World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v7.i7.747

World J Gastrointest Endosc 2015 June 25; 7(7): 747-757
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Clinical Trials Study

Management of liver transplantation biliary stricture: Results from a tertiary hospital

Fernanda Prata Martins, Michel Kahaleh, Angelo P Ferrari

Fernanda Prata Martins, Angelo P Ferrari, Endoscopy Unit, Hospital Israelita Albert Einstein, São Paulo-SP 05652-900, Brazil
Michel Kahaleh, Division of Gastroenterology and Hepatology, Department of Medicine, Weill Cornell Medical College, New York, NY 10021, United States
Angelo P Ferrari, Division of Gastroenterology, Universidade Federal de São Paulo, São Paulo-SP 05652-900, Brazil

Author contributions: Martins FP contributed to the design, acquisition of data and wrote the manuscript; Kahaleh M contributed to the writing and revision of the manuscript; Ferrari AP designed the aim and contributed to the writing and revision of the manuscript; all authors provided final approval of the version to be published.

Supported by Boston Scientific, EMcison, Xlumena, MaunaKea Tech, MI Tech, Apollo Endosurgery, Cook Endoscopy, W.L. Gore Associates, GI Dynamics and ASPIRE Bariatrics (Kahaleh M).

Ethics approval: The study was reviewed and approved by the Hospital Israelita Albert Einstein Institutional Review Board. This study is registered at https://clinicaltrials.gov.
Clinical trial registration: The registration identification number is NCT01148199.
Informed consent: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.
Conflict-of-interest: Fernanda Prata Martins has no conflict of interest to disclosure. Angelo Paulo Ferrari is a Medical Advisory Board Member for Boston Scientific do Brasil.
Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at https://datadryad.org. Consent for data sharing was not obtained but the presented data are anonymized and risk of identification is low. No additional data are available. Statistical data analysis was performed by the author (Martins FP) and reviewed by Hospital Israelita Albert Einstein Statistics Department.

Correspondence to: Fernanda Prata Martins, MD, PhD, Endoscopy Unit, Hospital Israelita Albert Einstein, Rua Barata Ribeiro, 490 cj 118, São Paulo-SP 05652-900, Brazil. fernandapbm@gmail.com
Telephone: +55-11-981936251
Fax: +55-11-38877997

Received: August 28, 2014
Peer-review started: August 28, 2014
First decision: September 16, 2014
Revised: April 30, 2015
Accepted: May 8, 2015
Article in press: May 10, 2015
Published online: June 25, 2015

Abstract

AIM: To review results of endoscopic treatment for anastomotic biliary strictures after orthotopic liver transplantation (OLT) during an 8-year period.

METHODS: This is a retrospective review of all endoscopic retrograde cholangiopancreatographys (ERCPs) performed between May 2006 and June 2014 in deceased OLT recipients with anastomotic stricture at a tertiary care hospital. Patients were divided into 2 groups, according to the type of stent used (multiple plastic or covered self-expandable metal stents), which was chose on a case-by-case basis and their characteristics. The primary outcome was anastomotic stricture resolution rate determined if there was no more than a minimum waist at cholangiography and a 10 mm balloon could easily pass through the anastomosis with no need for further intervention after final stent removal. Secondary outcomes were technical success

rate, number or ERCPs required per patient, number of stents placed, stent indwelling, stricture recurrence rate and therapy for recurrent anastomotic biliary stricture (AS). Stricture recurrence was defined as clinical laboratorial and/or imaging evidence of obstruction at the anastomosis level, after it was considered completely treated, requiring subsequent interventional procedure.

RESULTS: A total of 195 post-OLT patients were assessed for eligibility. One hundred and sixty-four (164) patients were diagnosed with anastomotic biliary stricture. ERCP was successfully performed in 157/164 (95.7%) patients with AS, that were treated with either multiple plastic (n = 109) or metallic billiary stents (n = 48). Mean treatment duration, number of procedures and stents required were lower in the metal stent group. Acute pancreatitis was the most common procedure related complication, occurring in 17.1% in the covered self-expandable metal stents (cSEMS) and 4.1% in the multiple plastic stent (MPS) group. Migration was the most frequent stent related complication, observed in 4.3% and 5.5% (cSEMS and MPS respectively). Stricture resolution was achieved in 86.8% in the cSEMS group and in 91% in MPS group. Stricture recurrence after a median follow up of 20 mo was observed in 10 (30.3%) patients in the cSEMS and 7 (7.7%) in the plastic stent group, a statistically significant difference (P = 0.0017). Successful stricture resolution after secondary treatment was achieved in 66.6% and 62.5% of patients respectively in the cSEMS and plastic stents groups.

CONCLUSION: Multiple plastic stents are currently the first treatment option for AS in patients with duct-to-duct anastomosis. cSEMS was associated with increased pancreatitis risk and higher recurrence rate.

Key words: Biliary stricture; Benign; Liver transplant; Endoscopic retrograde cholangiopancreatographys; Endoscopic treatment; Plastic stent; Self-expandable metal stent

Core tip: Endoscopic treatment is effective and safe in the management of post liver transplant biliary complications, mainly for anastomotic strictures. Progressive dilation and multiple plastic stenting have been demonstrated as the best endoscopic therapeutic modality with high success rates and low recurrence. Fully covered stent-expandable metal stents may be an option for endoscopic therapy potentially reducing the number and procedures lowering the costs, however their complication rate needs to be further evaluated.

Martins FP, Kahaleh M, Ferrari AP. Management of liver transplantation biliary stricture: Results from a tertiary hospital. *World J Gastrointest Endosc* 2015; 7(7): 747-757 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i7/747.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i7.747

INTRODUCTION

Biliary complications have been considered for a long time the "Achilles' heel" of orthotopic liver transplantation (OLT), due to its elevated incidence, need for long-term therapy and major impact on graft survival and quality of life. Despite the advances in surgical techniques, organ selection, preservation and immunosuppression, the biliary tract remains the most common site for postoperative complications[1-4].

The incidence of biliary complications varies from 6% up to 40% of patients and includes strictures, leakages, stones, casts, sludge and sphincter of Oddi dysfunction[1-5].

Among the risk factors enrolled in the development of biliary complications the most important are: type of liver transplant procedure, reconstruction technique, organ preservation, technical factors during surgery, reperfusion injury, infection, prolonged cold and warm ischemia, hepatic artery thrombosis or stenosis, chronic rejection, ABO incompatibility, underlying disease, donation after cardiac death and older age donor[2-4,6-8].

Diagnosis of biliary complications after liver transplantation is challenging. Patients usually present asymptomatic elevations of bilirubin, alkaline phosphatase, gamma-glutamyl transferase and/or liver enzymes. Non-specific symptoms such as anorexia, fever, pruritus, jaundice and rarely pain (due to immunosuppression and hepatic denervation) can be observed.

The evaluation should start with an abdominal ultrasound (US) with Doppler of hepatic vessels. If hepatic artery thrombosis or stenosis is suspected, angiography should be indicated for specific treatment (Figure 1). If bile duct dilation, stones and/or leakage are identified by US the patient should be referred to therapeutic endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous trans-hepatic cholangiography (PTC)[7,9-13]. In case of normal abdominal US, a liver biopsy should be performed to exclude rejection. Finally, in patients with normal US and rejection ruled out by liver histology, a magnetic resonance cholangiopancreatography (MRCP) should precede more invasive procedures (Figure 1)[14]. Those patients who have a stricture or leakage confirmed by MRCP will be referred to therapeutic ERCP or PTC according to the type of biliary reconstruction.

