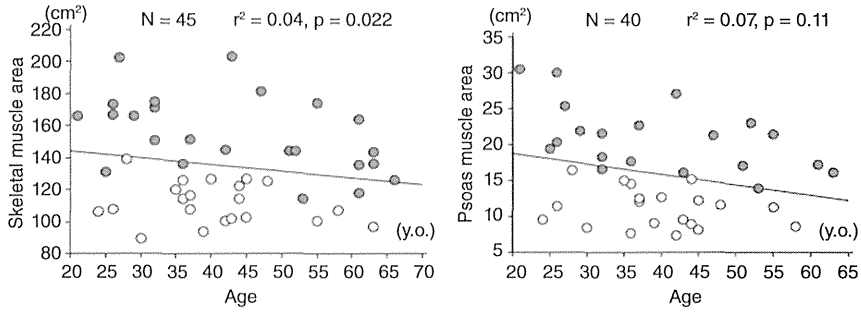

Figure 5 Relationship between age and measured skeletal or psoas muscle area in healthy adults. The measured muscle area was not significantly correlated with age. Closed circles for males, open circles for females.

accurately able to estimate sarcopenia, in contrast to psoas muscle area. A simple and new formula for estimating skeletal muscle area in each sex was established using data from healthy adults.

As shown in Table 1 and Figure 2, skeletal muscle area of males was significantly larger than that of females. Therefore, we established a separate formula for each sex. Although psoas muscle area is sometimes used to estimate sarcopenia,[11,12] we found that psoas muscle area did not correlate with any body size parameter. As shown in Figure 4, r^2 was relatively small compared with that of skeletal muscle. This suggests that the size of psoas muscle area is associated with individual variation and is not a reliable predictor of sarcopenia. Therefore, we used skeletal muscle area data in our validation of the formulae consisting of BSA.

Body surface area is a parameter frequently used in physiology and clinical medicine to normalize measures of biological function with respect to variations in body size and conformation.[13] Caloric needs, total body water and extracellular water are more closely related to BSA than to BW.[12] BSA correlates well with liver weight and has been used to calculate standard liver weight in the partial liver transplant setting,[14] first reported by Urata *et al.*[10,13] In patients with advanced cancer, severe muscle wasting, ongoing catabolism and abnormal metabolism can occur, which results in a negative balance of energy and protein.[1,7] Such a relationship between sarcopenia and abnormal metabolism suggested a correlation between muscle area and BSA.

Previous studies have shown a correlation between age and skeletal muscle mass.[15,16] However, a significant correlation was not obtained between age and skeletal muscle area in this study, as shown in Figure 5. A possible reason for this discrepancy is the difference in the distribution of age. The oldest donor in this study was 66 years old who would have been placed in the young group in a previous study.[15] Another reason may be that all donor candidates were healthy without any disease. Thus, the bias of the present study might have caused discrepancy between this and previous studies. Further studies including more aged patients are required to fully explain the discrepancy.

In the validation subjects, r^2 was relatively low as shown in Figure 6. The goal of this study was to establish a formula to define sarcopenia. Differences between the calculated mass and measured mass were between −22.8 and 18.7 cm^2 for males and between −2.5 and 21.3 cm^2 for females in this study. Thus, for example, when a patient has a measured muscle mass of 25 cm^2 fewer than the calculated mass using our formula like our representative case, the patient is sarcopenic. Addi-

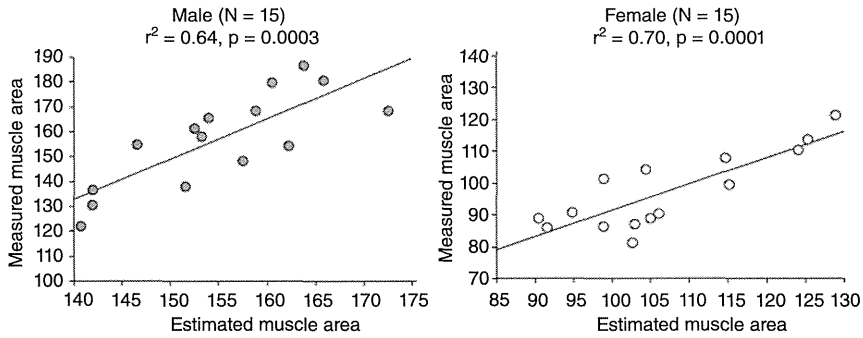

Figure 6 Relationship between measured skeletal muscle area and estimated skeletal muscle area in each sex. Estimated muscle area was correlated linearly with measured muscle area (left, $r^2 = 0.64$ for males, and right, $r^2 = 0.70$ for females). Closed circles for males, open circles for females.

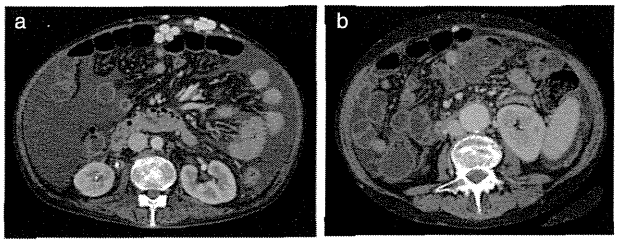

Figure 7 Two representative cases of sarcopenia. Computed tomography scans demonstrating two representative cases of sarcopenia. The patient in (a) had massive ascites and a remarkable depletion of skeletal muscle area. Measured skeletal muscle area in this patient was 69.3 cm^2. The patient in (b) also had remarkable depletion of skeletal muscle mass. Measured skeletal muscle area was 63.1 cm^2.

tional studies are needed to evaluate diagnostic ability, sensitivity, specificity, accuracy, positive predictive value and negative predictive value in patients with liver disease.

There may be some potential concerns in using skeletal muscle for sarcopenia in liver disease. For instance, in patients with non-alcoholic fatty liver disease, fat deposition in muscle may affect the estimation of skeletal muscle.[17] In addition, a recent study reported that mid-arm muscle circumference, an index for skeletal muscle, did not correlate with severity of liver disease.[18] The relationship between mid-arm muscle circumference and CT-based skeletal muscle area should be compared in patients with liver disease.

In conclusion, we analyzed skeletal muscle area using CT data from healthy adults and found that BSA significantly correlated with skeletal muscle area. Sarcopenia can be defined as a difference between measured and calculated data using the newly established formula.

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ELSEVIER

Chronic Immune-Mediated Reaction Syndrome as the Cause of Late Graft Mortality in Living-Donor Liver Transplantation for Primary Biliary Cirrhosis

N. Harimoto[a,*], T. Ikegami[a], H. Nakagawara[a], Y.-I. Yamashita[a], T. Yoshizumi[a], H. Uchiyama[a], Y. Soejima[a], T. Ikeda[a], K. Shirabe[a], S. Aishima[b], Y. Oda[b], and Y. Maehara[a]

From the Departments of [a]Surgery and Science and [b]Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

ABSTRACT

Introduction. Few studies to date have investigated the causes of late graft mortality after living-donor liver transplantation (LDLT) for primary biliary cirrhosis (PBC).

Patients and Methods. Fifty-five LDLTs for PBC were retrospectively reviewed. Factors prognostic of graft survival after LDLT were investigated, and histologic findings in patients with late graft loss were assessed.

Results. The 1-, 5-, and 10-year cumulative graft survival rates were 85.1%, 82.5%, and 66.9%, respectively. Multivariate Cox regression analysis found that male donor and ≥4 HLA mismatches were independently associated with poor graft survival. Among the 13 grafts lost, 5 were lost >1 year after LDLT, including 1 each due to chronic rejection, veno-occlusive disease, and obliterative portal venopathy, and 2 to other causes. Pathologic reviews of the serial biopsy specimens and explanted grafts from these 5 patients, with graft rejections from "chronic immune-mediated reaction syndrome," showed reciprocal changes over time. No patient died of recurrent PBC.

Conclusions. Male donor and ≥4 HLA mismatches were independent factors associated with poor graft survival. Late graft mortality after LDLT for PBC in some patients was due to chronic immune-mediated reaction syndrome, including chronic rejection, veno-occlusive disease, and obliterative portal venopathy, but not to recurrent PBC.

PRIMARY biliary cirrhosis (PBC) is a cholestatic disease characterized by granulomatous destruction of the bile ducts and the appearance in serum of antimitochondrial antibodies. The disease is progressive and leads to liver failure in many patients. Liver transplantation (LT) has shown efficacy in patients with PBC, with good survival outcomes and improvements in quality of life [1–3]. Improvements in surgical techniques and organ preservation in Japan has enhanced long-term survival after living-donor LT (LDLT) in patients with PBC. PBC recurrence rates after LT have been reported in 0.6% to 32% of grafts [4–10], although PBC recurrence has little influence on graft and patient survival [11]. One study reported that the proportion of grafts lost due to PBC recurrence 10 years after LT was 2% [12], whereas another study reported that recurrent PBC was not associated with graft loss in patients followed up for 20 years [13].

Although needle biopsy is necessary for the differential diagnosis of recurrent PBC, its histologic diagnosis is much more difficult in transplanted livers because of the occurrence of many graft abnormalities, including rejections and

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*Address correspondence to Norifumi Harimoto, MD, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: nharimotoh1@fukuoka.email.ne.jp

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adverse drug reactions, as well as biliary strictures. There is little information regarding long-term clinical outcome of LDLT for PBC. We therefore retrospectively reviewed investigated factors associated with graft survival in patients who underwent LDLT for PBC and examined entire explanted livers for the cause of graft loss.

