHF, fulminant hepatic failure; C-LC, HCV cirrhosis; HCC, hepatocellular carcinoma; F, female; M, male; LLS, left lateral segment; RL, right lobe; ELL, extended left lobe; LL, left lobe; RLS, right lateral sector; GI, gastrointestinal.

performed LDLT; however, this man eventually died from HCC recurrence. The other patient, a 50-yr-old male with multiple HCCs beyond the Milan criteria, underwent an LDLT after informed consent. He died of multiple lung metastases after unsuccessful sorafenib treatment, without intrahepatic recurrence.

Rejection. Of the seven patients who developed acute cellular rejection, all recovered with increased immunosuppression that included steroid bolus therapy. Four are alive and well, two are alive with slightly abnormal liver function, and one pediatric patient died of Langerhans hystiocytosis 35 months after the LDLT. One patient developed chronic rejection and died of liver failure 23 months after the LDLT.

Infections. All but one mentioned infected patient recovered with appropriate treatment (i.e., conservative treatment for the enteritis cases, antibiotic therapy for cellulitis and spontaneous bacterial peritonitis, acyclovir for herpes zoster, and surgical resection for *Aspergillus* sinusitis). One patient who developed stable HAM experienced gradual progression of voiding problems and gait disturbance.

Mortality over one yr after LDLT. Ten patients died more one yr post-LDLT, at a median time post-LDLT of 35 months (range, 18–66 months) (Table 1). The causes of transplantation related death were: liver failure from biliary stricture in four patients, gastrointestinal bleeding in two, HCC recurrence in two, liver failure due to alcohol abuse in one, and chronic rejection in one. Both cases of gastrointestinal bleeding were pediatric. Each patient developed sudden massive bleeding due to portal vein obstruction. An attempted recanalization of the portal vein via a percutaneous transhepatic approach failed in one patient. We could not procure a second graft for LDLT, so only one patient underwent repeat LDLT for graft failure from biliary stricture.

Liver function at the last follow-up. Current liver function in our surviving patients has been maintained with median alanine aminotransferase and total bilirubin levels of 23 IU/L (range, 7–546) and 0.9 mg/dL (range, 0.3–8.6), respectively. Overall, a majority of patients (43/55, 78%) had normal alanine aminotransferase and total bilirubin levels.

Assessment of daily activity. Most patients surviving more than one yr post-LDLT have a normal daily Karnofsky activity score of 100% (50/55, 91%). The other five patients are experiencing slightly diminished activity (40–90%), from general fatigue related to liver dysfunction (three patients), chronic renal dysfunction and gait disturbance with HAM.

Discussion

We attempted to determine the long-term results of LDLT by analyzing the complications requiring hospitalization more than one yr post-LDLT. Most complications were transplantation related. Treatment of surgical complications and original disease recurrence were major reasons for hospitalization. Biliary stricture is well documented as one of the major surgical complications after LDLT (6, 7) and generally develops several months after surgery. Four of the 15 patients requiring treatment for biliary stricture died, while most of the surviving patients maintained good liver function. Timing of the treatment of biliary stricture is important so patients should be followed carefully in order to not miss an appropriate opportunity for re-transplantation. Other surgical complications included portal and hepatic vein stenosis,

each successfully treated with balloon dilatation or stent placement. Other studies have also reported promising results with this procedure (8, 9).

Hepatitis C virus and HCC disease recurrence were major causes of hospitalization. Our original strategy for HCV was to preemptively treat patients with interferon and ribavirin (10), consequently the majority of our HCV patients had already undergone therapy within one yr post-LDLT. As a result, patients requiring treatment more than one yr post-LDLT usually had refractory HCV recurrence and their HCV clearance was diminished. Other current studies have indicated that preemptive therapy may be associated with a lesser efficacy for controlling HCV recurrence (11), so the optimal strategy for preventing HCV recurrence is unresolved.

Hepatocellular carcinoma recurrence was a cause for hospitalization and death in two patients, one beyond the Milan criteria, the other within the Milan criteria but who had undergone a percutaneous ethanol injection pre-transplantation. Percutaneous therapy or biopsy may cause dissemination of HCC (12); even if patient imaging is within the Milan criteria, they should be carefully evaluated before LDLT, possibly including a laparoscopic assessment.

Late-onset infections were observed, despite most patients receiving reduced immunosuppression. Although infection is a major cause of early post-transplantation death, late-onset infections were simply controlled with appropriate treatment and the majority of patients survived. One patient with HAM experienced a gradual progression of urinary problems and gait disturbance.

Late-onset acute rejection was observed in seven patients and each recovered with reinforced immunosuppression. In liver transplantation, although weaning from immunosuppression is often possible (13, 14), late-onset rejection may lead to graft loss (15). Even well-functioning grafts years after transplantation should have immunosuppression levels checked to identify possible late-onset acute cellular rejection.

The main cause of death more than one yr post-LDLT was liver failure related to biliary stricture followed by gastrointestinal bleeding, in two pediatric cases. Both pediatric patients were doing well with acceptable liver function, but died from massive, sudden-onset, bleeding due to portal obstruction. Late-onset portal vein complications are a recognized possible cause of death in liver transplantation (16). Liver function is maintained, even when the portal flow is disturbed, so these patients should be followed closely with imaging and/or endoscopy. We annually endoscope both adult and pediatric cases, now, based on this experience.

The cause of death within the first yr after LDLT in this patient population was mostly infection-related multi-organ failure: no patients died of liver failure due to biliary stricture, HCV/HCC recurrence, or gastrointestinal bleeding (data not shown). So, these complications seem specific to long-term patients and care providers should be aware and on the lookout for these complications in the outpatient clinic. There is a limited number of DDLTs in Japan so re-transplantation is difficult and potential complications merit careful patient monitoring post-LDLT in outpatient clinics. Perhaps, LDLT patients should be treated with greater vigilance with hospitalization for even relatively minor complications, compared to DDLT patients.

