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ENDOSCOPIC VS SURGICAL TREATMENT OF BILIARY STENOSIS AFTER LIVER TRANSPLANTATION.

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TRATTAMENTO ENDOSCOPICO VS TRATTAMENTO CHIRURGICO DELLE STENOSI BILIARI DOPO TRAPIANTO DI FEGATO.

Abstract

BACKGROUND:

L'anastomosi biliare è spesso considerata come il tallone d'Achille di trapianto di fegato (LT). Anche se l'incidenza è diminuita negli ultimi dieci anni, i pazienti sottoposti a trapianto di fegato sono ancora affetti da complicanze biliari. La gestione diagnostica e terapeutica della stenosi biliare anastomotica (ABS) è controverso. La diagnosi precoce è fondamentale per la sopravvivenza del paziente e del trapianto.

METODI:

Nel nostro studio ci siamo concentrati sul ruolo del trattamento endoscopico e chirurgico nel paziente trapiantato di fegato, nell' Ospedale Universitario Henry Mondor (Creteil, Francia), che aveva sviluppato ABS. I dati che abbiamo raccolto retrospettivamente dai file dei pazienti sono stati: caratteristiche dei pazienti e organi, indicazioni per il trapianto, tipo di intervento, test di funzionalità epatica, risultati di bili-IRM e ERCP e necessità di un intervento chirurgico, con gli esiti correlati. Se una complicazione biliare era sospettato, sulla base dei dati clinici e di laboratorio, una risonanza magnetica o TAC sono state eseguite. Nel nostro centro, per l'ABS il trattamento endoscopico è preferito ad eccezione controindicazioni. Il protocollo di studio contempla di mantenere uno stent metallico completamente coperto per 1 anno, con sostituzione dello stent ogni sei mesi o di emergenza in caso di migrazione o occlusione prima della sostituzione programmata. In caso di fallimento dell'endoscopia, i pazienti sono stati sottoposti a trattamento chirurgico. La sensibilità e la specificità della bili-IRM è stato testato e confrontato con ERCP.

RISULTATI:

Tra il 2010 e il 2015, sono stati eseguiti 465 trapianti di fegato: tra questi, 55 pazienti hanno sviluppato una ABS che necessitava di un trattamento. Le caratteristiche dei pazienti sono state analizzate e confrontate al fine di scoprire i fattori di rischio di sviluppo di ABS. Nella nostra analisi, il genere maschile è associato a tassi significativamente più elevati di complicanze biliari. 42 pazienti di 55 sono stati sottoposti trattamento endoscopico e 26 di questi hanno concluso 1 anno di stenting metallico: Il numero medio di ERCP per paziente è stato 3.77. Nessun complicazione maggiore è stata osservata. 4 pazienti dei rimanenti 16 e 1 dei 26 sono stati operati con buoni risultati. 14 di 26 hanno un follow up minimo di 1 anno (follow-up medio di 24 mesi); solo 1 paziente è stato necessario un ulteriore trattamento 20 mesi dopo la rimozione dello stent. La recidiva della stenosi, messa in evidenza con la bili-IRM di controllo, è fortemente associata alla lunghezza del ABS e alla dilatazione dei dotti biliari intra-epatici. La normalizzazione dei test di funzionalità epatica è influenzato da l'età dell'organo e dal MELD score. Nella nostra serie, la sensibilità e la specificità della bili-IRM nel rilevare stenosi biliare Erano il 95% e il 100% rispettivamente. Per il diametro, la congruenza della misura tra bili-IRM e ERCP era del 84%, meno per gli altri parametri.

CONCLUSIONI:

ERCP per il trattamento di ABS è fattibile e sicura. Risultati positivi a lungo termine sono stati ottenuti in 93% dei casi trattati con endoscopia e 100% dei casi trattati con endoscopia seguita da chirurgia. Tuttavia uno dei cinque pazienti sottoposti ad intervento chirurgico è morto in conseguenza al trattamento. Massimi vantaggi nel trattamento endoscopico sono stati osservati nei pazienti con stenosi di piccola lunghezza e senza dilatazione dei dotti biliari intra epatici. E' ancora necessario lavorare sul corretto albero decisionale terapeutico e sui fattori predittivi di ABS. La bili-IRM è un metodo accurato per esaminare l'albero biliare nei pazienti sottoposti a trapianto con sospetta complicanze biliari.

LE TRAITEMENT ENDOSCOPIQUE ET CHIRURGICAL DES STENSOSE BILIAIRE APRES TRANSPLANTATION DU FOIE.

Abstract

RESUME:

L'anastomose biliaire est souvent considérée comme le talon d'Achille de la transplantation hépatique (LT). Bien que l'incidence ait diminué au cours de la dernière décennie, les patients subissant une transplantation hépatique sont toujours affectés par des complications biliaires. La gestion diagnostique et thérapeutique du rétrécissement biliaire anastomotique (ABS) est controversée. Le diagnostic précoce est crucial pour la survie du patient et du greffon.

MÉTHODES:

Nous avons concentré notre étude sur le rôle du traitement endoscopique et chirurgical chez le patient transplanté du foie, dans l'hôpital universitaire Henry Mondor (Creteil, France), qui avait développé une ABS. Les données que nous avons recueillies rétrospectivement à partir des dossiers des patients étaient: caractéristiques des patients et des organes, indications pour la transplantation, type d'intervention, tests de la fonction hépatique, résultats du MRCP et du CPRE et besoin d'une intervention chirurgicale, avec les résultats correspondants. Si une complication biliaire était suspectée, en fonction de données cliniques et de laboratoire, une résonance magnétique ou une tomodensitométrie ont été effectuées. Dans notre centre, pour l'ABS le traitement endoscopique est préféré, sauf les contre-indications. Le protocole d'étude prévoit de maintenir un stent métallique entièrement recouvert pendant 1 an, avec remplacement du stent tous les six mois ou en urgence en cas de migration ou d'occlusion avant le remplacement prévu. En cas d'échec endoscopique, les patients ont subi un traitement chirurgical. La sensibilité et la spécificité du MRCP ont été testées et comparées avec la CPRE.

