Article Type: Original Articles

**Handling Associate Editor: Espen Melums**

# Endo-therapies for biliary duct-to-duct anastomotic stricture after liver transplantation: outcomes of a nationwide survey.

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/liv.14010

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Short title: BASALT study

Abbreviations: endoscopic retrograde cholangiopancreatography, ERCP; liver transplanted, LT; self-expandable metal stent, SEMS; post-ERCP pancreatitis, PEP; self-expandable metal stents, SEMS; IQR, inter quartile range.

Conflict of interest: none.

Financial support: none

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ABSTRACT

**Background.** The most appropriate endo-therapeutic approach to biliary anastomotic strictures is yet to be defined.

**Aim.** To retrospectively report on the endo-therapy of duct-to-duct anastomotic strictures during 2013 in Italy.

**Methods.** Data were collected from 16 Endoscopy Units at the Italian Liver Transplantation Centers (BASALT study group).

**Results.** Complete endo-therapy and follow-up data are available for 181 patients: 101 treated with plastic multistenting, 26 with fully covered self-expandable metal stenting (SEMS) and 54 with single stenting. Radiological success was achieved for 145 patients (80%), i.e. 88% of plastic multistenting, 88% of SEMS and 61% of single stenting ($p<0.001$ *vs* plastic multistenting; $p<0.05$ *vs* SEMS)]. After first-line endo-therapy failure, the patients underwent a second-line endo-therapy with plastic multistenting for 25%, fully covered SEMS for 53% and single stenting for 22% of cases, and radiological success was achieved for 84%, i.e. 100%, 85%, and 63% with plastic multistenting, SEMS and single stenting ($p<0.05$ *vs* plastic multistenting or SEMS), respectively. Procedure-related complications occurred in 7.8% of ERCP. Overall clinical success was achieved in 87% of patients after a median follow-up of 25 months.

**Conclusion.** Plastic multistenting is confirmed as the preferred first-line treatment, while fully covered SEMS as rescue option for biliary anastomotic strictures. Single stenting has sub-optimal results and should be abandoned.

**Key words:** Liver transplantation, biliary anastomotic stricture, ERCP, plastic multistenting, fully covered metal stenting.

**Summary**

In the field of biliary anastomotic stricture after liver transplantation, a high rate of success is achieved by endoscopic therapies.

Present data do not support the use of fully covered metal stent as first line treatment.

BACKGROUND

Biliary complications are reported in up to 35% of patients following liver transplantation. The stricture of duct-to-duct anastomosis is the most common complication in such patients (1) leading to liver dysfunction. Endo-therapy is considered the reference standard treatment for this condition due to the possible incidence of only a few major complications (1). While waiting for the release of international guidelines, the type of endo-therapy is center-based, according to local expertise. Across Europe, only a few high-volume tertiary centers have reported data on the follow-up of patients who underwent different endo-therapies (2-4). A larger database would be of great interest in order to better illustrate the types of proposed endo-therapies and the results of these approaches on a wider national basis. With the aim of building a larger team for future guidelines, the BASALT working study group was set up among the active endoscopic units at Liver Transplantation Centers across Italy in 2013. The aims of the present study are to retrospectively analyze the available data on the workload and types of endo-therapies dedicated to the anastomotic stricture of liver transplanted (LT) patients, and to report the medium-term outcome data of this national series.

## MATERIALS AND METHODS

### *Patient selection*

A dedicated electronic datasheet was designed by one Author (P.C.) and then independently reviewed by another two Authors (R.R. and R.P.) to collect the characteristics of secreted LT patients who had undergone endoscopic management in 2013 (i.e. age, sex, ethiology of cirrhosis, time from liver transplantation, first- and second-line treatment types, radiological and clinical outcomes). LT patients managed with non-endoscopic first-line treatments (radiology or surgery) were excluded. All the participants signed the informed consent form. The selection criteria for anastomotic stricture were homogenous among all centers, as recently assessed by a national survey among the same endoscopic units (BASALT study group) working with the Italian Liver Transplantation Centers (5), LT patients were considered for anastomotic stricture treatments in case of any alteration of liver tests persisting within three months and magnetic resonance or Kehr cholangiography being consistent with anastomotic stricture. Severity of the stricture was defined according to international criteria. In brief, severe stricture was defined in case of a reduction of the diameter of the common bile duct by more than 90% at the level of the anastomosis, while mild stricture in case of a reduction by less than 90%.

