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Original Article

Cholangiographic features and endoscopic treatment of biliary strictures

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Abstract: Objectives: The most commonly occurring complications following orthotopic liver transplantation procedures are associated with the biliary tract. Endoscopic technique has become the primary modality for the treatment of biliary strictures after liver transplantation. The objective of this study was to assess the role of cholangiographic features of the initial cholangiogram in endoscopic treatment success and stricture recurrence. Methods: Patients who underwent endoscopic therapy for biliary strictures after orthotopic liver transplantation (OLT), from 2006 to 2009 were included in this retrospective study. Results: The initial success rate after endoscopic treatment was achieved in 85.53% patients. However, recurrence of biliary strictures occurred in 24.62% of the patients. Patients with successful anastomotic biliary strictures (AS) after treatment were characterized by shorter stricture length as compared to patients who have not achieved success ($p < 0.01$). Of the 42 patients with AS, patients with recurrence had larger initial stricture length ($p < 0.01$) and smaller narrowing diameter ($p < 0.01$) than those without recurrence. Patients treated with NAS for multiple strictures experienced increased rate of recurrence than those with single narrowing, but failed to achieve statistical significance (50% vs. 23.08%, $p = 0.18$). Patients for whom dilation failed to eliminate the waist, experienced higher recurrence rate than those without stricture waist (70% vs. 16.63%, $p < 0.01$). Conclusions: Endoscopic procedure using endoscopic retrograde cholangiopancreatography was found to be an effective modality for treating biliary strictures after OLT.

Keywords: Biliary strictures, cholangiographic features, endoscopic retrograde cholangiopancreatography, liver transplantation

Introduction

Orthotopic liver transplantation (OLT) is a definitive treatment procedure for patients with end-stage liver disease. The most commonly occurring complications following OLT procedures are associated with the biliary tract. Biliary complications are considered as the "Achilles' heel" of liver transplantation because of high frequency and fatal effects on the survival of grafts and recipients [1]. Complications of biliary tract in patients undergoing transplantation occur at an incidence of up to 34% with a mortality rate of 5% [2, 3]. The most commonly occurring biliary complications are biliary leaks and strictures (abnormal narrowing of common bile duct). Other complications include incidence of biloma, sphincter of Oddi dysfunction, biliary stone or debris, common bile duct filling defects, and choledocholithiasis [1].

Biliary strictures, as the major biliary complications occur in 4% to 13% of the patients after OLT [2-5]. Biliary strictures after liver transplantation are classified into anastomotic and non-anastomotic strictures based on localization and pathogenesis. Anastomotic biliary strictures (AS) are localized in anastomosis region and are caused due to fibrotic shrinkage by use of improper surgical techniques, small caliber of the bile ducts, use of inappropriate suture material, and infection [6, 7]. Non-anastomotic biliary strictures (NAS) are located at the hilar bifurcation and/or peripheral ducts and are caused more frequently by ischemia due to hepatic artery thrombosis and prolonged graft cold ischemia time and less frequently due to immunological responses [8, 9].

Management of post-liver transplantation biliary strictures poses a great challenge. The

Table 1. Indications for liver transplantation

Indications	Number of patients (%), N = 76
Hepatitis B liver cirrhosis	34 (44.74)
Alcoholic liver cirrhosis	11 (14.47)
Primary biliary cirrhosis	8 (10.53)
Hepatocellular carcinoma	10 (13.16)
Cholangiocarcinoma	4 (5.26)
Fulminant hepatitis	9 (11.84)

strictures can be treated either with endoscopic retrograde cholangiopancreatography (ERCP), percutaneous (percutaneous trans-hepatic cholangio drainage [PTCD], or surgical repair (traditional approach). In recent times, endoscopic technique has become the primary modality for the treatment of biliary strictures after liver transplantation. The high success rates and low morbidity and mortality rates, has made ERCP with dilation and stent placement the preferred diagnostic tool and therapeutic procedure for the treatment of biliary strictures after OLT [10, 11]. However, recurrence of biliary strictures is a serious consequence following endoscopic treatment in patients with OLT. Several studies have found that the stricture recurrence rate after successful endoscopic treatment ranges from 10%-31% [10, 12, 13].

Factors influencing success of endoscopic treatment and recurrence of biliary strictures after ERCP intervention have not been well evaluated. Therefore, the aim of this study was to assess the relationship between cholangiographic features and success of endoscopic retrograde cholangiopancreatography or recurrence of biliary strictures following orthotopic liver transplantation in China.