RÉSULTATS:

Entre 2010 et 2015, 465 transplantations hépatiques a été faites: parmi elles, 55 patients ont développé un ABS besoin de traitement. Les caractéristiques de ces patients ont été analysées et comparées afin de connaître les facteurs de risque pour le développement d'un ABS. Le sexe masculin est associé de façon significative avec un taux plus élevé de complications biliaires dans notre analyse. 42 de 55 patients ont bénéficié d'un traitement endoscopique et 26 d'entre eux onr conclu 1 an de stenting métallique: le nombre de CPRE par patient moyen était de 3,77. Aucune complication majeure n'a été observée. 4 entre 16 et 1 de 26 autres ont été opérés avec de bons résultats. 14 de 26 ont un suivi minimum de 1 an (la moyenne de suivi est de 24 mois); seulement 1 patient a eu besoin d'autres traitements et a été opéré 20 mois plus tard l'ablation du stent. La récidive de la sténose, mise en évidence par le contrôle MRCP, est fortement associée à la longueur de l'ABS et à la dilatation de la voie biliaire intra-hépatique. La normalisation des tests de la fonction hépatique est influencée par l'âge d'organe et le score MELD. La sensibilité et la spécificité de MRCP dans notre série pour détecter une sténose biliaire étaient de 95% et 100% respectivement. Pour le diamètre, la concordance de la mesure entre MRCP et CPRE était de 84%, moins les autres paramètres.

CONCLUSIONS:

La CPRE pour le traitement de l'ABS est réalisable et sécurisée. Des résultats positifs à long terme ont été obtenus dans 93% des cas traités par endoscopie et 100% des cas traités par endoscopie suivie d'une intervention chirurgicale. Néanmoins, l'un des cinq patients ayant eu une chirurgie est mort en conséquence du traitement. Les plus hauts avantages du traitement endoscopique ont été observés chez les patients ayant une petite taille de sténose et sans dilatation des voies biliaires intra-hépatiques. Il est encore nécessaire de travailler sur l'arbre de décision thérapeutique approprié, y compris les facteurs prédictifs pour l'ABS. Le MRCP est une méthode précise pour examiner l'arbre biliaire chez les patients transplantés avec des complications biliaires présumées.

ENDOSCOPIC VS SURGICAL TREATMENT OF BILIAR STENOSIS AFTER LIVER TRANSPLANTATION.

Abstract

BACKGROUND:

The biliary anastomosis is often considered as the Achilles' heel of liver transplantation (LT). Although the incidence has decreased over the last decade, patients undergoing liver transplantation are still affected by biliary complications. The diagnostic and therapeutic management of the anastomotic biliary stricture (ABS) is controversial. Early diagnosis is crucial for patient and graft survival.

METHODS:

We focused our study on the role of the endoscopic and surgical treatment on liver transplanted patients, at Henry Mondor University Hospital (Creteil, France), who had developed ABS. The data we have retrospectively collected from patients' files were: characteristics of patients and organs, indications for transplantation , type of intervention, liver function tests, MRCP and ERCP results and need of surgery, with related outcomes. If a biliary complication was suspected, based on clinical and laboratory data, a magnetic resonance or CT scan were performed. In our center, for ABS, the endoscopic treatment is preferred unless contraindications . The study protocol contemplate to maintain a fully covered metallic stent for 1 year with replacement of the stent every six months or in emergency in case of migration or occlusion before the planned replacement. In case of endoscopic failure, patients underwent surgical treatment. The sensibility and specificity of MRCP was tested and compared to ERCP.

RESULTS:

Between 2010 and 2015, 465 liver transplantations have been done: among them, 55 patients developed an ABS needing a treatment. The characteristics of those patients were

analyzed and compared in order to find out the risk factors of development an ABS. Male gender is significantly associated with higher rate of biliary complications in our analysis. 42 of 55 patients underwent endoscopic treatment and 26 of them concluded 1 year of metallic stenting: mean number of ERCP per patient was 3.77. No major complications were observed. 4 of the remaining 16 and 1 of 26 were operated with good results. 14 of 26 have a minimum follow up of 1 year (mean follow-up is 24 months); only 1 patient needed other treatment and was operated 20 months after the ablation of the stent. The recurrence of the stenosis, evidenced by the control MRCP, is strongly associated to the length of the ABS and to the dilatation of the intra hepatic bile duct. The normalization of liver function tests is influenced by the organ age and MELD score. The sensitivity and the specificity of MRCP in our series in detecting biliary stenosis were 95% and 100% respectively. For the diameter, the congruence between MRCP and ERCP measurement was of the 84%, less for other parameters.

CONCLUSIONS:

ERCP for treatment of ABS is feasible and safe. Successful long-term results have been obtained in 93% of cases treated by endoscopy and 100% of cases treated by endoscopy followed by surgery. Nevertheless one of the five patients who underwent surgery died consequently to the treatment. Highest advantages in endoscopic treatment were observed in patients with small stenosis length and without dilatation of the Intra hepatic bile ducts. It is still necessary to work on the correct therapeutic decision tree including predictor factors for ABS. MRCP is an accurate method to examine the biliary tree in transplant patients with suspected biliary complications.

ENDOSCOPIC VS SURGICAL TREATMENT OF BILIARY STENOSIS AFTER LIVER TRANSPLANTATION.

Abbreviation: Magnetic Resonance Cholangiopancreatography (MRCP); Endoscopic Retrograde Cholangio-Pancreatography (ERCP); Liver Transplantation (LT); Donation-After-Death Liver Transplantation (DCD-LT); Donation-After-Brain Death Liver Transplantation (DBD-LT); Living Donor Transplantation (LDT); Orthotopic Liver Transplantation (OLT); Anastomotic Biliary Stricture (ABS); Non Anastomotic Stricture (NAS); Hepatic Artery Thrombosis (HAT); Primary Sclerosing Cholangitis (PSC); Fully Covered Self-Expandable Metallic Stent (FCSEMS); Partially Covered Metallic Stent (PSCEMS); Total Bilirubin (Tot-Bil); Direct Bilirubin (Dir-Bil); Alkaline Phosphatase (PAL); Gamma Glutamyltransferase (GGT); Aspartate Aminotransferase (ASAT); Alanine Aminotransferase (ALAT); Roux-en-Y hepatico-jejunostomy (R-Y).

1. Introduction

The biliary anastomosis is often considered as the Achilles' heel of liver transplantation (LT). Although the incidence has decreased over the last decade, patients undergoing liver transplantation are still affected by biliary complications.

The main early complication, occurring within a few weeks after transplantation, is bile leakage. Late complications, which become evident after few months up to years after transplantation, include strictures, stones, intraductal debris or sludge formation, kinking, and ampullary dysfunction [1].The cumulative risk of Anastomotic Biliary Strictures (ABS) after 1, 5, and 10 years was 6.6%, 10.6%, and 12.3% respectively [2]. Early diagnosis is crucial for patient and graft survival, and several attempts have been made to identify the best diagnostic and therapeutic strategy.

