

Role of protocol ultrasonography for detecting biliary stricture in adult living donor liver transplantation recipients

Yanhong Que^{1,2}, Junichi Kaneko¹, Yasuhiko Sugawara^{1,*}, Sumihito Tamura¹, Masatoshi Makuuchi¹

¹Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan;

²Department of Ultrasound, First Affiliated Hospital, China Medical University, Shenyang, China.

SUMMARY The role of protocol ultrasonography (US) in detecting biliary stricture (BS) after adult living donor liver transplantation (ALDLT) remains to be clarified. We reviewed 268 ALDLT cases with BS to assess the role of protocol US. The sensitivity and specificity of serum values of gamma-glutamyl transpeptidase (G-GTP) and alkaline phosphatase (ALP) as indicators of BS were evaluated and compared with the US findings. Diagnosis of BS was made by drip-infusion cholangiography or direct endoscopic retrograde cholangiography. Fifty patients (19%) developed BS; anastomotic stricture in 46 and non-anastomotic in 4. The incidence of BS was not affected by the method of bile duct reconstruction or the type of graft. Protocol US detected dilated bile ducts (≥ 3 mm) in 45 cases (90%) with BS. The mean diameter of bile ducts in the BS group was 5 ± 2 mm, which was greater than that of patients without BS (2 ± 1 mm, $P < 0.001$). When the bile duct diameter was over 3 mm, the sensitivity and specificity of protocol US for the diagnosis of BS was 96% and 91%, respectively, whereas those of G-GTP were 60% and 74% when the values were more than 5-fold greater than the upper normal limit, and those of ALP were 56% and 62% when the values were 3-fold greater than the upper normal limit. The bile duct diameter and the G-GTP and ALP values did not correlate. US might be a useful and efficient imaging method to follow-up patients after ALDLT.

Key Words: Live donor, bile duct, stenosis

Introduction

Adult living donor liver transplantation (ALDLT) is now one of the most common effective treatments for end stage liver failure, because of a severe cadaver graft shortage. In ALDLT, thinner bile ducts and multiple holes make the bile duct anastomosis procedure more challenging than that in whole liver transplantation (1). Biliary stricture (BS) remains one of the most common postsurgical complications.

Early diagnosis of BS is critical for preventing septic cholangitis and graft failure in liver transplantation

patients. A definite diagnosis based on clinical and laboratory features alone is often difficult, as these abnormal features also occur with other complications, such as acute or chronic rejection, exacerbation of hepatitis, non-biliary septicemia origin, and recurrence of primary biliary cirrhosis or sclerosing cholangitis.

Ultrasonography (US) is a non-invasive imaging modality that can be performed quickly at the bedside. It is now the most frequently used imaging procedure to monitor many post-operative complications in ALDLT. Its role in the diagnosis of BS, however, remains controversial.

In whole liver transplantation, Hussaini and colleagues (2) reported US as a valuable tool to diagnose BS with a sensitivity and specificity of 77% and 67%, respectively. Other studies (3-6), however, reported that the sensitivity was only 34% to 54%, and concluded that the role of US to detect BS is

*Correspondence to: Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; e-mail: yasusugatky@yahoo.co.jp

Received June 5, 2007

Accepted July 19, 2007

was limited. The role of protocol US in ALDLT has not yet been reported. A comparison of protocol US findings and the laboratory values of gamma-glutamyl transpeptidase (G-GTP) or alkaline phosphatase (ALP) has not been discussed in detail. In this study, we analyzed the ALDLT cases with BS in our database to assess the role of protocol US.

Patients and Methods

Patients

Clinical information was retrospectively obtained from hospital charts. From January 1996 to December 2005, 280 patients (156 men, 124 women; average age 47 years) underwent ALDLT at Tokyo University Hospital, Japan. The indications included hepatitis B and C-related cirrhosis ($n = 130$), cholestatic liver diseases ($n = 77$), fulminant hepatic failure ($n = 24$), biliary atresia ($n = 16$), metabolic disease ($n = 9$), alcoholic liver cirrhosis ($n = 3$), and others ($n = 21$). The most commonly used graft was right liver graft ($n = 144$) and left liver with or without the caudate lobe ($n = 117$), followed by the right lateral sector ($n = 19$). During this period of time, 12 patients failed to come in for long - term follow-up at our hospital and were therefore excluded from the study. In 268 cases of ALDLT, duct to duct anastomosis was performed in 193 and right liver graft was used in 157.

