the recent period. Moreover, the more times hepatectomy was repeated, the shorter the recurrence-free interval became. These results indicate the limits of repeat hepatectomy for cure of recurrent HCC.

Liver transplantation is the best option for patients with decompensated cirrhosis and with single HCC smaller than 5 cm or showing up to 3 nodules, each of which is less than 3 cm.[15] A major controversy persists over whether primary LT or partial hepatectomy is the optimal initial treatment for patients with resectable and transplantable HCC who have preserved liver function. Results of several retrospective studies showing that primary LT was associated with superior recurrence-free survival are the basis for the argument in favor of primary LT for resectable and transplantable HCC even in patients with preserved liver function, whereas overall long-term survival after partial hepatectomy was similar to that after primary LT.[16-18] Application of primary LT for patients with resectable HCC and preserved liver function would result in a greater shortage of deceased donor livers and an increase in the dropout rate on waiting lists. Partial hepatectomy is applicable immediately and results in a cure of HCC in some patients. The establishment of a strategy of primary LT for patients with resectable HCC might result in patients undergoing unnecessary LT and subsequent unnecessary immunosuppression. Without solving these problems, the approach is not realistic. There have been no prospective, randomized studies comparing partial hepatectomy with primary LT for early HCC in patients who could be eligible for both treatments.

In contrast, LT for patients with recurrent HCC or decompensated liver cirrhosis after curative hepatectomy, a concept that has been called "salvage LT" in the broad sense of the word "salvage," also has been debated for cure of HCC.[28-32] Initial studies suggested that salvage LT would offer poorer results.[28] Belghiti et al[29] reported that the survival after salvage LT was not significantly less; indeed, the 5-year survival rate after salvage LT in their study was 61%. Moreover, the Barcelona Clinic Liver Cancer Group[30] proposed salvage LT for patients in whom pathologic examination of a resected specimen indicated a high risk of recurrence even in the absence of proven residual disease. This concept is salvage LT in the narrow sense of the word "salvage." This approach may reduce the dropout rate on a waiting list and the effect of a long waiting list and donor shortage by selection of patients with HCC who are likely to obtain the maximum benefit from LT.[31] Expectations from the scenario depend on various assumptions and have not been proven by a prospective study.

Controversy also exists about whether salvage LT or repeat hepatectomy is the optimal surgical treatment for patients with resectable and transplantable recurrent HCC who have preserved liver function. The majority of patients with recurrent HCC after initial hepatectomy for small HCC have transplantable recurrent tumors in the remnant liver.[31-33] Considering our results showing the 5-year recurrence-free survival rate after the second hepatectomy was only 10%, and our results showing that the more times hepatectomy was repeated, the shorter the recurrence-free interval became, salvage LT may be the best treatment choice even for patients with resectable recurrent HCC and preserved liver function. If salvage LT is indicated for patients with recurrent HCC meeting the Milan criteria[15] who are younger than 60 or 65 years, only 10% or 15% of patients with HCC who underwent a second hepatectomy in this study would have benefited from salvage LT (data not shown), because the mean age of the patients with recurrent HCC at the time of the second hepatectomy was 66 years. Actually, LT has been performed in less than 20% of patients with recurrent HCC.[21,28,30,34] The low applicability of salvage LT for patients with recurrent HCC results from the older ages of the candidates at diagnosis of recurrence.[34]

Living-donor LT offers the potential for earlier transplantation for patients with HCC, which would result in lesser dropout rates and improved outcomes. Modeling studies have suggested that acceptable life expectancy and cost-effectiveness could be reached if waiting-time exceeded 7 months for patients with early HCC.[35] Thus, living-donor LT, even for patients with recurrent HCC, seems justified when there is little likelihood of a cadaveric organ becoming available in a timely manner. If a cirrhotic patient with recurrent HCC that is resectable and transplantable has a suitable living donor, living-donor LT can result in long-term survival without HCC recurrence. However, when a patient with recurrent HCC has no suitable living donor or has no indication for LT due to advanced age or associated diseases, repeat hepatectomy, which might enable total removal of cancer tissue, remains the first line of treatment for patients with resectable recurrent HCC and preserved liver function, even if the possibility of re-recurrence is extremely high.

In conclusion, repeat hepatectomy for patients with recurrent HCC resulted in good long-term survival and had survival benefits especially

for patients without microscopic vascular invasion. The incidence of re-recurrence after the second hepatectomy, however, was very high, and the recurrence-free interval was short, even in the subgroup with good long-term survival. The effectiveness of repeat hepatectomy for curing patients with recurrent HCC is limited. Salvage LT might be appropriate for treating patients with recurrent HCC, even if recurrent HCC in patients with preserved liver function is resectable.

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Biliary Complications after Duct-to-duct Biliary Reconstruction in Living-donor Liver Transplantation: Causes and Treatment

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Abstract
Background In living-donor liver transplantation (LDLT), biliary complications are recognized as a significant cause of post-transplantation morbidity.
Methods Eighty patients who underwent LDLT with duct-to-duct biliary reconstruction at Hiroshima University Hospital were enrolled in this study. The mean follow-up was 24 months (range, 3–72 months). Eighteen patients underwent the basiliximab-based immunosuppressive therapy, and 62 patients underwent non-basiliximab-based immunosuppressive therapy. The development of biliary complications after LDLT was retrospectively analyzed. Biliary complications were initially treated by endoscopic or radiological modalities.
Results Biliary leakages and strictures occurred in 12 (15%) and 20 (25%) of the 80 patients, respectively. Stepwise multivariate analysis demonstrated bile leakage to be an independent risk factor for the development of biliary stricture ($p = 0.001$) and basiliximab-based immunosuppressive therapy to be an independent protective factor for postoperative biliary leakage ($p = 0.005$). The 1-week total doses of steroids were significantly lower in the basiliximab-based immunosuppressive regimes (mean dose: 573mg) than in the non-basiliximab-based ones (mean dose: 1,121mg) ($p = 0.01$). All patients with biliary leakage were successfully treated with endoscopic or radiological modalities, except one patient who was treated by surgical treatment. Endoscopic or radiological modalities were successful as primary treatment modalities in 12 (60%) of 20 patients with biliary strictures. Lastly, six patients were treated surgically with long-term success, except for one patient with chronic cholangitis who died after 16 months.
Conclusions Steroid-sparing basiliximab-based immunosuppressive therapy reduced the incidence of biliary leakage, and biliary leakage was the independent factor for biliary stricture. The non-surgical and surgical treatments for biliary complications were satisfactory.

Various refinements in surgical techniques, postoperative management, and immunosuppressive management have reduced the incidence of complications after liver transplantation. Biliary complications, however, continue to be a significant cause of morbidity after liver transplantation [1, 2]. In living-donor liver transplantation (LDLT), the biliary system is usually reconstructed by performing a Roux-en-Y hepaticojejunostomy (RYHJ), which results in biliary complications in 12%-18% of recipients [3, 4]. In 1998, Wachs et al. first reported duct-to-duct reconstruction for LDLT [5]. Duct-to-duct direct biliary reconstruction has been performed in many institutes, and the advantages of duct-to-duct biliary reconstruction over hepaticojejunostomy have been pointed out in several reports. For example, it preserves the physiological bilio-enteric and bowel continuity, thus preventing delayed bowel movements. Further, it permits easy endoscopic access to the biliary tree for diagnostic and therapeutic instrumentation and assists the prevention and management

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of ascending cholangitis [6–9]. As the number of patients who have undergone LDLT with duct-to-duct biliary reconstruction has increased, however, a variety of biliary complications have emerged [10–12]. Some reports have addressed the occurrence of late biliary complications, particularly biliary strictures, in many patients with a significant median follow-up duration (>12 months) [9, 13]. In the present study, to evaluate the safety of duct-to-duct biliary reconstruction in LDLT, we retrospectively analyzed the biliary complications observed, with focus on biliary leakage and stricture.

Materials and methods

Patients and surgical procedures

Between May 2000 and September 2006, 85 patients underwent LDLT at Hiroshima University. Among these patients, the 80 patients who underwent duct-to-duct biliary reconstruction along with LDLT were enrolled in this study. Patient, graft, and operative characteristics are summarized in Table 1. The series comprised 47 men and 33 women (average age: 50 years). The most common indications for LDLT were viral hepatitis and cirrhosis with or without hepatocellular carcinoma (n = 54), followed by fulminant hepatic failure (n = 10), primary biliary cirrhosis (n = 8), autoimmune hepatitis (n = 6), and others (n = 2). The most commonly used graft type was a right hemi-liver (n = 66), followed by a left hemi-liver (n = 14). The donors included 49 men and 31 women (average age: 35 years).