Concerning management, although surgical repair used to be the standard treatment in the past, non-operative therapy of biliary complications has become the first line option in the last two decades[3,6]. Endoscopic approach is well established as the preferred therapeutic modality for patients with duct-to-duct anastomosis[15].

This paper will summarize the results of endoscopic treatment for anastomotic biliary strictures after

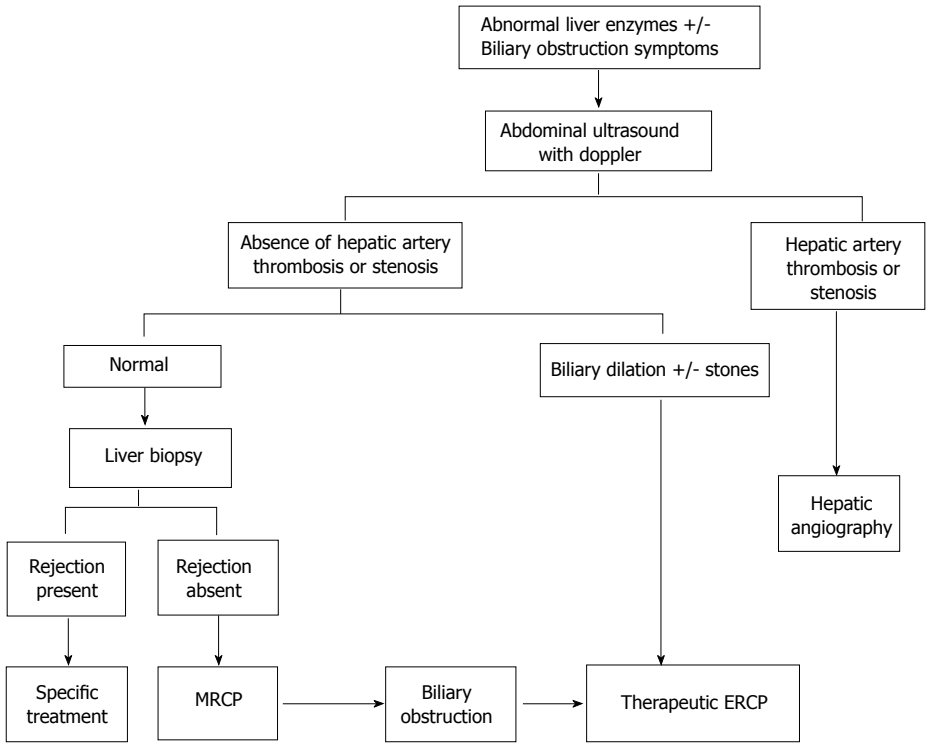

Figure 1 Algorithm for evaluation of suspected biliary obstruction after orthotopic liver transplantation in patients with duct-to-duct reconstruction. MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatographys.

deceased OLT in a tertiary center during an 8-year period and review the literature with future therapy considerations.

MATERIALS AND METHODS

Hospital Israelita Albert Einstein, São Paulo, Brazil, is a tertiary care hospital where around 120 liver transplantations are carried out annually. The study was reviewed and approved by the Hospital Israelita Albert Einstein Institutional Review Board. We retrospectively evaluated all ERCPs performed between May 2006 and June 2014 in deceased orthotopic liver transplant recipients with duct-to-duct anastomosis and suspected biliary complications. This paper reports our overall experience in such patients. All study participants, or their legal guardian, provided informed written consent prior to study enrollment. Procedures were performed under monitored care anesthesia.

Anastomotic biliary stricture (AS) was defined as a dominant short narrowing at the anastomotic site. Patients with AS were individually treated according to standardized protocols either with multiple plastic or single metal stents.

Briefly, plastic stents were initially placed after sphincterotomy and stricture balloon dilation. ERCP was repeated at 3-mo intervals for stent exchange, following a progressive balloon dilation and increasing number of stents protocol at each session, until 12 mo of therapy.

Covered self-expandable metal stents (cSEMS) were deployed with or without sphincterotomy and removed after a 3-mo period if a partially covered metal stent-expandable metal stents (PCSEMS) was used or after 6 mo in case of a fully covered stent-expandable metal stents (FCSEMS). In our early experience, biliary SEMS were placed without sphincterotomy, which we started to perform after recognizing a high rate of pancreatitis in these patients. PCSEMS were also used in our early experience, when fully covered SEMS were not available in Brazil.

Complications after ERCP (pancreatitis, cholangitis, hemorrhage, perforation) were defined by established criteria[16].

Initial technical success was the ability to obtain a cholangiogram and accomplish stent placement at ERCP alone or with a trans-hepatic *rendezvous* procedure. The investigators determined successful stricture resolution if there was no more than a minimum waist at cholangiography and a 10 mm balloon could easily pass through the anastomosis with no need for further intervention after final stent removal. All patients were followed at the institution transplant clinic through a combination of routine laboratory testing and clinical examination protocol. Stricture recurrence was defined as the return of clinical symptoms and/or elevated liver function tests with imaging evidence of obstruction at the anastomosis level causing biliary flow impairment requiring a subsequent interventional procedure in a patient previously considered successfully treated.

The primary outcome was anastomotic stricture resolution rate. Secondary outcomes were technical success rate, number or ERCPs required per patient,

Table 1 Summary of patients characteristics

	Multiple plastic stents	cSEMS
n	109	48
Sex		
Male	76 (69.7%)	36 (75.0%)
Female	33 (30.3%)	12 (25.0%)
Age (yr)		
Mean (± SD)	48.8 (± 14.5)	54.5 (± 12.9)
Median	50	56.8
Range	10-75	17-73
Time of anastomotic stricture after orthotopic liver transplantation (d)		
Mean (± SD)	214.2 (± 411.4)	221.6 (± 263.3)
Median	72	115.5
Range	6-2663	8-1339
Hepatic artery associated lesions		
Stenosis	3 (2.8%)	3 (6.3%)
Thrombosis	8 (7.3%)	1 (2.1%)
Associated biliary lesions		
Anastomotic fistula	5 (4.6%)	2 (4.2%)
Non-anastomotic fistula	1 (0.9%)	0 (0.0%)
Non-anastomotic stricture	1 (0.9%)	0 (0.0%)
Cholangitis	2 (1.8%)	0 (0.0%)
Stones	2 (1.8%)	0 (0.0%)

cSEMS: Covered self-expandable metal stents.

number of stents placed, stent indwelling, follow-up duration, stricture recurrence rate and therapy for recurrent AS.

Descriptive statistics were used to summarize data. Data was reported as the mean, standard deviation and range. Recurrence data was analyzed by the Kaplan-Meier method. Statistical data analysis was performed by the author (Martins FP) and reviewed by Hospital Israelita Albert Einstein Statistics Department.

RESULTS

A total of 195 post-OLT patients were referred to our Endoscopy Unit with a suspected biliary complication between May 2006 and June 2014. One hundred and sixty-four (164) patients were diagnosed with anastomotic biliary stricture (Figure 2).

