Management of Biliary Anastomotic Strictures After Liver Transplantation (BASALT Study): A Nationwide Italian Survey

TO THE EDITOR:

Anastomotic stricture (AS) can occur in 10%-30% of liver transplantation (LT) patients leading to liver dysfunction.[1] Its diagnostic workup does not rely on a standard protocol or any international consensus of experts, thus AS management can considerably differ among centers. This affects the selection of patients after LT for endotherapy and, ultimately, results. Endotherapy is considered the reference standard treatment for AS,[2,3] but approach differs among centers depending on local expertise.

The aim of the present retrospective survey was to report both the volume of endoscopic retrograde cholangiopancreatographies (ERCPs) dedicated to duct-to-duct AS treatment and the extent of variability in the management of AS at the Italian units involved in endotherapy of LT patients.

Abbreviations: AS, anastomotic stricture; BASALT, Biliary Anastomotic Strictures After Liver Transplantation; ERCP, endoscopic retrograde cholangiopancreatography; HCV, hepatitis C virus; LT, liver transplantation; MRC, magnetic resonance cholangiography; PM, plastic multistenting; SEMS, self-expandable metal stent.

Address reprint requests to Paolo Cantù, M.D., Ph.D., Gastroenterology and Endoscopy Unit, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda, Ospedale Maggiore Policlinico, Department of Pathophysiology and Transplantation, Università Degli Studi di Milano, Via F. Sforza 35, 20122 Milan, Italy. Telephone: + 39-02-55036375; FAX: + 39-02-55032140; E-mail: paolo.cantu@policlinico.mi.it

Additional author affiliations are listed in the Supporting Information.

Received July 14, 2016; accepted October 30, 2016.

Additional supporting information may be found in the online version of this article.

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DOI 10.1002/lt.24701

Potential conflict of interest: Nothing to report.

Patients and Methods

A dedicated questionnaire designed by 1 author (P.C.) and then independently reviewed by 4 authors (I.P., M.M., M.T., and R.P.) included 5 sections delineating the annual workload of ERCPs (year 2013), the selection criteria (clinical, biochemical, radiological) for duct-to-duct AS endotherapy, the criteria to confirm the presence of AS, the type of endotherapy, and the AS treatment in case of recurrence.

The study was approved by the ethics committee of the Fondazione Istituto di Ricovero e Cura a Carattere Scientifico 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. All the endoscopy units working with the 21 Italian LT centers were officially invited to take part in the survey. In detail, all endoscopists involved in LT patient endotherapy were asked to fill in the questionnaire with the contribution of hepatologists and surgeons. Questionnaires were coded and blinded for analysis.

Data were expressed as median (range), and a chi-square test was used to assess any association between the use of fully covered self-expandable metal stent (SEMS) and high-volume activity of the centers, defined as $\geq$250 ERCPs/year.

Results

PARTICIPATING CENTERS

Nineteen units (90%) returned the questionnaire. A total of 12 out of 19 (63%) units had high-volume

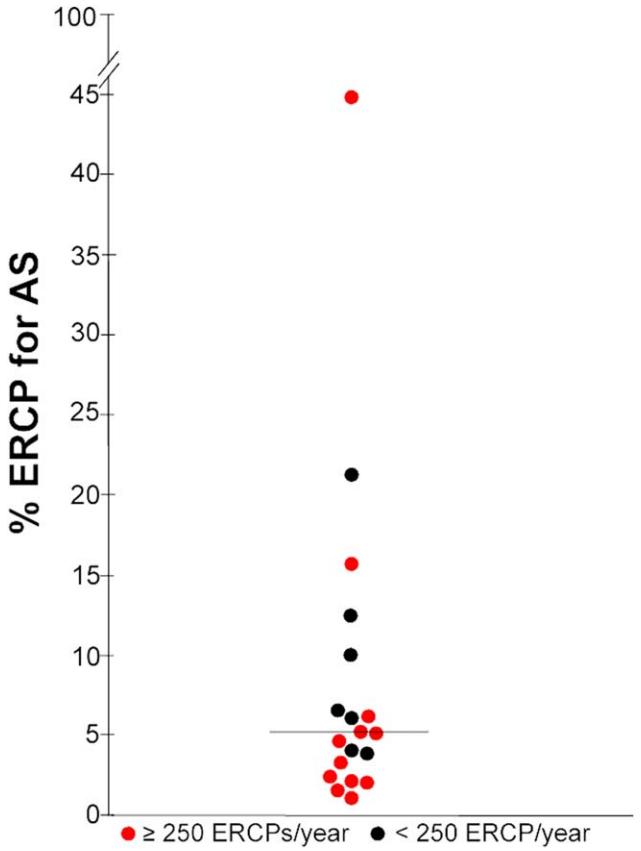

FIG. 1. Percentage of ERCPs dedicated to AS on the overall workload among endoscopic units working with the LT centers in Italy.

activity. During 2013, a total of 7679 ERCPs were performed with unit workload ranging from 80 to 1133 ERCPs (median of 330) and a total of 939 patients undergoing LT at the 19 participant units (Table 1; Fig. 1).