The mean model for end-stage liver diseases (MELD) score at the time of LDLT was 17.9 (range: 5–50). The mean graft-to-recipient weight ratio (GRWR) was 1.08 (range: 0.5–2.4); moreover, none of the grafts included a middle hepatic vein. The mean operative time was 12 h 8 min (range: 9–25 h). The mean total ischemic time was 108 min (range: 43–240 min), and the warm ischemic time was 45 min (range: 32–220 min).

The immunosuppressive regimen comprised cyclosporine with mycophenolate mofetil (MMF) and methylprednisolone and basiliximab (n = 18), or cyclosporine with MMF and methylprednisolone (n = 8), or tacrolimus with methylprednisolone (n = 56). The steroid-sparing basiliximab-based immuosuppressive therapy was indicated for viral hepatitis, because the steroid might contribute to the acceleration of hepatitis viral replication. Basiliximab 20 mg was given intravenously on both day 0 and day 4 after surgery. Tacrolimus was administered with a level of 5 ng/ml for the first 48 h postoperatively in order to maintain renal function. Then, the dose of tacrolimus was adjusted to maintain a level of 10–15 ng/ml during the first month, and afterward tapered to achieve a level of 5–10 ng/ml. Cyclosporine was also administered at a level of 50–100 ng/ml for the first 48 h postoperatively in order to maintain renal function. Then, the dose of cyclosporine was adjusted to maintain a level of 250–300 ng/ml during the first month, after which it was tapered to achieve a level of 150–250 ng/ml. Dose reductions of both tacrolimus and cyclosporine were performed primarily on the basis of renal and liver function. For patients with renal insufficiency, tacrolimus or cyclosporine was not given until renal function improved. After oral medication capsules were tolerated, MMF was given at a dose of 500–1,000 mg a day. Mycophenolate mofetil was tapered and discontinued, based on gastrointestinal toxicity and myelosuppression. Treatment with steroids was discontinued 2–3 months after LDLT. In basiliximab-based immuosuppressive therapy, patients either received no methylpredonisolone or they received 250 mg methylpredonisolone intravenously during surgery, followed by daily tapering (starting at 120 mg/day and ending at a baseline 40 mg/day, intravenously).

Table 1 Living-donor liver transplantation patient demographics

Characteristics	Number = 80
Age (range, years)	50 (20–69)
Male	47 (59%)
MELD (range)	17.9 (5–50)
Indication	
Liver cirrhosis (HCC)	54 (35)
Cholestatic disease	8
Fulminant hepatic failure	10
Autoimmune hepatitis	6
Others	2
Donor	
Age (range, years)	35 (18–64)
Male	49 (31)
Graft	
Left lobe	14
Right lobe	66
GRWR	1.08 (0.5–2.4)
Immunosuppresive therapy	
Tac + steroid	54
CyA + steroids + MMF	8
CyA + steroids + MMF + Bax	18
Operation	
Time (range)	12 h 8 min (9h–25h)
Blood loss (range)	4875ml (345–39500)
Total ischmic time (range)	108min (43–240)
Warm ischmic time (range)	45min (32–220)

MELD model for end-stage liver disease; GRWR graft: recipient weight ratio; Tac tacrolimus; CyA cyclosporin; MMF mycophenolate mofetil; Bax basiliximab

Treatment with oral methylpredonisone (32 mg/day) was initiated on postoperative day 7–10. In non-basiliximab based immunosuppression therapy, patients received 500 mg methylpredonisolone intravenously during surgery, followed by daily taper (starting at 250 mg/day and ending at a baseline 40 mg/day, intravenously). Treatment with oral methylpredonisone (32 mg/day) was initiated on day 7–10. Subsequent adjustment in maintenance methylpredonisolone was dependent on the patient's clinical course.

Donor assessment and surgery

The donors underwent several preoperative examinations, including computed tomography (CT) and drip-infusion cholangiography-CT, in order to assess the biliary and vascular system. The surgical techniques for donor hepatectomy have been described elsewhere [14]. Briefly, prior to parenchymal transection, routine intraoperative cholangiography was performed with fluoroscopy to determine the transection point of the hepatic duct. Minimal dissection was performed at the hilar plate around the hepatic duct. The liver was then transected with an ultrasonic dissector without inflow occlusion. The hepatic duct was sharply severed near the confluence, and the remnant stump was carefully closed with 6–0 polydioxanone monofilament sutures (PDS; Ethicon, Inc., Tokyo, Japan). The liver graft was perfused with University of Wisconsin (UW) solution. The diameters of the bile duct and vessels of the graft and the graft weight were directly measured. The average intraoperative blood loss was 310 ml. None of the 80 donors were given a blood transfusion.

Recipient surgery

In total hepatectomy, the hilar plate was dissected sharply at or distal to the second-order branch of the bile duct. In the dissection, careful attention was paid in order to preserve as much as possible of the surrounding tissues with an adequate blood supply to the bile duct. To maintain the blood supply to the bile duct from the right hepatic artery, dissection between the right hepatic artery and the bile duct was avoided. Bile duct anastomosis was performed after completion of all vascular anastomoses and reperfusion of the liver graft. Wherever possible, we prospectively performed duct-to-duct biliary reconstruction. An end-to-end anastomosis between the graft and recipient bile ducts was performed using an interrupted 6–0 PDS, beginning from the posterior wall and terminating at the anterior wall. In the case of more than one ductal opening in the graft, if the openings were adjacent to each other, ductoplasty was performed to suture them to form a single orifice. If two ductal openings in the graft were far apart, separate duct-to-duct anastomoses were performed without ductoplasty. A stent tube was routinely placed through the anastomosis as a splint and was pulled out through the common bile duct above the duodenum. A cholangiogram was obtained by using the inserted stent tube 1 month after LDLT, and then the stent tube was clamped. The tubes for bile duct stenting were removed 3 months after LDLT.

Diagnosis and treatment of biliary complications

Biliary leakage was diagnosed clinically and radiologically on the basis of a bile leak through abdominal drains, evacuation of extrahepatic biloma through a newly inserted drain under ultrasound guidance, or identification of a leak by endoscopic retrograde cholangiography (ERC) or cholangiography via an inserted stent tube. For biliary leakage, endoscopic retrograde nasobiliary drainage (ENBD) or percutaneous drainage under ultrasound guidance were the techniques most commonly undertaken.

Biliary stricture is primarily suspected when cholestatic enzymes that are assessed by liver function tests, including alkaline phosphatase and γ-glutamyl transpeptidase, are elevated and/or if there is sonographic evidence of a dilated biliary system. If the total bilirubin was not elevated, drip-infusion cholangiography-CT was performed. The presence of strictures was confirmed by ERC and/or percutaneous transhepatic cholangiography (PTC). Biliary stenosis was diagnosed on the basis of an abrupt luminal narrowing with an overt dilatation of the intrahepatic duct.

Primary transpapillary intervention was attempted in all patients who underwent duct-to-duct biliary reconstruction. Endoscopic retrograde balloon cholangioplasty was performed; this was followed by the placement of a plastic internal stent tube. When endoscopic treatment failed, percutaneous management of the biliary stricture was undertaken. Surgical revision was indicated when both these modalities failed.

Statistical analysis

Category variables were compared with the chi-square test. Continuous data were compared by the Mann-Whitney test. Patient survival after liver transplantation was analyzed by the Kaplan-Meier survival method. The statistical comparison of survival data was performed with the log-rank test. Stepwise logistic regression analysis was carried out in order to identify the independent predictors of biliary complications. A p value < 0.05 was considered to be significant. All statistical analyses were performed with the statistical software package SPSS version 11.0 (SPSS Inc Chicago, IL).

Results

Type of biliary reconstruction

Table 2 shows the type of bile duct reconstruction with the corresponding incidence rate of biliary stricture. Forty-eight (60%) grafts had a single duct for anastomosis, 29 grafts (36%) had two ducts, and 3 grafts (4%) had three ducts. After ductoplasty in 14 grafts, 62 grafts had a single duct for anastomosis, 15 grafts had two ducts for anastomosis, 2 grafts had three ducts for anastomosis, and 1 graft had two ducts for anastomosis.