Patients were divided into 2 groups, according to the type of stent used (multiple plastic or covered self-expandable metal stents), which was chosen on a case-by-case basis (Table 1). Both groups were similar concerning gender, age, time from OLT to anastomotic stricture and associated biliary or hepatic artery lesions.

Among the 164 patients with confirmed post-OLT anastomotic biliary stricture, initial technical success was obtained in 157 (95.7%); 109 individuals being treated with plastic stents and 48 with cSEMS (16 PCSEMS and 32 FCSEMS). Percutaneous trans-hepatic cholangiography was required in 11 (7.0%) patients to achieve access due to high-grade stricture or sharp angulation at the anastomosis. After percutaneous approach cSEMS were used in 7 and plastic stents in 4 cases.

Seven patients failed initial ERCP: 3 were referred to surgery (hepatic-jejunal anastomosis), 2 received external trans-hepatic biliary drainage, one was referred to re-transplantation and one died due to multiple organ failure after an episode of severe acute pancreatitis.

Table 2 Summary of treatment characteristics *n* (%)

	Multiple plastic stents	cSEMS
Total number of ERCP	271	70
Stent treatment duration (d)		
Mean (± SD)	282.7 (± 135.4)	124.2 (± 67.9)
Median	322	107.5
Range	3-767	9-269
Number of ERCP per patient		
Mean (± SD)	3.9 (± 1.5)	2.0
Median	4	2.0
Range	1-7	-
Number of stents per ERCP session		
Mean (± SD)	2.9 (± 1.5)	1
Median	3.0	1
Range	1-10	-
Total number of stents per patient		
Mean (± SD)	10.0 (± 7.2)	1
Median	10	1
Range	1-30	-
Complications	26 (9.6)	17 (24.3)
Acute pancreatitis	11 (4.1)	12 (17.1)
Bleeding	7 (2.6)	0 (0.0)
Perforation	2 (0.7)	0 (0.0)
Cardiorespiratory	2 (0.7)	0 (0.0)
Bacteremia	4 (1.4)	1 (1.4)
Pain	0 (0.0)	4 (5.7)
Stent related complications		
Migration	15 (5.5)	3 (4.3)
Occlusion	5 (1.8)	0 (0.0)

cSEMS: Covered self-expandable metal stents; ERCP: Endoscopic retrograde cholangiopancreatographys.

A total of 341 ERCPs were performed. Ten patients in the cSEMS group and 9 in the plastic stent group still have the stents in place and were excluded from analysis. Mean treatment duration, number of procedures and stents required were lower in the metal stent group (Table 2).

Acute pancreatitis was the most common procedure related complication, occurring in 17.1% in the cSEMS and 4.1% in the plastic stent group (Table 2). Other 4 patients (5.7%) presented abdominal pain without pancreatitis, requiring hospital admission to receive intravenous analgesics. Among stent related complications, migration was the most frequent, observed in 4.3% and 5.5% of patients with metal and plastic stents respectively.

There was one death (0.3%) related to severe acute pancreatitis in one patient who was also a technical failure.

There was no lost of follow-up until the primary outcome. Stricture resolution was achieved in 86.8% in the cSEMS group (Figure 3) and in 91% in the multiple plastic stents group (Figure 4). There were 5 failures in the cSEMS group, two of them presented spontaneous distal stent migration (Figure 5).

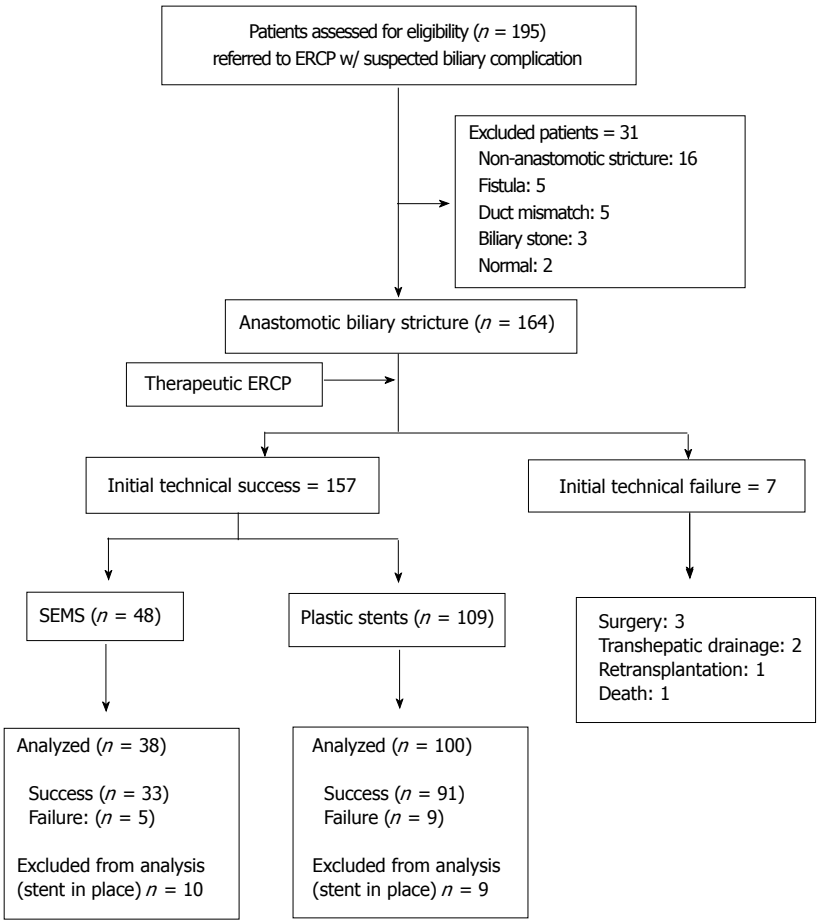

Figure 2 Flow chart of patients in the study. ERCP: Endoscopic retrograde cholangiopancreatographys; SEMS: Stent-expandable metal stents.

Table 3 Summary of the patients outcomes *n* (%)

	Multiple plastic stents	cSEMS
n	100	38
Stricture resolution rate		
Success	91 (91.0)	33 (86.8)
Failure	9 (9.0)	5 (13.2)
Follow-up (d)		
Mean (± SD)	690.8 (± 632.6)	620.3 (± 540.7)
Median	538	479
Range	0-2823	0-1615
Recurrence rate	7 (7.7)	10 (30.3)
Time to recurrent anastomotic stricture (d)		
Mean (± SD)	296.9 (± 259.5)	310.0 (± 348.4)
Median	240	124
Range	73-667	27-975
Re-treatment after failure or recurrent anastomotic stricture		
Success	10 (62.5)	10 (66.6)
Failure	6 (37.5)	1 (6.7)
In treatment	0 (0.0)	3 (20.0)
Lost of follow-up	0 (0.0)	1 (6.7)

cSEMS: Covered self-expandable metal stents.

Late stricture recurrence was observed in 10 (30.3%) patients in the cSEMS and 7 (7.7%) in the plastic stent group (Table 3). A Kaplan-Meier analysis (Figure 6) disclosed a statistically significant difference in the recurrence rate between both groups ($P = 0.0017$).

In the cSEMS group, 8 patients received re-treatment with multiple plastic stents, 2 received another cSEMS, 4 were referred to surgery and 1 lost of follow-up. In the multiple plastic stents group, secondary treatment consisted of cSEMS in 9 patients, multiple plastic stents in 4, surgery in 2 and PTC in 1 (choice of treatment in patients who failed initial treatment was decided by the referring physician). The results are summarized in Table 3.