### *Endoscopic therapy*

Endoscopic retrograde cholangiopancreatographies (ERCPs) of LT patients were planned under deep sedation (i.v. propofol, or general anaesthesia) in most units (75%), with conscious sedation (i.v. midazolam and petidine) performed in the remaining units

(25%). In 14 centres, aminosalicylic acid was used as the preventive medical therapy for hepatic artery thrombosis, and in 10 centers aminosalicylic acid was stopped before the ERCPs of LT patients. Sphincterotomy was performed before any first-line stenting procedure.

The choice of stenting type depended on local expertise and the availability of stents at the time of endo-therapy. When multistenting was applied, 89% of units progressively increased the number of plastic stents at three-month intervals and, as for the remaining units (11%), at the occurrence of obstructive symptoms. At 81% of units, all the stents were removed at every session, whereas in 19% of units only the dysfunctional ones (clogging, partial migration) were removed.

When a metallic stent was considered, a fully covered model was always chosen to secure its easy removal at the end of endo-therapy. Anti-migration systems were not available to all units during 2013 and brand types were varied among the units and not defined by protocol. The maximum number of plastic stents and the diameter of fully covered SEMS were assessed according to the diameters of the native and donor common bile ducts. Balloon dilation was used at the endoscopists' discretion, as assistance to any stenting and to facilitate the increase of multistenting. The treatment duration for multistenting and metal stenting depended on each endoscopists' preference. In the five units using single stenting, the stent was changed by protocol at three-month intervals in two units, and in the other three units when obstructive symptoms were identified. The success of endo-therapy was assessed by radiological criteria in 14 units (88%), including the duct diameter at the anastomotic level being equal to the one below, the rapid flow of contrast medium through the anastomosis and the easy passage of a balloon catheter through the anastomosis. On

the contrary, Rx failure of the endo-therapy was considered. In the remaining two units, radiological criteria were combined with laboratory-clinical criteria (see below). In all of the units, clinical success was achieved in patients in whom there was absence of any new-onset increase of the laboratory markers of cholestasis secondary to anastomotic stricture and in those who did not need a re-treatment after stents removal. The follow-up strategies were different among centers (retrospective design). Timing of imaging tests, lab tests and clinical evaluations were also center-based ranging from three to six-months after LT and every six months thereafter. During follow-up imaging tests, i.e. magnetic resonance cholangiography and abdominal ultrasound, were also planned at the time of any new-onset alteration of liver tests with or without the occurrence of biliary obstructive symptoms. The diagnostic criteria for recurrent anastomotic stricture were the same as for *de-novo* anastomotic stricture. After the stenting period, treatment failure was assessed in case of any new-onset elevation of markers of cholestasis with or without obstructive symptoms associated with anastomotic stricture. After ruling out other possible relevant co-factors (HCV flare, chronic rejection, de novo autoimmunity, hepatic artery thrombosis), re-treatment was planned in such cases.

*Complications*

Peri-procedural complications were reviewed and defined according to the international guidelines (6). Post-ERCP pancreatitis (PEP) was assessed in cases of abdominal

pain of pancreatic origin within 24 hours of the procedure, with serum amylase ≥ 3x of normal value and prolongation of hospitalization; severe pancreatitis in cases of prolonged hospitalization > 10 days (7). Cholangitis was diagnosed in the event of new-onset fever > 38°C within 48 hours of the procedure; relevant bleeding was considered in the event of melena or hematemesis or of a drop in the level of hemoglobin, with need for transfusions or endoscopic hemostasis within ten days from ERCP. While waiting for the European guidelines to be published in 2014 (8), in 2013 the prophylaxis of PEP and sepsis were center-based. In particular, PEP prophylaxis was performed in 10 units and consisted in non-steroidal anti-inflammatory drugs in 7 units (*i.e.* 100 mg suppository indometacin or diclofenac in 5 and 2 units, respectively, with i.v. gabesate mesilate in 2 units and pancreatic stenting in one); while in 6 units, no prophylaxis was systematically applied to LT patients. Finally, antibiotic prophylaxis for preventing sepsis in LT patients was performed in 11 units.