Overall incidence of biliary complications, risk factors, and outcomes after LDLT

Biliary leaks developed in 12 patients (15%), and 20 (25%) of the 80 patients suffered from a post-transplantation biliary stricture (Table 2). The mean follow-up was 24 months (range: 3–72 months). The onset of biliary leakage was 20 ± 8 days. No patient developed a de novo biliary stricture beyond 20 months after LDLT. Seven patients (8.8%) developed both the biliary complications. None of the five patients that underwent hepaticojejunostomy developed a biliary stricture. Further, there were no hepatic arterial complications in our series. By univariate analysis, we found two variables to be associated with an increased risk of biliary stricture: a postoperative bile leakage and non-basiliximab-based immunosuppressive therapy (Table 3). After stepwise multivariate analysis, one variable remained significant, i.e., postoperative bile leakage ($p = 0.001$) (Table 3). There were no significant differences in the incidence of biliary stricture with respect to donor age, MELD score, graft type, the number of bile ducts, and ductoplasty. There was no significant difference in the incidence of biliary stricture with respect to the number and mode of anastomotic sutures. However, in the grafts that had three ducts, we observed a high incidence of biliary stricture (2/3, 66.6%) (Table 2). We next examined the incidence of biliary stricture according to the diameter of the anastomosis. Graft duct sizes were classified into small (diameter <4 mm), medium (diameter 4–5 mm), and large (diameter >5 mm). Recipients with two or three biliary ducts were excluded in order to avoid bias from complex biliary reconstructions. We observed no association between the diameter of the bile ducts and the incidence of anastomotic suture.

Interestingly, both biliary leaks and strictures developed less frequently in patients with basiliximab-based immunosuppressive regimes. In stepwise multivariate analysis, non-basiliximab-based immunosuppressive therapy was associated with an increased risk for postoperative bile leakage ($p = 0.005$) (Table 4). Further, we found that the 1-week doses of methylpredonisolone after LDLT were significantly lower in basiliximab-based immunosuppressive regimes than in non-basiliximab-based ones ($p = 0.01$) (Fig. 1).

Freedom from biliary stricture was 73% at 1 year and 69% at 2 years (Fig. 2). The 1-year and 5-year survival rates for patients with biliary stricture were 69% and 53%, respectively, compared with 79% and 70% for those without biliary strictures ($p = 0.31$) (Fig. 3).

Table 2 Biliary complications after duct-to-duct biliary reconstruction in living donor liver transplantation

	n	Leakage (%)	stricture (%)
Number of bile ducts and anastomoses	80	12 (15)	20 (25)
1 duct / 1 anastomoses	48	5 (10.4)	11 (22.9)
2 ducts / 1 anastomoses (plasty)	14	3 (21.4)	5 (35.7)
2 ducts / 2 anastomoses	15	2 (13.3)	2 (13.3)
3 ducts / 3 anastomoses	2	1 (50)	2 (100)
3 ducts / 2 anastomoses (plasty)	1	0	0

Table 3 Univariate and multivariate analysis of risk factors for biliary strictures

Risk factors	No. of patients with biliary stricture	*p* Value (Univariate)	*p* Value (Multivariate)
Immunosuppression		0.044	0.124
Bax (*n*=18)	1 (5%)		
Non-Bax (*n*=62)	19 (30.6%)		
Biliary leakage		0.0001	0.001
Yes (*n*=12)	7 (58%)		
No (*n*=68)	13 (19%)		
No. of bile ducts		0.501	0.165
Single (*n*=48)	11 (22.9%)		
Non-single (*n*=32)	9 (28.1%)		
Ductoplasty		0.216	0.121
Yes (*n*=15)	5 (33.3%)		
No (*n*=65)	15 (23.1%)		
Donor age		0.072	0.152
> 50 year (*n*=28)	10 (35.7%)		
< 50 year (*n*=52)	10 (19.2%)		
Graft		0.647	0.917
Right (*n*=66)	17 (25.7%)		
Left (*n*=14)	3 (21.4%)		
MELD		0.837	0.806
> 25 (*n*=17)	4 (23.5%)		
< 25 (*n*=63)	16 (25.3%)		

Table 4 Univariate and multivariate analysis of risk factors for biliary leakage

Risk factors	No. of patients with biliary leakage	*p* Value (Univariate)	*p* Value (Multivariate)
Immunosuppression		0.033	0.005
Bax (*n*=18)	0 (0%)		
Non-Bax (*n*=62)	12 (19%)		
No. of bile ducts		0.569	0.901
Single (*n*=48)	6 (12.5%)		
Non-single (*n*=32)	6 (19%)		
Ductoplasty		0.639	0.702
Yes (*n*=16)	3 (18.8%)		
No (*n*=64)	9 (14%)		
Donor age		0.066	0.065
> 50 year (*n*=28)	7 (25%)		
< 50 year (*n*=52)	5 (9.6%)		
Graft		0.636	0.512
Right (*n*=66)	9 (13.6%)		
Left (*n*=14)	3 (21%)		
MELD		0.674	0.42
> 25 (*n*=17)	2 (12.5%)		
< 25 (*n*=63)	10 (15.6%)		

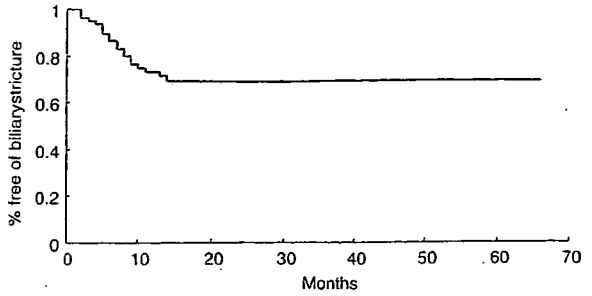

Fig. 2 Biliary stricture-free rate after LDLT

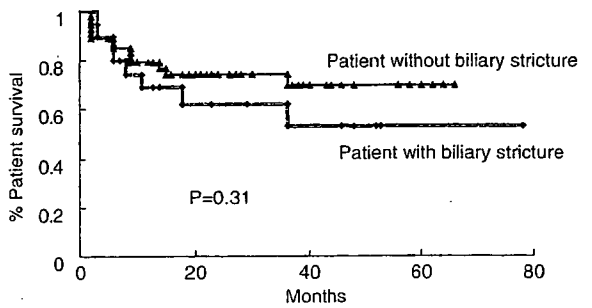

Fig. 3 Impact of biliary strictures on patient survival (Kaplan-Meier) in months

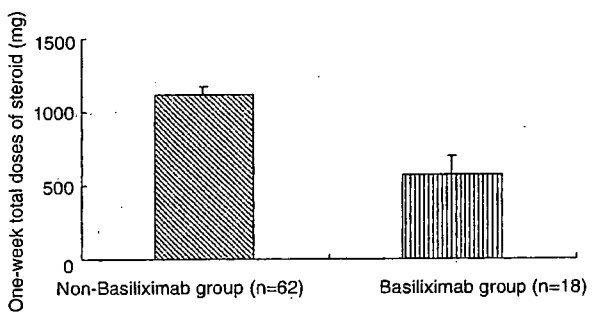

Fig. 1 Total doses of methylpredonisolone that were administered for one week after living donor liver transplant (LDLT). All values are expressed as the mean ± standard error

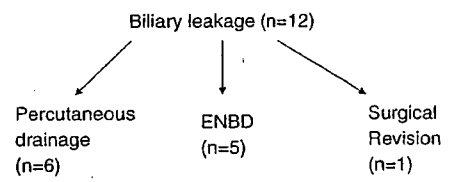

Fig. 4 Summary of the treatment modalities used for biliary leakage: endocsopic retrograde nasobiliary drainage (ENBD), percutaneous drainage, and surgical revision

Management of biliary complications

For biliary leakage, ENBD was possible in five patients. Six patients with bilairy leakage underwent percutaneous drainage under ultrasound guidance. One patient underwent Roux-en-Y hepaticojejunostomy. All patients were successfully treated by these modalities (Fig. 4).

Figure 5 shows the summary of the various modalities used for the treatment of biliary strictures. Initially, the patients with biliary strictures were referred for ERC. In 10 of the 20 patients, a guidewire could pass through the stricture, and these patients were treated by endoscopic internal stent placement. In the remaining 10 patients, the guidewire could not be passed through the biliary stricture because it was too tight and the bile ducts were too kinked. No symptoms of biliary stricture were observed in two patients after ERC. Seven patients required percutaneous transhepatic biliary drainage (PTBD), and five patients underwent stenting. Consequently, six patients underwent Roux-en-Y reconstruction to repair the stricture; however, 16 months after transplantation, one patient died of sepsis secondary to chronic cholangitis.

