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Sequential multistenting protocol in biliary stenosis after liver transplantation: a prospective analysis

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ABSTRACT

Background Biliary complications are a serious source of morbidity after orthotopic and living-related liver transplantation. Endoscopic retrograde cholangiography (ERC) is the gold standard for patients with duct-to-duct anastomosis because it allows a direct approach for interventional procedures. A retrospective study showed results of a sequential multistenting protocol, without stent removal/exchange, with promising results. We conducted a prospective analysis to assess the clinical success, recurrence rate, and adverse event rate related to this protocol.

Methods From May 2012 to April 2018, all consecutive patients with a diagnosis of anastomotic stenosis following liver transplantation were enrolled in the study, and were followed for a period of at least 6 months after the last ERC. During the first ERC, a maximum number of plastic stents (10 Fr) were placed. In subsequent ERCs, scheduled every 3 months up to a maximum of 1 year, additional stents were inserted, as many as possible, without removing the previously placed stents.

Results From May 2012 to May 2018, 87 patients were included in the study and treated with a sequential multistenting protocol. The mean number of stents placed was 3.7 (SD 1.0). Clinical success (stricture resolution and normalization of cholestasis) was achieved in 86 patients (98.9%). Seven patients (8.0%) developed complications. Recurrence was recorded in seven patients (8.0%) after a mean of 992.7 days (SD 622.1).

Conclusions This study represents the first prospective demonstration of the efficacy and safety of a sequential multistenting protocol. A key limitation of the study is the lack of a comparative group treated according to the traditional stent exchange approach.

Introduction

The risk factors for biliary complications after liver transplantation are well known: characteristics of the donor and recipient (e.g. prolonged ischemia, fibrosis, difference in bile duct caliber), tension on the anastomosis, use of cautery, and occurrence of biliary leak and infections [1–5].

Despite continual surgical improvement, biliary complications are a serious source of morbidity after orthotopic and living-related liver transplantation (OLT and LRLT), and a number of studies on endoscopic treatment of these complications have been published. The type of biliary reconstruction, ischemia and reperfusion injury, hepatic artery thrombosis, cytomegalovirus infection, and primary sclerosing cholangitis are the principal risk factors for the development of biliary morbidity after liver transplantation [6, 7].

The rate of biliary complications in transplant recipients in published series ranges from 8% to 35%. This complication rate is higher for LRLT than for OLT patients [8–10]. Depending on the type of surgical biliary reconstruction (Roux-en-Y choledocho-jejunostomy or duct-to-duct anastomosis), biliary complications can be treated by percutaneous transhepatic cholangiography or by endoscopic retrograde cholangiography (ERC).

The standard endoscopic treatment for anastomotic stenosis consists of sphincterotomy plus progressive pneumatic dilation with multiple stent placement. ERC should be repeated and the stent exchanged every 3 months [11] in order to obtain evidence of a morphological recovery of the stenosis [12, 13].

Another endoscopic approach that has been described is the placement of a fully covered self-expandable metal stent (FC-SEMS) across the stenosis. The technique has been shown to be safe, but the FC-SEMS migration rate is reported to be high,

and stricture recurrence occurs in 9 % – 47 % during a 5-year follow-up period [14 – 18]. A recent study showed, for the first time in a transplantation population, results of a sequential multistenting protocol, in which one additional stent is placed across the stricture during sequential ERC, without stent removal/exchange or stricture dilation. In this study, both methods had the same stricture resolution rate and adverse event rate, but the sequential approach was shorter and more cost-effective [19].

The aim of the current prospective study was to assess the clinical success, recurrence rate, and adverse event rate of the sequential multistenting protocol in patients with biliary anastomotic stenosis following liver transplantation.

Methods

The study was designed and conducted at IRCCS-ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione), a tertiary referral center in Palermo, Italy. The study protocol adhered to the principles of the Declaration of Helsinki, and was approved by our Institutional Research Review Board (IRRB No. IRRB/53). Written informed consent was obtained from all patients. All authors had access to the study data, and reviewed and approved the final manuscript.