In a period of 6 years, from 2010 to 2015, 465 liver transplantation have been carried out at our Centre and 55 developed a biliary stenosis needing treatment. We reviewed charts of those patients including: characteristics of patients and organs, indications, intervention, liver function test, Magnetic resonance cholangiopancreatography (MRCP) and Endoscopic Retrograde Cholangio-Pancreatography (ERCP) results and need of surgery, with related outcomes.

The objective of the present study is to research the causes of development and recurrence after treatment of ABS in our population. Moreover, we focused on indications, feasibility, safety and outcomes of the endoscopic and surgical treatment.

The study protocol contemplates to maintain a fully covered metallic stent for 1 year with replacement of the stent each six months or in emergency in case of migration or occlusion before the planned replacement. As a result, even if the stenosis was well calibrated at 6 months review, it was repositioned, to meet the criteria.

The endoscopic cholangiography and MRCP images have been compared to determinate the sensibility and specificity of MRCP on ABS and to evaluate the differences between the measures calculated with the two techniques.

2. Background

Biliary complications after liver transplantation (LT) occur in 5–34% of cases . The most common complication is anastomotic stricture, accounting for approximately 40% of all biliary complications[3]. Most problems related to biliary strictures can be subdivided into lesions involving the area immediately adjacent to the biliary anastomosis (anastomotic biliary strictures, ABS) and those occurring at extra-anastomotic sites (non-anastomotic strictures NAS)[4]. Other complications include biliary leakage, multiple ischemic strictures, sludge, stones, sphincter of Oddi dysfunction, mucoceles and hemobilia[5].

2.1 Risk factors responsible of ABS occurrence

Many risk factors have been identified in literature as responsible of ABS occurrence. These could be divided in factors depending by the patient, the organ and the surgical techniques. Some of them are worldwide accepted but the debate is still opened for others as we can see in the sequent variety.

<u>Risk factors depending on patient</u>.

Many studies focused on the characteristics of the patient. Some of those evidenced that recipient age[6-8] and smoking behavior are risk factors for ABS[9]. Also ABO blood group incompatibility seems to be associated to biliary complication [10,11]. However, an univariate and multivariate analyses demonstrated that neither recipient's features as MELD score, sex and age, nor donor age, and ABO blood group incompatibility can predict biliary complications[12]

Patients with hepatocellular cancer (HCC) had a 44% decreased risk of development of biliary complications. Although, if the etiology of HCC is viral or toxic, these patients had an increased risk of developing ABSs (p=0.003). Nevertheless chronic HCV infection alone didn't represent a significant risk factor for ABS occurrence[9].

Patients with primary sclerosing cholangitis (PSC) had a 2.8-fold increased risk of developing biliary problems. With the exception of PSC, autoimmune hepatitis and hepatocellular carcinoma, the primary liver disease of the recipients did not seem to affect the development of biliary complications[12].

<u>Risk factors depending on organ</u>.

The type of organ utilized for hepatic transplantation is largely discussed in literature. It depends on the difference between the demand of transplantation and the supply of organs. In reason of that, to increase the numbers of those, the organ can be donated after-death, after-brain death or by a living donor with, of course, different results. The biliary tree seems to be more sensitive to ischemia and ischemic-reperfusion injury than hepatocytes[13]. Donation-after-death liver transplantation (DCD-LT) carries higher complication rates compared to donation-after-brain death liver transplantation (DBD-LT) [14]. Patients who received a DCD graft had a 4.5-fold increased risk of development of a biliary complication[12]. Biliary complications after living donor transplantation (LDT) are more frequent, as their incidence is 28–32% compared to 5–15% after deceased donor LT [5,10,15-17]. However, an univariate and multivariate analyses demonstrated that warm and cold ischemic time can not predict biliary complications[12.]

Risk factors depending on surgical technique.

The surgical treatment is the last, and maybe most important, factor to reduce the incidence of the ABS. The two factors above could not be modified. Conversely, the surgical technique could improve the results of biliary complication. Many factors were studied. Considering the sensibility of biliary tree to the ischemia, time of warm and cold ischemia have been analyzed, with contrasting results. Some studies showed that it could be associated with biliary injury [10,11]. In contrast Albert et al. did not assess cold ischemia time a significant risk factors for ABS occurrence[9].

Operative criteria, such as the size of the bile duct, have been considered risk factors for ABS [6-8]. Technical factors such as, an interrupted rather than a continuous suture and performance of multiple biliary anastomoses, are known to favor the development of biliary complications after LDT [24,25]. Choledochojejunostomy has been associated with biliary problems (odds ratio, 1.5; p=0.05)[12] .In many centres, Duct-to-duct biliary reconstruction is favoured over hepatico-jejunostomy for LDT and DCD-LT to prevent ascending cholangitis and to facilitate endoscopic access to the bile ducts[18].

Take-back surgery, also for non-biliary indication, in the first month after liver transplantation (OR, 1.80; p=0.02)[12], hepatic artery thrombosis and chronic ductopenic rejection [10,19,20]increase the risk of developing ABSs.

2.2 Diagnosis and treatment

Early diagnosis is crucial for patient and graft survival, and several attempts have been made to identify the best diagnostic and therapeutic strategy. Periodical evaluation of liver function tests and, in case of abnormalities, the execution of US and MRCP, could be considered, at this moment, the best diagnostic follow-up. Defining the best therapeutic strategy is more difficult. Over the last 20 years studies have been focused on the endoscopic treatment of biliary complications in transplanted patients with duct-to-duct reconstruction, showing a success rate of 70% to 80% after orthotopic liver transplantation (OLT) and of 60% after LDT. Although not controlled studies are available comparing endoscopic and surgical treatment, ERCP with dilatation and stent placement have gained an increasing role in the management of biliary strictures after liver transplantation. Once the endoscopic approach has failed, surgical treatment with a Roux-en-Y choledocho-jejunostomy is the main alternative treatment [21]. Another possibility is available in rare case of long CBD: the resection of the ABS replaced with a new Duct-to-duct anastomosis. Surgical techniques offer a clear-cut possibility in the management of this problem. However, considerable rates of morbidity and mortality associated with surgical biliary reconstruction have been reported , included the recurrence of biliary stricture[22].

Many modified endoscopic approaches have been suggested for ABS. Time of appearing of stricture or association with a biliary leakage could influence the treatment.

Usually strictures are defined early if occurring within 3 months after LT and late if occurring after 3 months.