Patients and methods

Patients

Patients with biliary strictures after OLT were included in the study and medical, endoscopy, and radiology records were reviewed retrospectively. Patients were treated between 2006 and 2009 at the Department of Gastroenterology in the First People's Hospital affiliated to Shanghai Jiaotong University or in Changhai Hospital affiliated to the Second Military Medical University. Biliary reconstruction was performed in all the patients using end-to-end choledochocholedochostomy. Indications for ERCP included one or more of the following symptoms or signs: pruritus, jaundice, abnormal liver function tests, fever, abdominal pain (an indication of acute cholangitis), and abnormal imaging findings (such as a dilated bile duct). All patients also underwent liver biopsies before ERCP to exclude graft rejection. Patients with impaired hepatic artery flow were excluded from the study.

Biochemical parameters, including serum bilirubin, alkaline phosphatase, gamma-glutamyltransferase levels, and leukocyte count were determined before and after completion of endoscopic treatment. The study protocol was approved by the Institutional Review Board of the First People's Hospital affiliated to Shanghai Jiaotong University. Standard informed consent was obtained from all patients prior to ERCP procedure.

Endoscopic protocol

ERCP was performed with a therapeutic side-viewing endoscope (TJF240; Olympus, Tokyo, Japan) in the conventional manner with standard accessories by three experienced therapeutic endoscopists. Strictures were defined as clinically significant when a dominant narrowing was identified by cholangiography. The length and diameter of anastomotic stricture, as well as the location of non-anastomotic stricture in cholangiography were measured. After confirmation, a 0.035-inch guidewire was passed through the biliary strictures and the strictures were dilated with a balloon catheter followed by insertion of a 7-, 8.5-, 10-, or 11.5-Fr (French) plastic stent (Boston Scientific Inc.). The stent length varied, depending upon the location of the stricture. Depending upon the feasibility, a second or a third stent was placed alongside the first stent. The balloon was dilated to a diameter of 5 mm in the intrahepatic bile duct stricture and to 10 mm in extrahepatic bile duct stricture. After the dilation, sphincterotomy was performed with the standard technique and regardless of elimination of the waist the stent was placed across the stricture. To avoid stent occlusion, routine stent exchanges were scheduled once every 3 months until the bile duct strictures resolved. In case of increasing biochemical parameters such as fever or jaundice, stents were exchanged under emergency conditions. Patients treated successfully were followed-up after stent removal. During these routine visits. Patients underwent trans-abdominal

Table 2. Cholangiographic features and endoscopic treatment success

	Success	Failure	*p* value
AS, n (%)	42 (87.50)	6 (12.50)	0.52**
Stricture length, cm*	6.85 ± 2.33	11.67 ± 4.73	< 0.01
Stricture diameter, mm*	1.85 ± 0.38	1.58 ± 0.36	0.13
NAS, n (%)	23 (82.14)	5 (17.86)	
Single stricture	13 (91.67)	2 (8.33)	0.64***
Left hepatic duct	0	0	
Right hepatic duct	6 (86.67)	1 (13.34)	
Common hepatic duct	7 (100)	1 (0)	
Multiple strictures	10 (76.92)	3 (13.08)	
With waist, n (%)	10 (71.43)	4 (28.57)	0.11
Without waist, n (%)	55 (88.71)	7 (11.29)	

AS: Anastomotic biliary stricture; NAS: Non-anastomotic biliary stricture. *Data are presented as mean ± SD. **AS vs. NAS; ***Single stricture vs. Multiple strictures.

ultrasound, assessment of biochemical parameters assessment, and clinical evaluations were performed.

Evaluation of endoscopic management

"Success of endoscopic therapy" was defined as cholangiographic confirmed absence of stricture at the time of stent removal, clinical and biochemical improvement, and no subsequent requirement for further interventional procedures. "Recurrence" was defined by the presence of clinical symptoms, such as pruritus and cholangitis, and/or elevated serum alkaline phosphatase, and/or elevated bilirubin levels, along with an ERCP finding of a recurrent stricture that required further endoscopic therapy. Narrowing of bile flow without signs or symptoms of impairment was not indicative of stricture recurrence.

Statistical analysis

Continuous variables were compared using Student's t-test and categorical variables were compared either with Chi-square test or Fisher's exact test. Continuous variables were reported as mean ± standard deviation (SD). A *p*-value of less than 0.05 was considered as statistically significant.

Results

Study population

A total of 76 patients suffering from biliary strictures after OLT underwent endoscopic intervention. The mean patient age was 57.33 ± 5.61 years and the study group comprised of 46 (60.53%) men and 30 (39.47%) women. The indications for liver transplantation are provided in **Table 1**. Patients were followed-up for a mean duration of 18 (range, 4 to 30) months after stent removal.