From May 2012 to April 2018, all consecutive patients with a diagnosis of anastomotic stenosis following liver transplantation were enrolled in the study, and were followed for a period of at least 6 months from the last ERC. Inclusion criteria were: previous liver transplantation with duct-to-duct biliary anastomosis, age ≥ 18 years, new diagnosis of anastomotic stenosis or evidence of anastomotic stenosis recurrence after treatment with SEMS. Diagnostic evaluation was performed in cases of suspicion of biliary occlusion by biochemical testing and imaging such as ultrasonography and magnetic resonance cholangiopancreatography (MRCP). In accordance with our protocol, the clinical suspicion of anastomotic stenosis plus altered liver function tests was evaluated first by ultrasound (with and without Doppler), which also assessed arterial and portal blood flow. If the ultrasound was not conclusive, the next step was MRCP. When there were contraindications to magnetic resonance imaging (e.g. cardiac pacemaker, cerebral aneurysm clips, ocular or cochlear implants, and ocular foreign bodies), a computed tomography scan was done instead of MRCP. At ERC, anastomotic biliary stricture was defined as an isolated, short, dominant narrowing within 5 mm of the biliary anastomosis without passage of contrast dye during the cholangio sequences. Exclusion criteria were intrahepatic biliary stenosis or different caliber of donor and recipient biliary ducts at the anastomosis that was diagnosed as anastomotic stenosis by MRCP but with regular biliary outflow at ERC.

After acquiring informed consent according to the institutional guidelines, all included patients were treated with a sequential multistenting protocol. All ERCs were performed by senior endoscopists using a therapeutic video duodenoscope (TJF-Q180V or TJF-Q160V, Olympus Europe, Hamburg, Germany) in a standard fashion. Patients were placed in a supine position and under general anesthesia or deep sedation, according to the anesthesia protocols. Prophylactic antibiotic therapy was administered in all procedures.

During the first ERC, after deep biliary cannulation, a cholangiogram was performed to confirm the presence of an anastomotic stenosis, and sphincterotomy and balloon dilations (from 4 to 6 mm according to the caliber of the bile duct above the anastomotic stenosis) were subsequently performed. Multiple 10 Fr plastic stents were then inserted and placed side by side across the stricture. The maximum number of stents placed was dependent on the diameter of the residual bile duct.

After the first ERC, subsequent procedures were scheduled every 3 months, up to a maximum of 1 year. During each ERC, after bile duct cannulation and cholangiography, additional stents (as many as possible) were inserted without removing the previously placed stents (► **Fig. 1**). All plastic stents were removed when any further stent positioning was judged to be technically unfeasible (according to the residual room available across the anastomosis) or after 1 year.

Endoscopic evaluation was anticipated in cases of signs or symptoms of biliary obstruction. Unplanned hospital admission was recorded for adverse events related to ERC and biliary disease. The failure of multistenting was defined as the persistence of stenosis, confirmed fluoroscopically, after 12 months of treatment.