<u>Plastic stenting</u>

Thuluvath has found that strictures appearing within 1 year after transplantation have a very good response after 1 or 2 balloon dilatation and stent placement sessions (repeated every 2-3 months). Conversely, anastomotic strictures occurring after 12 months, require longterm stenting, although with an acceptable success rate (close to 70%). Other reports have shown the same success rate for OLT but lower rates for LDT[23-25]. However, in a study conducted by Alazmi et al.[26], the rate of cholestasis recurrence with evidence of biliary strictures at ERCP, after transitory initial success with endoscopic therapy, was around 18%.

Others approaches using endoscopic dilation followed by maximal stent placement (up to 9 plastic stents) were successful. That seems to be dependent on the maximal number of stents placed through the stricture, but the follow-up was less than 1 year in that study[27].

It is still unknown how long the stent should and could be kept in place to avoid recurrences. Trials of long-term stent insertion suggested that prolonged therapy often produced better outcomes [28], with the result that patients managed with subsequent cycles of balloon dilatation and continuous stenting over 12 months have the lowest failure rates reported in the literature[4]. According to studies using plastic stents, a one-year stenting time might be optimal [29,30].

The major factor limiting plastic stent patency is the formation of a bacterial biofilm that leads to do-conjugation of bile acid salts with sludge and stone formation. Efforts to prolong plastic stent patency by changes in stent design or by the administration of ursodesoxycholic acid, aspirin, or antibiotics, have had little impact on patency rates in vivo[27].

Metallic stenting

These are some of the reasons why the treatment of ABS, in the last years, has been done more frequently using metallic stenting. This technique is also associated with reduced duration of the procedure, since the fact that only one stent instead of nine is used.

Despite the procedure being easier, the problem concerning the duration of stenting is still debated. Some authors have suggested minimizing the treatment duration to less than 4 months and reported a success rate of 87% [31]. Some authors found that removal of a stent beyond 6 months could be more challenging due to tissue ingrowth at the uncovered part as well as a proximal migration of the partially covered metallic stent (PSCEMS)[32].

Analyzing this data we have noticed that no study on using a fully covered self-expandable metallic stent (FCSEMS) for 1 year consecutively have been conducted.

2.3 Risk factors responsible of ABS recurrence and overall survival

Independently by the type of endoscopic treatment (balloon dilatation, plastic or metallic stent) and by the stenting duration, the success is often not definitive. Many risk factors have been analysed to correlate to the patient, the characteristics of stenosis and the surgical technique with the recurrence of the stenosis and the overall survival.

Risk factors depending on patient.

Albert J. et all noticed that sex, age, were not identified as predictive for restenosis or overall survival. HCV infection is predominant in patients experiencing ABS recurrence (30% for HCV etiology versus 4% for non-HCV etiology) compared to patients not experiencing recurrence (36% for HCV etiology versus 30% for non-HCV etiology, $p>0.05$). But a competing risk analysis did not identify HCV as a risk factor for restenosis, but has been considered a factor for an increased incidence of death ($p=0.02$, HR55.4)[9].

Risk factors depending on characteristic of the stenosis:

The occurrence of an ABS 6 weeks or more after OLT is a significant predictor of recurrence [$p=0.04$, HR50.235]. The severity of the initial stricture predicted ABS recurrence ($p=0.046$, HR52.78), but it did not influence overall survival. A severe initial stricture (ie, a high-grade stricture versus a medium- or low-grade stricture) was associated with an increased incidence of ABS recurrence. A biliary leakage at the site of the anastomosis and duration of stent therapy were not predictive for restenosis or overall survival [9].

Risk factors depending on surgical technique:

Various risk factors have been identified, such as prolonged cold ischemia time, poor preparation of the donor organ, poor surgical anastomosis technique, insufficient local blood-supply, a history of postoperative bile leak, and bile duct size mismatch [6,9,15,33].

3. Materials &Methods

We performed a systematic and retrospective review of all LT patients that developed an ABS between the 1st January of 2010 and the 31st December of 2015 at Mondor Hospital (Creteil, France). Patients have been identified using computerized searches. Authorization for this research has been given by French National Commission on Liberty and Digital data (Commission Nationale de l'Informatique et des Libertés).

If a biliary complication was suspected, based on clinical and laboratory data, a magnetic resonance or CT scan were performed, after liver graft rejection and hepatic artery thrombosis had been excluded with histopathology and Doppler ultrasonography respectively.

In our center, for ABS, the endoscopic treatment is preferred except contraindications.

Data were retrospectively collected from patients' files: characteristics of patients and organs, indications, intervention, liver function tests , MRCP and ERCP results and need of surgery, with related outcomes.

3.1 Inclusion criteria:

- Patients transplanted, from January 2010 to December 2015, with donation-after-brain death liver transplantation (DBD-LT), Donation-after-death liver transplantation (DCD-LT) or living donor (LDT), that developed a stenosis proved by blood tests and/or MRCP.

- Patients endoscopically treated with fully covered self-expandable metallic stent (FCSEMS), eventually associated to a plastic stent in case of biliary leakage, enrolled in a protocol of 1 year continuous metallic stenting .
- Patients surgically treated, when endoscopic treatment failed.
- At least 1 year of follow-up after the end of the treatment .

3.2 Definitions:

- Normal liver tests: PAL 40-130 UI/L, ALAT <50 UI/L, ASAT <50 UI/L, tot Bili $<21\mu$mol/L, Direct Bili $< 3,4$ μmol/L, GGT < 60 UI/L
- Normalization of liver function test after the treatment: normal total Bilirubin, only one between ALAT, ASAT, PAL, GGT less than two times the normal.
- Biliary stenosis: is defined as an increase in liver function test results with definitive cholangiographic (endoscopic, percutaneous et MRCP) or surgical evidence of an anastomotic stricture.
- Biliary dilatation: common bile-duct (CBD) dilatation was considered when the recipient CBD measured more than 6 mm (+1 mm for every 10 yr above 60 yr of age) or when the donor CBD caliber was greater than the recipient CBD and accompanied by intrahepatic bile-duct dilatation.
- Technical endoscopic success : the ability to obtain a cholangiogram and accomplish stenting with or without previous stricture dilation at ERCP.
- Stricture resolution(SR). Cholangiographic evidence of absence of ABS or absence of dilatation of intra-hepatic bile duct.
- Stricture recurrence(R). cholangiographic evidence of ABS causing bile flow impairment, with or without dilatation of intra-hepatic bile duct.