Discussion

In the present study we observed that post-transplantation anastomotic biliary leakages and strictures occurred, respectively, in 15% and 25% of our patients who

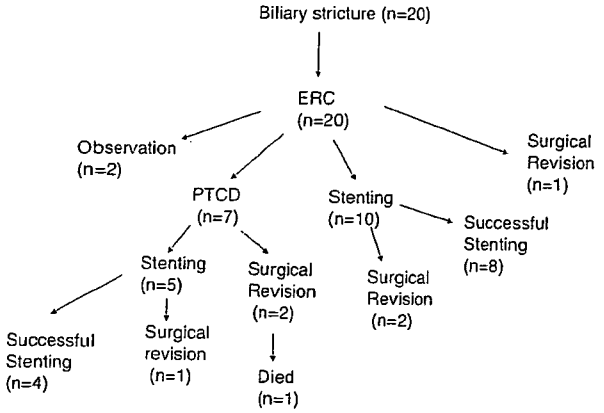

Fig. 5 Summary of the treatment modalities used for biliary stricture: endocsopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), and surgical revision

underwent LDLT with duct-to-duct biliary reconstruction. In previous reports the incidence of biliary stricture in patients who have undergone LDLT with duct-to-duct biliary reconstruction ranges from 20% to 60% [15, 16], whereas the reported incidence of biliary stricture in patients who have undergone cadaveric-donor liver transplantation with duct-to-duct biliary reconstruction is less than 30% [17–19]. Fan et al. reported that while the incidence of biliary leakage was comparable in the two groups, the incidence of biliary stricture was significantly higher in the LDLT group than in cadaveric whole-graft liver transplantation [20].

The present study sought to identify the risk factors for biliary leakage and stricture unique to duct-to-duct biliary reconstruction. We found that patients who developed biliary leakage were vulnerable to biliary stricture. Bile leakage after liver transplantation has previously been suggested as a risk factor for the development of anastomotic strictures [4, 21, 22]. It is likely that the leakage of bile causes local inflammation, thus increasing the risk of fibrosis. Further, the leakage of bile may merely represent ischemia of the extrahepatic bile duct, and in this manner, is associated with anastomotic stricture. The immunosuppressive regimes that included basiliximab were found to be a protective factor against anastomotic leakage. Biliary leakage developed less frequently in patients treated with the basiliximab-based immunosuppressive regimes than in those treated with the non-basiliximab-based ones. The initial 1-week doses of methylpredonisolone were significantly lower in the basiliximab-based immunosuppressive regimes than in those without basiliximab. In general, glucocorticosteroids impair fibroblast proliferation and collagen synthesis, and they delay wound healing [23]. Possibly, the steroid-sparing basiliximab-based immunosuppressive therapy contributed to protection against biliary leakage. Consequently, the development of biliary strictures tended to be less frequent in the basiliximab-based immunosuppressive therapy than in the non-basiliximab-based one. However, there was no significant difference in the incidence of biliary stricture with respect to the immunosuppressive therapies by using stepwise multivariate analysis.

In our series, 40% of the liver grafts had multiple bile duct orifices. The poor outcome might be related to the complicated procedures. The Kyoto Group has reported that they experienced a higher rate of biliary complications with the use of stents for biliary reconstruction; further, no difference was observed with respect to the presence of single or multiple biliary anastomoses [4]. Salvalaggio et al. studied the impact of multiple bile duct anastomoses on the development of biliary complications after liver transplantation in children. They demonstrated that patients with multiple ducts had a higher incidence of leaks as compared to those in the single duct group, but that the incidence of strictures, both early and late, was similar in the two groups [24]. Similarly, in our study, the presence of multiple or single hepatic ducts was not a significant risk factor for biliary stricture. The extensive dissection enabled us to overcome the technical difficulty encountered with multiple and widely separated bile ducts in the liver grafts, as the corresponding orifices in the recipient hilar plate could be freely selected. The use of a bile duct with a wide orifice might result in a good outcome. Hwang et al. reported that duct-to-duct biliary reconstruction involving a small-sized duct (diameter <4 mm) was a risk factor for anastomotic stenosis [25]. However, in our study, the diameter of the graft bile duct was not related to the incidence of biliary strictures.

Ischemic changes around the anastomosis are known to be a major cause of biliary stricture. In donor operations, particularly in cases of right lobe graft, the tissues surrounding the right hepatic duct at the bifurcation must be removed in order to correctly identify the anatomy of the anterior and the posterior segmental branches. The anterior branch of the hepatic duct might be more widely exposed than the posterior branch during the dissection. Dissecting these tissues might cause the biliary stump in the right-lobe graft to become ischemic, which may then facilitate formation of a biliary stricture. The arterial blood supply of the biliary system has been described by several investigators [26–29]. A fine arterial plexus covering the surface of the biliary tract is one of the main sources of the blood supply of the biliary system. Furthermore, the vascular supply for both hepatic ducts depends on an arterial network that is bilaterally fed by the plexus that is formed by the branches of both the right and left hepatic arteries. The blood supply to the bile duct of the graft tends to be tenuous. Shortening of the segment of the donor duct results in an improved circulatory status around the biliary anastomosis, and this technique is therefore suitable for LDLT with a limited length of the graft hepatic duct [9].

Our patients with biliary strictures were treated satisfactory by ERC, PTBD, surgery, or a combination of these. Hisatake et al. reported that 14 (73.4%) of their patients with strictures were treated endoscopically by inserting internal stents ranging from 7 to 12 Fr in size [13]. The complication of biliary stricture occurred only in one patient. Our initial treatment for duct-to-duct biliary reconstruction recipients was endoscopic stenting. Forty percent of our patients with anastomotic strictures failed to respond to endoscopic treatment because it was impossible to pass an endoscopic guidewire through the stricture because of the extreme narrowness of the duct. Those patients who failed to the respond to the endoscopic treatment were treated via a percutaneous transhepatic approach. The total success rate of stenting therapy was 60%. Surgical correction had been effectively performed in patients with recurrent symptoms of cholangitis after stent removal or in those patients for whom stenting was not possible. As demonstrated in several studies, balloon dilatation and stenting via either an endoscopic or percutaneous transhepatic approach were safe and effective. Nonetheless, surgical correction should be reserved for patients who fail to respond to nonsurgical treatment.

Our patients with biliary leakages were treated satisfactory by ENBD, percutaenous drainage, or surgery. We preferred interventional treatment rather than surgery as mentioned by Hwang et al [25]. All patients with biliary leakages were successfully treated by ENBD or percutaneous drainage, except one patient who was treated by surgery.

In summary, our experiences revealed that biliary stricture was associated with biliary leakage and that steroid-sparing basiliximab-based immunosuppressive therapy contributed to the decreased incidence of biliary leakage. The incidence of biliary stricture was not associated with the type or method of biliary reconstruction. The radiological, endoscopic, or surgical treatment for biliary complications was effective and satisfactory. However, the incidence rate of biliary stricture after LDLT is still high. Further improvements in surgical modalities and postoperative management should contribute to the decrease in the incidence of biliary complications.

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ORIGINAL ARTICLE

Microsurgical hepatic artery reconstruction during living-donor liver transplantation by using head-mounted surgical binocular system

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Keywords
hepatic artery reconstruction, living-donor liver transplantation, microsurgery, surgical telescope.

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Summary

We have described our experience with arterial reconstruction during living-donor liver transplantation by using Varioscope® AF3 – a head-mounted surgical binocular system with automatic focusing and continuous zoom magnification from 3.6× to 7.2×. From July 1996 to December 2006, 91 grafts were implanted in 89 living-donor liver transplantation recipients, including two that required retransplantation. For microsurgical reconstruction of the graft hepatic artery, a conventional operating microscope was used in the first 10 transplants and Varioscope, in the subsequent 81. The time required to complete arterial reconstruction while using a conventional operating microscope and Varioscope was 78.6 ± 44.6 min and 35.5 ± 15.5 min, respectively. No arterial complications, including hepatic artery thrombosis, occurred in any of the 89 patients during the observation period. In living-donor liver transplantation, successful hepatic artery reconstruction can be safely carried out using Varioscope.