For this study, 248 LT patients underwent endotherapy for duct-to-duct AS with a median of 7 (2-70) patients/unit. In order to treat AS, 560 (7.3%) ERCPs out of a total 7679 (median/center 16; range 5-204) were performed. When faced with unsuccessful ERCP, interventional radiology or surgery was used in 15 (6.0%) and 8 (3.2%) patients, respectively. In 24 LT patients managed in 4 units, interventional radiology was preferred as the first-line treatment.

TABLE 1. Workload of Participating Units in 2013

Characteristic	Value
Overall LT patients	939
LT patients/unit	40 (14-138)
Overall ERCPs	7679
ERCPs/unit	330 (80-1133)
ERCPs in LT patients/unit	25 (5-204)
% of ERCPs for AS, %/unit	5.1 (1.3-44.9)

NOTE: Note data are given as n or median (range).

SELECTION CRITERIA FOR THE ENDOTHERAPY OF BILIARY AS

In most units (16 of 19, 84%), the selection criteria for ERCP included any alteration of liver tests (see below) and AS documented by noninvasive imaging procedures; the remaining 3 units also included the presence of symptoms consistent with biliary obstruction.

Regarding liver tests alkaline phosphatase was used in 37%, bilirubin in 16%, transaminases in 5% of the units; in the remaining 42% any liver test was considered.

A persistent alteration was necessary for endotherapy in 84% of the units and the second evaluation varied from 1 to 6 months after the first one.

In order to diagnose AS, magnetic resonance cholangiography (MRC) or T-tube cholangiography was used in 90% of the units, whereas the diagnostic procedure was limited to ultrasound liver scan in the remaining ones. A progressive dilation of the donor's biliary ducts, a greater diameter of the donor duct compared with the recipient one, and a smaller diameter at the level of the anastomosis were used as markers of the presence of the AS in 42%, 16%, and 11% of the units, respectively. In the remaining ones, no consensus was reached concerning an accurate radiological marker of AS. Pre-endotherapy clinical workup did not include liver biopsy, performed only when necessary (eg, to evaluate post-LT hepatitis C virus [HCV] status). Moreover, histological findings did not influence the decision to proceed to endotherapy.

Criteria for AS confirmation at ERCP included the lack of visualization of native duct during pressure cholangiography (in 11% of the units), the difficult passage of the guidewire above the anastomosis (in 5%), the nil to poor outflow of the contrast medium to the duodenum (in 11%), the difficult passage of the balloon catheter throughout the anastomosis (in 11%), and visible waist on the hydrostatic balloon during inflation (in 11%). In the remaining 51% of the units, no consensus was found around this topic.

In order to define the clinical relevance of the radiologically confirmed AS, a stent trial period was considered useful in 68% of the units. For this purpose, LT patients underwent laboratory and clinical evaluation after a variable period between 2 weeks and 3 months, and the stent trial was considered positive for a clinically relevant AS in case of decrease or normalization

TABLE 2. Stenting for AS

	Units (n = 19)	High-Volume Units (n = 12)
PM only	10 (53)	7 (58)
Covered SEMS or PM	8 (42)	5 (42)
Covered SEMS only	0 (0)	—
Single plastic stent	1 (5)	0 (0)

NOTE: Data are given as n (%).

of liver tests. However, in 2 centers, only a positive stent trial was considered the most relevant criterion needed to select LT patients for endotherapy.

ENDOTHERAPY OF BILIARY AS

AS was treated with only plastic multistenting (PM) in 10 units, with fully covered SEMS or PM in 8, and with single plastic stenting in 1 (Table 2).

In 95% of the units, PM was used; in 53% PM was the only treatment and in 42% PM was used as an alternative to fully covered SEMS. During PM a progressive increase of the number of plastic stents (+1 stent/procedure) was reported in 11 units; maximal stenting from the beginning was proposed in 2 units. Noteworthy, all previous stents were removed in 13 units and the dysfunctional ones only (clogging, partial migration) in the other 4. Hydrostatic balloon dilation of the AS during PM was always used as a per-protocol maneuver in 26% of the units, when needed to increase the number of stents in 63%, and never used in order to avoid damage of the biliary tissue in 11%. PM was planned at 3-month intervals in 89% of the units, at 6-month intervals in 1 center, and at stent dysfunction only in the remaining center. During PM procedures, the long-wire technique to place multiple stents was preferred to the short one in 61% of units. The duration of endotherapy was planned up to radiological resolution of the stricture in 61% (11 units), at least for 1 year in 28% (5 units), and for 3 or 6 months in 11% (1 unit each).