PATIENTS AND METHODS

Patient Characteristics

Of the 401 LDLT operations performed at Kyushu University Hospital (Fukuoka, Japan) from October 1996 to December 2012, a total of 55 were adult-to-adult LDLTs for PBC. Mean ± SD follow-up time was 5.06 ± 4.17 years. The study protocol was approved by the Ethics and Indications Committee of Kyushu University.

Graft Selection

Grafts were selected as described previously [14]. Left lobe grafts were the primary graft if the graft volume/standard live volume (GV/SLV) ratio was ≥35%. Right lobe grafts were used if the simulated GV/SLV ratio of the left lobe graft was <35% and the donor's remnant liver volume was ≥35%. Posterior segment grafts were used if their GV/SLV ratio was ≥35% with isolated branching of the posterior pulmonary vein (PV).

Transplant Procedures

The transplant procedures for both the donors and recipients have been described previously [15]. Donor parenchymal transection was performed by using the Cavitron Ultrasonic Surgical Aspirator (Valleylab Inc, Boulder, Colo, United States) with the hanging maneuver. After donor hepatectomy, the graft was perfused, weighed, and stored in University of Wisconsin solution (Viaspan, DuPont Pharmaceuticals, Wilmington, Del, United States). After recipient hepatectomy, the grafts were transplanted in a piggyback fashion. The orifice of the recipient's hepatic vein was enlarged by making an incision on the vena cava to allow the venous anastomosis to provide sufficient outflow. The PV was reconstructed and reperfused, followed by arterial reconstruction under a microscope. Whenever possible, biliary reconstruction involved duct-to-duct biliary anastomosis.

Splenectomy

The indications for splenectomy during LDLT included hypersplenism and PV pressure of ≥20 mm Hg. Tieless splenectomy was performed by using a vessel-sealing system (LigaSure Atlas, Valleylab Inc) and endostapling devices (Echelon Staplers 60 2.5 mm, Ethicon Endo-Surgery Inc, Blue Ash, Ohio, United States) [16].

Immunosuppression

The basic immunosuppression protocol consisted of tacrolimus or cyclosporine with mycophenolate mofetil and steroids. Mycophenolate mofetil was used from patient #42 onward. The target tacrolimus and cyclosporine concentrations 1 month after LDLT were 10 to 14 ng/mL and 150 to 250 ng/mL, respectively, decreasing to 7 to 10 ng/mL and 100 to 150 ng/mL over the next few months. The initial dose of mycophenolate mofetil was 2 g/d, tapered to 1 g/d over 1 to 3 months and to 0 at 6 months. Each patient received 1 g of methylprednisolone immediately after reperfusion, which was decreased from 200 to 20 mg/d over the following week and was then switched to oral prednisolone, which was tapered off at 3 months.

Posttransplant Medical Care

Perioperative prophylaxis consisted of intravenous cefotaxime (4 g/d) and ampicillin sulbactam (6 g/d) 4 times per day for 3 days, starting 30 minutes before surgery. The central venous catheters that had been placed in the internal jugular vein before surgery were usually removed within 5 days after LDLT and replaced with peripheral catheters. Most patients required prolonged ascites drainage over 14 days after left lobe LDLT. The amount of ascites drained via the indwelling abdominal drains was recorded. Fluid loss due to ascites drainage was corrected by administration of intravenous saline containing 5% albumin to maintain a serum albumin level >3.5 mg/dL. All recipients were maintained on ursodeoxycholic acid (5–15 mg/kg per day) and methylprednisolone during the follow-up period. A liver biopsy was performed when patients showed clinical or biochemical signs of graft dysfunction. Protocol biopsies were not performed.

Histologic Assessments

All resected specimens were cut into serial 5- to 10-mm-thick slices and fixed in 10% formalin. After macroscopic examination, the slice with the greatest dimensions was trimmed, embedded in paraffin, and cut into 4-μm microscopic sections. The sections were stained with hematoxylin and eosin or Masson's trichrome. A diagnosis of acute or chronic rejection (CR) was based on the 1995 Banff criteria [17,18]. A diagnosis of recurrent PBC was confirmed by detection of florid duct lesions with mixed portal inflammatory infiltrates.

Statistical Analysis

Categorical variables were compared by using the χ^2 test or the Fisher exact test. Continuous variables were expressed as mean values ± SDs and compared by using the Student t tests. Graft survival was analyzed by using the Kaplan-Meier method and compared with the log-rank test. All statistical analyses were performed with Statview version 5.0 (Abacus Concepts, Inc, Berkeley, Calif, United States), with P values <.05 considered statistically significant.

RESULTS

The 1-, 5-, and 10-year cumulative graft survival rates were 85.1%, 82.5%, and 66.9%, respectively. Univariate analysis showed that male liver donor, ≥4 HLA mismatches, and absence of splenectomy were factors significantly associated with reduced graft survival after LDLT, whereas immunosuppressive regimens were not (Table 1). For example, the 5-year graft survival rates were 49% in patients with ≥4 HLA mismatches and 87.0% in patients with <4 HLA mismatches (Fig 1A) and 74.6% when donors were male and 100% when donors were female (Fig 1B). Multivariate Cox proportional hazards model of all clinical characteristics showed that male donor and ≥4 HLA mismatches were independent factors for poor graft survival, whereas lack of splenectomy was not (Table 2).

Of the 55 LDLT recipients, 13 (23.6%) died during the follow-up period. Eight of these patients (14.5%) died within 6 months after LDLT, including 3 from primary graft

Table 1. Univariate Analysis of Clinicopathologic Factors Associated With Graft Survival After LDLT

Factor	Patients	Survival at 3 Years (%)	*P* Value
Gender of recipient			
Male	7	100	.216
Female	48	80.2	
Age of recipient, y			
<50	21	88.0	.221
≥50	34	74.7	
Gender of donor			
Male	37	74.6	.039
Female	18	100.0	
Age of donor, y			
<40	22	66.6	.055
≥40	33	89.1	
Child-Pugh classification			
A + B	14	70.1	.299
C	41	86.3	
MELD			
≥25	8	87.5	.935
<25	47	81.8	
HLA mismatches			
≥4	14	49.0	.005
<4	32	87.0	
Splenectomy			
Yes	24	95.8	.0325
No	31	79.5	
GV/SLV, %			
>35	41	77.3	.246
≤35	14	100	
Mean portal pressure at closure, mm Hg			
≥25	36	80.9	.977
<25	10	78.7	
Graft			
Left	13	79.9	.564
Right	42	91.7	
CNI			
Cyclosporine	23	86.7	.425
Tacrolimus	32	76.4	
Antimetabolites (MMF, Aza)			
Yes	25	73.0	.080
No	30	87.1	
Postoperative biliary stricture			
Yes	9	100	.944
No	46	78.8	
Acute rejection			
Yes	21	85.7	.262
No	34	80.7	
CMV infection			
Yes	15	83.0	.780
No	40	78.3	

Abbreviations: AZA, azathioprine; CMV, cytomegalovirus; CNI, calcineurin inhibitor; GV/SLV, graft/standard liver volume; LDLT, living-donor liver transplantation; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil.

dysfunction (at 1, 1, and 2 months), 2 from intra-abdominal bleeding (at 1 and 3 months), 2 of liver infarction (at 2 and 4 months), and 1 of congestion of middle hepatic vein tributaries (at 4 months). Table 3 shows the cause of delayed graft loss after LDLT for PBC.

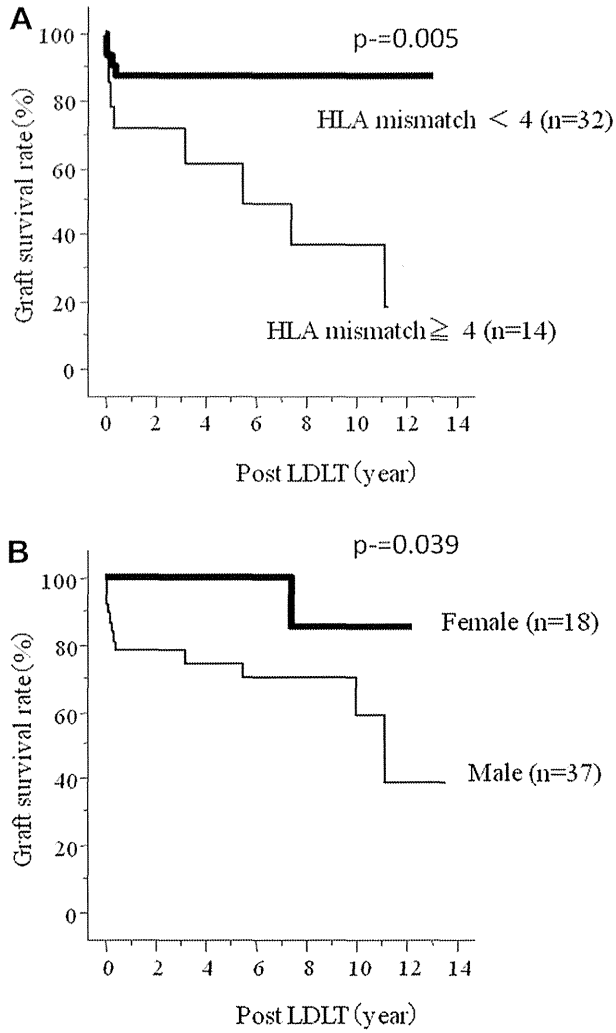

Fig 1. Graft survival after living-donor liver transplantation (LDLT) for primary biliary cirrhosis in patients receiving grafts from **(A)** donors with <4 and ≥4 HLA mismatches and **(B)** male and female donors. Graft survival was significantly poorer in patients with ≥4 HLA mismatches than <4 mismatches and in patients receiving grafts from male than female donors.