Although many patients required hospitalization more than one yr post-LDLT, most were found to enjoy active daily lives with good graft function at their most recent follow-up. With careful follow-up and adequate treatment, long-term outcomes after LDLT can be expected to further improve. Because HCV cirrhosis is a major indication for liver transplantation in both living and deceased donor liver transplantation, more effective and safe treatment for HCV recurrence after transplantation is essential to improve this group's long-term outcome.

Conclusions

In conclusion, many of our patients required hospitalization more than one yr post-LDLT for the treatment of complications, but most of them were able to maintain their quality of life and liver function with appropriate treatment.

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REVIEW ARTICLE

Liver transplantation for patients with human immunodeficiency virus and hepatitis C virus co-infection: update in 2013

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Abstract Because of the progress of anti-retroviral therapy (ART) for human immunodeficiency virus (HIV), mortality due to opportunistic infection resulting in AIDS has been remarkably reduced. However, meanwhile, half of those patients have died of end-stage liver cirrhosis due to hepatitis C virus (HCV) with liver cirrhosis and early occurrence of hepatocellular carcinoma. Recently, in 2013, non-cirrhotic portal hypertension due to ART drugs or still unknown mechanisms have become problematic with early progression of the disease in this patient population. Liver transplantation (LT) could be one treatment of choice in such cases, but the indications for LT perioperative management, including both HIV and HCV treatments and immunosuppression, are still challenging. In this review, we update the literature on HIV/HCV co-infection and LT as well as recent effort for modifying allocation system for those patients.

Keywords Co-infection · Hepatitis C virus · HIV · Human immunodeficiency virus · Liver transplantation

Introduction

The causes of death of human immunodeficiency virus (HIV) infected patients have dramatically changed since 1995. A major background factor behind these trends is the improved HIV control achieved with anti-retroviral therapy (ART) [1]. Despite dramatic reduction of death due to acquired immunodeficiency syndrome (AIDS), co-infected hepatitis C virus (HCV)-related death due to liver failure or hepatocellular carcinoma (HCC) became a serious problem, not only in Japan but all over the world, including England [2]. In Japan, in the late 1980s, contaminated blood products for hemophilia caused co-infection by HIV and HCV. In such cases, liver transplantation (LT) is the only possible treatment option to achieve long-term survival, but several modifications of perioperative management are required recently for better outcome.

In this review, the outcome and the points of management of LT for HIV/HCV co-infected patients were reviewed to save relatively young patients with HIV/HCV co-infection bearing HCC [3, 4], non-cirrhotic portal hypertension (NCPH) [5–7], and decompensated liver cirrhosis [8, 9]. An updated critical review of the literature in 2013 was performed, and new information on problems and results for LT for HIV/HCV co-infection were included.

Upcoming topics regarding LT indications for HIV/HCV co-infection in 2013

Non-cirrhotic portal hypertension

In HIV/HCV coinfected patients, liver failure due to HCV hepatitis was enhanced by ART-related hepatotoxicity, especially manifesting as non-cirrhotic portal hypertension [5–7]. One of the ART drugs, Didanosin (DDI), has been suspected for serious morbidity. Thus, not only in cases with deteriorated liver function, such as in Child–Pugh B or C cases, but also even in Class A cases, patients' liver function can easily deteriorate abruptly [10, 11]. The actual natural course of pure NCPH is unknown, because it can be modulated with HCV or other causes and reported as only case series. However, an important study regarding "Non-cirrhotic portal hypertension in HIV mono-infected patients without HCV" was published in 2012 [12]. All five patients had portal hypertensive symptoms such as ascites or variceal bleeding after ART medication. We need to await their prognostic information, since it can be extrapolated into HIV/HCV co-infected patients after successful HCV eradication.

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Therefore, all HIV/HCV co-infected patients should be carefully followed up so as not to miss the opportunity for LT. Recently, in Japan, a scoring system was created for listing a deceased donor LT for those patients with HIV/HCV co-infection due to previous contaminated blood products.

Hepatocellular carcinoma

Recently it became evident that HCC in HIV/HCV co-infected patients develop HCC at a very early stage of life, such as in the 30s and 40s [3, 4]. The molecular mechanism of its development still remains unclear, but surveillance in those patients should be considered for HCC strictly. In Japan, HIV/HCV co-infected hemophilic patients have been undergoing periodic examination for liver-related disease on a research basis. Early detection could contribute to treatment choices such as liver resection or liver transplantation. Regardless of the infectious status of HIV, treatment strategy for HCC in HIV/HCV infected patients should be the same in HCV mono-infected patients. Namely, whether liver resection could be performed or not should be based on the liver functional reserve. Also radio frequency ablation and transarterial chemoembolization can be selected according to the location, size and number of HCC.

Current results of LT for HIV/HCV co-infected patients in 2013

Indications for LT

As HCV mono-infected patients, LT should be considered when patients develop deteriorated liver function as indicated by a Child–Pugh score of class B or C in co-infected patients. Recently, Murillas et al. reported that the Model for End-stage Liver Disease (MELD) score is the best prognostic factor in HIV-infected patients [13]. HIV/HCV co-infected patients might be considered for LT before their MELD score increases to achieve comparable results with HCV mono-infected patients. Several studies showed that aggressive fibrosis in HIV/HCV co-infected patients compared with HCV mono-infected patients [14, 15], but the mechanism of this aggressive fibrosis remains unclear. Recently, transient elastography or acoustic radiation force impulse (ARFI) imaging to check for liver stiffness has been introduced as an effective and noninvasive modality to determine patients' candidacy for LT [16, 17].