Clinical and endoscopic characteristics

The median time period from liver transplantation to biliary stricture was 7.08 ± 2.83 months. Symptoms reported at the time of initial diagnosis were jaundice (n = 66, 86.84%), acute cholangitis (n = 29, 38.16%), and pruritus (n = 26, 34.21%). Altogether, 358 ERCPs were performed for the initial treatment of biliary stricture, with an average of 4.71 ± 1.71 for each patient. Further, an average of 8.17 ± 3.04 stents were inserted for individual patient. Based on the stricture location evaluated by cholangiography, biliary strictures were divided into two groups: AS (n = 49) and NAS (n = 27). Of the total patients, 10 (13.16%) experienced procedure-related complications; specifically, three had bleeding after endoscopic sphincterotomy and seven had pancreatitis. Overall, endoscopic treatment was successful in 65 (85.53%) patients after 11.58 ± 3.19 months post-treatment.

Treatment success and cholangiographic parameters

Data for treatment success and cholangiographic parameters are presented in **Table 2**. The success rates were similar between patients with AS and NAS (87.5% vs. 82.14%, p = 0.52). Among the 42 patients with AS, those who experienced treatment success were characterized by shorter stricture length (6.85 ± 2.33 cm vs. 11.67 ± 4.73 cm, p < 0.01) than those with unsuccessful resolution of the stricture. However, the stricture diameter in patients with successful AS was not statistically different from patients with failure of therapy (1.85 ± 0.38 mm vs. 1.58 ± 0.36 mm, p = 0.13). NAS patients with multiple strictures appeared to have a lower success rate than those with single narrowing, but this finding was not statistically significant (76.92% vs. 91.67%, p = 0.64).

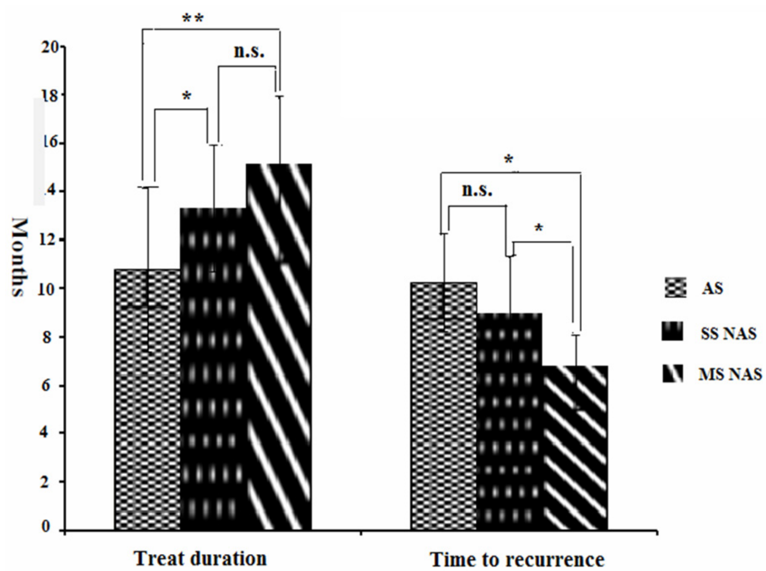

Figure 1. Treatment duration and time to recurrence after stent removal in patients with different types of strictures. AS: Anastomotic biliary strictures; MS NAS: Multiple strictures of nonanastomic biliary strictures; SS NAS: Single stricture of non-anastomotic biliary strictures. n.s.: Not significant; *p < 0.05; **p < 0.01.