The remaining 5 patients died >1 year after LDLT. Examination of the explanted livers showed that the causes of graft failure included CR (patient #1), veno-occlusive disease (VOD; patient #3), and obliterative portal venopathy (OPV; patient #4). The other 2 patients died of spontaneous retroperitoneal hematoma (patient #2) and secondary biliary cirrhosis due to biliary stricture (patient #5). Patient #1 exhibited elevated liver enzyme levels 3 months after LDLT, with liver biopsy specimens revealing evidence of VOD. Increased immunosuppression was not effective, and a second liver biopsy was performed. This patient was diagnosed with CR and VOD. The graft was lost 3.4 years after LDLT due to CR. Patient #3 exhibited increased alkaline phosphatase levels, beginning 6 years after LDLT,

Table 2. Multivariate Analysis of Factors Independently Predictive of Graft Survival

Variable	Hazard Ratio	95% CI	*P* Value
Gender of donor: male	8.5	1.1–67.0	.010
HLA mismatch: ≥4	5.0	1.5–17.2	.042
Splenectomy: no	5.2	0.7–41.8	.119

Abbreviation: CI, confidence interval.

followed by the development of liver dysfunction. Results of a liver biopsy revealed recurrent PBC and VOD. Despite increased immunosuppression, the liver failed, and the patient was diagnosed with VOD at the time of graft loss. Patient #4 experienced acute cellular rejection 4.2 years after LDLT and required steroid pulse therapy. Results of a liver biopsy revealed VOD and ACR. Alkaline phosphatase levels began to increase 7.6 years after LDLT, followed by the development of liver dysfunction. Results of a liver biopsy revealed recurrent PBC and VOD. Liver failure developed despite increased immunosuppression, and the patient was finally diagnosed with OPV at graft loss. Increased immunosuppression in these patients included the addition of mycophenolate mofetil. None of these 3 patients was diagnosed with recurrent PBC at the time of graft loss.

Of the 5 patients who died >1 year after LDLT, 2 (patients #3 and #4) were histologically diagnosed with cholangitis of the interlobular bile duct (suggesting PBC) before LDLT. After LDLT, acute CR was histologically observed in patients #2, #4, and #5; CR in patient #1; VOD in patients #1, #3, and #4; and OPV in patient #4. None of these patients underwent splenectomy at the time of first LDLT.

Figure 2 displays the histologic findings in these patients. Patient #1, who was diagnosed with CR at graft death, exhibited histologic evidence of duct loss with degenerative epithelial damage and centrilobular fibrosis. Patient #3 had centrilobular congestion, central venulitis, and obliteration and was diagnosed with VOD. Patient #4 exhibited histologic evidence of obliterative changes in the portal veins without fibrosis and was diagnosed with OPV.

DISCUSSION

Multivariate analysis of 55 retrospectively evaluated patients who underwent LDLT for PBC indicated that male liver donor and ≥4 HLA mismatches were independently prognostic of poor graft survival. Similarly, a previous study reported that the number of HLA mismatches between recipients and donors significantly affects postoperative survival rates after LDLT for PBC [19]. In contrast, HLA incompatibility did not seem to have a significant impact on patient survival after LDLT for end-stage liver disease [20–22]. The pathophysiology of PBC is strongly associated with humoral autoimmunity, and HLA mismatches may induce and/or exacerbate humoral immunoreactions. Four of the 5 patients who experienced late graft loss received grafts from non–blood-related donors. Moreover, 4 of these donors were males (all 4 were the husbands of the recipients). Cumulative postoperative survival rates after LDLT for PBC were found to be significantly higher when donors were not blood relatives of the recipients [19].

Lack of splenectomy was significantly associated with poor prognosis in univariate (not multivariate) analysis. Splenectomy reportedly prolonged the effects of corticosteroids in mouse models of autoimmune hepatitis (AIH) and suppressed the development of AIH [23]. Patients with severe AIH have a high potential for recurrence after LT, increasing the likelihood of graft loss. Splenectomy may overcome this insufficiency, inducing prolonged remission of AIH. The same mechanism may occur in patients who undergo LT for PBC. In these patients, splenectomy may decrease humoral immunoreactions induced by HLA mismatches.

Pathologic reviews of the serial biopsy specimens and explanted grafts in patients with late mortality from CR, VOD, and OPV, collectively termed "chronic immune-mediated reaction syndrome," revealed reciprocal changes among them over time. None of these patients, however, died of recurrent PBC as the final diagnosis. Late cellular rejection may cause late liver allograft dysfunction [24]. CR in a biopsy specimen was defined as: (1) biliary epithelial senescence changes affecting a majority of the bile ducts with or without bile duct loss; (2) foam cell obliterative arteriopathy; or (3) bile duct loss affecting >50% of the portal tracts. Inadequate immunosuppression was usually accompanied by CR but not always. Immunologic pathogens

Table 3. Causes of Delayed Graft Loss After LDLT for PBC

	Patient No.				
Factor	1	2	3	4	5
Recipient (age [y]/sex)	34/F	57/F	37/F	47/F	47/F
Donor (age [y]/sex)	52/M	47/M	51/M	19/M	49/M
Relationship between donor and recipient	NBR	NBR	NBR	BR	NBR
Graft type	Left	Left	Left	Left	Left
GRWR	0.88	0.81	0.77	1.07	1.17
GV/SLV, %	42.6	35.7	31.6	49.3	48.6
HLA mismatch	4	6	5	NA	6
Splenectomy	No	No	No	No	No
Time to death, y	3.2	5.5	7.5	10.1	11.3
Complications after LDLT					
ACR	×	○	×	○	○
CR	○	×	×	×	×
VOD	○	×	○	○	×
OPV	×	×	×	○	×
Recurrent PBC	×	×	○	○	×
Cause of graft loss	CR	Retroperitoneal hematoma	VOD	OPV	Secondary biliary cirrhosis

Abbreviations: ACR, acute cellular rejection; BR, blood relative; CR, chronic rejection; F, female; GRWR, graft recipient weight ratio; GV/SLV, graft volume/standard liver volume; LDLT, living-donor liver transplantation; M, male; NA, not available; NBR, non–blood relative; OPV, obliterative portal venopathy; PBC, primary biliary cirrhosis; VOD, veno-occlusive disease.

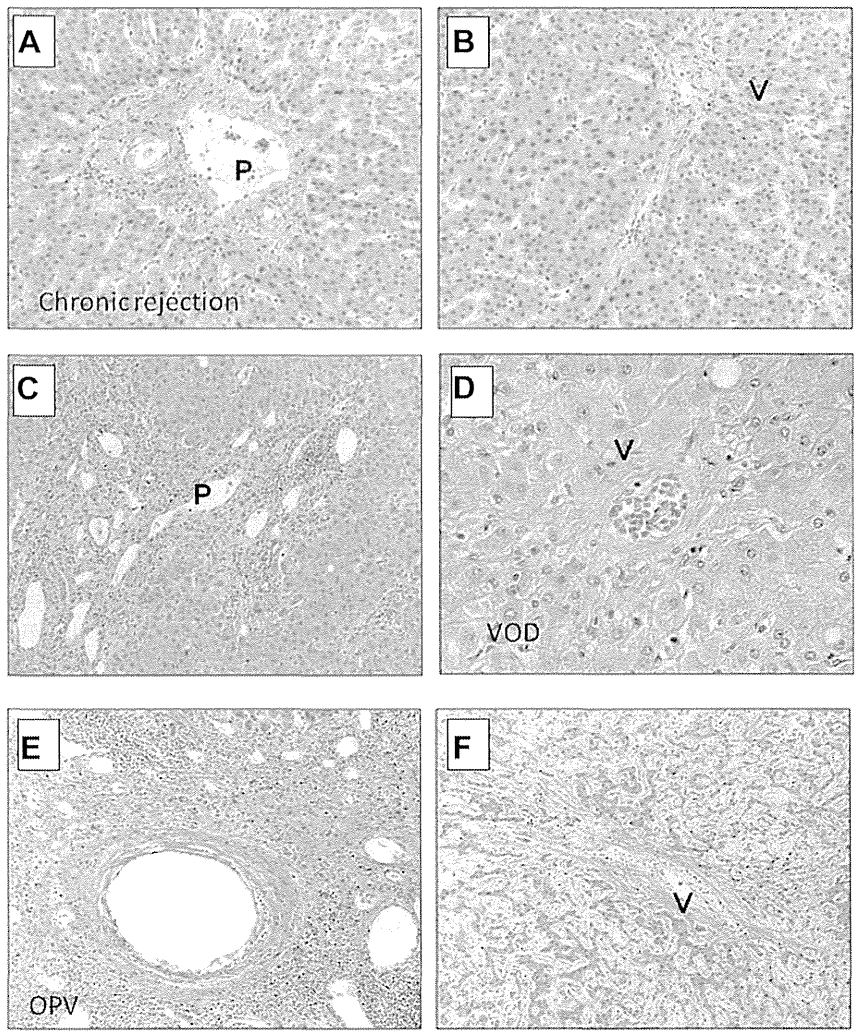

Fig 2. Histologic findings at the time of graft loss in (**A** and **B**) patient #1, (**C** and **D**) patient #3, and (**E** and **F**) patient #4. These 3 patients were diagnosed with chronic rejection, veno-occlusive disease (VOD), and obliterative portal venopathy (OPV), respectively. Hematoxylin and eosin staining; original magnification ×100 for **A**, **B**, **C**, **E**, and **F** and ×200 for **D**. Abbreviations: P, portal area; V, central vein area.