- Success of the treatment: liver blood chemistry improvement (normalization of direct bilirubin, only one between ALAT,ASAT,PAL,GGT less than two time the normal), with or without Cholangiographic evidence of absence of ABS and absence of subsequent interventional procedures.
- Failure of the treatment: deterioration of one of the liver function test superior to two times the normal, with or without associated cholangiographic evidence of ABS and the need for subsequent interventional procedures.
- Matching between MRCP and ERCP measures: difference not superior to 3mm for each single measure.

3.3 Laboratory Values

Laboratory values were collected 3 times: at the time of presentation of ABS (T0), between three and six months after the end of the treatment (T1)and the last one available, with a maximum of 56 months(T2). Six liver tests were analyzed: serum level of total bilirubin(tot-bili) and direct bilirubin (dir-bili), alkaline phosphatase (PAL), gamma glutamyltransferase (GGT), aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT)

3.4 MRCP

MRCP imaging was performed with 1.5 T MR Unit (AvantoFit, VE11, Siemens, Germany) and 3 T MR Unit (Skyra, VE11, Siemens, Germany) and a body coil. Intera MR scanner using a dedicated phase array coil and a thick-section, breath hold single shot/MRCP-RAD technique (slice thickness 40 mm in the coronal orientation, echo time 800 ms, TR/TE 8000/800 ms, image matrix 300 · 256, FOV 300 · 300 mm). No additional preparation was required. The measurements were done on MRCP images reconstructed from 3D or 2D Biliary MRCP sequence or from coronal T2 FSE weighted images in patients with no MRCP images or when the interpretation of the MRCP was limited by motion artifacts.

The images were retrospectively reviewed and the characterization of the ABS was done at the end of all the procedure, by an experienced radiologist. Its length, diameter, and distance from the biliary convergence, the presence or not of intra hepatic biliary dilatation, the maximal size of the bile duct proximal to the stenosis and the presence of stones were calculated before and after the treatment.

A stricture was identified when there was a significant disproportion in the duct caliber between two segments and there was a dilatation of the proximal segment. In patients with normal difference in caliber between the donor and the recipient bile duct, no stricture has been identified at the anastomosis.

A cutoff of 6mm was used to consider common bile duct dilatation. This value was adjusted to age in patients older than 60 years (+1 mm for every 10 years). The intra hepatic bile ducts were considered dilated if the intra hepatic ducts were identified beyond the second biliary division. The distance of the stenosis from the biliary convergence was measured from the proximal end of the stenosis.

3.5 Endoscopy

All ERCPs were performed under general anesthesia by experienced therapeutic biliary endoscopists after routine administration of antibiotic prophylaxis.

Deep biliary cannulation was attempted by using a sphincterotome (Olympus ® KD-V211M-0725) pre loaded with an hydrophilic guidewire (0.025 inch). After successful cannulation of the bile duct, cholangiography was performed following by biliary sphincterotomy. If the upper part of the stricture did not involve the hilum, the patient was considered suitable for biliary stenting with a FCEMS measuring 60 or 80 mm (Boston Scientific Co., Cook Medical) stricture. Strictures were sometime dilated, using 8 or 10 mm in diameter balloon catheters (Hurricane; Boston Scientific Co.) only if there was impossible to insert directly the stent, due to the importance of the anastomotic narrowing.

With the help of fluoroscopy, the stent was deployed inside the bile duct, covering the narrowed segment. After stent delivery, effective drainage of the radiographic contrast, from both intra hepatic side, was checked before withdrawing the endoscope to avoid selective drainage . The risk of a selective drainage is higher for the stenosis developed close to the bifurcation (< 15mm).

We applied a protocol of stenting of minimum one year with replacement of the stent each six month or in emergency in case of migration or occlusion before the planned replacement.

During the second procedure, a Fogarty biliary balloon (Olympus®) was used to evaluate the percentage of calibration, but a new stent was systematically inserted if the stenting duration was less than one year . After one year, the evaluation of the permeability of the anastomosis was performed after retrieval of the stent. A good calibration of the stenosis was attested by pulling the Fogarty biliary balloon catheter, inflated to 10 mm, without resistance through the anastomosis followed by the spontaneous drainage of the intra-hepatic radiographic contrast, after deflation of the balloon . In case of persistence of a ABS a new stent was inserted for six month more . After eighteen months of calibration if there was a persistence of biliary stenosis patient was referred for surgical biliary reparation.

When ERCP has been performed, the number of sessions was registered, as well as technical details of the procedure: sphincterotomy, dilatation procedures, and stenting. The characterization of the stenosis have been done at the end of the procedures, by the same endoscopist, using the images of cholangiography before and after the placement of the stent. The image of the cholangiography without stent has been used to measure the length of the stenosis and the distance from the confluence of right and left intra-hepatic bile ducts. The one with the stent for the width of the stenosis. The metallic stent needs 48 hours to expand, except to the edges, completely distended at the moment of release in the CBD. The edge of the stent has been considered as a unit in the image (10mm). The width of the stenosis is the rapport between the edge of the stent and the narrowest part of the ABS.

3.6 Surgery

All operations were performed under general anesthesia by experienced pancreatic and hepato-biliary surgeons, after routine administration of antibiotic prophylaxis.

The two main types of intervention, well codified in literature and accepted by most of the equips, were the duct-to-duct biliary reconstruction and the Roux-en-Y hepatico-jejunostomy.

Surgery was performed in case of endoscopic failure for patients with a low surgical risk, in where disease appears to be localised, or in those with duodenal or gastric outlet obstruction.

The duct-to-duct biliary reconstruction was favored in case of long CBD. In this case, some stenosis were associated with a "S" shape of the common bile duct , cause of a "syphon effect". The long common bile duct was resected and a new T-T anastomosis was confectioned.

The Roux-en-Y hepatico-jejunostomy was preferred in the others cases of endoscopic failure.The duct-to-duct anastomosis, done at the time of liver transplantation, was left. The research of the common bile duct was done with the "needle test" and, proximally to the stenosis, a latero-lateral hepatico-jejunostomy was performed.

3.7 Overall survival

Patient survival and need for re-transplantation were evaluated. Causes of death were recorded when linked to the treatment or its complications.

3.8 Risk Factor Analysis

Many possible risk factors possibly associated with biliary stenosis were selected. These included:

- Donor and recipient variables: sex, age, MELD, CMV infection
- Surgical variables: type liver donor, organ type, combined transplantation, age of the organ, cold ischaemia time, time of LT
- Postoperative course variables: months between LT and stenosis development, liver function test at the moment of the stenosis diagnosis, MRCP stenosis length, diameter, distance by the confluence of intra hepatic bile duct, dilatation and size of intra-hepatic bile duct, presence of stones, endoscopic and surgical success and failure, recurrence of stenosis to the MRCP of control, normalization of liver function test.