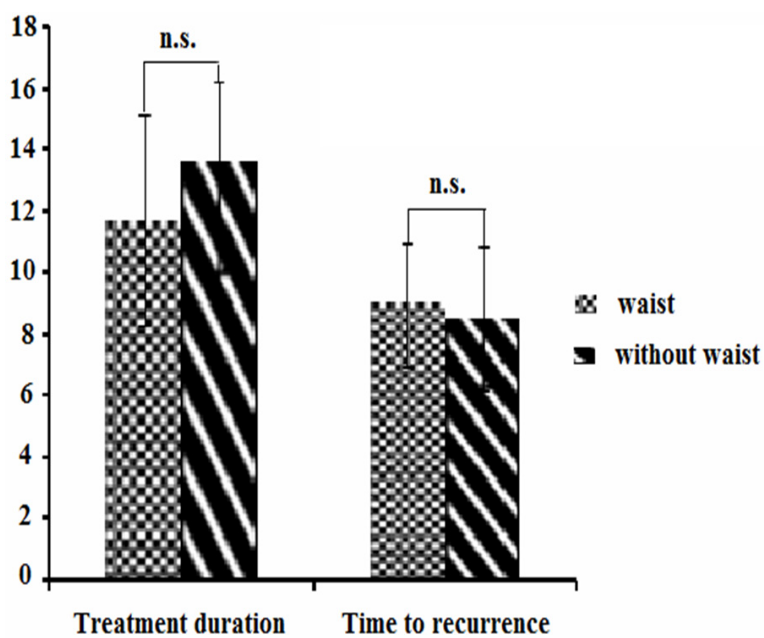

Figure 2. Treatment duration and time to recurrence after stent removal in patients with or without stricture waist. n.s.: Not significant.

The AS group required a less treatment duration from the initial presentation to treatment success as compared to the single ($p < 0.05$) or multiple strictures NAS group ($p < 0.01$), as shown in **Figure 1**. There was no significant difference between the NAS single stricture and multiple strictures groups. Treatment durations were not statistically significant between patients with or without waist, as illustrated in **Figure 2**.

The success rate was lower among 10 patients for whom dilation failed to eliminate the waist than the patients for whom elimination of the waist was achieved. However, this trend was not statistically significant (71.43% vs. 88.71%, $p = 0.11$) (**Table 2**).

Stricture recurrence and cholangiographic parameters

Among 65 patients who showed initial resolution of the biliary duct narrowing, 19 (24.62%) developed recurrent cholestasis and ERCP showed the evidence of recurrence of the bile duct narrowing that required intervention. The mean time to stricture recurrence after stent removal was 9.00 ± 2.79 months. The cholangiographic features of the patients with or without stricture recurrence are presented in **Table 3**. Patients with NAS had a higher recurrence rate than those with AS, but this trend was not statistically significant (34.78% vs. 19.05%, $p = 0.47$). Among the 42 patients with AS, patients with recurrence had larger stricture length (9.73 ± 1.27 cm vs. 6.16 ± 2.66 cm, $p < 0.01$) and smaller narrowing diameter (1.45 ± 0.62 mm vs. 1.93 ± 0.34 mm, $p < 0.01$) than those without recurrence. NAS patients with multiple strictures experienced more recurrence than those with single narrowing; however, this difference was not statistically significant (50% vs. 23.08%, $p = 0.18$). Among the 10 patients for whom the initial dilation failed to eliminate the waist, seven experienced recurrence, translating to a higher frequency than those without

Table 3. Cholangiographic features and biliary stricture recurrence

	Recurrence	Non-recurrence	*p* value
AS, n (%)	8 (19.05)	34 (80.95)	0.47**
Stricture length, cm*	9.73 ± 1.27	6.16 ± 2.66	< 0.01
Stricture diameter, mm*	1.45 ± 0.62	1.93 ± 0.34	< 0.01
NAS, n (%)	8 (34.78)	15 (65.22)	
Single stricture	3 (23.08)	10 (76.92)	0.18***
Left hepatic duct	0	0	
Right hepatic duct	2 (33.33)	4 (66.67)	
Common hepatic duct	1 (14.29)	6 (85.71)	
Multiple strictures	5 (50.00)	5 (50.00)	
With waist, n (%)	7 (70.00)	3 (30.00)	< 0.01
Without waist, n (%)	9 (16.36)	46 (83.64)	

AS: Anastomotic biliary stricture; NAS: Non-anastomotic biliary stricture. *Data are presented as mean ± SD. **AS vs. NAS; ***Single stricture vs. Multiple strictures.

stricture waist (70.00% vs. 16.63%, p < 0.01) (**Table 3**).

Figure 1 shows that the AS group along with single stricture NAS group had a longer interval from the time of treatment success to recurrence, as compared with the multiple strictures NAS group ($p < 0.05$); whereas, there was no difference between the AS and single stricture NAS groups. The comparison of time to recurrence after removal of stents in patients with or without stricture waist is presented in **Figure 2**. The median time to recurrence was not significantly different between the two groups.

Discussion

Biliary stricture complications following liver transplantation are an important contributor to morbidity and mortality in transplant recipients. Endoscopic intervention due to high success rate and low incidence of complications has emerged as a first-line therapy for biliary stricture after OLT. The success rate of endoscopic therapy reported in previous studies varies from 69% to 100% (14-16), which is in line with to the findings in our study (85.53%). However, recurrence of biliary strictures represents a significant burden to the patients who experienced initial successful endoscopic treatment, as it is associated with prolonged hospital stay and increased medical cost. The published recurrence rates of biliary strictures range between 3% and 31% (11, 17-19). Our study also reported a similar recurrence rate (24.62%) following endoscopy.