have not been identified to date. VOD has been defined as sinusoidal or perivenular fibrosis with inflammation, necrosis, hemorrhage, and/or endothelialitis in zone 3. Although VOD rarely causes liver graft loss, life-threatening VOD has been reported after LDLT [25]. Moreover, histologic features of VOD after LT have been observed in 2.3% of patients, with VOD possibly being immune mediated [26]. OPV has been defined as primary occlusion of the intrahepatic portal veins in the absence of cirrhosis, inflammation, and hepatic neoplasia [27]. Portal vasculopathy is prominent in medium-sized and preterminal veins, which are easily accessible on liver biopsy. OPV is considered a thrombotic- or immune-mediated disorder. Several studies have assessed the relationship between portal venopathy and PBC [28,29]. Our patient with OPV also experienced recurrence of PBC, suggesting that OPV may be a subtype of recurrent PBC. The pathophysiology of each of these conditions (CR, VOD, and OPV) is strongly associated with autoimmunity, although the mechanisms are not clear.

In conclusion, this retrospective analysis revealed causes of graft loss in patients who underwent LDLT for PBC. Male donor and ≥4 HLA mismatches were independent predictors of poor graft survival. CR, VOD, and OPV were found to be causes of graft loss, whereas recurrent PBC was not, suggesting that chronic immune-mediated reactions were among the pathologic conditions associated with graft loss. The mechanisms linking chronic immune reaction with long-term graft loss in patients with PBC require further investigation.

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CASE REPORT

Thrombotic microangiopathy caused by severe graft dysfunction after living donor liver transplantation: report of a case

Daisuke Matsuda · Takeo Toshima · Toru Ikegami · Norifumi Harimoto · Yo-ichi Yamashita · Tomoharu Yoshizumi · Yuji Soejima · Tetsuo Ikeda · Ken Shirabe · Yoshihiko Maehara

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Abstract Thrombotic microangiopathy (TMA) is a life-threatening complication after transplantation including liver transplantation, and its typical clinical picture is characterized by hemolytic anemia, thrombocytopenia, renal dysfunction, neurological abnormalities, and fever. We report the case of a 56-year-old female with end-stage liver disease who underwent living donor liver transplantation (LDLT), and whose postoperative course was characterized by renal failure and progressive hyperbilirubinemia. Two weeks after LDLT, she started to show progressive thrombocytopenia, anemia, oliguria, and encephalopathy. From these clinical manifestations, she was diagnosed as having TMA and underwent plasma exchanges with continuous hemodialysis under temporary holding calcineurin inhibitors. The patient promptly responded to the treatment, with improved hematological, hepatic, and renal conditions, and was discharged from hospital a month later in a stable condition. We describe this case of TMA after LDLT with poor graft function and extensively review the disease in liver transplant recipients.

Keywords Living donor liver transplantation · Thrombotic microangiopathy · Graft dysfunction · Plasma exchange

Abbreviations

TMA	Thrombotic microangiopathy
LDLT	Living donor liver transplantation
AIH	Autoimmune hepatitis
PBC	Primary biliary cirrhosis
CNI	Calcineurin inhibitor
POD	Postoperative day
PE	Plasma exchange
CHDF	Continuous hemodiafiltration
ADAMTS13	A disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13
vWF	von Willebrand factor

D. Matsuda · T. Toshima (✉) · T. Ikegami · N. Harimoto · Y. Yamashita · T. Yoshizumi · Y. Soejima · T. Ikeda · K. Shirabe · Y. Maehara
Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
e-mail: toshima@surg2.med.kyushu-u.ac.jp

Introduction

Living donor liver transplantation (LDLT) has been established as a modality to treat end-stage liver diseases, especially in Eastern countries, where the lack of deceased donors has restricted the number of liver transplants [1, 2]. However, functional recovery of a partial living donor liver graft is not always satisfactory through a combination of factors, including small graft volume, higher donor age, and deteriorated recipient condition [1, 2]. Because of their poor metabolic condition with such dysfunctional LDLT grafts, patients may suffer from secondary life-threatening diseases.

Thrombotic microangiopathy (TMA) is a systemic microvascular occlusive disorder that is characterized by progressive hemolytic anemia, thrombocytopenia, renal dysfunction, encephalopathy, and sometimes fever [3]. It has been reported that secondary TMA could occur in association with various disorders, including bacterial infection, systemic inflammation, and drug interactions, especially with calcineurin inhibitors [3, 4]. We describe a case with a typical clinical presentation of TMA with decreased ADAMTS-13 (the 13th member of the 'a

disintegrin-like and metalloprotease with thrombospondin repeats' family of metalloproteases) secondarily caused by severe primary graft dysfunction after LDLT. The case was successfully treated by plasma exchanges.

Case report

A 56-year-old female with end-stage liver disease caused by primary biliary cirrhosis was referred to our hospital for possible LDLT. Her hepatic profile included total bilirubin 26.1 mg/dl, albumin 2.9 g/dl, aspirate aminotransferase 77 IU/l, creatinine 0.81 mg/dl, and international normalized ratio (INR) 1.69. Her model for end-stage liver disease score was 25. Because of the pneumonedeme and bilateral moderate pleural effusion, the blood gas examination in 7 l/min oxygen mask revealed unfavorable results with pH 7.441, pCO_2 29.5, pO_2 70.0, HCO_3 21.7, and BE −3.2; in addition, the patient required dopamine with 5γ for blood pressure sustention. Therefore, she was transferred to the intensive care unit owing to her deteriorated general condition. The patient underwent LDLT using a left lobe graft donated by her 51-year-old brother, who had the identical blood type. The weight of the liver graft was 426 g, which represented 41.0 % of the standard liver weight of the recipient. The surgical field during LDLT was bloody owing to her severe coagulopathy. The operating time was 583 min, and the blood loss was 3,140 ml. The patient received 8 units of matched arterial platelets (MAP), 10 units of fresh frozen plasma (FFP), and 20 units of platelets to maintain an INR of ≥1.5.

After LDLT surgery, the patient developed acute renal failure and was put on continuous hemodiafiltration for 3 days after postoperative day (POD) 3. After recovery from the renal failure by vigorous supportive treatment, including infusion of fluids and FFP, she was transferred to an in-patient ward on POD 12 and received regular immunosuppression treatment, which included tacrolimus,

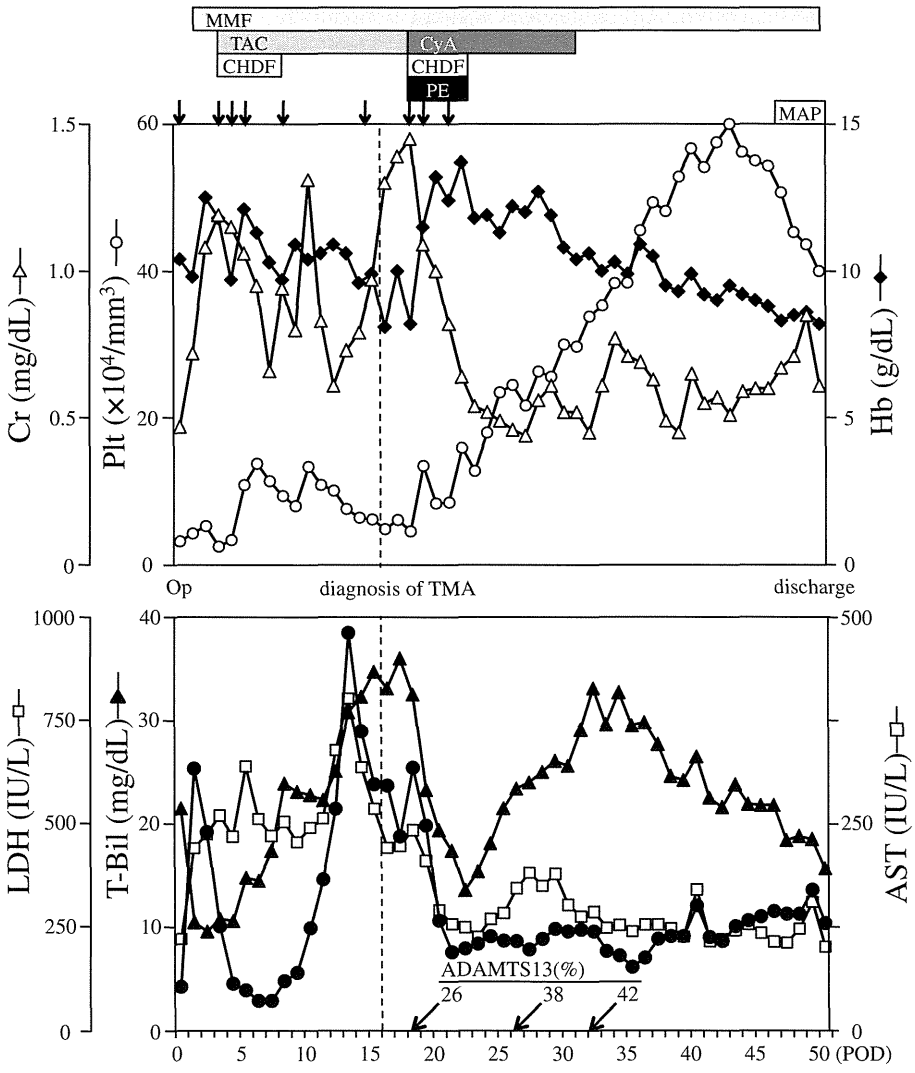

Fig. 1 Postoperative course. On postoperative day 16, the patient showed aberrant blood works and symptoms indicating thrombotic microangiopathy: anemia, thrombocytopenia, increased serum creatinine, apparent somnolence, hyperbilirubinemia, increased lactate dehydrogenase, and deteriorated activity of a disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13. *ADAMTS13* a disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13, *CHDF* continuous hemodiafiltration, *Cr* creatinine, *CyA* cyclosporine, *Hb* hemoglobin, *LDH* lactase dehydrogenase, *MMF* mycophenolate mofetil, *PE* plasma exchange, *Plt* platelet, *POD* postoperative day, *TAC* tacrolimus, *T-Bil* total bilirubin