The possible influence of these variables on the risk of developing ABS and its recurrence after treatment were evaluated as well as the influence on the success of the treatment.

3.9 Statistics

Continuous baseline descriptive variables were expressed as means with standard deviation (SD) and were compared using the t-Student test. Categorical variables were expressed as absolute numbers and proportions. We used the $\chi 2$ statistic for most categorical variables, whereas the Fisher exact test was used for small numbers. Univariate and multivariate conditional logistic regression analyses procedures were used to obtain crude and adjusted odds ratios (ORs) and 95% confidence intervals (95% CI) after controlling simultaneously for potential confounders. P-values less than 0.05 were regarded as statistically significant and those factors associated with mortality with p-value setting at 0.06 or less were included in multivariate analysis using the Cox proportional hazards model. Survival analyses were performed using the Kaplan – Meier method and compared by log-rank test.

A two-sided P value < 0.05 was defined as significant. All analyses were performed using R.

4. Results

Between 2010 and 2015, 465 liver transplantation has been done. The characteristics of patients, organs and of transplantation are summarized in *Table 1*. The first tree reasons of transplantation were HCC 37%, followed by 23% of alcoholic cirrhosis and 6% of HCV cirrhosis.

Table 1: Baseline demographic and clinical characteristics of all patients transplanted.

Patients n=465	
Recipient variables	
Age (years)	53.3 (10) (20;70)
Gender F	118 (25,4%)
Gender M	347 (74,6%)
Age of hepatic transplantation (years)	53.6(11.9) (18.8;70.9)
MELD	19(10.6) (6;40)
Number of transplantations for patient	
Number of patients to the first Hepatic transplantation	410 (88.2%)
Number of patients to the second Hepatic transplantation	50 (10.8%)
Number of patients to the third Hepatic transplantation	5 (1.1%)
Type Liver Donor	
DBD-LT	458 (98.5%)
DCD-LT	1 (0.2%)

Domino	6 (1.3%)
TH-DV	0 (0%)
NA	2
Organ Type	
Total Liver	412 (99.6%)
Right Liver	13 (2.8%)
Right Liver +IV	35 (7.5%)
Left Liver	5 (1.1%)
NA	1
Organ age (years)	55.6 (14;89)
Transplantation Characteristics	
Cold ischemia time	7.6 (2.2) (2;17)
Time of Intervention	7.6(2.3) (2.7;30.8)
Combined Transplantation	
Heart	4 (0.9%)
Kidney	23 (4.9%)
None	438 (94%)
NA	1
	mean (SD) (min;max)

55 (11.8%) patients developed an ABS needing a treatment. The characteristics of those patients were analyzed and compared to the transplanted population without stenosis to evidence the risk factors to develop an ABS. Male gender is statistically significant in the univariate analysis (p=0.016). *Table 2*

Table 2: Univariate analysis of risk factors to develop an ABS

Covariate	Patient without stenosis(N=410)	Patient without stenosis (N=55)	p-value
Recipient variables			
Age TH	53.6 (12.2) (18.8;70.9)	54.1 (9.6) (20.4;69.9)	0.723
Gender F	112 (27.3%)	6 (10.9%)	0.016
Gender M	298 (72.7%)	49 (89.1%)	
CMV infection	69 (16.8%)	5 (9.1%)	0.206
MELD	18.9 (10.5) (6;40)	19.9 (11.4) (6;40)	0.576
Surgical factors			
Cold ischemia time	7.6 (2.2) (2;17)	7.5 (2.2) (3.2;13.7)	0.758
Time for TH	7.6 (2.4) (2.7;30.8)	8 (1.9) (4.3;15)	0.133
Number of transplantations for patient			
1	359 (87.6%)	51 (92.7%)	0.796
2	46 (11.2%)	4 (7.3%)	
3	5 (1.2%)	0 (0%)	
Type Liver Donor:			
SME	405 (98.8%)	53 (96.3%)	0.228
Domino	5 (1.2%)	2 (3.7%)	
Organ Type			
Total Liver	361 (88.%)	51 (92.7%)	0.957
Left Liver	5 (1.2%)	0 (0%)	

Right Liver +IV	32 (7.9%)	3 (5.4%)	
Right Liver	12 (2.9%)	1 (1.9%)	
			mean (SD) (min;max)

42 (76%) patients underwent the endoscopic treatment. mean age of our cohort (of 42 patients) was 53.3 years (20 to 70 years) and 36 patients were men (86%). *Table 3*

Table 3: Characteristics of the population treated by endoscopy.

Patients n=42	
Recipient variables	
Age (years)	53.3 (10) (20;70)
Gender F	6 (14.3%)
Gender M	36 (85.7%)
Age of hepatic transplantation (years)	53.3 (10.2) (20.4;69.9)
MELD	20.2 (11.4) (6;40)
Months between TH and stenosis development	7.4 (10.5) (0;54)
Type Liver Donor	
DBD-LT	40 (100%)
DCD-LT	0 (0%)
Domino	0 (0%)
TH-DV	0 (0%)
NA	2
Organ Type	
Total Liver	36 (90%)
Right Liver	1 (2.5%)

Right Liver +IV	3 (7.5%)
Left Liver	0 (0%)
NA	2
Organ age (years)	54.5 (19.5) (19;89)
Transplantation Characteristics	
Cold ischemia time	7.7 (2.2) (4.1;13.7)
Time of Intervention	7.9 (1.9) (4.5;15)
Combined Transplantation	
Heart	0 (0%)
Kidney	3 (7.3%)
None	38 (92.7%)
NA	1
	mean (SD) (min;max)