DISCUSSION

Bile duct strictures after OLT are the most common biliary complication and have been classified according to their location into anastomotic strictures and non-anastomotic. They will be discussed separately in this paper as they differ in pathogenesis, presentation, natural history and response to treatment.

Anastomotic strictures present as a thin, short, localized and isolated narrowing in the area of biliary anastomosis as a result of fibrotic healing arising from ischemia at the end of both the donor and recipient bile duct[4,6,17]. They occur in 5% to 15% of patients after deceased OLT and 19% to 32% after living donor liver transplantation (LDLT)[3,4,6,18,19]. Early presentation

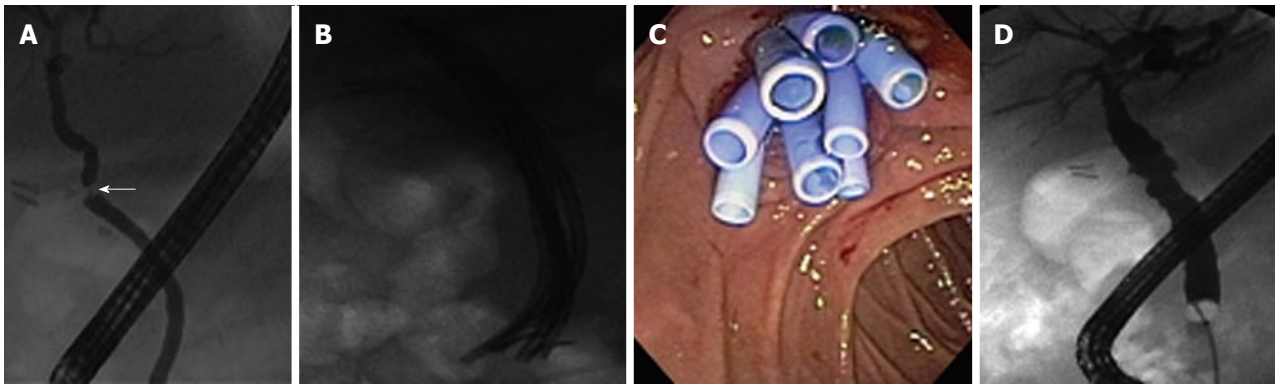

Figure 3 Patient with post-orthotopic liver transplantation anastomotic stricture from index endoscopic retrograde cholangiopancreatographys. A: Retrograde cholangiogram demonstrating post-OLT anastomotic stricture (arrow); B: Patient was treated with progressive multiple plastic stents; C: Patient was treated with progressive multiple plastic stents; D: Final cholangiogram revealing complete stricture resolution. OLT: Orthotopic liver transplantation.

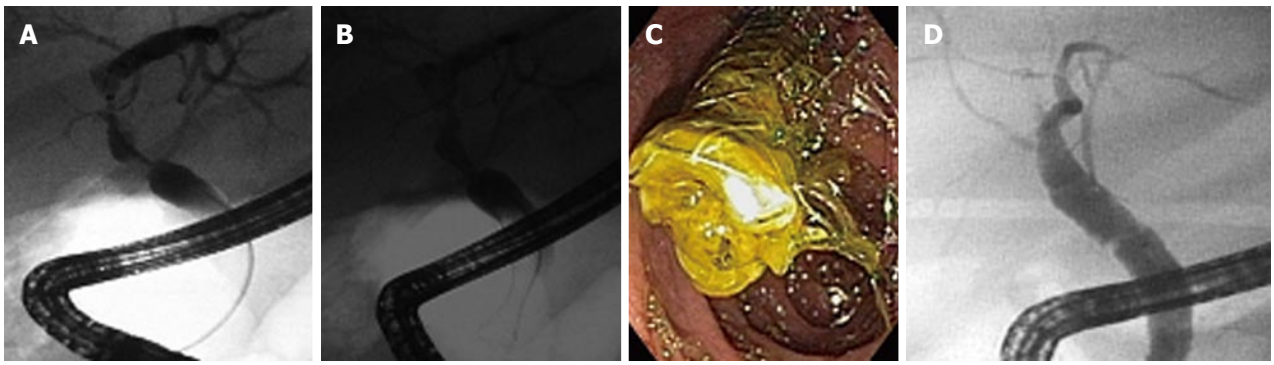

Figure 4 Patient with post-orthotopic liver transplantation anastomotic stricture. A: Post-OLT anastomotic biliary stricture; B: Placement of a fully covered SEMS across the stricture as a primary therapy option; C: Endoscopic view of the FCSEMS after 6 mo in place; D: Fluoroscopic image revealing enlargement of the common hepatic duct after SEMS removal. OLT: Orthotopic liver transplantation; FCSEMS: Fully covered stent-expandable metal stents.

Figure 5 Recurrent anastomotic stricture after fully covered stent-expandable metal stents distal migration.

(within 12 wk) of anastomotic strictures have been related to technical issues, such as, small caliber of bile ducts, mismatch in size between donor and recipient ducts, inappropriate surgical techniques including suture material, tension at the anastomosis and excessive use of electrocautery[20]. The presence of bile leak has been reported as an independent risk factor for the development of AS; the underlying process may be related to the inflammation and subsequent fibrosis as a local effect caused by the bile itself or it may be a marker of poor vascularity in those patients in whom the leak is not originated from the cystic stump[8,21]. Late strictures are mainly due to vascular insufficiency, ischemia and problems with healing and fibrosis[12,22].

The majority of anastomotic stricture develops within the first year after OLT. In our series, the mean time between OLT and biliary stricture presentation was about 7 mo. Patients usually present asymptomatic or may have non-specific symptoms with abnormalities in liver function chemistries. Clinical suspicious must be confirmed by imaging diagnostic tools and patients are then referred to treatment, accordingly to the algorithm presented above.

There has been a transition over the past two decades in the primary management of benign biliary strictures from surgery to minimally invasive *via* ERCP. Endoscopic therapy presents a lower complication rate and shorter hospital stay when compared to surgery, not compromising the option of operation in case of failure[23,24]. Percutaneous therapy is still considered a second line option for patients with duct-to-duct anastomosis, though reserved to failed endoscopic

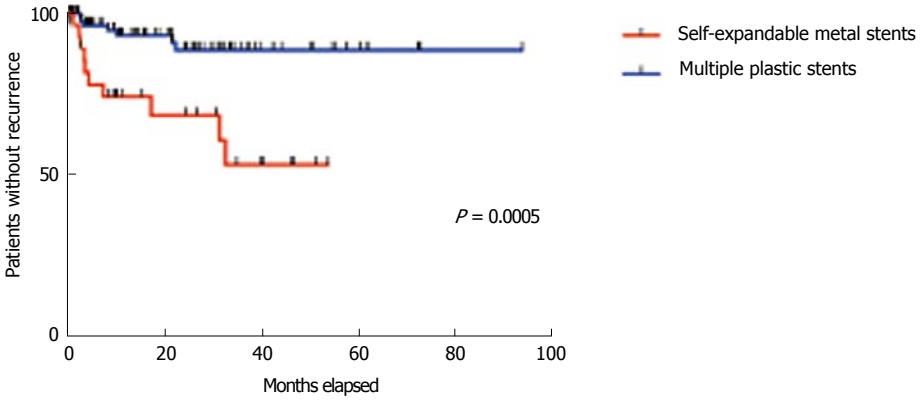

Figure 6 Stricture recurrence after resolution.

access to the anastomotic stricture, and patients with hepaticojejunostomy or choledochojejunostomy reconstruction. Currently surgical revision is confined for patients who have failed endoscopic and percutaneous therapy with re-transplantation being the final option.