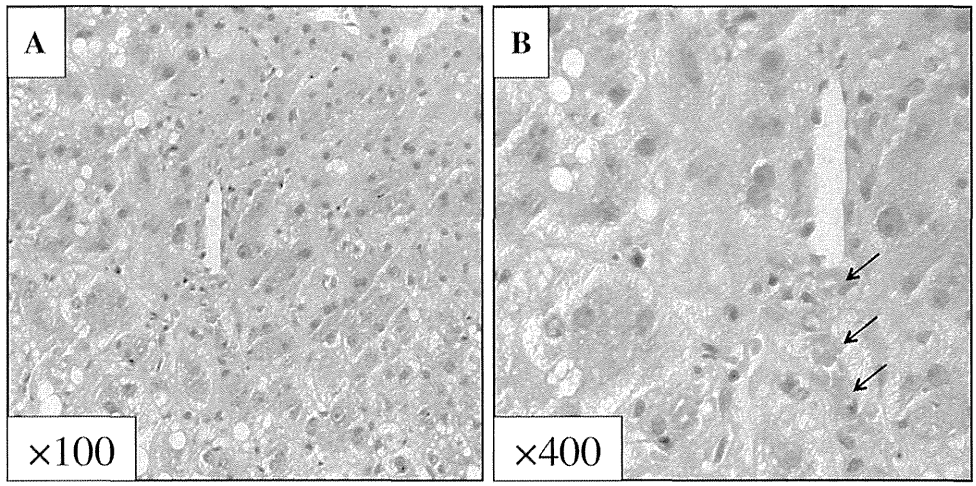

Fig. 2 **a** Lower and **b** higher magnification views of the liver biopsy. Marked ballooning hepatocytes and mild cholestasis were evident not around the portal tracts but at the central veins. Associated red blood cells (*arrows*), which accumulated and showed a rolling appearance at the central veins, indicate thrombotic microangiopathy. Little lymphoid aggregation around the central vein was noted

mycophenolate mofetil, and steroids (Fig. 1). Because of progressive elevation of serum total bilirubin level of 30.8 mg/dl on POD 13, a percutaneous graft liver biopsy was performed. The biopsy findings were compatible with primary graft dysfunction, which is characterized by hepatocyte ballooning and cholestasis without lymphocyte aggregations and bile duct damage (Fig. 2). Thus, we continued supporting treatment only with the infusion of fluids and albumin for ascites drainage.

On POD 16, however, the patient started to develop anemia (hemoglobin dropped from 11.2 to 8.1 g/dl over 24 h, minimum 7.6 g/dl), thrombocytopenia (platelet count dropped from 7.8 to 3.3 over 24 h), oliguria (450 ml/day), and apparent somnolence. Blood work showed decreased ADAMTS-13 (26 %) and increased lactate dehydrogenase (497 IU/l). The blood smear revealed the presence of fractionated erythrocytes on POD 16. The liver biopsy examination (Fig. 2) and blood smear results indicated TMA with red blood cells fractioned and accumulated. From her clinical symptoms, we diagnosed the patient as suffering from TMA, and we transferred her to the intensive care unit. There, she received daily plasma exchanges with 40 units of FFP for 4 days, with continuous hemodiafiltration under holding tacrolimus (Fig. 1).

After the treatment, the progression of anemia and thrombocytopenia apparently stopped, and there was improved renal function and recovery of the graft hepatic function, even after induction of cyclosporine. The patient was discharged from hospital with a stable graft function, and she showed a remarkably improved general condition.

Discussion

TMA is a rare but life-threatening secondary disorder caused by various factors, including bacterial infection, systemic inflammatory processes, and drug interactions [3–5]. It has been supposed that the decrease in ADAMTS-13, which has a metalloproteinase activity and specifically cleaves the multimeric von Willebrand factor (vWF), plays a major role in TMA [4]. vWF is a glycoprotein that is essential for platelet adhesion. It is produced by endothelial cells as multimeric vWF with higher biological activity [4, 6], and this multimeric vWF has the ability to induce platelet aggregation under high shear stress of blood flow [4, 6]. ADAMTS-13 is produced mainly by hepatocytes, and it cleaves multimeric vWF into monomeric forms with lower coagulation activity [6].

In the congenital absence of ADAMTS-13 or with acquired immunoglobulin production against ADAMTS-13, the disease process of TMA is clear [3]. In the majority of clinical cases with TMA, however, the pathogenesis for the decrease in ADAMTS-13 is not fully understood. For example, TMA caused secondary to *Escherichia coli* infection with hemorrhagic colitis is possibly mediated by the production of Shiga toxin by bacteria [7]. The mechanisms whereby Shiga toxin causes the decrease in ADAMTS-13 have not been elucidated.

The diagnostic criteria for TMA are [4–6]—(1) the presence of thrombocytopenia (platelet count $<5.0 \times 10^4/mm^3$) or the progressive decline in platelet counts (decrease of $>3.0 \times 10^4/mm^3$ within 24 h); (2) microangiopathic hemolytic anemia (hemoglobin <8.0 g/dl); (3) sharply elevated levels of serum lactate dehydrogenase (typically >500 IU/l); (4) the presence of fractionated erythrocytes in a blood smear; and (5) severe deficiency in ADAMTS-13 activity (<5 % in normal plasma) or prevalence of ADAMTS-13-specific antibodies categorized as immunoglobulin G isotypes. In this case, all of items (1–4) were met on POD 16; however, item (5) was not clear. Considering the marked response to the treatment of daily plasma exchanges, which was not effective therapy for TMA subtypes with severe deficiency in ADAMTS-13 activity, it might be highly possible that the patient has ADAMTS-13-specific antibodies.

The development of TMA after organ transplantation as being possibly due to calcineurin inhibitors has been well documented with kidney transplants [8, 9]. The pathogenesis could be attributed to the vasoconstriction and endothelial injuries caused by calcineurin inhibitors, including both tacrolimus and cyclosporine. Effective treatment in such TMA cases caused by calcineurin inhibitors is also temporary, and it involves holding or switching such medications and implementing plasma exchanges [9].

In the case presented here, TMA was caused secondary to severe graft dysfunction, with hyperbilirubinemia and lower protein production. Primary graft dysfunction was defined as graft insufficiency with possible in-hospital mortality, without technical, anatomical, immunological, or hepatitis-related issues [10, 11], and graft insufficiency was defined as hyperbilirubinemia (total serum bilirubin $\geq$20 mg/dl), occurring at least 7 days after surgery and persisting for $\geq$7 consecutive days [10, 11]. Other clinical factor also indicated primary graft dysfunction—severe coagulopathy, increased ammonia concentration, and massive ascites with severe distended abdomen and increased body weight. Therefore, we believe that the plasma exchanges in this case compensated for the decrease in ADAMTS-13, which should have been produced by hepatocytes in a well-functioning liver graft. Nakazawa et al. [12] hypothesized that the severity of the ADAMTS-13 deficit affects the occurrence of TMA in LDLT recipients because ADAMTS-13 is exclusively synthesized in the liver [13]; reduction in ADAMTS-13 with an increase in vWF after LDLT was reported in a recent study [14].

Other possible mechanisms involved in the pathogenesis of this case could be severe shear stress in dysfunctional partial liver grafts, resulting in endothelial injuries [15]. Although increased shear stress may indicate liver regeneration after hepatectomy, its negative impact on excessive endothelial stress, resulting in severe damage, has also been reported in small-graft transplantation models, both in humans and rodents [1, 15].

A group at The University of Tokyo [16] recently made an extensive review of their cases, and found that the administration of FFP and sensitization against human leukocyte antigens were not closely related to the occurrence of TMA. The same group also showed that the incidence of TMA was significantly increased in LDLT compared with whole liver transplants from deceased donors. In the light of this evidence, LDLT using a partial graft increases the chance of TMA owing to insufficient protein synthesis and endothelial injuries in a dynamically regenerating graft [12]. Additional insults, including immunological, infectious, or drug-induced factors, may cause clinically apparent TMA.

In conclusion, this experience was of a case of TMA secondarily caused by severe graft dysfunction after LDLT. This case could be clearly treated by plasma exchanges.