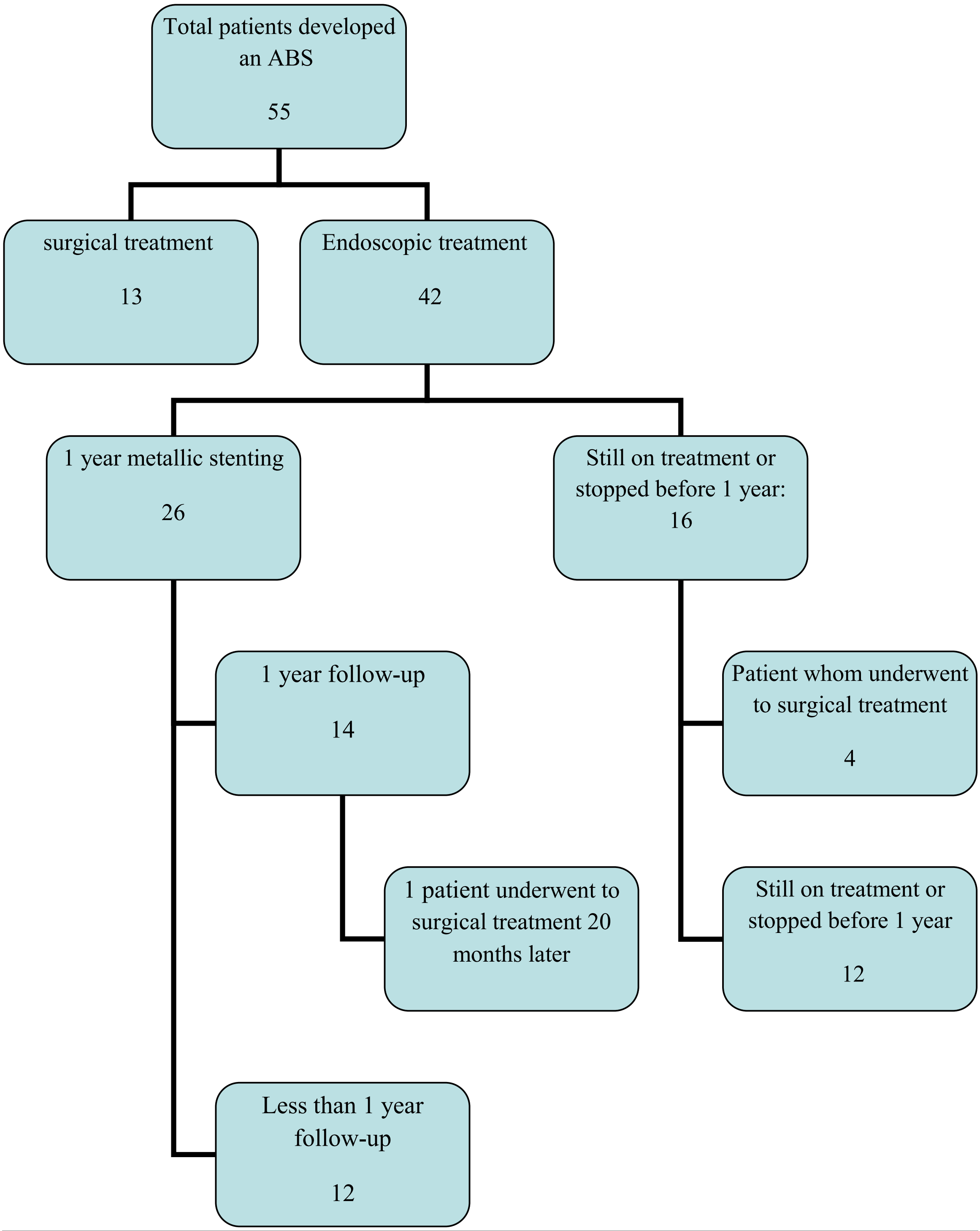
26 (61.9%) of them concluded 1 year of metallic stenting; 1 of those was operated 20 months later for stricture recurrence. In this group, the mean number of ERCP per patient was 3.77, from 2 to 7 exams for a total of 83 exams. 16 (38.1%) are still on treatment or stopped the treatment before 1 year; 4 of those were operated: 2 for many stent migrations, and 2 for a long CBD cause of an "S" shape, that made impossible the stenting in 1 case and a fast stent migration in the other.

The stenosis was discovered medially 7.4 months after the transplantation (0-54 months), and in 22 patients in the first 3 months.

Tree patients died. In the endoscopic group, one for reactivation of the CHC with multiple metastasis and the other committed suicide. The one in the surgical group, consequently to the operation, 3 weeks later the second intervention.

13 (24%) patients directly underwent surgical treatment. Those were not analyzed because not comparable to the population underwent endoscopy. *Figure 1*

Figure 1: analysis of population developing an ABS



All patients with pathologic liver function tests underwent to magnetic resonance cholangiography or CT scan after exclusion of liver graft rejection and of hepatic artery thrombosis, at histopathology and Doppler ultrasonography. ERCP was performed in 40% of the cases (n=17) for an icteric cholestasis (total bilirubin > 21μmol/l). In the rest of patients, the bilirubin was normal, but the others cholestasis exams were pathologic.*Table 4*

<u>Table 4: liver function tests at the time of presentation of ABS (T0) and last one available after the end of the treatment (T2)</u>

Covariate	T0 (N=55)	T2 (N=14)
PAL	329.8 (204.6) (62;1077)	111.4 (84) (20;362)
ALAT	133.4 (133.2) (10;523)	29.6 (29.3) (11;129)
ASAT	84.4 (91) (14;526)	26.2 (10) (17;52)
Total Bilirubin	47 (81.5) (3;362)	8.5 (3.9) (5;16)
Direct Bilirubin	36.8 (66.9) (1;322)	4 (1.8) (2;8)
GGT	588.5 (461.8) (44;1639)	114.2 (121.7) (15;378)
		mean (sd) (min;max)

Among the 118 ERCP, nearly the 97.5% were successful with incannulation of the papilla, good opacification of the Biliary tract, catheterization of the stenosis and release of the stent. Only 2 patients needed a radiologic RVand1 underwent to surgery. 83 ERCP have been done for the 26 patients that concluded the protocol (mean 3.77; 2 to 7). During the procedure 36 ABS and 7 bile leakage were diagnosed and treated. In 4 patients the leakage was associated with the stenosis, in 3 cases the stenosis developed after the treatment of the biliary fistula.

Regarding the type of stents 95 FCSEMS were used, of which 64 in the group of patient that concluded the protocol (mean 2.46) and 13 made of plastic, of which 5 in association with the metallic one.

20 times the stent was glided, 15 in the patients who concluded the protocol (18 % of the ERCP). No complications were registered.