Regardless of the presence of hemophilia, the indications and methods for performing liver transplantation remains unchanged for patients with HIV/HCV co-infection. In fact, after a successful liver transplantation, hemophilia can normally be cured. Usually, the conditions for liver transplantation are as follows: (1) AIDS symptoms have not surfaced; (2) CD4+ T lymphocyte count is 150–200/μl or above; and (3) as a result of ART, the amount of HIV RNA in the blood by PCR method is below the level of sensitivity of the assay.

In HIV/HCV co-infected patients, current studies show that a count of more than 100/μl CD4+ T lymphocytes is acceptable [18, 19], because patients generally have portal hypertension, which can cause leukocytopenia. In such patients, the ratio of CD4/CD8 is reported to be a realistic marker to predict postoperative complications including opportunistic infections. When the ratio is less than 0.15, the incidence of infectious complications is significantly higher [20].

In 2013, based on the evidence of rapid progression of the liver cirrhosis and portal hypertension in patients with HIV/HCV co-infection, a ranking system for waiting list of deceased donor LT has been set up in Japan. Even HIV/HCV co-infected liver cirrhotic patients with Child–Pugh class A can be listed for LT as "point 3" because of NCPH nature. Also co-infected patients with Child–Pugh class B and C can be listed as "point 6" and "point 8" based on the data from our HIV/AIDS project team of the Ministry of Health, Labor, and Welfare of Japan, and world literatures [21–23]. It is basically considered for previous victims of contaminated blood products for hemophilia.

Results of LT for patients with HIV/HCV co-infection

In the United States and Europe, liver transplantation from deceased donors has been performed in HIV patients since the 1980s. At that time, the outcomes of LT were very poor [11]. Recent series of reports are listed in Table 1 [24–31]. The reality is that, in addition to those listed therein, there have been many sporadic reports, such as reviews, expectations for liver transplantation, and assessment of indications.

In general, most reports concluded that the results were 10% worse than in the cases with HCV mono-infection, with a 3-year survival of around 60–70%. Recently, a 5-year patient survival of around 50% was reported, and there is debate whether these results can be accepted for patients of a younger age and were co-infected through previous use of a contaminated blood product. In Japan, the Tokyo group reported six cases of living donor liver transplantation (LDLT) between 2001 and 2004 [32]. Terrault et al. reported that older donor age, combined kidney-liver transplantation, an anti-HCV positive donor, and a body mass index <21 kg/m^2 were independent predictors of graft loss [33]. After LT, several studies showed that acute cellular rejection was more frequent and more severe in HIV/HCV co-infected patients than in HCV mono-infected patients, possibly due to difficulties in achieving optimal immunosuppression because of interactions between antiretroviral agents and immunosuppression.

Table 1 Updated outcome of liver transplantation for HIV positive recipients

Authors	Year	Country	*n*	Patient survival (%)			
				1 year	3 years	5 years	
Duclos-Vallee et al. [25]	2008	France	35	–	73	51	
Tsukada et al. [32]	2011	Japan	6	66	66	50	Only LDLT, only hemophilia
Terrault et al. [33]	2012	US	89	76	60	–	
Miro et al. [26]	2012	Spain	84	88	62	54	
Anadol et al. [27]	2012	Germany	32	90	65	60	
Harbell et al. [28]	2012	USA	125	91	67	–	
Baccarani et al. [31]	2012	Italy	32	–	79	69	
Di Benedetto et al. [46]	2012	Italy	30	75	65	50	with HCC
Ragni et al. [29]	2013	USA	15	71	38	–	only hemophilia

HCC hepatocellular carcinoma, *LDLT* living donor liver transplantation

Lowered outcome can be presumed from previous reports. Final mortality (graft loss) after LT was usually due to infection and multiorgan failure. As in Miro's report the causes due to the higher proportion of organs from donation after cardiac death (DCD) donors, higher rate of combined liver-kidney transplantation, increased rate of acute cellular rejection, HBV co-infection and infection. However, it was of note that there was no death due to infections related to HIV.

Preoperative management of HIV/HCV in liver transplantation

The number of HIV-RNA copies before LT is suggested as an independent risk factor of postoperative mortality, so that HIV should be controlled sufficiently before LT [30]. Accordingly, in patients who are under consideration to receive LT, ART can be safely stopped before LT, because HIV is generally well controlled for a long period by ART. Also ART can be toxic for the virgin graft, which underwent ischemia/reperfusion injury and liver resection in a donor. Once it is settled down after liver transplant, especially in LDLT cases, ART can be resumed with meticulous adjustment with calcineurin inhibitors.

Actually, after LT, ART should be restarted as soon as possible, because HIV-RNA appears at 3 to 30 days after ART is stopped [34], but the timing of restart of ART depends on the patient's condition, including liver function [35]. As long as the liver function has not fully recovered, or partial liver graft such as in LDLT has not yet sufficiently regenerated, ART cannot be started. Castells et al. reported in their case-control study that ART was started at a median of 8 days after LT (range 4–28 days) [36]. ART administered after LT should be the same as the preLT regimen, but the majority of ART drugs, including protease inhibitors and non-nucleoside reverse transcriptase inhibitors, have interactions with calcineurin inhibitors (CNI) or mammalian target-of-rapamycin (mTOR) [37], so that the monitoring of blood levels of immunosuppression is extremely important to avoid infectious complications or rejection. It can easily overshoot beyond the therapeutic level. Currently, a novel HIV-1 integrase inhibitor, raltegravir, is expected to be a feasible drug because it has no interactions with CNI, unlike other drugs [38, 39]. Therefore, the current recommended strategy in the light of LT could be to try raltegravir as ART before LT and see if HIV can be controlled with raltegravir. If it is the case, CNI could be used as usual after LT. However, if raltegravir cannot control HIV or cannot be applied due to other reasons, meticulous management of CNI (e.g. once a week administration with frequent trough monitoring) or Mycophenolate mofetil protocol should be considered. In fact, the novel protease inhibitor anti-HCV drug, telapreir, has the same character as ART drugs for HIV, and transplants team learn to overcome such drug interactions when post-LT HCV mono-infected patients are treated with telaprevir.