Most patients with anastomotic stricture require multiple endoscopic interventions at 3-mo intervals for 12 to 24 mo with balloon dilation and long-term stenting[4,6,7,19,25-29]. The rational for multiple biliary stents placement through the stricture is to maintain the maximal expansion in luminal diameter achieved during balloon dilation, possibly promoting the re-modelation of bile ducts over the stents and preventing duct narrowing when stents are still in place[27,30]. In addition, the use of multiple stents may reduce complications related to stent occlusion, such as obstructive jaundice and cholangitis by adding biliary drainage through interstent channels[27,30,31].

A recent systematic review showed that stricture resolution rates were 78.3% for stent indwelling of less than 12 mo, compared with 97% for those longer than 1 year. The corresponding recurrence rates were 14.2% and 1.5% respectively[32].

In our center, we adopted an aggressive multiple plastic prophylactic stent exchange protocol over 1 year period, achieving a stricture resolution rate of 91%, which compares favorably with literature results. Recurrence rate after a mean follow-up of approximately 2 years is as low as 7.7%, reinforcing the benefits of extending the treatment up to 1 year.

A recent multivariate regression analysis was published assessing the outcome of endoscopic treatment of biliary complications after OLT[5]. Patients who received a graft from living donor or from a donor after cardiac death and those who had a reoperation for a non-biliary indication within the first month after liver transplantation were less likely to respond to endoscopic therapy[5]. Another factor apparently associated to stricture recurrence is the presence of a biliary leakage at initial ERCP[33]. On the other hand, early onset strictures seem to respond better and this finding may be related to the fact that those with late-onset are likely to be more fibrotic and therefore tighter and more resistant to therapy[8,27,33,34]. However, in case of recurrence, patients appear to respond well to repeated endoscopic treatment[8,27,30,35].

The major drawbacks of endoscopic treatment with balloon dilation and multiple plastic stents placement are the need of multiple procedures. Partially or fully covered SEMS were introduced on the market and became a very appealing option for benign biliary strictures due to their removability[36-49].

Post OLT biliary strictures offer an anatomical advantage for the placement of SEMS, which is the presence of the graft duct, permitting enough space above the stenosis to accommodate the metal stent distant from the hepatic confluence. Kahaleh *et al*[44] have been pioneer in the use of SEMS for benign biliary strictures of different etiology. Firstly, by describing metallic stent removability[44] and afterwards testing partially and fully covered SEMS in different clinical and technical settings[42,43,50-52].

Temporary placement of FCSEMS in patients with post-OLT anastomotic strictures refractory to conventional endoscopic therapy reached 87.5% to 100% initial success rate with a 4.5% to 7.4% recurrence. The major drawback of FCSEMS use was migration; occurring in 27.2% to 37.5%, even though with no clinical consequences[36,40,46].

In a systematic review that included 21 studies, multiple plastic stents were compared with metal stents in post liver transplant anastomotic stricture. There was significant heterogeneity in stent protocols, types of SEMS used, the use of balloon dilation or plastic stents before SEMS placement, primary outcome and stent free follow-up. There were no randomized controlled trials or non-randomized studies comparing these two modalities. Two hundred patients treated with SEMS were analyzed and stricture resolution rate was 80% to 94% when stent indwelling was longer than 3 mo, very similar to a 94% to 100% rate seen with multiple plastic stent for at least 12 mo. Moreover SEMS were used as a second line therapy for refractory strictures in 125 of these patients, what can be considered a

selection bias for more difficult strictures. The main problem with SEMS was stent migration, occurring in 16% of cases[32]. The rate of stricture resolution is lower in patients with FCSEMS migration[32,46,48].

In our study, we analyzed 38 post OLT patients with anastomotic stricture treated with cSEMS as a first line approach, reaching a stricture resolution of 86.8% after a mean stent indwelling of 124.2 d. Although the initial success was comparable with the currently standard multiple plastic stent treatment, there was a 30.3% recurrence rate after a mean of 310 d. We wonder if this higher recurrence rate was due to the shorter stent indwelling or the smaller final diameter of a 10 mm (30 French) cSEMS compared with the maximum number of plastic stents (up to 90 French per ERCP session) achieved in the other group.

We presented a mid-term evaluation of our randomized controlled trial comparing cSEMS with multiple plastic stents at DDW 2013. Although success rate was similar between groups, mean treatment duration and number of procedures required were statistically lower in cSEMS group ($P < 0.001$ for both comparisons). Moreover in our prospective trial, the mean total diameter for plastic stent group was 59 French (range 20 to 104.5 French)[47].

In summary, temporary placement of FCSEMS has been demonstrated effective and safe in the treatment of post OLT anastomotic strictures and should be considered for patients with refractory strictures[36,40,42,43,49]. On the basis of the current data, FCSEMS may allow anastomotic biliary stricture resolution with fewer procedure sessions possibly reducing treatment global cost, with the initial high price of a SEMS being compensated by the reduction in the number of ERCPs and the total number of plastic stents used during the 12-mo treatment period[53].

Questions remain about the optimal stenting interval and ideal metal stent. Concerning the first question, FCSEMS may be left in place for longer periods than partially covered ones, but prospective randomized studies with long-term follow-up are necessary to confirm this concept. The pursue for the ideal SEMS is still ongoing, it should be fully covered with an inert and resistant coating and have no fins, which seem to be associated to significant tissue reaction.

Concerning complications rate, in our study, the rate of post procedure acute pancreatitis in the plastic stent group was 4.1%, which compares favorably with the literature reports[54,55]. However, the rate of pancreatitis in the cSEMS group was 17.1%, which is exceedingly high even for a high-risk population.

Biliary sphincterotomy is usually not performed before SEMS placement in malignant biliary obstructions and therefore in the first 16 cases in our study cSEMS were deployed without one. The high incidence of acute pancreatitis (50% in the first 16 cases) came to our attention raising a debate over the impact of the sphincterotomy preceding metal stent deployment in a benign biliary stricture. Moreover, the severity of the event after cSEMS placement without sphincterotomy was also alarming, since 1 case was severe, 5 moderate and 2 mild.

The main hypothesis was that placing a trans-papillary metal stent in a native papilla without prior sphincterotomy was the main reason for the high rate of post procedure pancreatitis. Differently from patients with malignant obstruction that probably have already pancreatic parenchymal atrophy secondary to insidious pancreatic distal obstruction and therefore do not present acute pancreatitis after trans-papillary SEMS[56] Currently in our practice, all cSMES are placed after a biliary sphincterotomy in the post-OLT anastomotic stricture what drastically decreased acute pancreatitis rate to 12.5% (4/32) and all events were mild.