Introduction

Hepatic artery thrombosis after liver transplantation is a life-threatening event and is associated with high mortality. It has been reported that the incidence of hepatic artery thrombosis varies widely (approximately 2–15%); however, because of recent technical advances, it has generally decreased, even in the case of split liver transplantation or living-donor liver transplantation [1–7]. One of the most important advances in hepatic artery reconstruction is the introduction of microsurgical techniques involving an operating microscope. Generally, a conventional operating microscope comprising a binocular head, counterbalanced pantographic arm, and floor stand is used for microsurgical hepatic artery reconstruction. However, this type of operating microscope has certain drawbacks: it is bulky, requires tilting, and presents difficulties for focusing in the abdominal cavity. As a substitute for this device, we used Varioscope® AF3 (Varioscope; Life Optics®, Vienna, Austria) – a head-mounted surgical binocular system with automatic focusing and continuous zoom magnification from 3.6× to 7.2×. It is operated using a footswitch and can provide a wide field of view at any working distance (300–600 mm) and any magnification (Fig. 1). Here, we describe our experience of hepatic artery reconstruction by using Varioscope in a series of 91 living-donor liver transplantations for 89 adult patients; we have focused on the microsurgeon's perspective.

Patients and methods

Patient population

From July 1996 to December 2006, 91 grafts were implanted in 89 living-donor liver transplantation recipients

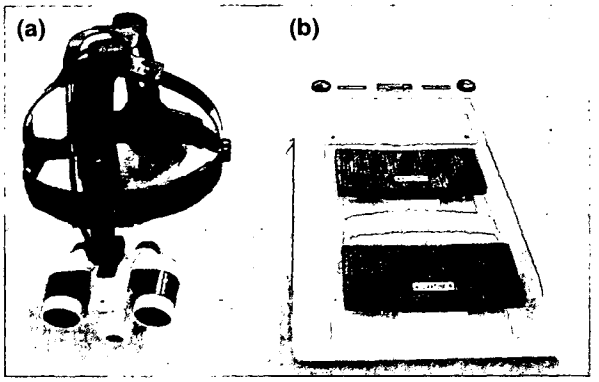

Figure 1 The Varioscope® AF3 is a head-mounted surgical telescope with automatic focusing and continuous zoom magnification from 3.6× to 7.2× that can be operated using a footswitch. This device refocuses if the working distance changes, and the surgeon has almost unlimited mobility without any corresponding loss of sharpness in the obtained three-dimensional images. (a) Head-mounted surgical telescope. (b) Footswitch for focusing and zoom magnification.

comprising 52 men and 37 women whose age ranged from 20 to 69 years (mean age 50). The indications for living-donor liver transplantation included hepatitis virus-related cirrhosis in 52 patients, cholestatic liver disease including primary biliary cirrhosis and autoimmune hepatitis in 14, fulminant hepatitis in 10, retransplantation in two, and others in 13. Of 41 patients with hepatocellular carcinoma, 22 had a history of transcatheter arterial chemoembolization prior to living-donor liver transplantation. The types of liver grafts included those of the right liver lobe (n = 72), left liver lobe (n = 18), and right lateral sector (n = 1).

Surgical technique

Prior to microsurgical hepatic artery reconstruction, the implanted graft was reperfused in the recipients after the portal veins were reconstructed [8]. For microsurgical reconstruction of the graft hepatic artery, a conventional operating microscope was used for the first 10 transplants and Varioscope, for the subsequent 81. The recipient artery was selected according to its patency, extent of intimal damage, and caliber consistency with the graft artery caliber. End-to-end vessel anastomosis was carried out between the recipient and graft hepatic arteries with interrupted 8-0 monofilament nylon sutures. In all 91 implants, we used microvascular double clamp type A-II comprising two bulldog clamps fitted to a sliding bar; it can be used to anastomose vessels of diameters ranging from 0.5 to 5.0 mm without injuring the vessel wall (Fig. 2) [9]. After reconstruction, the intrahepatic arterial signals were verified using color Doppler ultrasonography. Postoperative anticoagulation management was carried out via heparin infusion (the target activated clotting time was 150–200 s for 2 weeks). To determine the adequacy of blood flow and velocity during the first two post-transplant weeks, color flow Doppler ultrasound was performed daily, on alternate days in the third week, and once a week thereafter until discharge.

Results

The details and sizes of the graft/recipient hepatic arteries used for anastomosis are shown in Tables 1 and 2. Double arterial reconstructions were performed in three transplant patients. In one of the right lobe grafts, the

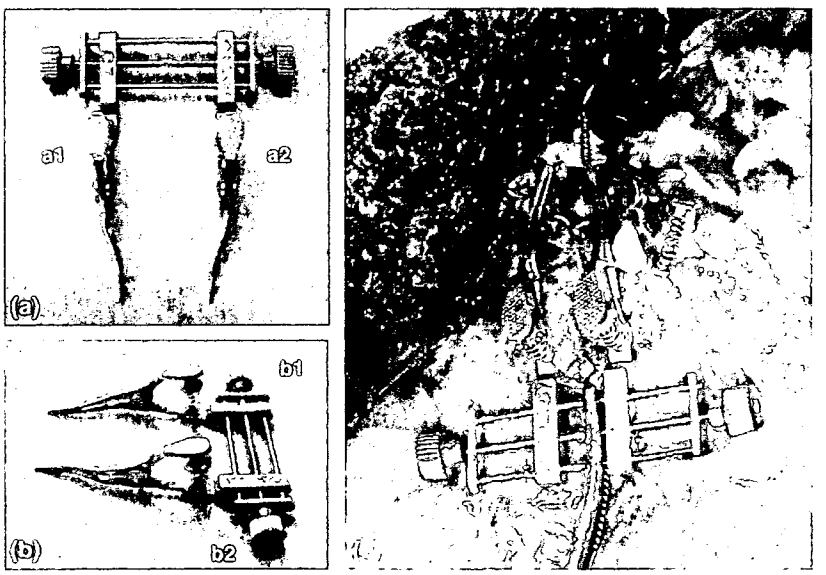

Figure 2 The microvascular double clamp type A-II device comprising 4.2 cm long bulldog clamps and weighing 17 g. By rotating b1 or b2, the distance of the two tips can be freely adjusted from 0 to 25 mm. By rotating a1 and a2, the pressure required to open the tips can be adjusted from approximately 40–250 g. (a) Frontal view. (b) Oblique view. (c) Use of the device during end-to-end anastomosis of the hepatic artery for living-donor liver transplantation with a right lobe.

Table 1. Details of graft/recipient hepatic arteries anastomosed.

Graft	Recipient	No
Right lobe graft		
RHA	RHA	60
RHA	LHA	7
RHA	CHA	2
RHA	Paramedian branch b of RHA	2
Lateral branch of RHA	Lateral branch of RHA	2
Paramedian branch b of RHA	Paramedian branch of RHA	1
Paramedian branch b of RHA	LHA	1
Left lobe graft		
LHA	LHA	13
LHA	RHA	4
LHA	CHA	1
MHA	RGEA	1
Total		94

RHA, right hepatic artery; CHA, common hepatic artery; LHA, left hepatic artery; RGEA, right gastroepiploic artery; MHA, middle hepatic artery.

Table 2. Diameters of hepatic arteries anastomosed (n = 94).

Diameters	Graft	Recipient
2 mm and less	42 (44.7)	26 (27.7)
2–3 mm	39 (41.9)	48 (51.1)
Over 3 mm	13 (13.8)	20 (21.3)
Mean	2.72 mm	2.92
SD	0.95 mm	0.75

Values indicated in parentheses are percentage.

paramedian and lateral branches of the donor's right hepatic artery were anastomosed to those of the recipient's right hepatic artery, respectively. In another right lobe graft, these branches were anastomosed to the recipient's left and right hepatic arteries, respectively. In one of the left lobe grafts, the left hepatic artery and middle hepatic artery were anastomosed to the recipient's left hepatic artery and right gastroepiploic artery, respectively. Vascular interposition grafts were not used in this series.