In the 8 centers where fully covered SEMS and PM were both used, the choice of stenting policy was secondary to the degree of the stricture (ie, plastic stent for a tight AS) in 50% of the units, the anatomic features of the AS (ie, plastic stent for angulated AS) in 75%, and the availability of the stents in 25% (multiple answers were accepted for this issue in the questionnaire). The use of covered SEMS was independent of both the overall ERCP workload of the units and the burden of patients after LT with AS. In the units using SEMS, fully covered ones were generally preferred, with flaps in 25%, with a single or double retrieval loop in 50% and 12%, respectively. In half of the units, only 10-mm fully covered SEMS were used, and in the other half, both 8- or 10-mm diameters were used. Only the transpapillary position was used for fully covered SEMS. The removal of SEMS was planned after 3 or 6 months in 3 and 5 of the units, respectively.

The success of endotherapy was assessed by radiological criteria in 89% of the units (n = 17), including the duct diameter at the anastomotic level being equal to the one below it in 47% (n = 9), the rapid flow of contrast medium through the anastomosis in 32% (n = 6), and the easy passage of a balloon catheter through the anastomosis in 11% (n = 2). In 2 centers, only clinical and laboratory findings were used to evaluate endotherapy success after stent removal.

FOLLOW-UP AND MANAGEMENT OF RECURRENT AS

During follow-up, as a first imaging test, MRC was used in 68% of the units (n = 13), abdominal ultrasound in 26% of the units (n = 5), and ERCP in the remaining 6% of the units (n = 1). The diagnostic criteria for recurrent AS were the same as for de novo AS in most units. Recurrent AS was treated endoscopically in 79% of the units (n = 15) and surgically in the other 21% (n = 4). As rescue endotherapy, PM and fully covered SEMS were proposed in 42% (n = 8) and 6% of the centers (n = 1), respectively. Crossing-over endotherapy was proposed in 26% of the units (n = 5), ie, PM if fully covered SEMS failed as first-line treatment or vice versa. The duration of rescue endotherapy was planned up to the time of radiological success in 66% of the units (n = 10) or for at least 1 year in the others.

Discussion

In the field of managing biliary complications after LT, no pertinent guidelines are currently available. As a result, questions around the selection and treatment of biliary-diseased patients after LT arise in daily practice. Accordingly, the present nationwide survey endorsed by the Italian Society of Digestive Endoscopy was conceived to report on the current practice and to build a network of physicians involved in the treatment of this condition.

Despite the high number of questions included in the final version of the survey, the 90% rate of

participation clearly indicates the need of sharing both data and experiences among centers.

As to the annual workload, more than half of the participating units are considered high-volume (ie, ≥ 250 ERCPs/year) ones for biliary endotherapy, and the other 4 units ranged from 200 to 250 ERCPs/year. Among the units a relevant variability in the number of patients after LT treated for anastomotic biliary stricture has been recorded secondary to different annual LT workloads and different criteria for the selection of patients (use of trend of liver tests, stent trial, etc.).

Regarding the selection of patients for endotherapy, the criteria applied were not homogeneous across the units. The trend of liver tests and noninvasive imaging procedures were combined in all the units. Among liver tests, alkaline phosphatase was mostly used, but there was no agreement about both the timing to calculate the trend of liver tests and the cutoff values of variation of such tests along time for decision making. In most units, MRC was considered the appropriate examination to test for the presence of AS after LT. Overall, findings at noninvasive cholangiography associated with persistent alterations of liver tests have the most relevant role for referral of LT patients to ERCP. We feel that there is need of a consensus on a decision-making chart for patients with abnormal liver tests after LT including the appropriate role of liver biopsy. Variability in patient selection and the exclusion of liver biopsy findings from among the factors influencing the decision to resort to endotherapy are likely to have impacted both on the variability and often on the rate of endoscopic intervention and on clinical success of endotherapies in our units. As previously shown, during ERCP, dynamic evaluation can be performed by contrast medium injection under variable pressure and by instrumentation at the level of the anastomosis (ie, the pneumatic balloon passing through without resistance or in the absence of waist during hydrostatic dilation), thus excluding the presence of an anastomotic biliary stricture in up to 50% of cases. No consensus was, however, recorded on this aspect. Moreover, laboratory alterations can be multifactorial in most LT patients, being secondary to HCV status, rejection, hepatic artery thrombosis, de novo autoimmunity, or infections. In order to select patients with a clinically relevant AS among multiple factors leading to liver damage, 2 centers had planned the use of a stent trial, ie, the evaluation of the trend of liver tests after stenting an AS. In the other units, a stent trial was carried out, but subsequent AS management was independent of trial results. Its role in a more accurate selection of LT patients with clinically relevant AS remains to be elucidated.