Although advances in surgical technique, organ preservation and selection have been made, biliary complications remain a significant source of morbidity in post liver transplant patients. Endoscopic treatment is already established as standard first line therapy. Progressive balloon dilation and multiple plastic stenting have been considered the first treatment option for biliary stricture in patients with duct-to-duct anastomosis. Our study shows encouraging results regarding placement of biliary cSEMS as the therapeutic endoscopic choice aiming to reduce the number of procedures and thus have a positive impact in cost, morbidity and quality of life of these patients, however their complication rate needs to be further evaluated.

COMMENTS

Background

Biliary complications have been considered for a long time the technical "Achiles heel" of orthotopic liver transplantation (OLT), with biliary strictures incidence up to 40% of patients. The standard strategy for post OLT biliary strictures in patients with duct-to-duct anastomosis has been balloon dilation followed by insertion of multiple plastic stents. Recently, covered self-expandable metal stents (cSEMS) has been increasingly used in the management of benign biliary strictures.

Research frontiers

The major drawback of conventional endoscopic treatment with multiple plastic stents placement is the need of multiple procedures. cSEMS have removability previously demonstrated in published studies and longer patency. In the area of benign biliary lesions, the current research hotspot is to evaluate the effectiveness and adverse events related to cSEMS.

Innovations and breakthroughs

Current evidence does not suggest a clear advantage of SEMS use over multiple plastic sten. In the study although success rates were similar, mean treatment duration and number of procedures required were statistically lower in cSEMS group. On the basis of the current data, fully covered stent- EMS may allow anastomotic biliary stricture resolution with fewer procedure sessions possibly reducing treatment global cost, with the initial high price of a SEMS being compensated by the reduction in the number of endoscopic retrograde cholangiopancreatographys and the total number of plastic stents used during the 12-mo treatment period.

Applications

Conventional endoscopic treatment with progressive balloon dilation and multiple plastic stenting has been considered the first option for post-OLT biliary stricture for decades. The study shows encouraging results regarding placement of biliary cSEMS as the therapeutic endoscopic choice aiming to reduce the number of procedures and thus have a positive impact in cost, morbidity and quality of life of these patients, however the complication rate

needs to be further evaluated.

Terminology

Anastomotic biliary strictures in the post-OLT scenario present as a short narrowing at the area of choledochal anastomosis. Endoscopic therapy can be performed by standardized protocols either with multiple plastic or single metal stents. Multiple plastic stents are placed after sphincterotomy and stricture balloon dilation, exchanged at 3-mo interval, until 12 mo of therapy. cSEMS are deployed at the index procedure and removed after approximately 6 mo.

Peer-review

This is a good descriptive study in which the authors analyzed the effectiveness and safety of endoscopic therapy in the management of post-OLT anastomotic biliary stricture. The results are interesting and suggest that cSEMS is a potential therapeutic option to multiple plastic stents that could be used for reducing the number of procedures and overall costs.

REFERENCES

1 **Fogel EL**, McHenry L, Sherman S, Watkins JL, Lehman GA. Therapeutic biliary endoscopy. *Endoscopy* 2005; **37**: 139-145 [PMID: 15692929 DOI: 10.1055/s-2004-826146]

2 **Chang JM**, Lee JM, Suh KS, Yi NJ, Kim YT, Kim SH, Han JK, Choi BI. Biliary complications in living donor liver transplantation: imaging findings and the roles of interventional procedures. *Cardiovasc Intervent Radiol* 2005; **28**: 756-767 [PMID: 16160754 DOI: 10.1007/s00270-004-0262-7]

3 **Akamatsu N**, Sugawara Y, Hashimoto D. Biliary reconstruction, its complications and management of biliary complications after adult liver transplantation: a systematic review of the incidence, risk factors and outcome. *Transpl Int* 2011; **24**: 379-392 [PMID: 21143651 DOI: 10.1111/j.1432-2277.2010.01202.x]

4 **Sharma S**, Gurakar A, Jabbour N. Biliary strictures following liver transplantation: past, present and preventive strategies. *Liver Transpl* 2008; **14**: 759-769 [PMID: 18508368 DOI: 10.1002/lt.21509]

5 **Buxbaum JL**, Biggins SW, Bagatelos KC, Ostroff JW. Predictors of endoscopic treatment outcomes in the management of biliary problems after liver transplantation at a high-volume academic center. *Gastrointest Endosc* 2011; **73**: 37-44 [PMID: 21074761 DOI: 10.1016/j.gie.2010.09.007]

6 **Williams ED**, Draganov PV. Endoscopic management of biliary strictures after liver transplantation. *World J Gastroenterol* 2009; **15**: 3725-3733 [PMID: 19673012 DOI: 10.3748/wjg.15.3725]

7 **Rerknimitr R**, Sherman S, Fogel EL, Kalayci C, Lumeng L, Chalasani N, Kwo P, Lehman GA. Biliary tract complications after orthotopic liver transplantation with choledochocholedochostomy anastomosis: endoscopic findings and results of therapy. *Gastrointest Endosc* 2002; **55**: 224-231 [PMID: 11818927 DOI: 10.1067/mge.2002.120813]

8 **Verdonk RC**, Buis CI, Porte RJ, van der Jagt EJ, Limburg AJ, van den Berg AP, Slooff MJ, Peeters PM, de Jong KP, Kleibeuker JH, Haagsma EB. Anastomotic biliary strictures after liver transplantation: causes and consequences. *Liver Transpl* 2006; **12**: 726-735 [PMID: 16628689 DOI: 10.1002/lt.20714]

9 **Verdonk RC**, Buis CI, Porte RJ, Haagsma EB. Biliary complications after liver transplantation: a review. *Scand J Gastroenterol Suppl* 2006; **(243)**: 89-101 [PMID: 16782628 DOI: 10.1080/00365520600664375]

10 **Pfau PR**, Kochman ML, Lewis JD, Long WB, Lucey MR, Olthoff K, Shaked A, Ginsberg GG. Endoscopic management of postoperative biliary complications in orthotopic liver transplantation. *Gastrointest Endosc* 2000; **52**: 55-63 [PMID: 10882963 DOI: 10.1067/mge.2000.106687]

11 **Thuluvath PJ**, Pfau PR, Kimmey MB, Ginsberg GG. Biliary complications after liver transplantation: the role of endoscopy. *Endoscopy* 2005; **37**: 857-863 [PMID: 16116539 DOI: 10.1055/s-2005-870192]

12 **Pascher A**, Neuhaus P. Biliary complications after deceased-donor orthotopic liver transplantation. *J Hepatobiliary Pancreat Surg* 2006; **13**: 487-496 [PMID: 17139421 DOI: 10.1007/s00534-005-1083-z]

13 **Thethy S**, Thomson BNj, Pleass H, Wigmore SJ, Madhavan K, Akyol M, Forsythe JL, James Garden O. Management of biliary tract complications after orthotopic liver transplantation. *Clin Transplant* 2004; **18**: 647-653 [PMID: 15516238 DOI: 10.1111/j.1399-0012.2004.00254.x]

14 **Jorgensen JE**, Waljee AK, Volk ML, Sonnenday CJ, Elta GH, Al-Hawary MM, Singal AG, Taylor JR, Elmunzer BJ. Is MRCP equivalent to ERCP for diagnosing biliary obstruction in orthotopic liver transplant recipients? A meta-analysis. *Gastrointest Endosc* 2011; **73**: 955-962 [PMID: 21316670 DOI: 10.1016/j.gie.2010.12.014]