Figure 3 shows the chorographical comparison of the time required to complete arterial reconstruction. Overall, the time required for hepatic artery reconstruction by using a conventional operating microscope and Varioscope was 78.6 ± 44.6 min (n = 10) and 35.5 ± 15.5 min (n = 81), respectively. All the anastomoses were patent and yielded a 100% patency rate. Twenty-six patients died postoperatively of multiple organ failure, sepsis, recurrence of hepatic tumor, and chronic rejection. However, arterial complications did not develop even in these 26 patients. In the remaining 63 (74.2%) patients, the hepatic artery anastomoses remained patent during a mean follow-up period of 28.7 ± 19.4 months. Thus, no arterial

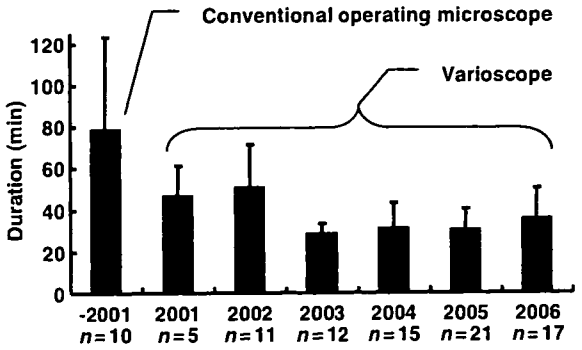

Figure 3 Chorographical comparison of the time required to complete arterial reconstruction. Average values ± SD in each year from 1996 to 2006 are shown.

complications, including hepatic artery thrombosis and hepatic artery stenosis, occurred in any of the 89 patients during the observation period.

Discussion

The introduction of microsurgical techniques in living-donor liver transplantation has resolved the problem associated with the high risk of hepatic artery thrombosis, enabled the reconstruction of arteries of different calibers, and reduced the incidence of arterial complications because of the delicate manipulation required in living-donor liver transplantation. The widely used operating microscope, which needs to be covered with a sterile plastic bag and adjusted depending on the operator's position, provides an operating field of view at a certain prefixed angle (usually a vertical view) but does not allow the operating field to be viewed sideways. This takes time and occasionally causes difficulties in the precise observation of the hepatic artery intima that are sequestered by the outer tunica. An additional problem is the movement of the vessels due to ventilation; the upper abdominal organs together with the recipient artery move in accordance with ventilation. During suturing performed with the aid of an operating microscope, it is occasionally difficult to adjust continuously the operative field of view. Therefore, when required, respiration needs to be withheld during suture placement. Because of this inconvenience, high-power surgical loupes are sometimes preferred to operating microscopes. It has been reported that microvascular hepatic artery reconstruction with 4× or 6× loupe magnification can yield results as good as those obtained with an operating microscope [10,11]. We employed the Varioscope – a device that is more sophisticated than surgical loupes; this instrument combines a miniature high-end microscope with a flexible head-

mounted system. The Varioscope can simply be mounted on the head, thereby saving setup time. It enables the surgeon to easily adapt to the motion of the operative field due to respiration. Temporary termination of artificial respiration to prevent motion of the operative field was not required when the Varioscope was used.

Previously, a liver graft with a fine hepatic artery of diameter <2 mm was regarded as a risk factor for hepatic artery thrombosis. As shown in Table 2, approximately 45% of the graft hepatic arteries and 28% of the recipient hepatic arteries were of diameter ≤2 mm. Our procedure using Varioscope enables the reconstruction of such relatively small arteries. Microvascular double clamp type A-II was used in most transplants in the present series. Both ends of the graft and recipient hepatic arteries were immobilized using the clamps, and the distance between the tips of the two clamps was adjusted such that the ends of the arteries were in contact. After the anterior wall of the hepatic artery had been anastomosed using interrupted sutures, the double clamp was rotated, and the posterior wall was then similarly anastomosed. In two cases wherein the graft hepatic artery was short, we employed the posterior-wall-first anastomotic technique using smaller single-clamp devices. In this technique, microsutures are first placed in the posterior wall of the vessel, and turning over of the microclamp is thereby eliminated; it is known to have significant advantages for such short hepatic artery reconstruction in living-donor liver transplantation [6]. For both anastomotic techniques, Varioscope could provide sufficient magnification at an appropriate working distance. Although vascular interposition grafts for hepatic artery reconstruction were not used in this series, they may be occasionally required when a suitable recipient's artery is not available for reconstruction [12,13]. The utility of the Varioscope in such cases remains to be tested.

In conclusion, we have described our experience with the successful use of Varioscope for arterial reconstruction in living-donor liver transplantation, instead of using a convectional microscope that has positioning and tilting problems.

Authorship

HO and HT performed hepatic artery reconstruction; HO, HT, KI, KI, MS, TI, MO, HT, TI and TA performed recipient transplantation; TI and T.A performed donor hepatectomy; HO analyzed the data and wrote the paper.

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Surveillance Program for Early Detection of Hepatocellular Carcinoma in Japan

Results of Specialized Department of Liver Disease

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Objective: Surveillance of cirrhotic patients enables early detection of hepatocellular carcinoma (HCC) and possibly prolongs survival. The aim of this study was to explore whether early-stage HCC can be detected earlier at a specialized department of liver disease than in other institutions.

Methods: The study subjects were 574 patients with HCC. Patients were subdivided into 3 groups according to the manner of HCC detection: group A, HCC was detected in 91 patients during periodic examination at Kurume University School of Medicine; group B, HCC was detected in 301 patients during periodic examination at other institutions; group C, HCC was detected incidentally or because of symptoms in 182 patients.

Results: The HCC detected in group A was significantly of smaller size (20.4 mm) compared with groups B (27.1 mm, $P < 0.0001$) and C (57.8 mm, $P < 0.0001$). The frequency of receiving treatment (surgery or local ablation therapy) was significantly higher in group A (73%) than in groups B (52%, $P = 0.002$) and C (26%, $P < 0.0001$). The 5-year survival rates were 52% for group A, 40% for group B, and 23% for group C, respectively. The survival of group A was significantly better than that of groups B ($P = 0.0157$) and C ($P < 0.0001$).

Conclusions: Surveillance for HCC at specialized Department of Liver Disease can detect early-stage HCC, resulting in a higher chance of receiving promising treatment.

Key Words: hepatocellular carcinoma, surveillance, ultrasonography, computed tomography, tumor markers

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Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world, and the third most common cause of cancer-related death.[1] HCC has become the leading cause of death among patients with liver cirrhosis.[2] The incidence of HCC has increased in the United States over the past 2 decades.[3] HCC commonly occurs in patients with chronic liver diseases related to hepatitis C virus (HCV) or hepatitis B virus (HBV) and the incidence of HCC in patients with HCV was reported to be 1.5% to 8% per annum.[4–7] Several studies have shown that surveillance with ultrasonography (US) and α-fetoprotein (AFP) for patients with liver cirrhosis can detect early-stage HCC, resulting in higher chance of receiving early treatment.[4–11] However, some studies showed that surveillance for HCC has a limited value in prolonging survival of patients with HCC including cost effectiveness,[12,13] and there is no randomized controlled trial to establish the value of surveillance of HCC in increasing survival of patients with chronic liver disease. Nowadays, such a study is almost impossible for ethical reasons. Discrepancies in the results of surveillance of HCC are related to differences in the incidence of HCC, target population of surveillance, frequency of surveillance, effective treatment of HCC, management of liver cirrhosis, and possibly also US equipment and skill of US examiner. The improvement of US equipment and increased proficiency of US examiner for surveillance of HCC have allowed early diagnosis of HCC, and resulted in prolonging survival of patients with liver cirrhosis over 3 quinquennia.[10] US equipment and skill of US examiner vary among institutions. However, no controlled trial has compared the results of surveillance of HCC among institutions.

Three-phase computed tomography (CT) and magnetic resonance imaging (MRI) might be potentially more sensitive and specific for the diagnosis of HCC.[14] Studies from the United States indicated that the screening for HCC with CT could be a cost effective strategy in transplant-eligible patients with cirrhosis.[15] Des-γ-carboxy prothrombin (DCP), a new tumor marker of HCC is more specific or equally specific to AFP.[16,17] However, surveillance studies using 3-phase CT, MRI, and DCP have not been reported.

The aims of the present study were (1) to determine differences in detecting early-stage HCC among various departments of liver disease, (2) if such differences have an impact on survival of patients with chronic liver disease, and (3) compare the values of regular 3-phase CT or regular DCP and conventional method of surveillance program of HCC in the detection of early-stage HCC.

PATIENTS AND METHODS

Patients

The study subjects were 574 Japanese patients with HCC diagnosed at Kurume University School of Medicine between January 1995 and December 2000. The diagnosis of HCC was established by histopathology and/or imaging studies (US, CT, angiography, CT-angiography, and MRI), and/or based on high plasma levels of tumor markers such as AFP and DCP. Patients were subdivided into 3 groups according to the manner of HCC discovery: group A, 91 patients were found to have HCC during periodic follow-up examination at Kurume University School of Medicine; group B, 301 patients were found to have HCC during periodic follow-up examination in other institutions; and group C, 182 patients were found to have HCC incidentally or because of symptoms.