Disclosures

Conflict of Interest: The authors declare that they have no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

Informed Consent: Informed consent was obtained from all patients for being included in the study.

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Clinical Science

Trends in surgical results of hepatic resection for hepatocellular carcinoma: 1,000 consecutive cases over 20 years in a single institution

Yo-ichi Yamashita, M.D., Ph.D.[a,b,*], Eiji Tsuijita, M.D., Ph.D.[a], Kazuki Takeishi, M.D.[a], Teruyoshi Ishida, M.D., Ph.D.[b], Toru Ikegami, M.D., Ph.D.[b], Takuhiro Ezaki, M.D., Ph.D.[b], Takashi Maeda, M.D., Ph.D.[a], Tohru Utsunomiya, M.D., Ph.D.[a], Naofumi Nagasue, M.D., Ph.D.[b], Ken Shirabe, M.D., Ph.D.[b], Yoshihiko Maehara, M.D., Ph.D.[b]

[a]*Department of Surgery, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Hiroshima, Japan;*
[b]*Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan*

KEYWORDS:
5-year disease-free survival;
5-year survival;
Hepatocellular carcinoma;
Hepatic resection;
Morbidity and mortality

Abstract

BACKGROUND: Surgical results have been reported to be improved in hepatic resections for hepatocellular carcinoma (HCC) in recent years, but the detailed trends in surgical results for HCC in a single high-volume center are still not clear.

METHODS: Surgical results in 1,000 hepatic resections for HCC performed at a single medical center from 1989 to 2011 were analyzed. Patients were divided into 3 groups: those performed in the early period (1989 to 1995, n = 181), the middle period (1996 to 2004, n = 391), and the late period (2005 to 2011, n = 428).

RESULTS: Hospital mortality (3.9%, 1.0%, and .5%; $P = .0027$) and morbidity (45%, 24%, and 15%; $P < .0001$) rates were significantly decreased. The overall survival rates were significantly improved (50%, 72%, and 78% at 5 years; $P = .0021$), but there was no significant difference in the disease-free survival (29%, 34%, and 31% at 5 years; $P = .7823$).

CONCLUSIONS: Surgical results of hepatic resections for HCC were significantly improved, with the mortality rate nearly reaching 0%. The 5-year survival rate after hepatic resections for HCC was also improved to 78%, but the consistently high rate of HCC recurrence after hepatic remains a problem.

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, with an annual occurrence of at least 1 million new cases.[1] The mainstay of curative treatment for HCC is hepatic resection. In the 1980s, hepatic resections for HCC were associated with a high mortality rate in the range of 10%.[2,3] Over the past decade, many large studies have documented better perioperative results, with operative mortality rates typically less than 2% and trending toward 0% in high-volume centers in Japan[4–6] and around 5% in other countries.[7,8] The decline in operative mortality is attributable to the improvement in

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* Corresponding author. Tel.: +81-92-642-5469; fax: +81-92-642-5482.
E-mail address: yamashi@surg2.med.kyushu-u.ac.jp

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careful patient selection,[9,10] meticulous surgical techniques,[4,5] and intensive perioperative care.[11,12]

Because of the advances in hepatic resection,[13,14] postoperative surveillance for recurrence, management of HCC recurrence, and interferon (IFN) therapy,[15,16] long-term surgical results such as the 5-year survival rates after hepatic resections for HCC have been improved and are now in the range of 50% to 60%.[17,18] Our colleges reported an improvement of 5-year survival to 70.3% in hepatitis C virus antibody-positive patients with HCC after hepatic resections over the years 2000 to 2006.[19]

The present study analyzed 1,000 consecutive patients who underwent hepatic resections for HCC from 1989 to 2011 at a single institution and clarified trends in the operative mortality, morbidity, and prognosis of patients with hepatic resection for HCC by dividing the treatment into 3 periods of 6 to 8 years each.

Methods

Patients

A total of 1,000 hepatic resections for HCC were performed at the Department of Surgery, Hiroshima Red Cross and Atomic Bomb Survivors Hospital, Hiroshima, Japan, between January 1989 and December 2011. Thirty-eight patients (.38%) received lipiodolization,[20] and 8 patients (.08%) received ablation therapy before hepatic resection. Only 1 patient (.01%) received percutaneous transhepatic portal embolization in order to perform an extended right lobectomy for HCC. In the same timeframe, 124 ablation therapies and 283 lipiodolizations[20] for HCC were performed at our department, and 2 liver transplantations for patients with end-stage liver cirrhosis and HCC were performed at the transplantation center in Japan according to our recommendation using the previously described strategy.[21] According to the changing of directors, perioperative management, and surgical techniques, this period was divided into 3 periods: the early period (1989 to 1995, n = 181), the middle period (1996 to 2004, n = 391), and the late period (2005 to 2011, n = 428). All directors at our department were trained in liver surgery at the same institution (Kyushu University, Fukuoka, Japan); therefore, the differences of the management policy for patients with HCC caused by the surgeons were thought to be minimal. The medical records of all patients were followed up; we collected patient data through March 2012. Twenty-four patients (2.4%) were lost to follow-up. The median follow-up period in this series was 52 months. This study was conducted in accordance with the Declaration of Helsinki after approval from our institutional review board.

Surgical techniques and follow-up methods

Details of the surgical techniques and patient selection criteria have been reported previously.[10,14] We considered surgical indication based on patients' activity of daily living, patients' age, fitness degree of tumor invasion, extent of resection, and remnant liver function. Simply speaking, patients with an indocyanine green dye retention rate at 15 minutes less than 40% were selected for hepatic resection, and patients with an indocyanine green dye retention rate at 15 minutes less than 35% were selected for anatomic resection.[14] Anticoagulant drugs, such as nafamostat mesilate,[11] were administered perioperatively since the middle period, and preoperative steroid administration was routinely performed during the late period.[12] Intravenous antibiotics for surgical prophylaxis were given for 3 days or more in the early and middle period and for 2 days or less in the late period.

In almost all hepatic resections, the intermittent Pringle maneuver consisting of clamping the portal triad for 15 minutes and then releasing the clamp for 5-minute intervals or hemivascular occulusion[22,23] was applied. The clump-crushing method was used to transect the liver parenchyma from the early period to the early part of the middle period, and an CUSA system (Valleylab, Boulder, CO) was used since the later part of the middle period, with the addition of a VIO soft-coagulation system (ERBE Elektromedizin, Tübingen, Germany) since 2010.[24] During the late period, hepatic venous backflow control,[25] which was typically achieved extrahepatically before dividing the liver, and the Belghiti hanging maneuver,[26] in which a tape was introduced behind the caudate lobe through the groove between the right and middle hepatic vein, were performed. An intraoperative bile leakage test has been routinely performed during the late period.[27]

Five surgical outcomes were mainly examined: postoperative mortality, morbidity, duration of hospital stay, overall survival, and disease-free survival. Any death that occurred in the hospital after operation was recorded as a mortality. Complications such as liver failure, encephalopathy, gastrointestinal bleeding, intraperitoneal abscess, abdominal hemorrhage, bile leakage, pleural effusion, intractable ascites, and wound infection were evaluated using the Clavien-Dindo classification[28] of surgical complications, and a grade of II or more, which required pharmacologic treatment with drugs or invasive surgical/endoscopic/radiologic interventions, was defined as positive. After discharge, all patients were examined for recurrence by ultrasonography and tumor markers such as α-fetoprotein and des-γ-carboxy prothrombin every month and by dynamic computed tomographic imaging every 3 or 4 months.[17] No patients received adjuvant chemotherapy or adjuvant lipiodolization at our institution. We treated recurrent HCC with repeat hepatectomy,[29] ablation therapy, and lipiodolization according to the previously described strategy.[30]

Statistical analysis

Continuous variables were expressed as means ± standard deviation and compared using an analysis of variance test. Categorical variables were compared using either the chi-square test or the Fisher exact test as appropriate. Survival curves were generated by the Kaplan-Meier

method and compared with the log-rank test. All analyses were performed with StatView 5.0 software (Abacus Concepts, Berkeley, CA). *P* values less than .05 were considered to indicate statistical significance.

Results

Annual changes in hepatic resections between 1989 and 2011

Table 1 shows the annual changes in hepatic resections over the years 1989 to 2011 based on the 1,000 cases analyzed. The first hepatic resection for HCC at our institution was performed in 1981 by one of the present authors (N.N.), and the number of hepatic resections for HCC has gradually increased since that time. A patient database of hepatic resections was established in 1989 at our department. In the early period (1989 to 1995), H.Y. headed this department, and cases usually exceeded 20 annually. In the middle period (1996 to 2004), T.E. and T.M. headed the department, and annual hepatic resections for HCC exceeded 40 cases. In the late period (2005 to 2011), T.U. and Y.Y. headed the department, and annual hepatic resections for HCC exceeded 80 cases. In 2011, the annual number of hepatic resections, including resections for other diseases such as intrahepatic cholangiocarcinoma and liver metastasis, reached 109 cases.