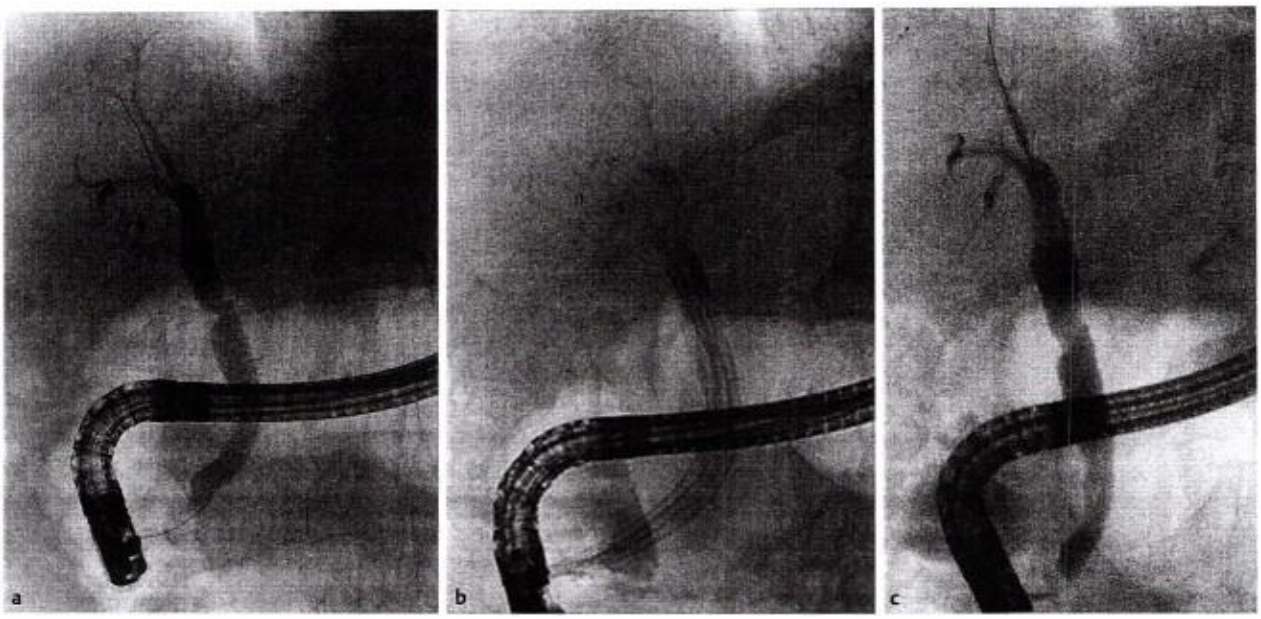
Follow-up

All patients were successively evaluated with close follow-up at our institute, with periodic monitoring of clinical conditions by biochemical testing and imaging (ultrasound/MRCP/ERC) according to our standard post-transplantation protocol. After stent removal, patients were called by our clinical coordinators every 15 days to check on clinical conditions. Liver function tests were recorded immediately after stent removal and every 3 months during the follow-up period. Recurrence of anastomotic stenosis was diagnosed when an increase in the cholestatic indices was associated with imaging test results that were diagnostic for stenosis. After the established diagnosis of relapse by a new real-time cholangiogram, endoscopic re-treatment was defined as clinically indicated.

Outcomes

The primary outcome was resolution of anastomotic stenosis, defined as no or only a minimum waist discerned on cholangiography and easy passage of a 12 mm extraction balloon through the anastomosis, together with the normalization of cholestatic indices maintained for more than 1 month after the last ERC procedure.

Secondary outcomes were recurrence rate and adverse event rate. Recurrence was diagnosed when an increase in the cholestatic indices associated with imaging tests that were diagnostic for stenosis was observed in patients with a minimum follow-up of 6 months, with or without sign of cholangitis. Adverse events included stent migration, cholangitis, fever, abdominal pain, and/or all events clinically related to ongoing endoscopic treatment. In addition, the need for urgent hospital admission for adverse events related to anastomotic stenosis and/or endoscopic treatment was recorded.



► **Fig. 1** Sequential multistenting for anastomotic stricture following orthotopic liver transplantation. **a** Cholangiogram at time zero. **b** Fluoroscopic image after placement of four side-by-side 10 Fr plastic stents across the stricture. **c** Final cholangiogram with resolution of anastomotic stenosis.

Statistical analysis

Continuous variables are summarized as means with standard deviation (SD) or range, as appropriate. Categorical variables are summarized as frequency and percentage. For comparison of qualitative variables, a chi-squared test was done. For comparison of quantitative variables, Student's *t* test was used. Adverse events, success, and recurrence rates were coded as binary data, and reported as percentages and 95 % confidence intervals (CIs). Logistic regression was used to explore associations between success and recurrence with patient demographics (sex and age), type of transplantation, number of biliary anastomoses, time between transplant and detection of complications, number of stents, number of ERC, etc. The Kaplan–Meier method was used to assess recurrence of anastomotic stenosis.

Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA). Differences were considered significant at a *P* value of <0.05 (two-sided).

Results

From May 2012 to May 2018, 395 patients underwent liver transplantation at our institute. After transplantation, 91 patients had a diagnosis of anastomotic stenosis on duct-to-duct anastomosis. Three of these showed a discrepancy of caliber between donor and recipient biliary ducts at the anastomosis that was misdiagnosed as anastomotic stenosis by MRCP, and were therefore excluded from the study. One patient had experienced previous failure of a traditional multistenting protocol, and was also excluded from the analysis. The remaining 87 patients were consecutively included in the study, and treated with our sequential multistenting protocol.

The mean age was 57.2 years (SD 12) and 68 patients (78.2 %) were male. The median time to anastomotic stenosis diagnosis after transplantation was 7 months (IQR 13 months). A total of 59 patients were naive (67.8 %), and 28 patients (32.2 %) had undergone previous treatment with FC-SEMS, which had failed. Patient characteristics are summarized in ► **Table 1**.

The median duration of endotherapy (time from index to final ERC) was 8 months (IQR 4 months). The mean number of ERCs (including index and final ERC) was 4.7 (SD 1.1). The mean number of plastic stents placed was 3.7 (SD 1.0).

Initial stricture resolution was achieved in all 87 patients (100 %). All but one patient (86/87) showed normalization of cholestasis after 1 month from the end of endotherapy treatment (clinical success 98.9 %). The patient with failed resolution was treated with a new FC-SEMS for 6 months, with initial success but early recurrence of the stenosis.

During the treatment period, 7 of 87 patients (8.0 %, 95 %CI 2.3 %–13.8 %) developed a complication that required hospital admission: five cholangitis, one stent migration, and one recurrence of jaundice with increase in cholestatic index (► **Table 2**). The mean follow-up period after anastomotic stenosis resolution was 992.7 days (SD 622.1). During this period, seven recurrences were recorded in the 86 patients with clinical success. The median time to recurrence was 4.0 months (IQR 1.0–10.0) (► **Fig. 2a**).