15 **Balderramo D**, Bordas JM, Sendino O, Abraldes JG, Navasa M, Llach J, Cardenas A. Complications after ERCP in liver transplant recipients. *Gastrointest Endosc* 2011; **74**: 285-294 [PMID: 21704993 DOI: 10.1016/j.gie.2011.04.025]

16 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393 [PMID: 2070995 DOI: 10.1016/S0016-5107(91)70740-2]

17 **Ostroff JW**. Post-transplant biliary problems. *Gastrointest Endosc Clin N Am* 2001; **11**: 163-183 [PMID: 11175980]

18 **Zoepf T**, Maldonado-Lopez EJ, Hilgard P, Schlaak J, Malago M, Broelsch CE, Treichel U, Gerken G. Endoscopic therapy of posttransplant biliary stenoses after right-sided adult living donor liver transplantation. *Clin Gastroenterol Hepatol* 2005; **3**: 1144-1149 [PMID: 16271347 DOI: 10.1016/S1542-3565(05)00850-5]

19 **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 [PMID: 16482553 DOI: 10.1002/lt.20644]

20 **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 [PMID: 16628684 DOI: 10.1002/lt.20753]

21 **Welling TH**, Heidt DG, Englesbe MJ, Magee JC, Sung RS, Campbell DA, Punch JD, Pelletier SJ. Biliary complications following liver transplantation in the model for end-stage liver disease era: effect of donor, recipient, and technical factors. *Liver Transpl* 2008; **14**: 73-80 [PMID: 18161843 DOI: 10.1002/lt.21354]

22 **Testa G**, Malagó M, Valentín-Gamazo C, Lindell G, Broelsch CE. Biliary anastomosis in living related liver transplantation using the right liver lobe: techniques and complications. *Liver Transpl* 2000; **6**: 710-714 [PMID: 11084056 DOI: 10.1053/jlts.2000.18706]

23 **Dumonceau JM**, Devière J, Delhaye M, Baize M, Cremer M. Plastic and metal stents for postoperative benign bile duct strictures: the best and the worst. *Gastrointest Endosc* 1998; **47**: 8-17 [PMID: 9468417 DOI: 10.1016/S0016-5107(98)70292-5]

24 **Tocchi A**, Mazzoni G, Liotta G, Costa G, Lepre L, Miccini M, De Masi E, Lamazza MA, Fiori E. Management of benign biliary strictures: biliary enteric anastomosis vs endoscopic stenting. *Arch Surg* 2000; **135**: 153-157 [PMID: 10668872 DOI: 10.1001/archsurg.135.2.153]

25 **Costamagna G**, Tringali A, Mutignani M, Perri V, Spada C, Pandolfi M, Galasso D. Endotherapy of postoperative biliary strictures with multiple stents: results after more than 10 years of follow-up. *Gastrointest Endosc* 2010; **72**: 551-557 [PMID: 20630514 DOI: 10.1016/j.gie.2010.04.052]

26 **Krok KL**, Cárdenas A, Thuluvath PJ. Endoscopic management of biliary complications after liver transplantation. *Clin Liver Dis* 2010; **14**: 359-371 [PMID: 20682241 DOI: 10.1016/j.cld.2010.03.008]

27 **Pasha SF**, Harrison ME, Das A, Nguyen CC, Vargas HE, Balan V, Byrne TJ, Douglas DD, Mulligan DC. Endoscopic treatment of anastomotic biliary strictures after deceased donor liver transplantation: outcomes after maximal stent therapy. *Gastrointest Endosc* 2007; **66**: 44-51 [PMID: 17591473 DOI: 10.1016/j.gie.2007.02.017]

28 **Zoepf T**, Maldonado-Lopez EJ, Hilgard P, Malago M, Broelsch

CE, Treichel U, Gerken G. Balloon dilatation vs. balloon dilatation plus bile duct endoprostheses for treatment of anastomotic biliary strictures after liver transplantation. *Liver Transpl* 2006; **12**: 88-94 [PMID: 16382450 DOI: 10.1002/lt.20548]

29 **Holt AP**, Thorburn D, Mirza D, Gunson B, Wong T, Haydon G. A prospective study of standardized nonsurgical therapy in the management of biliary anastomotic strictures complicating liver transplantation. *Transplantation* 2007; **84**: 857-863 [PMID: 17984838 DOI: 10.1097/01.tp.0000282805.33658.ce]

30 **Tabibian JH**, Asham EH, Han S, Saab S, Tong MJ, Goldstein L, Busuttil RW, Durazo FA. Endoscopic treatment of postorthotopic liver transplantation anastomotic biliary strictures with maximal stent therapy (with video). *Gastrointest Endosc* 2010; **71**: 505-512 [PMID: 20189508 DOI: 10.1016/j.gie.2009.10.023]

31 **Morelli J**, Mulcahy HE, Willner IR, Cunningham JT, Draganov P. Long-term outcomes for patients with post-liver transplant anastomotic biliary strictures treated by endoscopic stent placement. *Gastrointest Endosc* 2003; **58**: 374-379 [PMID: 14528211 DOI: 10.1067/S0016-5107(03)00011-7]

32 **Kao D**, Zepeda-Gomez S, Tandon P, Bain VG. Managing the post-liver transplantation anastomotic biliary stricture: multiple plastic versus metal stents: a systematic review. *Gastrointest Endosc* 2013; **77**: 679-691 [PMID: 23473000 DOI: 10.1016/j.gie.2013.01.015]

33 **Alazmi WM**, Fogel EL, Watkins JL, McHenry L, Tector JA, Fridell J, Mosler P, Sherman S, Lehman GA. Recurrence rate of anastomotic biliary strictures in patients who have had previous successful endoscopic therapy for anastomotic narrowing after orthotopic liver transplantation. *Endoscopy* 2006; **38**: 571-574 [PMID: 16802268 DOI: 10.1055/s-2006-925027]

34 **Thuluvath PJ**, Atassi T, Lee J. An endoscopic approach to biliary complications following orthotopic liver transplantation. *Liver Int* 2003; **23**: 156-162 [PMID: 12955878 DOI: 10.1034/j.1600-0676.2003.00823.x]

35 **Morelli G**, Fazel A, Judah J, Pan JJ, Forsmark C, Draganov P. Rapid-sequence endoscopic management of posttransplant anastomotic biliary strictures. *Gastrointest Endosc* 2008; **67**: 879-885 [PMID: 18178206 DOI: 10.1016/j.gie.2007.08.046]

36 **García-Pajares F**, Sánchez-Antolín G, Pelayo SL, Gómez de la Cuesta S, Herranz Bachiller MT, Pérez-Miranda M, de La Serna C, Vallecillo Sande MA, Alcaide N, Llames RV, Pacheco D, Caro-Patón A. Covered metal stents for the treatment of biliary complications after orthotopic liver transplantation. *Transplant Proc* 2010; **42**: 2966-2969 [PMID: 20970584 DOI: 10.1016/j.transproceed.2010.07.084]

37 **Chaput U**, Scatton O, Bichard P, Ponchon T, Chryssostalis A, Gaudric M, Mangialavori L, Duchmann JC, Massault PP, Conti F, Calmus Y, Chaussade S, Soubrane O, Prat F. Temporary placement of partially covered self-expandable metal stents for anastomotic biliary strictures after liver transplantation: a prospective, multicenter study. *Gastrointest Endosc* 2010; **72**: 1167-1174 [PMID: 20970790 DOI: 10.1016/j.gie.2010.08.016]