The study was approved by the Ethics Committee of the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan (Italy) and endorsed by the National Committee of the Italian Society of Digestive Endoscopy (SIED). All the Endoscopy Units working with the 19 Liver Transplantation Centers in Italy were officially invited to take part in the survey.

*Statistical analysis*

Data were expressed as median (IQ range) or mean (±SEM). Student's T and Chi square tests were used when appropriate to compare the patients' characteristics among

multistenting, fully covered SEMS and single stenting and to assess any association between the types of endo-therapy and high-volume activity of the Centers, which is defined as >250 ERCPs/year. Kaplan-Meier's survival analysis was done for the clinical outcome of: a) the whole cohort after undergoing both first and second-line treatments, b) the three groups according to the type of endotherapy, separately for the first and second-line treatment. In the latter analysis, patients were considered from the start of treatments. Rx failures and anastomotic stricture recurrences comprised drop-out events.

## RESULTS

### *Participating Endoscopic Units*

Sixteen (84%) out of the 19 units working with Italian Liver Transplantation Centers participated in the study. Eleven of the 16 units (69%) had high-volume workloads. All the endoscopists working at these units were experienced ($\geq$ 1000 ERCPs/life). During 2013, a total of 6654 ERCPs were performed in the 16 units, ranging from 80 to 1133 ERCPs per unit (median 328). Two hundred and sixty LT patients underwent endo-therapy for duct-to-duct anastomotic stricture. In order to treat anastomotic stricture, 524 (7.9%) ERCPs out of a total 6654 (median/center 18; range 7-204) were performed.

*Study LT population*

Complete data on 221 LT patients were received and reviewed by the coordinating center. Among this group of LT patients, 40 (18%) were excluded from the analysis. Of these 40, 20 presented with biliary complications after liver transplantation other than anastomotic stricture; 15 had anastomotic stricture recurrence after a previous treatment with fully covered SEMS prior to 2013 (non-naïve patients); and 4 died during first-line endo-therapy. Patient deaths occurred three months after fully covered stenting and at 3, 7 and 27 months during single stenting first-line treatment, secondary to liver failure in three and to PEP-related sepsis in the fourth case. This last case was included in the complication rate. In one case, the anastomotic stricture was not passed and the patient underwent surgery. The remaining 181 LT patients comprised the study population and their data were appropriately analyzed. Complete endo-therapy and follow-up data were available for all the LT study patients after reminders to participating centers, when required. Thirty-six LT patients were treated at the ISMETT Hospital Palermo, 27 at the Papa Giovanni XXIII Hospital Bergamo, 19 at the Niguarda Ca' Granda Hospital Milan, 13 at the Gemelli Hospital Rome, 12 at the Cardarelli Hospital Naples, 11 at the Borgo Trento Hospital Verona, 10 at the United Hospitals Ancona, 10 at the Molinette Hospital Turin, 9 at the Ca' Granda Maggiore Policlinico Hospital Milan, 7 at the Sant'Agostino Estense Hospital Modena, 7 at the Medical School Hospital Pisa, 6 at the Policlinico Modena, 4 at the INT Hospital Milan, 4 at the Santa Maria della Misericordia Hospital Udine, 4 at the University Hospital Bari and 2 at the Universital Hospital Padua. Characteristics of the study population have been summarized in Table 1.

*First-line treatments*

*Multistenting*

One-hundred and one LT patients (56%) underwent multistenting. A median 4 ERCPs/patient (IQR 3-5) were performed (p<0.0001 *vs* covered SEMS and single stenting) and a median 4 (IQR 3-5) 10-Fr stents were placed as the maximum stenting procedure. The median duration of multistenting therapy was 9 (IQR 6-12) months (p<0.0001 *vs* SEMS). Radiological success was achieved in 89 patients (88%) (p<0.001 *vs* single stenting). Anastomotic stricture recurrence after radiological success was recorded for 10 patients (11%) (p<0.001 *vs* SEMS) after a median of 8 (IQR 4-9) months from the removal of all stents (Table 2). Re-treatment was needed in 22 patients (22%) because of radiological failure (12 patients) or recurrent anastomotic stricture (10 patients) after radiological success.