The treatment strategy for HCV in HIV/HCV co-infected patients is the same as in HCV mono-infected patients. Combination therapy of pegylated interferon (Peg-IFN) and ribavirin is the standard treatment both before and after LT in 2013. The treatment should be started as soon as possible, because in HIV/HCV co-infected patients, HCV recurrence may be accelerated in an immunocompromised state [40, 41]. As mentioned above, the novel protease inhibitor telaprevir is currently being introduced as an effective drug to achieve sustained viral response (SVR) of 70%, even in genotype 1b, with Peg-IFN/ribavirin in a non-transplant setting [42], but this drug is metabolized via cytochrome P450, as are CNI and various protease inhibitors of ART for HIV. Close monitoring of the CNI trough level should be performed, and although triple therapy with telaprevir/Peg-IFN/ribavirin or even without Peg-IFN is currently reported to be effective to prevent HCV recurrence after LT in HCV mono-infected cases, special attention should be paid when

this regimen is adapted for HIV/HCV co-infected patients. Additionally, mutational status of the IL28 B genotype should be investigated before interferon therapy for both donor and recipient.

Immunosuppression

Several reports have demonstrated both the in vitro and in vivo effectiveness of rapamycin in reducing HIV replication [43–45]. Di Benedetto et al. found that rapamycin monotherapy was significantly beneficial in long-term immunosuppression maintenance and HIV control after LT [46]. Mycophenolate mofetil is expected to be an effective immunosuppressive drug because of its efficacy in reducing HIV infection by both virological and immunological mechanisms. Mycophenolic acid, a selective inhibitor of the de novo synthesis of guanosine nucleotides in T and B lymphocytes, has been proposed to inhibit HIV replication in vitro by depleting the substrate (guanosine nucleotides) for reverse transcriptase. Using these drugs, a more effective regimen of immunosuppression with ART may be established. However, more information needs to be obtained to establish concrete immunosuppressive protocol.

As to steroids, several studies proposed that a steroid-free regimen can be safely applied and effective in LT for HCV cirrhosis. In HIV/HCV co-infected patients, a steroid-free protocol may play a beneficial role in preventing both HIV and HCV recurrence after LT [47, 48].

Hepatocellular carcinoma

Liver transplantation has been performed also for indication of HCC. The most updated study indicated that the existence of HCC did not change the outcome of LT provided that HCC was downstaged preoperatively for UCSF criteria [49]. Also for these cases sirolimus tended to be used as primary immunosuppressive agents. This encouraging result awaits further reports [50].

Conclusions

The above is an overview of liver transplantation performed to date in HIV/HCV- co-infected patients. Although, the results are 10% lower in patient survival after LT than those for HCV mono-infected patients, LT could be feasible in selected cases with HIV/HCV co-infection after careful evaluation within suitable stages of the disease. In light of the fact that most HIV/HCV co-infected patients in Japan are the victims of contaminated blood products, it is believed that the importance of liver transplantation will increase in the future in the context of medical relief as well. Our investigating team under the Ministry of Health, Labor, and Welfare of Japan has made all possible efforts to clarify the appropriate timing to put HIV/HCV co-infected patients on a waiting list for LT.

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Conflict of interest None declared.

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A hybrid method of laparoscopic-assisted open liver resection through a short upper midline laparotomy can be applied for all types of hepatectomies

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Abstract
Background Although hepatectomy procedures should be designed to provide both curability and safety, minimal invasiveness also should be pursued.
Methods We analyzed the data related to our method for laparoscopy-assisted open resections (hybrid method) through a short upper midline incision for various types of hepatectomies. Of 215 hepatectomies performed at Nagasaki University Hospital between November 2009 and June 2012, 102 hepatectomies were performed using hybrid methods.
Results A hybrid method was applicable for right trisectionectomy in 1, right hemihepatectomy in 32, left hemihepatectomy in 29, right posterior sectionectomy in 7, right anterior sectionectomy in 1, left lateral sectionectomy in 2, and segmentectomy in 7 patients, and for a minor liver resection in 35 patients (12 combined resections). The median duration of surgery was 366.5 min (range 149–709) min, and the median duration of the laparoscopic procedure was 32 min (range 18–77) min. The median blood loss was 645 g (range 50–5,370) g. Twelve patients (12 %) developed postoperative complications, including bile leakage in three patients, wound infections in two patients, ileus in two patients, and portal venous thrombus, persistent hyperbilirubinemia, incisional hernia, local liver infarction each in one patient. There were no perioperative deaths.
Conclusions Our method of hybrid hepatectomy through a short upper midline incision is considered to be applicable for all types of hepatectomy and is a reasonable approach with no abdominal muscle disruption, which provides safe management of the hepatic vein and parenchymal resection even for patients with bilobular disease.

Keywords Hepatectomy · Minimally invasive liver resection · Hybrid method · Living-donor hepatectomy · Midline incision

Liver resection is one of the most challenging fields of minimally invasive surgery. In 2007, Koffron et al. [1] reported 300 minimally invasive liver resections (MILR) for hepatic lesions. In their report, they employed three different methods of liver resection: pure laparoscopic liver resection, hand-assisted laparoscopic resection, and laparoscopy-assisted open resection (hybrid) as the MILR. Compared with open hepatic resection, all of their MILR procedures were less invasive and were associated with a shorter operation time, lower blood loss, and shorter hospital stay, with the same rates of local recurrence and complications.

In a worldwide review of laparoscopic liver resection performed in 2009, pure laparoscopic resections were performed in 75 % of cases, hand-assisted laparoscopic resections in 17 %, and a hybrid procedure was done in only 2 % of cases [2]. However, according to the review, the resected area of the liver was a wedge resection in 45 % and left lateral section in 20 %, revealing that only 23 % of procedures were performed for anatomical resections larger than a sectionectomy.