With regards to endotherapy, the majority of the units performed multistenting to treat AS after LT. Multistenting is the traditional endotherapy and optimal results at the medium term have been reported.[4] Multistenting at 3-month intervals for 1 year at least or until radiological success was the preferred strategy. Again, the policy to remove all previous plastic stents, the progressive increase of the number of stents, and balloon dilation when needed to force stents across the AS were used in most of the units.

The use of SEMS in benign biliary strictures has widely been reported. In the field of AS after LT, the use of these stents can hopefully reduce the number of procedures compared with the multistenting policy thus decreasing the overall treatment cost. A few studies have reported short-term results of SEMS; in most series, patients with benign biliary strictures secondary to various conditions were mixed with those with AS after LT. A relevant rate of dysfunction for covered metal stents, ie, migration and/or secondary strictures, has been reported in up to 20% of cases.[5] At the present, there are no controlled randomized trials comparing the longterm results in the use of covered metal stents with traditional multistenting. In daily practice, the use of a covered metal stent is limited to one-third of the units where they are proposed not as an exclusive, but rather as an alternative therapy to multistenting for some LT patients. Their use is not limited to high-volume units, and in some of them, it was proposed outside controlled studies. Selection for multistenting or fully covered SEMS was based on variable factors, ie, anatomical features or degree of the stricture in most cases and availability of the stent in a minority. We cannot therefore draw conclusions on criteria for SEMS use.

The results of the present survey indicate the common attitude to consider endotherapy as the first-line step to treat anastomotic biliary strictures after LT, even if no randomized controlled series comparing endotherapy and surgery has been approved yet, which is probably due to both the relevant mortality and the severe morbidity rates of the surgical approach. Moreover, the retreatment of recurrent AS was approached by endotherapy in the majority of the centers. Overall, radiology and surgery play a role of rescue therapies[1] independently of the ERCP workload.

The outcome data on LT patients who have undergone ERCP in 2013 are currently being collected from the participating endoscopic units. Hopefully, the

Biliary Anastomotic Strictures After Liver Transplantation (BASALT) survey could represent the starting point of further initiatives on this topic among the participating endoscopic units, such as prospective studies, on one side, and on the other, a platform of experts' consensus on the relevant issues of endotherapy in LT patients.

Acknowledgments: This survey is dedicated to the memory of Gianluca Rotondano, M.D., a brilliant friend of all of us, who prematurely passed away in November 2015.

Paolo Cantù, M.D.
Ilaria Parzanese, M.D.
Valerio Balassone, M.D.
Antonio Di Sario, M.D.
Fiammetta Soggiu, M.D.
Giovanni Lombardi, M.D.
Federico Barbaro, M.D.
Antonio Pisani, M.D.
Anna Baldan, M.D.
Giulio Cariani, M.D.
Valentina Boarino, M.D.
Alberto Fasoli, M.D.
Helga Bertani, M.D.
Edoardo Forti, M.D.
Milutin Bulajic, M.D.
Davide Ghinolfi, M.D.
Elena Nadal, M.D.
Angelo Cerofolini, M.D.
Luca Barresi, M.D.
Giorgia Catalano, M.D.
Italo Stroppa, M.D.
Sara Traini, M.D.
Vincenzo Mazzaferro, M.D.
Livio Cipolletta, M.D.
Andrea Tringali, M.D.
Guido Costamagna, M.D.
Paolo Ravelli, M.D.
Franco Bazzoli, M.D.
Alberto Merighi, M.D.
Maria Caterina Parodi, M.D.
Rita Conigliaro, M.D.
Massimiliano Mutignani, M.D.
Maurizio Zilli, M.D.
Franco Filipponi, M.D.
Alberto Fantin, M.D.
Luca Rodella, M.D.
Ilaria Tarantino, M.D.
Mario Traina, M.D.
Mauro Salizzoni, M.D.
Roberto Rosa, M.D.
Federica Malinverno, M.D.
Federica Invernizzi, M.D.
Matteo Angelo Manini, M.D.
Maria Francesca Donato, M.D.
Massimo Colombo, M.D.
Dario Conte, M.D.
Giorgio Rossi, M.D.
Roberto Penagini, M.D.

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