Comparisons of patients' background characteristics according to the 3 periods

The comparison of patients' characteristics according to the 3 periods is summarized in Table 2. There were significant differences in the patients' ages (early: 61 ± 9 years, middle: 66 ± 10 years, and late: 69 ± 10 years; $P < .0001$) and body mass index (early: 22.4 ± 2.0, middle: 23.1 ± 3.2; and late: 23.1 ± 3.0; $P = .0164$). There were no significant differences in the positive rate of hepatitis B surface antigen (early: 17%, middle: 19%, and late: 19%; $P = .6812$) and hepatitis C virus antibody (early: 69%, middle: 71%, and late: 64%; $P = .1143$). Patients in the middle and late periods maintained liver function better than those in the early period, with a lower total bilirubin level (early: 1.0 ± .4 mg/dL, middle: .8 ± .4 mg/dL, and late: .8 ± .3 mg/dL; $P < .0001$), higher albumin level (early: 3.7 ± .4 g/dL, middle: 3.9 ± .4 g/dL, and late: 4.0 ± .4 g/dL; $P < .0001$), lower indocyanine green dye retention rate at 15 minutes (early: 20.8% ± 13.0%, middle: 17.2% ± 9.6%, and late: 19.0% ± 10.4%; $P = .0007$), and better Child classification (early: A in 87%, middle: A in 94%, and late: A in 96%; $P = .0002$).

Comparisons of short-term surgical outcomes according to the 3 periods

The comparisons of short-term surgical outcomes according to the 3 periods are summarized in Table 3. Repeat hepatic resection for recurrent HCC was significantly increased both in the middle and the late period (early: 2%, middle: 16%, and late: 34%; $P < .0001$), and operation time was significantly prolonged (early: 170 ± 74 minutes, middle: 229 ± 98 minutes, and late: 252 ± 99 minutes; $P < .0001$). Other surgical stressors such as surgical blood loss (early: 1,087 ± 601 g, middle: 612 ± 601 g, and late: 362 ± 664 g; $P < .0001$), intraoperative transfusion rates (early: 53%, middle: 16%, and late: 4%; $P < .0001$), and resected liver volume (early: 175 ± 296 g, middle: 130 ± 182 g, and late: 114 ± 149 g; $P = .0030$) were significantly decreased both in the middle and the late period. There were significant differences in hospital mortality rate (early: 3.9%, middle: 1.0%, and late: .5%; $P = .0027$), postoperative morbidity rate (early: 45%,

Table 1 Annual changes in cases of 1,000 hepatic resections during 1989 to 2011

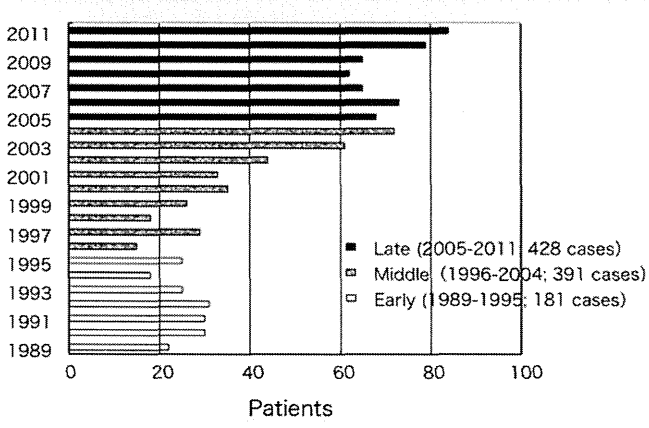

Table 2 Comparisons of patients' background characteristics

Variables	Early (n = l81)	Middle (n = 391)	Late (n = 428)	*P* value
Age (y)	61 ± 9	66 ± 10	69 ± 10	<.0001
Male/female	128/53	278/113	290/138	.5462
BMI	22.4 ± 2.0	23.1 ± 3.2	23.1 ± 3.0	.0164
DM (%)	48 (27)	98 (25)	133 (31)	.1483
Drinking (%)	48 (27)	98 (25)	133 (31)	.1080
HBsAg (+) (%)	30 (17)	73 (19)	83 (19)	.6812
HCV-Ab (+) (%)	125 (69)	277 (71)	274 (64)	.1143
Pit (× $l0^4$/μL)	1 8.7 ± 27.3	20.9 ± 50.9	21.3 ± 6.3	.0078
T-bil (mg/dL)	1.0 ± .4	.8 ± .4	.8 ± .3	<.0001
Alb (g/dL)	3.7 ± .4	3.9 ± .4	4.0 ± .4	<.0001
AST (IU/L)	63 ± 40	51 ± 25	43 ± 36	<.0001
ALT (IU/L)	68 ± 47	51 ± 33	41 ± 31	<.0001
PT (%)	87 ± 1 9	86 ± 16	90 ± 1 3	.0022
ICG1 5R (%)	20.8 ± 13.0	17.2 ± 9.6	1 9.0 ± 10.4	.0007
Child A (%)	1 58 (87)	366 (94)	412 (96)	.0002
Liver damage A	110 (61)	266 (68)	350 (82)	<.0001

Alb = albumin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DM = diabetes mellitus; HBsAg = hepatitis B surface antigen; HCV-Ab = hepatitis C antibody; ICG15R = indocyanin green retention rate after 15 minutes; Pit = platelet counts; PT = prothrombin time; T-bil = total bilirubin.

middle: 24%, and late: 15%; $P < .0001$), and the mean duration of hospital stay (early: 40 ± 23 days, middle: 18 ± 11 days, and late: 13 ± 17 days; $P < .0001$).

Comparisons of tumor-related factors according to the 3 periods

The comparisons of tumor-related factors according to the 3 periods are summarized in Table 4. There were significant differences in tumor diameter (early: 4.0 ± 3.0 cm, middle: 3.1 ± 2.2 cm, and late: 2.6 ± 1.6 cm; $P = .0043$) and tumor number (early: 1.1 ± .4, middle: 1.4 ± .8, and late: 1.5 ± 1.1; $P = .0023$). The rate of poorly differentiated HCC was significantly decreased (early: 34%, middle: 29%, and late: 22%; $P = .0049$), but there were no significant differences in the positive rate of portal venous infiltration ($P = .2345$) and intrahepatic metastasis ($P = .1002$). The positive rate of histological cirrhosis (lc) was decreased both in the middle and the late period (early: 66%, middle: 49%, and late: 54%; $P = .0008$).

Survival after hepatic resections for hepatocellular carcinoma according to the 3 periods

The overall survival curves after hepatic resection for HCC of the 3 periods are shown in Fig. 1. The overall survival rates were significantly improved, with the 5-year survival rate in the late period reaching 78% (early: 50% and middle: 72%, $P = .0021$). The disease-free survival curves

Table 3 Comparisons of surgical outcomes

Variables	Early (n = l 81)	Middle (n = 391)	Late (n = 428)	*P* value
Surgical outcomes				
Repeat hepatic resection (%)	4 (2)	61 (16)	148 (34)	<.0001
Operation time (min)	170 ± 74	229 ± 98	252 ± 99	<.0001
Blood loss (g)	1,087 ± 601	612 ± 601	362 ± 664	<.0001
Resected volume (g)	175 ± 296	130 ± 182	114 + 149	.0030
Transfusion (%)	96 (53)	61 (16)	17 (4)	<.0001
Hr 0:S:1 -2	113:33:35	250:32:109	276:68:84	.0527
Anatomic resection (%)	68 (38)	141 (36)	152 (36)	.8899
tw (mm)	5.1 ± 5.6	3.9 ± 6.5	4.3 ± 5.2	.1345
Postoperative courses				
Mortality (%)	7 (3.9)	4 (1.0)	2 (.5)	.0027
Morbidity (%)	81(45)	92 (24)	65 (15)	<.0001
Hospital stay (days)	40 ± 23	18 ± 11	13 ± 17	<.0001

Hr = hepatic resection; tw = surgical margin.

Table 4 Comparisons of tumor-related factors

Variables	Early (n = l 81)	Middle (n = 391)	Late (n = 428)	*P* value
Tumor diameter (cm)	4.0 ± 3.0	3.1 ± 2.2	2.6 ± 1.6	.0043
Tumor number	1.1 ± .4	1.4 ± .8	1.5 ± 1.1	.0023
Poorly differentiated (%)	62 (34)	115 (29)	96 (22)	.0049
fc (+) (%)	122 (67)	244 (62)	255 (60)	.2383
fc-inf (+) (%)	91 (50	182 (47)	218 (51)	.7304
vp (+) (%)	92 (51)	197 (50)	227 (53)	.2345
im (+) (%)	29 (16)	40 (10)	57 (13)	.1002
Stage III or IVA (%)	93 (51)	175 (45)	206 (48)	.0744
AFP (ng/mL)	39 ± 34	55 ± 25	48 ± 29	.6462
PIVKA-ll (mAU/mL)	28 ± 91	22 ± 54	49 ± 73	.6897
lc (+) (%)	120 (66)	191 (49)	231 (54)	.0008

AFP = α-fetoprotein; fc = fibrous capsule; fc-inf = infiltration to fibrous capsule; im = intrahepatic metastasis; lc = histological liver cirrhosis; PIVKA-ll = protein induced by Vitamin K abscence or antagonists-II; vp = portal venous infiltration.

after hepatic resection for HCC of the 3 periods are shown in Fig. 2. There were no significant differences among the 3 periods, and the 5-year disease-free survival rate of the late period remained quite low at 31% (early: 29% and middle: 39%, $P = .7823$). The survival curves after HCC recurrence of the 3 periods are shown in Fig. 3. The survival rates after the recurrence of HCC were significantly improved, and the 5-year survival rate after HCC recurrence was quite high at 47% in the late period (early: 20% and middle: 37%; $P < .0001$).