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We have employed hybrid liver resection with hand-assisted laparoscopic liver mobilization and subsequent liver resection with the hanging maneuver [3] and a two-surgeon technique through a short upper midline incision. Our initial data on hybrid liver resection were herein analyzed to clarify the parameters related to their use for various types of hepatectomies.

Patients and methods

Of 215 hepatectomies performed between November 2009 and May 2013 at Nagasaki University Hospital, we employed laparoscopy-assisted open resections (hybrid method) for 102 patients (47 %).

The contraindications for the hybrid procedure were as follows: (1) cases with a previous history of upper abdominal laparotomy; (2) tumor involvement of the diaphragm or a tumor large enough to require an anterior liver resection; and (3) cases with portal or hepatic venous tumor thrombus. The resections for small tumors located in the anterocaudal side of the liver and left lateral sectionectomy were performed under pure laparoscopic liver resection. As a standardized anatomical resection of the normal liver, we chose living-donor left hemihepatectomy for comparison of the surgical outcomes of the hybrid technique and the open procedure.

Among the analyzed patients who underwent hybrid resection, the median age (62 males, 40 females) was 59 years (range 21–85) years (Table 1). The patients' median height was 161 cm (range 145–181) cm, and the median weight was 60 kg (range 37–88) kg. The body mass index (BMI) was 22.8 (range 16.5–31.6).

Table 1 Patient characteristics

Age (years)	59 (range, 21–85)
Sex (M:F)	62:40
Height (cm)	161 (145–181)
Weight (kg)	60 (37–88)
BMI	22.8 (16.5–31.6)
Indications	Number
Hepatocellular carcinoma	32
Metastatic liver tumor	14
Hilar cholangioma	3
Intrahepatic cholangioma	5
Epithelial hemangioendothelioma	1
Hepatic carcinoid	1
Cystoadenoma	1
Caroli's disease	1
Living donor	44

All but one patient had Child-Pugh grade A status; one patient was considered to have Child-Pugh grade B disease. The liver functional reserves were as follows: the indocyanine retention rate at 15 min (ICGR15) had a median of 11 % (range 1–30 %), and the median 99mTc-GSA scintigraphy receptor index [ratio of the liver to heart-plus-liver radioactivity at 15 min (LHL15)] was 0.922 (range 0.826–0.975). The liver functional reserve evaluations, including the ICG retention test and 99mTc-GSA scintigraphy, were not performed for living liver donors.

The primary reasons for the operations were hepatocellular carcinoma in 32, metastatic liver cancer in 14, hilar cholangiocarcinoma in 3, intrahepatic cholangiocellular carcinoma in 5, hepatic epithelial hemangioendothelioma in 1, hepatic carcinoid in 1, cystadenoma in 1, Caroli's disease in 1, and living liver donor in 44 (Table 1). The surgical methods employed were a right trisectionectomy in 1, right hemihepatectomy in 32, left hemihepatectomy in 29, right posterior sectionectomy in 7, left-lateral sectionectomy in 2, and segmentectomy (S5, 6, 7) in 7 patients, and a minor liver resection was performed in 35 patients (combined in 12; Table 2). We evaluated surgical outcomes in the patients who underwent the hybrid procedure. We also compared the surgical outcomes of the hybrid procedure and open procedure for living-donor hemihepatectomy.

The Mann–Whitney U test was applied to compare the groups. $P < 0.05$ was considered to be statistically significant.

Surgical techniques

Patients were placed in the supine position with their arms adducted, and a urinary catheter and arterial and central venous lines were inserted. An 8-cm upper midline laparotomy was made, followed by a 5-mm umbilical incision for the laparoscope. The round, falciform, and coronary ligaments were divided, and a wound retractor was installed. Before starting the laparoscopic procedure, a surgical towel was inserted through the upper midline incision to displace the small intestine and colon away

Table 2 Types of hepatectomies

Types of hepatectomies	Number
Right trisectionectomy	1
Right hemihepatectomy	32
Left hemihepatectomy	29
Anterior sectionectomy	1
Posterior sectionectomy	7
Left lateral sectionectomy	2
Segmentectomy	7
Minor liver resection	35 (combined in 12)

from the surgical site. A GelPort (Applied Medical, CA, USA) was attached to the wound retractor at the 8-cm incision, and a 5-mm trocar was placed in the right lateral upper abdomen under pneumoperitoneum (CO_2 at 8 mmHg; Fig. 1A). This configuration enabled the first assistant surgeon, who stood on the left side of the patient, to use the hand port for liver manipulation. The primary surgeon stood on the right side and used the right lateral 5-mm port for dissection. Using laparoscopic electrocautery and a hand assist, the right lobe of the liver was mobilized until the inferior vena cava (IVC) was recognized for all types of hepatectomies. The IVC does not need to be exposed fully at this stage to avoid incidental massive bleeding.

For patients indicated for left-side hepatectomy, the left triangle ligament also was dissected through the 5-mm port placed through the GelPort (Fig. 1B). After these mobilizations, the midline incision was extended to 10 cm for left-side anatomical resection and 12 cm for right-side anatomical resection, and a wound retractor was applied. For minor partial resections, even for multiple lesions, the 8-cm incision was still used. The wound was retracted and opened with the Omnitract retractor. For a right-side hepatectomy, the short hepatic veins were divided under direct view, and the right hepatic vein was encircled and a 6-mm Penrose drain was placed for a subsequent liver hanging maneuver through a midline incision (Fig. 2A). For an extended left hemihepatectomy, the common trunk of the middle and left hepatic veins was carefully encircled. The left hepatic vein was isolated and encircled in advance of parenchymal resection, when it could be performed safely. A Penrose drain also was placed between the hepatic veins for the liver hanging maneuver for left hemihepatectomies.

When cholecystectomy was necessary, we performed it by an open procedure. Hilar dissection was conducted through the midline incision under direct vision (Fig. 2B).