Protocol ultrasonography examination

Protocol Doppler US was performed once or twice per day for 2 weeks postoperatively and several times per week after the initial 2 weeks using a color Doppler US instrument (SSD 2000 or SSD 6500, Aloka Co. Ltd., Tokyo, Japan) in B, M, and Doppler modes. Protocol US was performed every 3 months in the outpatient clinic and when aspartate aminotransferase (AST), alanine aminotransferase (ALT), G-GTP, and ALP levels were above the upper normal limits, or when AST, ALT, G-GTP, or ALP values were abnormal and the intrahepatic biliary duct was dilated more than 3 mm. We examined all the bile ducts in the graft and chose the point where the intrahepatic bile duct was the most dilated and measured the diameter.

G-GTP, ALP, AST, and ALT were measured twice per day during the first 2 weeks postoperatively and once a day thereafter until discharge. In the outpatient clinic, these data were collected on a weekly basis during the first 3 months and every month in the succeeding period.

Diagnosis and treatment of biliary stricture

The final step of diagnosis consisted of three-dimensional reconstruction done by helical computed

tomography on drip-infusion cholangiography or direct endoscopic retrograde cholangiography. Type of stricture, anastomotic or non-anastomotic, was determined using these examinations.

Balloon dilatation under endoscopic retrograde cholangiography or percutaneous transhepatic biliary drainage was first applied when feasible. If the stricture was not resolved by conservative methods, surgical revision was performed.

Statistical analysis

Data were expressed as percent and mean \pm standard deviation or median and range. We compared categorical variables using the chi-square test and, when appropriate, the Mann-Whitney U test. A Spearman correlation test was used to analyze the relation between the bile duct diameter and the cholestatic liver enzyme values. A P value of less than 0.05 was considered significant. Statistical analysis was performed using SPSS software version 10.0.6 (SPSS Inc., Chicago, IL, USA).

Results

Incidence of biliary stricture

Fifty patients (19%) developed BS (20 women, 30 men); anastomotic stricture in 46 (17%) and non-anastomotic stricture in 4 (2%). The median time from ALDLT to the diagnosis of BS was 7.5 (range, 0.1-87) months and median follow-up of each patient from the first treatment to the last follow-up visit or death was 23.8 (range, 1-92) months. The different bile duct reconstruction types ($P = 0.3$) and graft types (right vs. left, $P = 0.7$) did not relate to the occurrence of BS.

G-GTP and ALP

In the patients with BS (BS group), 16 (34%) had clinical symptoms of cholestasis such as high fever, jaundice, and itching. On the other hand, the other 34 (68%) remained asymptomatic. G-GTP and ALP values exceeded the upper normal limit in 47 (94%) and 48 (96%) patients, respectively. The differences were statistically significant compared with the maximum values in the control group (Table 1). There was no correlation between bile duct diameter and G-GTP or ALP ($P = 0.8$ or 0.7). Sensitivity and specificity for multiple discriminatory thresholds of G-GTP were 60%

Table 1. G-GTP and ALP levels in BS group (before treatment) and control

Liver Enzymes	BS Group	Control	P
G-GTP (IU/l)	502 \pm 368	302 \pm 324	< 0.001
ALP (IU/l)	680 \pm 336	384 \pm 348	< 0.001

Abbreviations: G-GTP, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase

Table 2. Sensitivity and specificity to diagnose biliary stricture for multiple discriminatory thresholds of G-GTP

Threshold	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)
ULNL	47	15	203	3	94	7
5-folded of ULNL	30	161	57	20	60	74
10-folded of ULNL	15	200	18	45	25	92

Abbreviations: ULNL, Upper limit of normal level; TP, true positive; TN, true negative; FP, false positive; FN, false negative; G-GTP, gamma-glutamyl transpeptidase

Table 3. Sensitivity and specificity to diagnose biliary stricture for multiple discriminatory thresholds of ALP

Threshold	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)
ULNL	48	7	211	2	96	3
5-folded of ULNL	28	136	82	22	56	62
10-folded of ULNL	10	192	26	40	20	88

Abbreviations: ULNL, Upper limit of normal level; TP, true positive; TN, true negative; FP, false positive; FN, false negative; ALP, alkaline phosphatase

Table 4. Sensitivity and specificity for multiple discriminatory thresholds of ultrasound to diagnose biliary stricture

Threshold	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)
≥ 3 mm	45	198	20	5	90	91
≥ 5 mm	24	216	2	26	48	99

Abbreviations: TP, true positive; TN, true negative; FP, false positive; FN, false negative

and 74% when the values were more than 5-fold greater than the upper normal limit (Table 2); those for ALP were 56% and 62% when the values were more than 3-fold greater than the upper normal limit (Table 3).