*Fully covered SEMS*

Twenty-six LT patients (14%) were treated with fully covered SEMS as first-line endo-therapy. A median of 2 ERCPs/patient (IQR 2-3) were performed (p<0.0001 *vs* plastic multistenting). A 10-mm metal stent was used in 24 patients (92%) and 8-mm metal stent was used in the remaining two (8%) patients. The median duration of metal stenting was 5 (IQR 3-6) months. Radiological success was achieved in 23 patients (88%, p<0.05 *vs* SS). Anastomotic stricture recurrence after radiological success was recorded in 11 patients (48%) after a median of 20 (IQR 4-11) months (Table 2). Re-treatment was needed in 14 patients (54%) for Rx failure (3 patients) or anastomotic stricture recurrence (11 patients).

*Single stenting*

Fifty-four LT patients (30%) were treated with single stenting as first-line endo-therapy. At the time of the first procedure, a 10 Fr stent has been placed in 87% of single stenting LT patients, a 8.5 Fr and 7 Fr have been placed in 5.5% both, and a 11.5 Fr was used in 2% of cases. A median of 2 ERCPs/patient (IQR 1-3) were performed ($p<0.0001$ *vs* plastic multistenting) and a 10-Fr stent was used as the maximum diameter procedure in 94% of cases. The median duration of single stenting therapy was 4 (IQR 2-12) months. Radiological success was achieved in 33 (61%) patients (*i.e.* $p< 0.001$ *vs* plastic multistenting and $p<0.05$ *vs* SEMS). Anastomotic stricture recurrence after radiological success was recorded in 9 patients (27%) after a median of 9 (IQR 7-12) months. Re-treatment was needed for 30 patients (56%) following Rx failure (21 patients) or anastomotic stricture recurrence (9 patients).

*Second-line treatments*

Overall, re-treatment was required for 65 patients (36%) out of the 181 naïve LT patients. One patient was removed from the study as a result of death unrelated to endo-therapy. Endoscopic treatment was applied to 49 out of the 65 patients requiring re-treatment. Multistenting was performed in 12 patients, *i.e.* 25% of endoscopic re-treatments, after radiological failure (6 patients) or following anastomotic stricture recurrence (6 patients) in 7 plastic multistenting patients; 4 fully covered SEMS patients and 1 single stenting patient of first-line endo-therapies. As second-line treatment, plastic multistenting achieved radiological success in all patients (Table 3). Fully covered metal stenting was performed in 26 patients, i.e. 53% of re-treatments, after Rx failure (10 patients) or following anastomotic

stricture recurrence (16 patients) in 12 plastic multistenting patients, 6 SEMS patients and 8 single stenting patients of first-line endo-therapies. Metal stenting achieved Rx success in 22 (85%) out of the 26 patients treated with SEMS as second-line treatment. Single stenting was applied to 11 patients (in 22% of endoscopic re-treatments), after failure (5 patients) or following anastomotic stricture recurrence (6 patients) in 3 SEMS and 8 single stenting patients of first-line endo-therapies. Single stenting achieved Rx success in 7 cases (63%, $p<0.05$ *vs* plastic multistenting).

Non-endoscopic treatments were proposed in the remaining 16 patients. In this series, surgery was performed in 14 patients (2 plastic multistenting and 12 single stenting patients) after Rx failure (12 patients) and following anastomotic stricture recurrence (2 patients) in 7 units, 5 of which were high-volume ones. Percutaneous drainage was performed in 2 patients, after Rx failure of SEMS in one patient and single stenting in the other patient, respectively.

*Complications*

Complications were recorded following 51 of the 656 (7.8%) ERCPs performed on LT patients who underwent first-line or second-line endo-therapies to treat an anastomotic stricture. Considering the overall rate of complication, no difference between plastic multistenting and SEMS patients was found. PEP occurred after 17 of the 656 (2.6%) procedures, corresponding to 12 PEP episodes out of the 181 (6.6%) ERCPs performed on endoscopy-naïve patients and 5 PEP episodes out of 474 (1.1%) ERCPs performed on endoscopy-non-naïve LT patients ($p<0.0001$). One severe PEP occurred in one non-naïve

patient after a single stenting procedure, followed by sepsis of pancreatic origin leading to death, in spite of nonsteroidal anti-inflammatory prophylaxis.