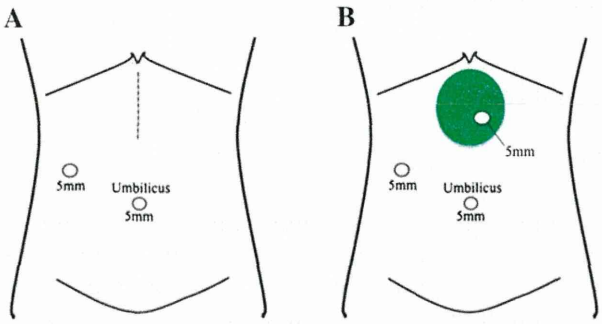

Fig. 1 The trocar placement. **A** *Dotted line* shows the upper midline incision. A 5-mm camera port is inserted from the umbilicus. Another 5-mm trocar is used for dividing the ligaments for mobilization of the right lobe. **B** When mobilizing the left lobe of the liver is necessary, a 5-mm trocar is inserted through a GelPort handport device

By placing surgical towels in the right subphrenic space, the liver can be stabilized in an ideal position by setting the intended transection line in the middle of the incision (Fig. 3).

The 4-0 polypropylene stay sutures were placed at the anterocaudal edge of the liver along the plane of the intended transection. The chief surgeon dissected the hepatic parenchyma from the patient's right side using a Cavitron ultrasonic surgical aspirator (CUSA) system (Integra Life Sciences, Plainsboro, NJ, USA), whereas the assistant surgeon used a saline-linked cautery device (Dissecting Sealer DS 3.5; Salient Surgical Technologies, Portsmouth, NH, USA) from the patient's left side. The occlusion of the hepatic arterial and portal inflow was not performed in any of the cases. The liver parenchyma was dissected with the CUSA, and the intraparenchymal vascular anatomy was defined so that a decision on the hemostatic technique could be made based on the vessel size. The saline-linked cautery device was used to coagulate and divide the dissected vessels that were 3 mm or smaller in diameter. Vessels larger than 3 mm in diameter were ligated with 3-0 or 4-0 synthetic polyester ties and were sharply divided. The few larger vessels were ultrasonically dissected and controlled with 4-0 absorbable monofilament transfixing sutures and were then sharply divided. The traction on the stay sutures was used to separate and to expose the deepening transection plane. During the parenchymal dissection, the upward traction on the tape (hanging maneuver) allowed the surgeon to follow a direct plane and facilitated the exposure and hemostasis of the deeper parenchymal plane in front of the IVC [5, 13]. A closed suction drain was inserted at the conclusion of each procedure.

Preparations for an open hepatectomy were always executed as a backup plan before surgery.

Results

The median length of the operation was 366.5 min (range 149–709) min. The median duration of the laparoscopic procedure was 32 min (range 18–77) min. The median blood loss was 645 g (range 50–5,370) g. There were no macroscopic or microscopic-positive margins seen in any of the patients. No cases were converted to conventional open hepatectomy with subcostal incision. The postoperative complications included surgical site infections in two patients, bile leakage in three patients, ileus in two patients, local liver infarction, portal venous thrombus, incisional hernia, and postoperative hyperbilirubinemia each in one patient. According to the Clavien–Dindo classification [4], the patient with portal venous thrombus and the patient with ileus was a grade III complication, whereas the others

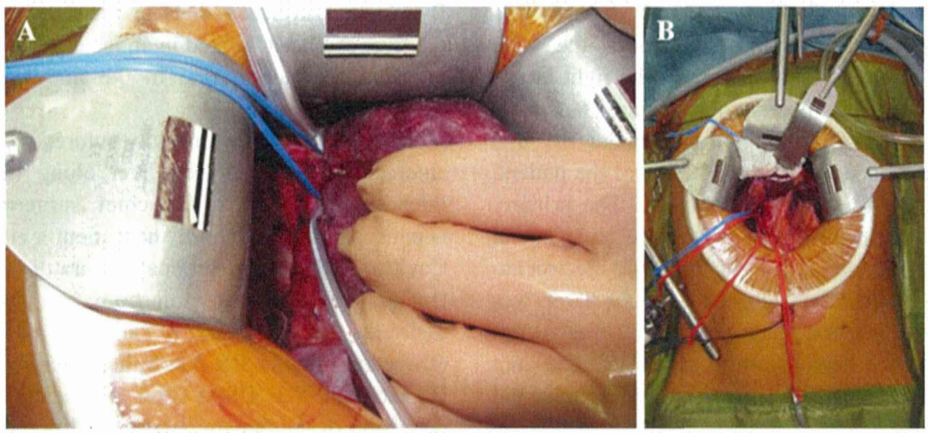

Fig. 2 **A** When mobilizing the right lobe of the liver, the surgeon can manage short hepatic veins, the right hepatic vein, and the inferior vena cava through the upper midline incision with adequate exposure. The *blue vessel loop* is encircling the right hepatic vein, and a Penrose drain also was passed around the right hepatic vein for the later hanging maneuver during parenchymal resection. **B** Hilar dissection under direct vision from the 12-cm upper midline incision. An Omni-tract surgical retractor is useful to maintain a good surgical field (Color figure online)