The results were similar when we analyzed the subgroup of 59 naïve patients (► **Table 2**, ► **Fig. 2b**).

▶ **Table 1** Patient characteristics (n = 87).

Male sex, n (%)	68 (78.2)
Age, mean (SD), years	57.2 (12)
Etiological indication for liver transplantation, n (%)	
• HCC	37 (42.5)
• HCV-related cirrhosis	18 (20.7)
• HBV\HDV-related cirrhosis	4 (4.6)
• Nonalcoholic fatty liver disease	9 (10.3)
• Alcohol-related cirrhosis	4 (4.6)
• Acute hepatitis	6 (6.9)
• Others	9 (10.3)
Time from transplant to anastomotic stenosis diagnosis, median (IQR), months	7 (3 – 16)
Previous endoscopic treatment, %	28 (32.2)

SD, standard deviation; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; HDV, hepatitis D virus; IQR, interquartile range.

Anastomotic stenosis recurrence was treated with the same sequential multistenting approach in six patients, achieving technical and clinical success. In the remaining patient, we decided to place an FC-SEMS as per patient preference, which is still in place.

Logistic regression was used to explore associations between success, recurrence, and adverse events with patient demographics (sex and age), number of biliary anastomoses, time between transplantation and detection of complications, number of stents, and number of ERCs. The only statistically significant association was between the number of ERCs and the adverse event rate: this rate was 4.7 times higher for each additional ERC (odds ratio [OR] 4.7, 95 %CI 1.7 – 13.4). The same association was found in the naïve subgroup analysis (OR 4.9, 95 %CI 1.5 – 16.5).

Discussion

ERC is the gold standard for treatment of duct-to-duct anastomotic stenosis following liver transplantation. Over the past two decades, several approaches have been evaluated, with some differences between them [20]. Anastomotic pneumatic dilation alone, without stent placement, was abandoned because of the low clinical success (40 %) and high rate of anastomotic stenosis recurrence [21].

In a recent systematic review [20], ERC with multiple plastic stents, exchanged every 3 months over a 12-month period, showed high technical and clinical success, with a recurrence rate ranging from 3 % to 37 % over a mean of 6 – 10 months' follow-up, and with the number of ERCs ranging from 3 to 4.5. Several studies have evaluated this endoscopic treatment, and have shown a success rate of approximately 70 % – 80 % in cases of OLT and of about 60 % following LRLT [11].

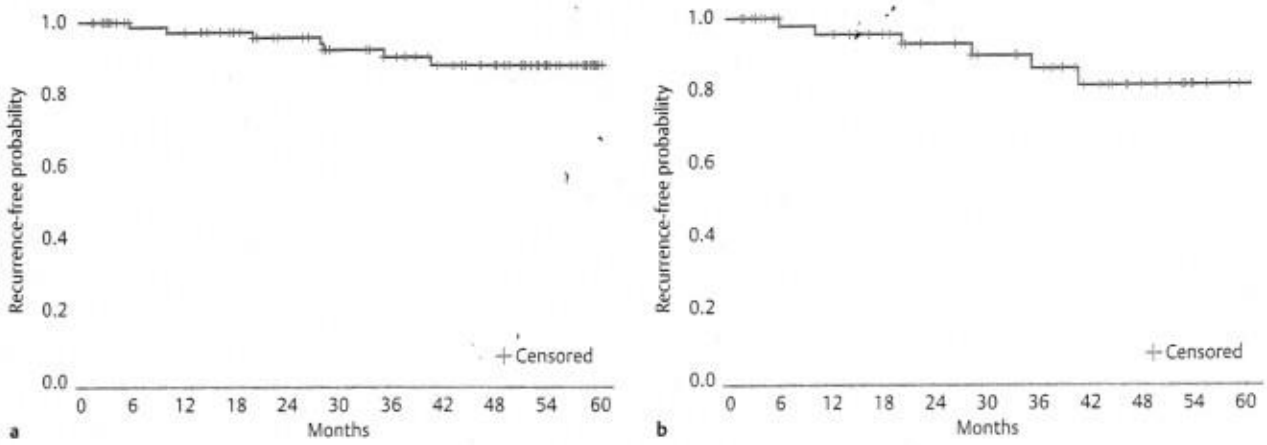
In patients successfully responding to endoscopic therapy, there is still the risk of biliary stricture recurrence. In a study by Alazmi et al. [14], the rate of cholestasis recurrence with evidence of biliary strictures at ERC, after transitory initial success with endoscopic therapy, was approximately 18 %.