Surveillance Program

Surveillance of 91 patients of group A included patients with chronic liver disease irrespective of age, liver cirrhosis, or etiology (HCV, HBV, alcoholic and other chronic liver diseases). Regular surveillance program of 91 patients of group A was as follows: US + AFP, 20 patients; US + AFP + DCP, 20 patients; US + AFP + CT, 15 patients; and US + AFP + CT + DCP, 36 patients. The frequency of monitoring using US, AFP, CT, DCP were 3, 6 to 12, and 3 to 6 months, respectively. During the subsequent surveillance period, imaging studies and tumor markers, together with physical examination and routine biochemical test, were repeated every 3 months. If 1 diagnostic modality indicated possible HCC, the other modalities were then performed on an out-patient basis. When nodular liver lesion was depicted by US or CT in such patients, they were admitted to Kurume University School of Medicine, and the diagnosis of HCC was confirmed by histopathology and/or imaging studies conducted based on high plasma levels of tumor markers.

The 301 patients of group B were found to have nodular liver lesions during periodic follow-up examination at other institutions at least 6-month interval by means of direct interview of the patients. The surveillance program of the 301 patients of group B was unknown. Classification of 182 patients as group C was based on finding a nodular liver lesion incidentally or at examination for symptoms and interview of patients but not at periodic follow-up examination.

Treatment Strategy

When a diagnosis of HCC was established at Kurume University School of Medicine, the following treatment options were assessed. Liver transplantation (LT)[18,19] was not considered because of very small number of donor resources and insurance system in Japan from January 1995 to December 2000. (1) Hepatic resection (HR)[20] was assessed especially for patients with localized HCC and preserved hepatic reserve capacity. (2) Nonsurgical treatments, such as percutaneous ethanol injection (PEI),[21] microwave coagulation therapy (MCT),[22] radiofrequency ablation (RFA),[23,24] transarterial chemoembolization (TACE),[25] hepatic arterial infusion chemotherapy (HAIC),[26] and systemic chemotherapy[27] were assessed when HR was contraindicated or the patient refused surgical treatment. The most appropriate therapeutic procedure was selected according to the tumor status and the underlying liver cirrhosis. Local ablation therapies (LAT) such as, PEI, MCT, and RFA were considered in patients with 1-3 tumor nodules, each measuring $\leq$30 mm in diameter that were devoid of vascular invasion and not associated with extrahepatic metastasis. (3) TACE, HAIC, or systemic chemotherapy was considered in patients with maximum tumor size of > 30 mm, number of tumors > 3, presence of vascular invasion and/or presence of extrahepatic metastasis. (4) Best supportive care was assessed when patient had little hepatic reserve capacity or patient refused any treatment of HCC.

Outcome Measures

Outcome measures were analyzed retrospectively in groups A to C as follows: (1) tumor characteristics including size and number of HCC nodules, presence of vascular invasion, and presence of extrahepatic metastasis; (2) UNOS (The United Network for Organ Sharing) criteria for HCC[28]; (3) treatment of HCC; and (4) cumulative survival of patients with HCC.

Differences of Surveillance Program at Kurume University School of Medicine

In 91 patients of group A, 51 patients underwent regular CT (15 US + AFP + CT and 36 US + AFP + CT + DCP) and 56 patients underwent regular DCP (20 US + AFP + DCP and 36 US + AFP + CT + DCP) in addition to US and AFP for surveillance program of HCC, respectively. (1) Tumor characteristics; (2) UNOS criteria for HCC; (3) treatment of HCC; and (4) cumulative survival of patients with HCC was also compared in 51 patients with regular CT [regular CT (+) group] and 40 patients without regular CT [regular CT (−) group], and in 56 patients with regular DCP [regular DCP (+) group] and 36 patients without regular DCP [regular DCP (−) group].

Statistical Analysis

We used the χ^2, Fisher exact, and Mann-Whitney tests, where appropriate, to evaluate differences in clinical features of patients and in tumor characteristics. Survival was analyzed by the Kaplan-Meier method[29] and survival curves were compared by the log-rank test. Survival was

TABLE 1. Clinical Profile of 572 Patients With HCC

	Group A	Group B	Group C
No. patients	91	301	182
Age (y, mean ± SD)	65.4 ± 7.4	65.2 ± 8.8	63.5 ± 9.3
Sex			
Male (%)	54 (59)	214 (71)	158 (87)
Female (%)	37 (41)	87 (29)	24 (13)
		$P = 0.035$	$P < 0.0001$
			$P < 0.0001$*
Etiology			
HCV-positive (%)	82 (90)	258 (86)	135 (74)
HBV-positive (%)	4 (4)	30 (10)	31 (17)
HCV-negative and HBV-negative (%)	5 (6)	13 (4)	16 (9)
			$P = 0.006$
			$P = 0.006$*
Total bilirubin (mg/dL: mean ± SD)	1.27 ± 0.64	1.22 ± 0.78	1.12 ± 0.86
Albumin (g/dL: mean ± SD)	3.39 ± 0.49	3.45 ± 0.47	3.50 ± 0.45
Child pugh class			
A (%)	53 (58)	186 (62)	126 (69)
B or C (%)	38 (42)	115 (38)	56 (31)
AFP (ng/mL)			
0 to 100 (%)	68 (75)	181 (60)	91 (50)
> 100 (%)	23 (25)	120 (40)	91 (50)
		$P = 0.011$	$P = 0.030$
			$P < 0.0001$*
DCP (mAU/mL)			
0 to 40 (%)	70 (77)	188 (62)	55 (30)
> 40 (%)	21 (23)	113 (38)	127 (70)

*Group B versus group C.

confirmed up to September 30, 2004. The statistical software package SPSS for Windows (version 10.0, SPSS Inc, Chicago, IL) was used for data analysis. A P value of < 0.05 was considered significant.

RESULTS

Patient Characteristics

Table 1 summarizes the clinical profile of 574 patients with HCC. The 3 groups were comparable for age, serum levels of total bilirubin and albumin, and Child Pugh class, whereas they significantly differed for sex (group A vs. B: $P = 0.035$; group A vs. C: $P < 0.0001$; group B vs. C: $P < 0.0001$) and etiology of liver disease (group A vs. C: $P = 0.006$; group B vs. C: $P = 0.006$). Serum levels of AFP (> 100 ng/mL) and DCP (> 40 mAU/mL) were significantly higher in group C than in groups A and B, and significantly higher in group B than in group A (AFP; group A vs. group B: $P = 0.011$, group A vs. group C: $P < 0.0001$, group B vs. group C: $P = 0.030$. DCP; group A vs. group B: $P = 0.011$, group A vs. group C: $P < 0.0001$, group B vs. group C: $P < 0.0001$).

HCC Features

The characteristics of HCC in the three groups are listed in Table 2. Significantly smaller size and fewer HCC nodules were detected in group A than in groups B and C, and significantly smaller in group B than in group C (tumor size: A, B, C; 20.4, 27.1, 57.8 mm, respectively, group A vs. group B: $P < 0.0001$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$. Number of tumors; group A vs. group B: $P < 0.0001$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$). A significantly higher proportion of tumors showed vascular invasion in group C than in groups A and B, and significantly higher in group B than in group A (group A vs. group B: $P = 0.020$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$). Extrahepatic metastasis was noted in 9 patients. A significantly higher proportion of extrahepatic metastasis was noted in group C than in groups A and B (group A vs. group C: $P = 0.042$; group B vs. group C: $P = 0.001$).