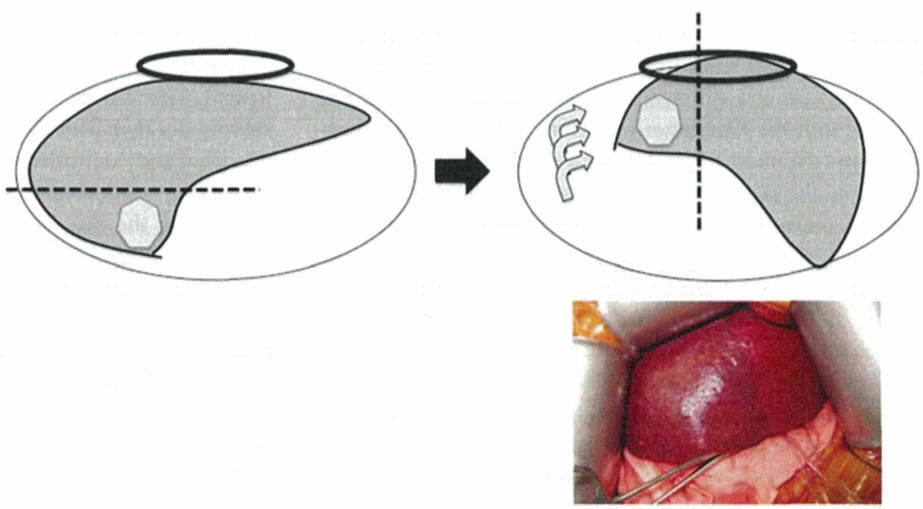

Fig. 3 With sufficient mobilization, the planned resection line can be exposed under an upper midline incision. The *dotted line* shows the planned resection line for a posterior sectionectomy. The photograph shows the demarcation line with control of the inflow to the posterior sector

were grade I. The median hospital stay was 13 days (range 8–123) days.

Comparing the findings for the hybrid technique and the open procedure for living donor left hemihepatectomy ($n = 24$ per group) and right hemihepatectomy ($n = 19$), no significant differences were seen in the duration of the operation [hybrid group: median 440 min (range 282–581) min; open hepatectomy: median 400 min (range 305–636) min]. In donor left hemihepatectomy, the intraoperative blood loss was significantly lower in the hybrid method group [median 510 g (range 50–1,950) vs. 637.5 g (range 250–3,150)]. No significant difference was seen in the intraoperative blood loss between open and hybrid donor right hemihepatectomy [median 625 g (range 320–1,800) vs. 710 g (range 234–2,550); Fig 4].

As a result, a hybrid method was successfully employed even in the cases that needed combined hepatectomy with hemihepatectomy and minor liver resection, or multiple minor liver resections for bilobular lesions, or a right posterior sectionectomy.

Case studies

Case 1

A 56-year-old male with hepatic carcinoid had multiple lesions in the right lobe and a lesion close to the middle hepatic vein. In addition, another tumor was present in the left-lateral section. The patient underwent right hemihepatectomy with local resection of the left-lateral section by a hybrid method. Radiofrequency ablation was performed for the lesion close to the middle hepatic vein with intraoperative ultrasound guidance (Fig. 5).

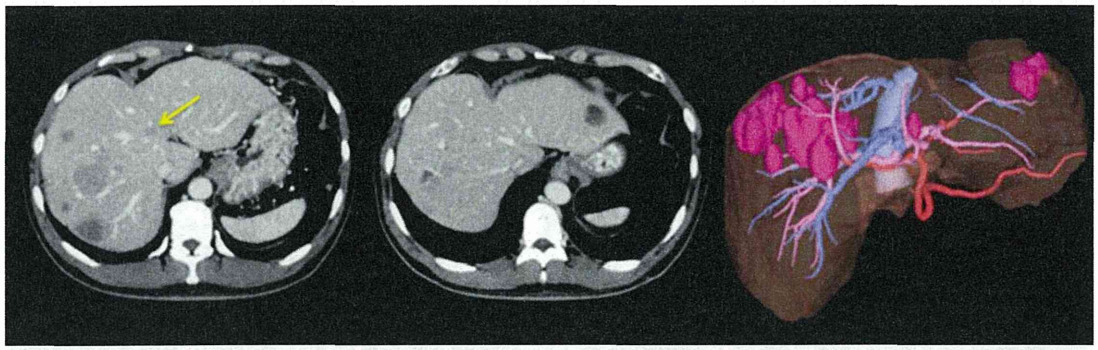

Fig. 4 CT images of multiple hepatic carcinoid tumors treated by hybrid resection, and a lesion treated by radiofrequency ablation (*arrow*). The *right panel* is a 3D reconstructed image made from CT scans obtained by a Synapse Vincent instrument (Fujifilm Medical, Tokyo, Japan)

Case 2

A 75-year-old male with multiple colorectal liver metastases. The tumors were located in segments 4, 6, and 7 (Fig. 6A). Because his hepatic functional reserve was disturbed as a result of the adverse effects of chemotherapy, a right hemihepatectomy was not possible. The patient underwent multiple local resections by a hybrid method through a 10-cm upper midline incision (Fig. 6B).

Case 3

A 74-year-old female with solitary hepatocellular carcinoma in segment 7 underwent an extended posterior sectionectomy by a hybrid method (Fig. 7).

Discussion

We herein reported the largest case series of hepatectomies performed by hybrid methods. To date, two other large case series employing hybrid methods have been reported [1, 5]. Our data further support the safety, feasibility, and efficacy of the hybrid approach for anatomical liver resection.

Although the term "hybrid method" is becoming common, there are some differences among institutions in terms of the following procedures: the location of the incision, the trocar locations, the extent of hand-assist procedures, etc. At our institution, we have adopted an upper midline incision for both the hand access and the open procedure. The hybrid method with an upper midline incision can be performed irrespective of the type of resection. Even posterior sectionectomies (S6 + 7) were consistently performed through the upper midline incision after hand-assisted right lobe mobilization. The benefits of anatomical resection for HCC have been reported [6, 7]. Hepatic parenchymal resection under direct vision in hybrid method can achieve meticulous and accurate resection with exposing vessels as well as conventional open procedure.

In addition to the effective application of the hybrid method for anatomical liver resections, we consider that a multiple partial hepatectomy is a good indication for the hybrid technique. Bilobular multiple liver tumors can be consistently managed through the short upper midline incision after the sufficient mobilization of the liver.