Ultrasonography in the detection of biliary stenosis

In our study, bile ducts were found to be dilated by US in 45 cases in the BS group (90%). The mean bile duct diameter in BS group was significantly greater than that of the control group (5 ± 2 mm and 2 ± 1 mm, $P < 0.001$). The sensitivity and specificity for discriminatory thresholds of US to diagnose BS are shown in Table 4. The cutoff value of the diameter of the bile duct was 3 mm with a sensitivity and specificity of 96% and 91%, respectively.

Follow-up after treatment

During the follow-up, 7 (14%) patients in the BS group died. One patient died because of pulmonary embolism, one had sepsis of biliary origin, three patients died due to recurrent malignancy, 1 due to multiple organ failure, and 1 secondary to pneumonia and peritonitis.

In the BS group, all patients with long-term survival eventually had satisfactory results and the dilated bile ducts returned to normal in 32 cases (64%) based on US at the last follow-up visit. The bile duct dilation remained unchanged in 22 cases (44%), based on US: 12 cases remained unresolved and the other 10 cases had recurrent bile duct dilatation and were treated more than 3 times. All these cases were confirmed to have recurrent or unresolved BS by helical computed tomography on drip-infusion cholangiography or endoscopic retrograde cholangiography and were

treated with the same or other modalities.

Discussion

Duct to duct anastomosis for biliary reconstruction in ALDLT has made endoscopic access to the biliary tree for diagnostic and therapeutic management more feasible. The method also provides a more physiologic situation for preventing ascending cholangitis and delayed bowel movement (7).

The relation between the type of reconstruction and the incidence of BS is a matter of controversy. Gondolesi and colleagues (8) reported that patients with duct to duct reconstruction had a higher incidence of BS (32%) than patients with hepaticojejunostomy. Soejima and colleagues (9) reported no association between these two groups. According to our data, the overall prevalence of BS was 19% (20% in duct to duct and 15% in hepaticojejunostomy with no intergroup difference). In contrast to the findings of Soejima (9), we did not detect a tendency towards an increased incidence of BS using left liver graft in ALDLT (20%) in our series, although the incidence of BS was higher than in those with right liver graft (18%).

Biliary stricture occurred at the anastomotic site in 92% of the patients. Previous studies (10,11) have demonstrated that technical issues are the most important etiologic factors for anastomotic stricture. Ischemic and immunologic injury to the biliary epithelium is suggested to have a role in causing non-anastomotic stricture (12-14). The need for more than one bile duct anastomosis in ALDLT can aggravate these technical difficulties and cause anastomotic stricture. Shorter ischemia time and good quality liver from living donors might contribute to the lower rate of

non-anastomotic stricture in our series compared with the rate in deceased donor liver transplantation (15), which is 18% of patients with BS.

In the present study, 68% of the patients with BS were asymptomatic. The finding supports our approach, in which protocol US is used as the first line imaging examination during follow-up after ALDLT. Intrahepatic bile ducts are not visualized by US in the absence of biliary obstruction. In 90% of the cases with BS, US successfully detected dilated intrahepatic bile ducts. The presence of the classical intrahepatic “parallel channel sign” and the combined use of color Doppler US to identify the vessels from bile ducts might contribute to this favorable result (16).

One concern in the condition of chronic hepatic disease is that enlargement of the intrahepatic branches of the hepatic artery might also result in the intrahepatic parallel channel sign. To avoid such a fundamental misinterpretation, Doppler ultrasonography is an indispensable tool to distinguish bile ducts from blood vessels (16). In combined application of M-mode Doppler examination with the conventional B-mode ultrasonography, the cutoff value of 3 mm had high specificity and sensitivity for predicting the presence of BS in our study.

Our findings suggest that caution is required in interpreting the elevated G-GTP and ALP levels. In our study, G-GTP and ALP exceeded the upper normal limit in 47 cases (94%) and 48 cases (96%), respectively, when BS was diagnosed. The sensitivity and specificity of G-GTP and ALP for the detection of BS, however, were poor; thus, a confirmatory study using US is mandatory for the diagnosis of BS.