To overcome the limitation of repeating ERC every 3 months, several studies have evaluated the efficacy of FC-SEMS placement across the stenosis. Because placement of a single FC-SEMS results in radial dilation of a stricture equivalent to that of at least three side-by-side plastic stents (which cannot generally be placed during the initial ERC), preliminary studies supported the hypothesis that deployment of FC-SEMS would be beneficial in patients with benign strictures. The use of FC-SEMS can reduce the duration of endoscopic treatment, as the stent is placed and then removed after 3 – 6 months, thus requiring only two ERC procedures. Removal of FC-SEMS is usually successful, although the need for a "SEMS-in-SEMS" technique

▶ **Table 2** Results of sequential multistenting for anastomotic stricture following liver transplantation.

Characteristics	Overall (n = 87)	Naïve (n = 59)
ERC, mean (range), n	4.7 (3 – 9)	4.8 (3 – 9)
Biliary plastic stents placed, mean (range), n	3.7 (2 – 6)	3.6 (2 – 6)
Clinical success, n (%)	86 (98.9)	58 (98.3)
Clinical failure, n (%)	1 (1.2)	1 (1.7)
Stent migration, n (%)	13 (14.9)	9 (15.2)
Follow-up, mean (SD), days	992.7 (622.1)	824.0 (588.0)
Recurrence, n (%) [95 %CI]	7 (8.1) [2.4 – 13.9]	6 (10.3) [2.5 – 18.2]
Recurrence time, median (IQR), months	4.0 (1.0 – 10.0)	6.5 (3.0 – 10.0)
Unplanned urgent hospital recovery due to biliary treatment, n (%) [95 %CI]	7 (8.1) [2.3 – 13.8]	5 (8.5) [1.4 – 15.6]

ERCP, endoscopic retrograde cholangiography; SD, standard deviation; CI, confidence interval; IQR, interquartile range.



► **Fig. 2** Kaplan-Meier estimates of anastomotic stenosis recurrence-free survival. **a** Overall population. **b** Naïve population.

has been reported for cases in which removal was challenging [22]. However, there is a higher migration rate with FC-SEMS than with the plastic stents, which affects the overall cost of treatment [20].

Martins at al. recently published a randomized controlled trial of FC-SEMS vs. multistenting technique with multiple stent exchanges in 64 patients with anastomotic stenosis. FC-SEMS were placed for 6 months in 32 patients, and in the multistenting group multiple stent exchanges were done over 12 months in 32 patients. The mean follow-up was 36.4 and 32.9 months, respectively. Clinical success was 83.3% in the FC-SEMS group and 96.5% in the multistenting group ($P=0.19$), but there were significant differences in recurrence rate (32% vs. 0%, respectively; $P<0.01$) and adverse events (23% vs. 6%, respectively; $P<0.01$) [23].

Finally, a study by our group showed higher rates of long-term recurrence with FC-SEMS than with multiple plastic stents [18].

Our present study showed excellent results in terms of clinical success and recurrence rate with the sequential multistenting protocol in a large prospective series of patients with anastomotic stenosis following liver transplantation. Our results show an adverse event rate of 8%; all of these events led to early planning of the ERC session compared with the protocol. These results are in line with published results of the traditional multistenting exchange approach over a very long-term follow-up period (7 years) [24], but with the advantage of a shorter procedure time, less complexity, and fewer stent placements.

These results confirm the findings of Barakat et al., whose retrospective comparative study compared the sequential approach with an incremental dilation and stent exchange approach. The authors described results in 32 patients and 45 patients treated with the two different approaches, respectively. They found similar rates of cholangitis, unplanned stent exchanges, or stent migration in both treatment groups, concluding that the addition of a single new stent during each procedure is sufficient to maintain safe biliary drainage even in this high risk group of immunocompromised patients. The additional protocol required fewer accessory devices, and exposed patients to less radiation [19]. Tabibian et al. achieved similar results, again in a retrospective study of 64 patients with late anastomotic stenosis (>3 months from the transplantation) who were treated with a sequential approach. The authors found anastomotic stenosis resolution in 94% of patients, with a recurrence rate of 3.1% and a mean follow-up of 12 months [25].

Finally, our study represents the first prospective demonstration of the efficacy and safety of the sequential multistenting protocol in a large cohort of patients with anastomotic stenosis following liver transplantation. The limitation of the study is the lack of a comparative group treated with a traditional stent exchange approach. Therefore, before this innovative approach can be accepted and incorporated into clinical practice, randomized studies with a traditional multistenting approach will be needed.

Competing interests

None

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