UNOS Criteria and Treatment

Of the 574, 334 patients (58%) presented with HCC within UNOS T2 criteria (Table 2). A significantly higher proportion of patients presented with HCC within UNOS T2 criteria in group A (91%) compared with group B (68%) and group C (26%), and in group B compared with group C (group A vs. group B: $P < 0.0001$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$). With regard to treatment, 10 (11%), 20 (7%), and 16 (9%) of groups A, B, and C were treated with HR, respectively. Furthermore, 56 (62%), 137 (45%), and 31 (17%) of group A, B, and C were treated with LAT including PEI, MCT, and RFA, respectively. In addition, 21 (23%), 132 (44%), and 122 (67%) of groups A, B, and C were treated with interventional radiology including TACE and HAIC, respectively. For other therapies, 2 of group C were treated with systemic chemotherapy, and 4 (4%), 12 (4%), and 13 (7%) of groups A, B, and C were

TABLE 2. Tumor Characteristics and Treatment of 572 Patients With HCC

	Group A	Group B	Group C
No. patients	91	301	182
Tumor size (mm; mean ± SD)	20.4 ± 9.5	27.1 ± 17.8 $P < 0.0001$	57.8 ± 34.0 $P < 0.0001$ $P < 0.0001$*
Tumor number			
1 (%)	57 (63)	133 (44)	43 (23)
2 (%)	30 (33)	100 (33)	54 (30)
> 3 (%)	4 (4)	68 (23) $P < 0.0001$	85 (47) $P < 0.0001$ $P < 0.0001$*
Vascular invasion			
Yes (%)	0 (0)	17 (6)	44 (24)
No (%)	91 (100)	284 (94) $P = 0.020$	138 (76) $P < 0.0001$ $P < 0.0001$*
Extrahepatic metastasis			
Yes (%)	0 (0)	1 (1)	8 (4)
No (%)	91 (100)	300 (99)	174 (96) $P = 0.042$ $P = 0.001$*
UNOS criteria			
T1-2 (%)	83 (91)	204 (68)	47 (26)
T3-4 (%)	8 (9)	97 (32) $P < 0.0001$	135 (74) $P < 0.0001$ $P < 0.0001$*
Treatment			
Surgery or local ablation (%)	66 (73)	157 (52)	47 (26)
TACE, HAIC, or systemic chemotherapy (%)	21 (23)	132 (44)	122 (67)
Supportive care (%)	4 (4)	12 (4)	13 (7)

*Group B versus group C.

followed-up conservatively without any specific treatment for HCC because of hepatic failure or patient refusal of any treatment for HCC. The frequency of receiving promising treatment (HR or LAT) was significantly higher in group A (73%) than groups B (52%) and C (26%), and significantly higher in group B than group C (group A vs. group B: $P = 0.002$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$).

Survival Rates

The cumulative survival rates according to the modality of HCC discovery are shown in Figure 1. The 3, 5, and 7-year cumulative survival rates were 67%, 52%, and 36% for group A; 60%, 40%, and 22% for group B; and 38%, 23%, and 9% for group C, respectively. The cumulative survival rates of group A were significantly better than those of groups B ($P = 0.0157$) and C ($P < 0.0001$), and those of group B were significantly better than those of group C ($P < 0.0001$).

Differences in Surveillance Program at Kurume University School of Medicine

The detected HCC in the regular CT (+) group tended to be smaller than the regular CT (−) group (mean tumor size: 18.7 mm vs. 22.4 mm; $P = 0.061$). However, the number of tumors, serum levels of AFP and DCP, frequency of meeting UNOS T1-2 criteria and frequency of receiving promising treatment were not significantly different between the 2 types of HCC discovery (Table 3). Furthermore, cumulative survival was comparable between regular CT (+) and CT (−)

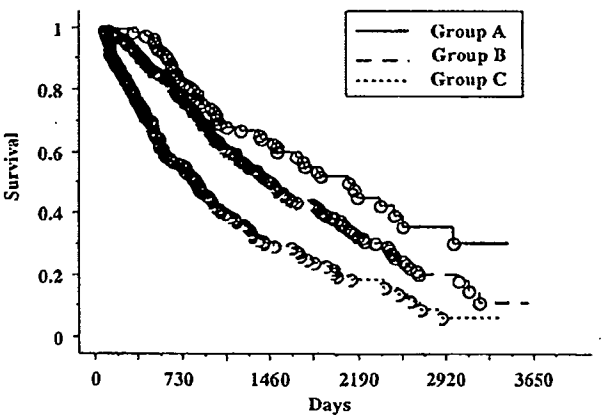

FIGURE 1. Kaplan-Meier survival curves of 574 patients with HCC according to the HCC diagnosis. The cumulative survival of group A was significantly better than that of groups B ($P=0.0157$) and C ($P<0.0001$), and group B was significantly better than that of group C ($P<0.0001$).

TABLE 3. Tumor Characteristics and Treatment of 91 Patients With HCC With Regular CT and DCP

	Regular CT (+)	Regular CT (−)	P	Regular DCP (+)	Regular DCP (−)	P
No. patients	51	40		56	35	
Tumor size (mm; mean ± SD)	18.7 ± 8.5	22.4 ± 10.1	0.0610	19.6 ± 8.7	21.5 ± 10.3	NS
Tumor size (mm)			0.0439			NS
0 to 20 (%)	35 (69)	18 (45)		35 (63)	18 (32)	
21 to 30 (%)	9 (17)	16 (40)		14 (25)	11 (31)	
> 31 (%)	7 (14)	6 (15)		7 (12)	6 (17)	
Tumor number			NS			NS
1 (%)	34 (67)	23 (58)		35 (63)	22 (63)	
2 (%)	15 (29)	15 (38)		17 (30)	13 (37)	
> 3 (%)	2 (4)	2 (5)		4 (7)	0 (0)	
AFP (ng/mL)			NS			NS
0 to 100 (%)	39 (76)	29 (73)		40 (71)	28 (80)	
> 100 (%)	12 (24)	11 (27)		16 (29)	7 (20)	
DCP (mAU/mL)			NS			NS
0 to 40 (%)	9 (18)	12 (30)		13 (23)	8 (23)	
> 40 (%)	42 (82)	28 (70)		43 (77)	27 (77)	
UNOS criteria			NS			NS
T1-2 (%)	47 (92)	38 (95)		51 (91)	34 (97)	
T3-4 (%)	4 (8)	2 (5)		5 (9)	1 (3)	
Treatment			NS			NS
Surgery or local ablation (%)	40 (78)	26 (65)		40 (72)	26 (74)	
TACE, HAIC, or supportive care (%)	11 (22)	14 (35)		16 (28)	9 (26)	

groups (Fig. 2A). Tumor size, number of tumors, serum levels of AFP and DCP, frequency of meeting UNOS T1-2 criteria, frequency of receiving promising treatment, and cumulative survival were comparable between regular DCP (+) and DCP (−) groups (Table 3, Fig. 2B).

DISCUSSION

HCC commonly occurs in patients with chronic liver diseases related to HCV or HBV.[4–7] Six months interval of surveillance including US and AFP for Child A-B cirrhotic patients is a conventional method used worldwide for early detection of HCC.[8–12] However, the results of surveillance are conflicting because of the annual incidence of HCC, target population of surveillance, frequency of surveillance, available treatment for HCC, management of liver cirrhosis, and possibly US equipment and skill of US examiner.[4–13] Trevisani et al[11] reported that the center that detected HCC during surveillance was an independent prognostic indicator for elderly Italian patients with cirrhosis in multicenter clinical studies. A small sample size could also contribute to the conflicting results. Our study attempted to define the difference in the outcome of patients with HCC retrospectively according to the manner of HCC discovery (group A, surveillance at Kurume University School of Medicine; group B, surveillance at other institutions; group C, control group).

The 3 groups were comparable for age, serum total bilirubin level, serum albumin level, and Child Pugh class (Table 1). Patients with symptomatic HCC had poorer hepatic reserve capacity than patients with HCC detected by surveillance, on the basis of the larger size of the tumors that exert a space-occupying effect despite the high proportion of patients without cirrhosis.[9,11] Variation of hepatic reserve capacity depends on the balance between existence of cirrhosis and tumors exerting a space-occupying effect.

A significantly higher proportion of patients unrelated to HCV (HBV-positive or HBV-negative and HCV-negative) were observed in group C compared with groups A and B (Table 1). Surveillance for HCC in patients with HCV-related chronic liver disease is commonly conducted across Japan.[5] HCC tends to be detected during surveillance in patients with HCV-related liver disease.

LT, HR, and LAT are promising therapeutic options for HCC[18–23] and suitable candidates for LT[18,19] and LAT[21–23] include HCC within UNOS T2 criteria[19,28] (single tumor; ≤5 cm in diameter and multiple tumors; no more than three tumor nodules, each ≤3 cm in diameter without vascular invasion or extrahepatic metastasis). Sangiovanni et al[10] concluded that a shift of more patients from HR toward LAT was favored by the application of strict criteria for patient selection to HR and that LAT contributed to prolongation of survival of patients with HCC over 3 quinquennia. In the present study, significantly smaller and fewer HCC were detected in group A than in groups B and C, and significantly smaller in group B than in group C. Moreover, a significantly higher proportion of patients of group A (91%) presented with HCC within UNOS T2 criteria than groups B (68%) and C (26%) and significantly higher proportion of group B than group C (group A vs. group B: $P < 0.0001$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$). Yuen et al[9] reported that