Comments

Hepatic resection represents the best and only curative treatment for HCC. This evolution is largely because of improvements in perioperative mortality and morbidity over the past 20 years. In our own institution, the mortality rate after hepatic resection for HCC significantly decreased to .5% in the late period (2005 to 2011). Many large studies documented better perioperative results, with an operative mortality rate typically less than 2% and trending toward 0% in high-volume centers in Japan[4–6] and around 5% in other countries.[7,8] The decrease of mortality of hepatic resection for HCC is caused by considerations for remnant liver functions and volume to prevent postoperative liver failure and the establishment of surgical indications for HCC.[5,9,14]

Relatively high morbidity rates remain problematic in hepatic resections for HCC. In contrast to hepatic resection for metastatic liver cancer, strict perioperative managements are required for hepatic resections for HCC because it usually occurs from liver cirrhosis.[4,6] In our own institution, the morbidity rate after hepatic resection for HCC significantly decreased to 15%, and the mean duration of hospital stay was also shortened to 13 days in the late period. This improvement of short-term surgical results is because of meticulous surgical procedures and perioperative managements, such as the bile leakage test,[27] preoperative steroid administration,[12] and perioperative use of nafamostat mesilate.[11] In particular, the decease of blood loss

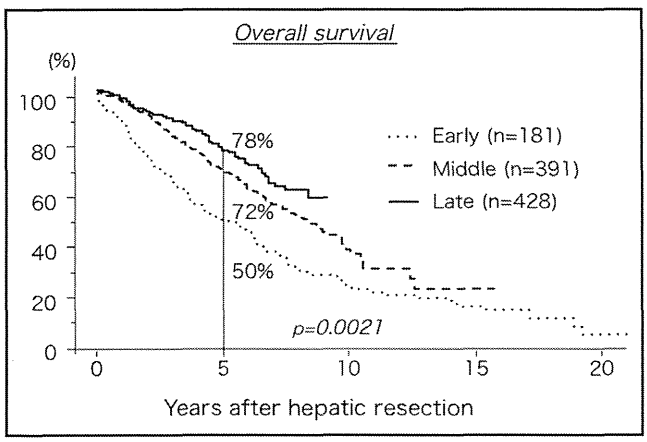

Figure 1 The overall survival curves of patients with hepatic resection for HCC according to the 3 periods are shown. The overall survival rates were significantly improved, and the 5-year survival rate for the early period is 50%, 72% for the middle period, and 78% for the late period ($P = .0021$).

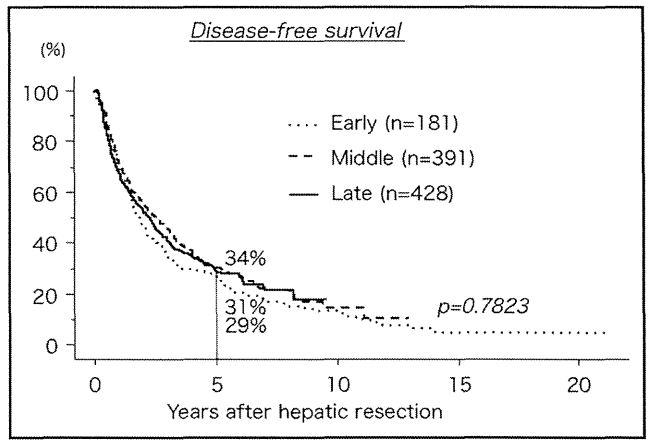

Figure 2 The disease-free survival curves after hepatic resection for HCC according to the 3 periods are shown. There were no significant differences in the disease-free rate, and the 5-year disease-free survival rate for the early period was 29%, 39% for the middle period, and 31% for the late period ($P = .7823$).

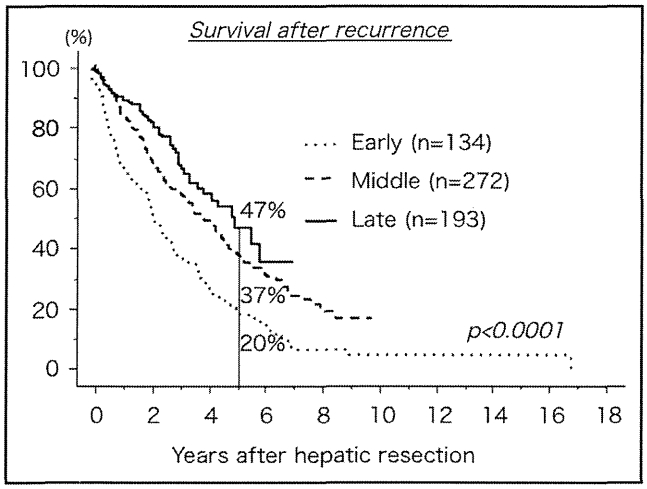

Figure 3 The survival curves after HCC recurrence according to the 3 periods are shown. The survival rates after the recurrence of HCC were significantly improved, and the 5-year survival rate after the recurrence of HCC for the early period was 20%, 37% for the middle period, and 47% for the late period ($P < .0001$).

and transfusion rates are most important. Many studies have reported that intraoperative blood loss and blood transfusion were predictive factors linked to postoperative mortality and morbidity.[2,4,8,10] In our institution, the mean blood loss was reduced to 362 g, and the blood transfusion rate was decreased to 4% in the late period. This reduction of blood loss during hepatic resections for HCC was caused by various devices used in surgical procedures during the divisions of the liver parenchyma, such as hepatic venous backflow control,[25] Belghiti hanging maneuver,[26] and CUSA with a VIO soft-coagulation system.[24] In not only pancreatic surgery[31] but also hepatic resection,[32] surgeons' and hospital volumes have been reported to impact mortality and morbidity. The increase of annual cases of hepatic resections for HCC in our institution may be one of the causes of improvements of short-term surgical results.

According to the results of trends in the backgrounds of the patients (Table 2), patients with hepatic resections for HCC preserved showed a better preservation of liver function in the later period. This difference of liver function among the 3 periods is the most important limitation of our study when comparing short-term and long-term surgical results of hepatic resections for HCC. We previously reported that liver dysfunction was a predictive factor linked to postoperative mortality and morbidity.[4,12] Makuuchi et al[33] reported the criteria used to select operative procedures in patients with HCC in 1993, and radiofrequency ablations for HCC were developed widely as an alternative therapy for patients with HCC and impaired liver function.[34] The improvements of short-term surgical results in hepatic resections for HCC are attributable to the adequate selection of surgical candidates and operative procedures for HCC.

The overall survival rates of patients with HCC after hepatic resections were significantly improved, and the 5-year survival rate in the late period reached 78% (early: 50% and middle: 72%, $P = .0021$). However, there were no significant differences in disease-free survival, and the 5-year disease-free survival rate of the late period remained fairly low (ie, 31%; early: 29% and middle: 39%; $P = .7823$). These results are contrary to existing reports.[18,19] We hypothesized that both overall and disease-free survival were improved in late periods at the outset. Poon et al[18] reported trends of improvement in 5-year overall survival (38% in 1989 to 1993 and 49% in 1994 to 1999) and disease-free survival (25% in 1989 to 1993 and 16% in 1994 to 1999). Our 5-year recurrence rate of 60% to 70% after hepatic resection for HCC is low compared with that after radiofrequency ablation (80% to 90%),[34] but our results indicated that the local control of HCC through improved techniques of hepatic resections for micrometastases around HCC were not particularly attributable to the trends of improvement in patient survival. HCC recurrence was mainly caused by micrometastases and multicentric recurrence. To improve patient survival after hepatic resections, the establishment of a strong adjuvant chemotherapy regimen for micrometastases and a potent IFN regimen[15,16,35] for multicentric recurrence is crucial. Sorafenib, an oral multikinase inhibitor, recently has been reported to be effective for the treatment of advanced HCC in the Sorafenib Hepatocellular carcinoma Assessment Randomized Protocol (SHARP) trial[36] and in a phase III trial of the Asia-Pacific regimen[37]; therefore, sorafenib should be one of the most important drugs for establishing a systemic adjuvant treatment regimen for HCC.

There are many reports that a large amount of intraoperative blood loss and transfusion promotes recurrence and is related to a poor prognosis of patients with HCC after hepatic resections.[38,39] The reduced blood loss and transfusion rate in our series are 2 of the causes of the improvement of long-term surgical results for HCC. In many reports, good liver function has been shown to be a strong predictor for good prognosis of patients after hepatic resections.[3,13,14,19,29,30] As mentioned previously and shown in Table 2, patients with hepatic resections for HCC exhibited a better preservation of liver functions in the later period (liver damage A: 82%). Patients with good liver function were able to receive curative treatment, such as repeat hepatic resections for recurrent HCC.[19,29,30] This "selection bias" is the main cause of the improvement of survival rates after the recurrence of HCC in the middle and late period and leads to remarkably longer patient survival (eg, 78%) at 5 years. In our previous report, the 5-year survival rates were 87% in the anatomic resection group and 76% in the limited resection group for patients with solitary HCC and liver damage A.[14]

In conclusion, the surgical results of hepatic resections for HCC were significantly improved, and a mortality rate of 0% was nearly achieved. The 5-year survival rate after hepatic resections for HCC was improved to 78%, but the consistently high rate of HCC recurrence after hepatic resection remains a problem. The improvements of surgical results for HCC were largely attributable to the adequate selection of surgical candidates for HCC and factors aimed at reducing blood loss.

Acknowledgment

This article is dedicated to Hiroshi Ogawa, M.D., and Hirofumi Yukaya, M.D.

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