Factors influencing success of endoscopic intervention and prevention of stricture recurrence have not been adequately assessed. The number of stents used in total and per ERCP in patients with AS may be related to a higher success rate [11]. Patients with biliary complications who had surgical procedures for non-biliary indications during the first month after liver transplantation (especially, for bleeding) as well as receiving a graft from either a donor after cardiac death or a living donor did not sufficiently respond to endoscopic therapy [20]. Bile duct leakages at the initial ERCP, prolonged time to initial presentation of stricture, and NAS have also been correlated to recurrence [21]. Longer time for occurrence of biliary strictures after OLT and presence of multiple strictures may also be linked with final endoscopic success [22, 23]. To date, however, very few studies have evaluated the relationship between cholangiographic features and success of endoscopic treatment or recurrence of biliary stricture after OLT.

In the current study, detailed features of biliary strictures in the initial cholangiogram were recorded. Our study did not demonstrate that AS patients had a higher success rate than NAS patients, as has been shown in previous studies [12, 19]. This may be due to the fact that patients with single NAS, who have a similar endoscopic response to AS patients, occupied a major proportion of the NAS group in our study. We demonstrated that, in the AS group, patients with longer biliary strictures had lower success rates and were more prone to recurrence. Stricture diameter was found to be closely associated with recurrence, even more than the initial treatment success. Our data showed that AS patients had a similar success rate as NAS patients, but a lower recurrence rate; although, these findings were not statistically significant. NAS patients with multiple strictures tended to have more unsuccessful treatments and more recurrences after initial successful treatment than those with single stricture. This finding is similar to that of the study performed by Barriga et al [22].

Nevertheless, Pasha et al. previously demonstrated that initial diameter of stricture was not related to recurrence [15]; although, their finding may have been influenced by their approach of utilizing excessive dilation and remarkably, more stents to persistently dilate the stricture. Considering our findings in light of those from previous publications, we concluded that treatment approaches may contribute to recurrence along with the relationship between cholangiographic features and endoscopic treatment. Therefore, to minimize the recurrence rate, as patients with long and narrow strictures, as well as NAS patients with multiple strictures, may need more dilation and increased duration of stent treatment.

Treatment and patency duration was also compared after stent removal among different types of strictures. Our results indicated that NAS patients with multiple strictures needed more time to achieve success but developed recurrence in a shorter duration of time than AS patients; however, compared to NAS patients with single stricture, AS patients required less treatment time and had similar patency duration.

In evaluating the relationship of treatment success and recurrence, stricture waist was also considered as an important cholangiographic feature. Biliary strictures require complete resolution of the "waist" for satisfactory dilation. In fact, waist can be eliminated in most patients who have biliary narrowing after OLT. Very few studies to date have analyzed the role of the waist in endoscopic treatment of biliary stricture after OLT. In one of the studies evaluating endoscopic treatment of AS with maximal stent utilization, Tabibian et al. performed an additional one minute dilation in an attempt to eliminate the waist, and then continued with other steps of the procedure regardless of effacement of the waist [11]. During the ERCP procedure in our study, we also attempted to eliminate biliary stricture waist through dilation. Although no dilation related complications occurred during the study, but failed to eliminate the waist in 10 patients. Our results showed that presence of a waist did not affect the endoscopic success rate, but was related to a significant biliary stricture recurrence. If we excluded the patients who failed to have the waist eliminated, the overall recurrence rate fell to only 16.36%, which emphasized the importance of complete dilation of biliary strictures. However, our results indicated that treatment duration and patency interval between patients with or without waist were not significantly different. These findings demonstrated that the waist plays a vital role in biliary stricture recurrence after successful endoscopic treatment. Therefore, sufficient dilation should be performed to resolve the waist as much as possible while accounting for the potential risks.

In conclusion, we used routine endoscopic dilation plus multiple stents to treat biliary strictures after OLT. The study concluded that endoscopic therapy was an effective modality for treating biliary stricture (narrowing) after OLT. Cholangiographic features were related to successful treatment and recurrence of biliary strictures; as such, they may aid in evaluation of strictures through the initial cholangiography. Since the current study was limited by the number of patients, further evaluation of a large patient cohort is required to confirm our findings.

Disclosure of conflict of interest

None.

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