In conclusion, protocol US is useful for detecting BS at the earliest stage. A bile duct diameter greater than 3 mm detected by US suggests the presence of BS with high rates of sensitivity and specificity.

Acknowledgements

The study was supported by a Grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan and Grants-in-aid for Research on HIV/AIDS, and China Sasagawa medical researcher system by Japan China Medical Association and the Nippon Foundation.

References

1. Salvalaggio PR, Whittington PF, Alonso EM, Superina RA. Presence of multiple bile ducts in the liver graft increases the incidence of biliary complications in pediatric liver transplantation. *Liver Transpl* 2005;11:161-166.

2. Hussaini SH, Sheridan MB, Davies M. The predictive value of transabdominal ultrasonography in the diagnosis of biliary tract complications after orthotopic liver transplantation. *Gut* 1999;45:900-903.
3. Jeffrey GP, Brind AM, Ormonde DG, Frazer CK, Ferguson J, Bell R, Kierath A, Reed WD, House AK. Management of biliary tract complications following liver transplantation. *Aust NZ J Surg* 1999;69:717-722.
4. St Peter S, Rodriguez-Davalos MI, Rodriguez-Luna HM, Harrison EM, Moss AA, Mulligan DC. Significance of proximal biliary dilatation in patients with anastomotic strictures after liver transplantation. *Dig Dis Sci* 2004;49:1207-1211.
5. Chahin NJ, De Carlis L, Slim AO, Rossi A, Groeso CA, Rondinara GF, Garnbitta P, Zanan G, Forti D. Long-term efficacy of endoscopic stenting in patients with stricture of the biliary anastomosis after orthotopic liver transplantation. *Transplant Proc* 2001;33:2738-2740.
6. Mahajani RV, Cotler SJ, Uzer MF. Efficacy of endoscopic management of anastomotic biliary strictures after hepatic transplantation. *Endoscopy* 2000;32:943-949.
7. Soejima Y, Shimada M, Suehiro T, Kishikawa K, Yoshizumi T, Hashimoto K, Minagawa R, Hiroshige S, Terashi T, Ninomiya M, Shiotani S, Harada N, Sugimachi K. Feasibility of duct-to-duct biliary reconstruction in left-lobe adult-living-donor liver transplantation. *Transplantation* 2003;75:557-559.
8. Gondolesi GE, Varotti G, Florman SS, Munoz L, Fishbein TM, Emre SH, Schwartz ME, Miller C. Biliary complications in 96 consecutive right lobe living donor transplant recipients. *Transplantation* 2004;77:1842-1848.
9. Soejima Y, Taketomi A, Yoshizumi T, Uchiyama H, Harada N, Ijichi H, Yonemura Y, Ikeda T, Shimada M, Maehara Y. Biliary strictures in living donor liver transplantation: incidence, management, and technical evolution. *Liver Transpl* 2006;12:979-986.
10. Koneru B, Sterling MJ, Bahramipour PF. Bile duct strictures after liver transplantation: a changing landscape of the Achilles' heel. *Liver Transpl* 2006;12:702-704.
11. Colonna JO 2nd, Shaked A, Gomes AS, Colquhoun SD, Jurim O, McDiarmid SV, Millis JM, Goldstein LI, Busuttil RW. Biliary strictures complicating liver transplantation. Incidence, pathogenesis, management, and outcome. *Ann Surg* 1992;216:344-350.
12. Guichelaar MM, Benson JT, Malinchoc M, Krom RA, Wiesner RH, Charlton MR. Risk factors for and clinical course of non-anastomotic biliary strictures after liver transplantation. *Am J Transplant* 2003;3:885-890.
13. Sankary HN, McChesney L, Hart M, Foster P, Williams J. Identification of donor and recipient risk factors associated with nonanastomotic biliary strictures in human hepatic allografts. *Transplant Proc* 1993;25:1964-1967.
14. Abt P, Crawford M, Desai N, Markmann J, Olthoff K, Shaked A. Liver transplantation from controlled nonheart-beating donors: an increased incidence of biliary complications. *Transplantation* 2003;75:1659-1663.
15. Graziadei IW, Schwaighofer H, Koch R, Nachbaur K, Koenigsrainer A, Margreiter R, Vogel W. Long-term outcome of endoscopic treatment of biliary strictures after liver transplantation. *Liver Transpl* 2006;12:718-725.
16. Willi UV, Teele RL. Hepatic arteries and the parallel-channel sign. *J Clin Ultrasound* 1979;7:125-127.