The upper midline incision contributes to the effective hand assist compared with access through a subcostal incision as a result of the wider working space. In terms of ergonomics, a hand-assist through the upper-midline incision may be more natural, because the rotation of the liver and the hand movement of the first assistant go in the same direction. Furthermore, the midline incision offers easy access to bilobular lesions. By using a GelPort hand device in place of trocar insertion, less port surgery can be achieved.

Hand-assisted procedures performed during the management of the area around the IVC and hepatic veins guarantees that there can be rapid emergency management of incidental massive bleeding. We consider that dividing the short hepatic veins and the subsequent encircling of the right hepatic vein or the common trunk of the middle hepatic vein and left hepatic vein can be more securely performed under direct vision compared to by a laparoscopic procedure. Once the right lobe is mobilized, the liver can be rotated to the left of the midline and retracted; therefore, the surgeon can easily approach the IVC and the right hepatic vein even through a minilaparotomy with a short upper midline incision. Because the IVC and hepatic hilum are basically located in the middle of the abdomen, the surgeon can approach these areas without stress through the midline under the exposure provided by the wound retractor and surgical retractor. The safety guaranteed by the hand-assist procedure seems to be superior to the magnification effect obtained during laparoscopy.

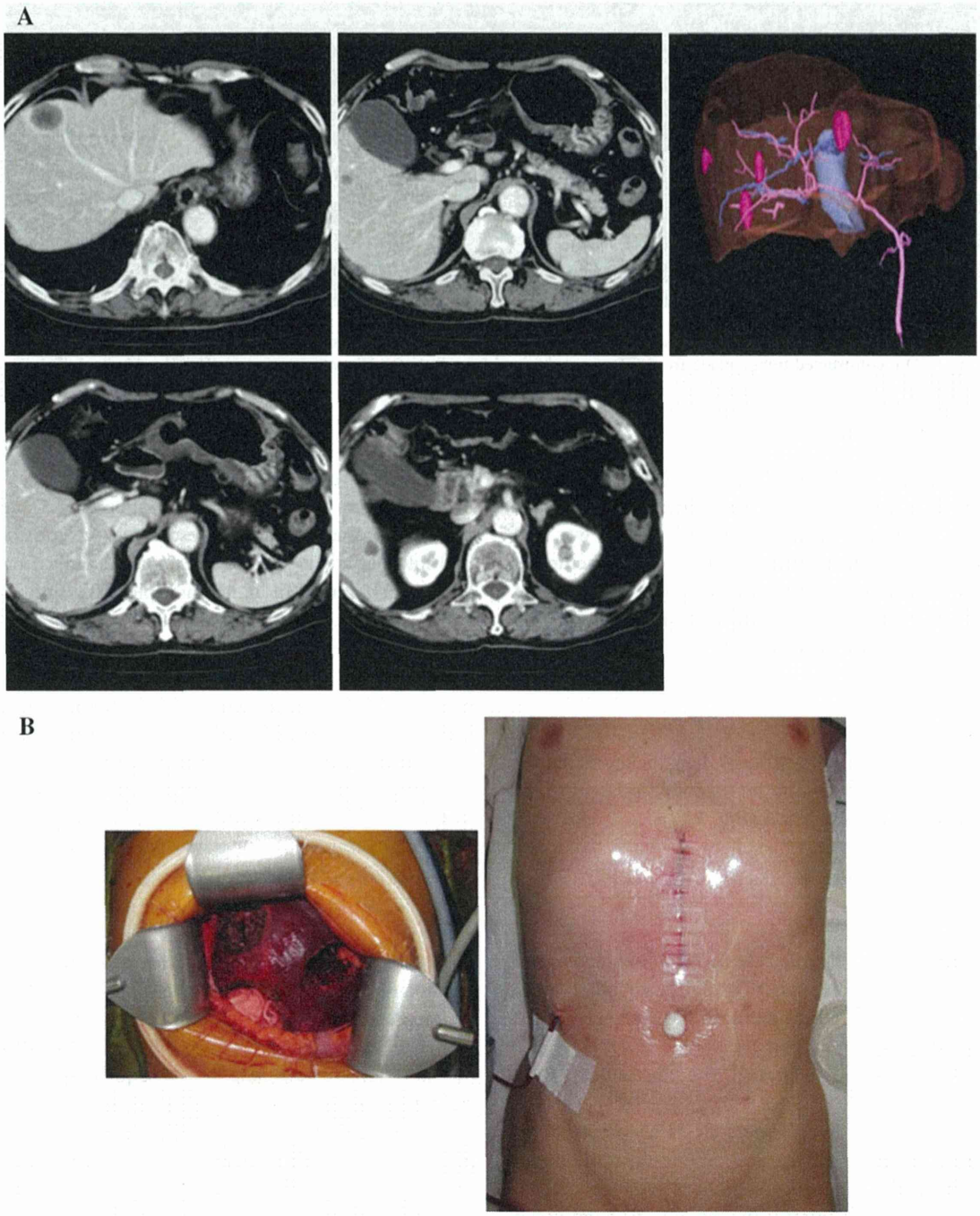

Fig. 5 **A** CT images of multiple colorectal metastases treated by a hybrid method. The *right panel* is a 3D reconstructed image made from CT scans obtained by a Synapse Vincent instrument (Fujifilm Medical, Tokyo, Japan). **B** Local resection was performed for four lesions because of insufficient liver functional reserve for major hepatectomy. A 10-cm upper midline incision was made for the hybrid method

Reducing blood loss is one of the goals of liver surgery, and several technical inventions have been introduced to achieve this, including the Pringle maneuver [8, 9] and selective vascular occlusion [10], among other techniques. Regarding surgical devices, the CUSA has contributed to the safety of hepatectomies by making it easy to identify the vessels during parenchymal transections. However, because the CUSA cannot seal tissues, meticulous ligation is required to avoid bleeding or bile leakage from the cut surface of the liver. Saline-linked electric cautery (SLC) is