Cholangitis occurred in 27 out of the 656 (4.1%) ERCPs performed, specifically in 5 cases out of 181 endoscopy-naïve patients and in 22 cases after 474 procedures in endoscopy-non-naïve patients (p=ns). All of these patients were successfully treated with antibiotics.

Relevant bleeding occurred in 6 cases out of the 656 (0.9%) ERCPs performed, specifically in 4 cases (2.2%) after sphincterotomy of naïve procedures and in 2 cases (0.4%) of non-naïve procedures ($p< 0.05$ *vs* naïve). Five of the 6 bleeding patients were not taking aminosalicylic acid therapy, whereas the remaining one was, at the time of the procedure. Thienopyridine platelet inhibitor and anticoagulation were stopped before ERCP in three and one LT patients, respectively and no bleeding, occured in this subgroup.

Migration of metal stents occurred in 5 of the 27 (19%) treatments. In four cases migration occurred during first-line treatment, partial (duodenal) in three and complete in one. Re-treatment was needed in three of such cases. In one LT patient complete migration occurred during second-line treatment and no re-treatment was needed. No intra-biliary migration was recorded. All metal stents which underwent migration were 10 mm-large.

*Clinical outcome and associated factors*

Overall, there was no need for surgery in 168 of the 181 (93%) LT patients with anastomotic stricture at a median of 25 months (IQR 15-34) following the end of endo-therapies (both first and second-line). In terms of intention-to-treat analysis, clinical success was achieved in 91%, 89% and 84% of the whole cohort at 12, 24 and 36 months of follow-up, respectively

(Fig.1). When assessing first-line endo-therapies separately, at 12 months of follow-up clinical success was achieved for 94% of patients after multistenting, 88% after fully covered SEMS and 70% after single stenting ($p<0.05$ *vs* multistenting and SEMS); at 24 months of follow-up clinical success was achieved in 82%, 65% and 59% of patients; and at 36 months in 77%, 54% and 48%, respectively (Fig.2). When second-line endo-therapies have been assessed, clinical success was achieved at 12 months of follow-up for 92%, 100% and 100%, and at 24 months for 92%, 100% and 73% ($p<0.05$ *vs* multistenting) for multistenting, SEMS and single stenting patients, respectively (Fig.3). It is worth noting that fully covered SEMS performed better as second-line rather than first-line treatment, i.e. 100% vs 88% at 12 months and 100% vs 65% ($p<0.05$) at 24 months, respectively. Alkaline phosphatase was $371 \pm 32$ before treatment, $220 \pm 29$ at the end of treatment ($p<0.0001$ vs pre) and $175 \pm 26$ at the end of the follow-up ($p<0.0001$ vs pre).

Regarding the characteristics of LT patients or the types of endo-therapies used, only the maximum number of stents during multistenting was associated with a higher rate of clinical success at 22 months, i.e. 91% (40 out of 44 patients) in the non-maximal (<3) stent group *vs* 100% (55 out of 55 patients) in the maximal ($\geq 4$) stent group ($p<0.05$). Severity of the stricture was not associated to type of treatment applied, radiological or clinical success.

## DISCUSSION

Today endoscopic therapies (1, 9) are the first-line treatment option for biliary complications after liver transplantation, however randomized trials comparing radiologic or surgical therapy *vs* endo-therapy are not yet available in this area. This point is firmly

confirmed by our national survey. The endo-therapies carried out, in fact, avoided surgery or percutaneous drainage for more than 90% of LT patients of the present study. The most appropriate endoscopic treatment of anastomotic stricture is far from being established and standardized. Traditionally, the progressive increase of the number of plastic stents to insert is proposed in order to treat this condition and high success rates have been confirmed in several studies (3, 4). Recently Tringali *et al.* reported clinical success in 98% of 51 LT patients at 5.8 years after multistenting as first- and second-line treatment, with a median of 4 large bore stents at the time of maximal dilation (4). The drawback of the multistenting approach is consistent with the need for several treatment sessions, which impacts on the number of hospitalizations, patients' compliance and, ultimately, on costs. More recently, fully covered metal stents have been approved for the treatment of benign strictures, with the certification of safe removal within 12 months for most of them (10). The rapid use of self-expandable stents with a progressive maximal diameter of 8 mm or 10 mm within 48 hours would potentially be more attractive than multistenting with regard to reducing the number of endoscopic procedures (insertion and removal sessions), hospitalizations, overall treatment duration, thus leading to a reduction of overall costs.