38 **Tee HP**, James MW, Kaffes AJ. Placement of removable metal biliary stent in post-orthotopic liver transplantation anastomotic stricture. *World J Gastroenterol* 2010; **16**: 3597-3600 [PMID: 20653071 DOI: 10.3748/wjg.v16.i28.3597]

39 **Marín-Gómez LM**, Sobrino-Rodríguez S, Alamo-Martínez JM, Suárez-Artacho G, Bernal-Bellido C, Serrano-Díaz-Canedo J, Padillo-Ruiz J, Gómez-Bravo MA. Use of fully covered self-expandable stent in biliary complications after liver transplantation: a case series. *Transplant Proc* 2010; **42**: 2975-2977 [PMID: 20970587 DOI: 10.1016/j.transproceed.2010.08.023]

40 **Traina M**, Tarantino I, Barresi L, Volpes R, Gruttadauria S, Petridis I, Gridelli B. Efficacy and safety of fully covered self-expandable metallic stents in biliary complications after liver transplantation: a preliminary study. *Liver Transpl* 2009; **15**: 1493-1498 [PMID: 19877248 DOI: 10.1002/lt.21886]

41 **Vandenbroucke F**, Plasse M, Dagenais M, Lapointe R, Lêtourneau R, Roy A. Treatment of post liver transplantation bile duct stricture with self-expandable metallic stent. *HPB* (Oxford) 2006; **8**: 202-205 [PMID: 18333277 DOI: 10.1080/13651820500501800]

42 **Mahajan A**, Ho H, Sauer B, Phillips MS, Shami VM, Ellen K, Rehan M, Schmitt TM, Kahaleh M. Temporary placement of fully covered self-expandable metal stents in benign biliary strictures: midterm evaluation (with video). *Gastrointest Endosc* 2009; **70**: 303-309 [PMID: 19523620 DOI: 10.1016/j.gie.2008.11.029]

43 **Kahaleh M**, Behm B, Clarke BW, Brock A, Shami VM, De La Rue SA, Sundaram V, Tokar J, Adams RB, Yeaton P. Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm? (with video). *Gastrointest Endosc* 2008; **67**: 446-454 [PMID: 18294506 DOI: 10.1016/j.gie.2007.06.057]

44 **Kahaleh M**, Tokar J, Le T, Yeaton P. Removal of self-expandable metallic Wallstents. *Gastrointest Endosc* 2004; **60**: 640-644 [PMID: 15472699 DOI: 10.1016/S0016-5107(04)01959-5]

45 **Trentino P**, Falasco G, d'orta C, Coda S. Endoscopic removal of a metallic biliary stent: case report. *Gastrointest Endosc* 2004; **59**: 321-323 [PMID: 14745419 DOI: 10.1016/S0016-5107(03)02685-3]

46 **Devière J**, Nageshwar Reddy D, Püspök A, Ponchon T, Bruno MJ, Bourke MJ, Neuhaus H, Roy A, González-Huix Lladó F, Barkun AN, Kortan PP, Navarrete C, Peetermans J, Blero D, Lakhtakia S, Dolak W, Lepilliez V, Poley JW, Tringali A, Costamagna G. Successful management of benign biliary strictures with fully covered self-expanding metal stents. *Gastroenterology* 2014; **147**: 385-395; quiz e15 [PMID: 24801350 DOI: 10.1053/j.gastro.2014.04.043]

47 **Martins FP**, Di Sena V, de Paulo GA, Contini ML, Ferrari Junior AP. Phase III randomized controlled trial of fully covered metal stent versus multiple plastic stents in anastomotic biliary strictures following orthotopic liver transplantation: midterm Evaluation. *Gastrointest Endosc* 2013; **77**: AB318 [DOI: 10.1016/j.gie.2013.03.1075]

48 **Kahaleh M**, Brijbassie A, Sethi A, Degaetani M, Poneros JM, Loren DE, Kowalski TE, Sejpal DV, Patel S, Rosenkranz L, McNamara KN, Raijman I, Talreja JP, Gaidhane M, Sauer BG, Stevens PD. Multicenter trial evaluating the use of covered self-expanding metal stents in benign biliary strictures: time to revisit our therapeutic options? *J Clin Gastroenterol* 2013; **47**: 695-699 [PMID: 23442836 DOI: 10.1097/MCG.0b013e31827fd311]

49 **Tarantino I**, Traina M, Mocciaro F, Barresi L, Curcio G, Di Pisa M, Granata A, Volpes R, Gridelli B. Fully covered metallic stents in biliary stenosis after orthotopic liver transplantation. *Endoscopy* 2012; **44**: 246-250 [PMID: 22354824 DOI: 10.1055/s-0031-1291465]

50 **Phillips MS**, Bonatti H, Sauer BG, Smith L, Javaid M, Kahaleh M, Schmitt T. Elevated stricture rate following the use of fully covered self-expandable metal biliary stents for biliary leaks following liver transplantation. *Endoscopy* 2011; **43**: 512-517 [PMID: 21618151 DOI: 10.1055/s-0030-1256389]

51 **Wang AY**, Ellen K, Berg CL, Schmitt TM, Kahaleh M. Fully covered self-expandable metallic stents in the management of complex biliary leaks: preliminary data - a case series. *Endoscopy* 2009; **41**: 781-786 [PMID: 19693751 DOI: 10.1055/s-0029-1215050]

52 **Ho H**, Mahajan A, Gosain S, Jain A, Brock A, Rehan ME, Ellen K, Shami VM, Kahaleh M. Management of complications associated with partially covered biliary metal stents. *Dig Dis Sci* 2010; **55**: 516-522 [PMID: 19267200 DOI: 10.1007/s10620-009-0756-x]

53 **Behm BW**, Brock A, Clarke BW, Adams RB, Northup PG, Yeaton P, Kahaleh M. Cost analysis of temporarily placed covered self expandable metallic stents versus plastic stents in biliary strictures related to chronic pancreatitis. *Gastrointest Endosc* 2007; **65**: AB211 [DOI: 10.1016/j.gie.2007.03.432]

54 **Rabenstein T**, Schneider HT, Bulling D, Nicklas M, Katalinic A, Hahn EG, Martus P, Ell C. Analysis of the risk factors associated with endoscopic sphincterotomy techniques: preliminary results of a prospective study, with emphasis on the reduced risk of acute pancreatitis with low-dose anticoagulation treatment. *Endoscopy* 2000; **32**: 10-19 [PMID: 10691266 DOI: 10.1055/s-2000-138]

55 **Wilcox CM**, Phadnis M, Varadarajulu S. Biliary stent placement is associated with post-ERCP pancreatitis. *Gastrointest Endosc* 2010;

72: 546-550 [PMID: 20633882 DOI: 10.1016/j.gie.2010.05.001]
56 **Tarnasky PR**, Cunningham JT, Hawes RH, Hoffman BJ, Uflacker R, Vujic I, Cotton PB. Transpapillary stenting of proximal biliary strictures: does biliary sphincterotomy reduce the risk of postprocedure pancreatitis? *Gastrointest Endosc* 1997; **45**: 46-51 [PMID: 9013169 DOI: 10.1016/S0016-5107(97)70301-8]

P- Reviewer: Kobayashi N, Zhu YL **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com