Randomized controlled trials comparing fully covered SEMS and plastic multistenting are few and numerically weak (11, 12). Kaffes *et al.* (11) prospectively treated 20 patients randomized to either treatment with a 80% clinical success after multistenting and 100% success after a short fully covered SEMS suspended into the common bile duct across the choledocho-choledocal stricture at 26 months of follow-up. Tal *et al*. (12) coordinated a multi-center prospective trial involving 5 European academic referral centers. In this study, 48 LT patients were randomized for traditional multistenting (24 patients) or fully covered

(24 patients). Short-term clinical success was achieved in 96% and 100% of cases, respectively, after multistenting or after fully covered SEMS of different models, both at the endoscopists' discretion. At a median of 17 months, re-treatment was needed in 10 patients after multistenting (5 patients) or after SEMS (5 patients). Contrary to this, a large case series focusing on the long-term follow-up of 70 LT non-naive patients showed a suboptimal 61% success rate after fully covered SEMS during a longer follow-up period of 4 years (13).

The present study represents the largest nationwide series of LT patients undergoing endo-therapy reported to date. In 2013, in the Italian referral units actively treating biliary complications following liver transplantation, multistenting was the most common first-line approach for anastomotic stricture. Medium-term results have confirmed a high rate of clinical success after multistenting, at best in the case of patients with more than 3 stents placed side-by-side in the view at the time of maximal dilation of the stricture. In such cases, the optimal rate of clinical success was maintained at almost 2 years after the end of multistenting. This treatment with maximal stenting was proposed by 7 of the 16 units in the study period. While anticipating pertinent international guidelines, the enthusiastic use of fully covered SEMS has been recorded in the survey. According to the sparse literature data discussed above, clinical success significantly decreased over time when covered SEMS was applied as a first-line endo-therapy. The hypothesis that large-diameter SEMS may possibly impair the vascular support during the rapid expansion within 48 hours from delivery across a very narrowed stricture, thus leading to an ischemic damage of the biliary wall, has yet to be tested. This condition could be among the factors leading to the sub-optimal clinical results of SEMS compared to multistenting, when proposed as the first-line treatment option. Our data have shown poor and similar results for fully covered and single

plastic stent, when used as first-line treatment, probably because of both the low number of LT patients in whom SEMS have been placed and the high rate of migration of these stents.

On the contrary, SEMS potentially has an optimal performance rate when the anastomotic stricture is not yet expected to be strictly narrowed. The data on the use of covered SEMSs as second-line treatment possibly support this view. A recent systematic review (14) reported better results after multistenting or SEMS, if the duration was at least 12 or 3 months, respectively. In the present survey, the duration of both treatments was appropriately planned in most units.

In order to prevent relevant commercial sponsorship on the study, brand type was not established in the protocol for either plastic or metallic stents. All metal stents implanted were fully covered ones in order to secure easy removal within 6 months. The migration of covered metal stents was appropriately named the Achilles's heel of the device (15), leading to its limited efficacy. While anti-migration systems are welcome, they were not available to all units at the time of the study and should be the object of testing in future studies.

At the time of the survey (2013), single stenting was proposed as the first-line treatment with sub-optimal results in 5 of the units working with Liver Transplantation Centers, as expected. With the objectives of improving LT patients' management in the meantime and abandoning the use of single stenting, three meetings have been held every year since 2013. During these meetings, a summary of the running data of the survey was discussed. Moreover, courses focused on the endo-therapies of this condition were delivered in one center.

Balloon dilation alone has previously proved to achieve short-term success in a minority of LT patients. Accordingly, in our series dilation has not been used alone, but only as an aid during stenting or to assist maximal increase of multistenting, at discretion of the endoscopist.

Limitations lie in the retrospective design of the present study and the lack of randomization among endo-therapies, thus leaving questions still unanswered regarding the most appropriate endo-therapy for anastomotic stricture. The retrospective design rules out the chance to define by protocol which selection criteria to apply for endo-therapy and for confirmation of anastomotic stricture, leaving those criteria variable among the centers, thus mirroring everyday practice. In addition, the relevant variability among the units of the number of patients treated secondary to different annual liver transplantation workloads has precluded the opportunity of testing any characteristics of patients or anastomotic strictures against a better selection of LT patients for metallic stent or, alternatively, for traditional multistenting. At present, the choice of endo-therapies remains based on both the center and endoscopists' discretion.

In summary, the present survey supports endo-therapy as the first-line approach for the treatment of anastomotic stricture by means of the overall valuable clinical results achieved, but on the basis of the aforementioned limitations, the present data are not conclusive in terms of defining the most appropriate endo-therapy as first- and second-line treatments. Among the endo-therapies utilised, multistenting has achieved optimal clinical results at medium-term follow-up and covered metal stenting can represent a good option as a second-line treatment. On the contrary, single stenting should be avoided secondary due to sub-optimal results. Randomized studies should be carried out to identify which LT patients

are treated best with the traditional plastic multistenting *vs* metallic stenting as first- and second-line endo-therapies.

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**Figure legends**

Fig.1. Kaplan-Meier's survival analysis of the clinical success rate, including overall endo-therapies for anastomotic stricture. Rx failures and anastomotic stricture recurrences comprised drop-out events.

Fig.2. Kaplan-Meier's survival analysis of the clinical success rate divided according to types of first-line endo-therapies. Rx failures and anastomotic stricture recurrences comprised drop-out events.

Fig.3. Kaplan-Meier's survival analysis of the clinical success rate divided according to types of second-line endo-therapies. Rx failures and anastomotic stricture recurrences comprised drop-out events.

| | Overall (n=181) | PM (n= 101) | CSEMS (n =26) | SS (n=54) | p |
|---|---|---|---|---|---|
| Age, yrs | 59 (52 - 64) | 59 (20 – 76) | 61 (38 – 68) | 60 (25 – 70) | |
| Sex, (M %) | 82 | 83 | 70 | 87 | ns |
| Viral etiology (%) | 77 | 83 | 100 | 67 | ns |
| HCC (%) | 23 | 17 | 50 | 33 | ns |
| Time from OLT, mos | 4 (3 – 9) | 4 (3 – 8) | 8 (1 – 14) | 14 (5 - 41) | ns |

**Table 1. Characteristics of study population.**

OLT: orthotopic liver transplantation; HCC: hepatocellular carcinoma; PM: plastic multistent; CSEMS: covered self-expandable metal stent; SS: single stent.

Data shown as percentage or median (IQ range)

| | PM (n= 101) | CSEMS (n =26) | SS (n=54) | p |
|---|---|---|---|---|
| ERCPs/pt, n | 4 (3 – 5) | 2 (2 – 3)† | 2 (1 –3)† | <0.0001† |
| Tp duration, mos | 9 (6 – 12) | 5 (3 – 6)† | 4 (2 – 12) | <0.0001† |
| Rx Success, n (%) | 89 (88) | 23 (88) | 33 (61)†‡ | <0.001†/<0.05‡ |
| AS recurrence, n (%) | 10 (11) | 11 (48)† | 9 (27)‡ | <0.001†/<0.05‡ |

**Table 2. First line endotherapies**

ERCP: endoscopic retrograde cholangiopancreatography; Rx: radiological; AS: anastomotic stricture; PM: plastic multistent; CSMES: covered self-expandable metal stent; SS: single stent.

Data shown as percentage or median (IQ range)

† vs PM

‡ vs CSEMS

| | PM (n= 12) | CSEMS (n =26) | SS (n=10) | p |
|---|---|---|---|---|
| Tp duration, mos | 9 (7 – 13) | 4 (3 – 6)† | 5 (2 – 13) | <0.001† |
| Rx success, n (%) | 12 (100) | 22 (85) | 6 (60)† | <0.05† |
| AS recurrence, n (%) | 0 (0) | 0 (0) | 0 (0) | ns |

**Table 3. Second line endotherapies**

Rx: radiological; AS: anastomotic stricture; PM: plastic multistent; CSEMS: covered self-expandable metal stent; SS: single stent

† vs PM