The 26 patients that concluded the protocol of 1 year consecutive metallic stenting had an improvement of liver function test during clinical course. *Table 5* Of these, 14 have a minimum follow up of 1 year. No significantly differences have been noticed between the groups with more or less than 1 year follow up. *Table 6*

Table 5: Characteristics of the population treated by 1 year metallic stenting

Covariate	**Total Patients n=26**
Recipient variables	
Age (years)	53.1 (10.3) (20;70)
Gender F	3 (11.5%)
Gender M	23 (88.5%)
Age of hepatic transplantation (years)	53.4 (10.4)(20.4;69.9)
MELD	19.3 (11) (6;40)
Months between TH and stenosis development	5.8 (10.8) (0;54)
Type Liver Donor	
DBD-LT	26 (100%)
DCD-LT	0 (0%)
Domino	0 (0%)
TH-DV	0 (0%)
Organ Type	
Total Liver	25 (96.2%)
Right Liver	0 (0%)
Right Liver +IV	1 (3.8%)
Left Liver	0 (0%)

Organ age (years)	54.5 (19.5) (19;89)
Cold ischemia time	7.7 (2.2) (4.1;13.7)
Time of Intervention	7.9 (1.9) (4.5;15)
Combined Transplantation	
Heart	0 (0%)
Kidney	3 (7.3%)
None	38 (92.7%)
T0 liver function tests	
PAL	330.1 (226.2) (62;1077)
ALAT	122 (125.7) (20;505)
ASAT	67.3 (58.1) (20;241)
Tot Bili	45.7 (78.5) (3;304)
Dir Bili	34.7 (58.7) (1;220)
GGT	528.7 (446.2) (101;1636)
T0 bili-IRM Characteristics of the stenosis	
Stenosis lenght	11.1 (7.3) (2;27)
Stenosis diameter	0.7 (1.2) (0;5)
Distance of stenosis by the confluence of I.H. bile ducts	24.2 (6.3) (14;35)
Intra-hepatic bile ducts dilatation	0.8 (0.4) (0;1)
Size of left IH bile duct	8 (3.5) (3.7;16)
Size of right IH bile duct	6.3 (2.8) (2.5;12.3)
Size of middle IH bile duct	5 (1.5) (2.8;7.3)

Table 6 :Characteristics of the populations treated by 1 year metallic stenting: groups with more or less than 1 year follow up

Covariate	Patients with 1 year follow-up n=14	Patients without 1 year follow-up n=12	p-value
Recipient variables			
Age (years)	53.3 (9.6) (36;70)	52.8 (11.4) (20;63)	0.915
Gender F	3 (21.4%)	0 (0%)	0.225
Gender M	11 (78.6%)	12 (100%)	0.842
Age of hepatic transplantation (years)	53 (9.7) (35.8;69.9)	53.8 (11.6) (20.4;62.7)	0.862
MELD	17.8 (11.4) (6;40)	21 (10.7) (6;39.8)	0.466
Months between TH and stenosis development	7.4 (14) (0;54)	4 (5.2) (0;15)	0.417
Type Liver Donor			
DBD-LT	14 (100%)	12 (100%)	1
DCD-LT	0 (0%)	0 (0%)	
Domino	0 (0%)	0 (0%)	
TH-DV	0 (0%)	0 (0%)	
Organ Type			
Total Liver	13 (92.9%)	12 (100%)	1
Right Liver	0 (0%)	0 (0%)	
Right Liver +IV	1 (7.1%)	0 (0%)	
Left Liver	0 (0%)	0 (0%)	
Organ age (years)	58.9 (22.1) (23;89)	57.5 (17.2) (19;80)	0.862

Transplantation Characteristics			
Cold ischemia time	7.5 (2.1) (4.1;12.3)	7.5 (2.1) (5.4;12.1)	0.968
Time of Intervention	7.2 (1.5) (4.7;11.1)	8.9 (2.2) (7;15)	0.034
Combined Transplantation			
Heart	0 (0%)	0 (0%)	
Kidney	1 (7.1%)	1 (7.1%)	
None	13 (92.9%)	13 (92.9%)	
T0 liver function tests			
PAL	363.2 (280.6) (67;1077)	291 (141.5) (62;552)	0.426
ALAT	111.2 (125.8) (33;505)	134.7 (130.3) (20;385)	0.658
ASAT	61.8 (55.4) (20;228)	73.8 (63.2) (21;241)	0.628
Tot Bili	59.9 (102.5) (5;304)	28.9 (31.7) (3;108)	0.318
Dir Bili	43.4 (75.2) (3;220)	24.4 (30.4) (1;99)	0.416
GGT	531.6 (434.6) (111;1554)	525.3 (480.9) (101;1636)	0.973
T0 bili-IRM Characteristics of the stenosis			
Stenosis lenght	8.9 (7.2) (3;27)	13.2 (7.1) (2;24)	0.195
Stenosis diameter	0.9 (1.6) (0;5)	0.5 (0.5) (0;1)	0.467
Distance of stenosis by the confluence of I.H. bile ducts	22.3 (6.2) (14;33)	26.1 (6.2) (17;35)	0.187
Intra-hepatic bile ducts dilatation	0.7 (0.5) (0;1)	0.9 (0.3) (0;1)	0.29
Size of left IH bile duct	8.6 (3.2) (3.7;12.6)	7.4 (3.8) (4;16)	0.428
Size of rightIH bile duct	6.2 (3.1) (2.5;11.1)	6.5 (2.6) (3.2;12.3)	0.774
Size of middle IH bile duct	4.9 (1.7) (2.8;7)	5.1 (1.3) (3;7.3)	0.797
			mean (SD) (min;max)

The mean follow-up is 24 months (12 to 58). The normalization of the liver function test is reached in 78.5% (11/14) but an improvement compared to the initial values was achieved in 92.8% (13/14). Ten patients on fourteen performed a control MRCP and a stricture recurrence was shown at in 40% (4/10). The success of the treatment, considered as absence of subsequent interventional procedures, is reached in 13 out of 14 (92.8%). One patient needed other treatment and was operated 20 months after the ablation of the stent.

The characteristics of patients were separately analyzed in function of the recurrence of the stenosis evidenced by the control MRCP, and the normalization of liver function test in order to find possible risk factors. The recurrence of stenosis is strongly linked to the length of the ABS and the dilatation of the intra hepatic bile duct (p= 0.053 and p=0.058 respectively) and lesser with cold ischemia time (p=0.06). The normalization of the liver function test is influenced by the organ age and by MELD score (p=0.003 and p=0.027 respectively). *Table 7-8*

None of the covariates analyzed in univariate analysis is statistically significant in multivariate analysis.

Table 7: Univariate analysis ofrisk factors of recurrence of stenosis based on Bili-IRM results

Bili-IRM n=10 (on 14 patient with 1 year metallic stenting and 1 year of follow up)			
Covariate	**No Stenosis Recurrence (n=6)**	**Stenosis Recurrence (n=4)**	**p-value**
Recipient variables			
Age (years)	57.2 (8) (47;70)	49.8 (10.4) (41;64)	0,279
Gender F	2 (33.3%)	0 (0%)	0,467

Gender M	4 (66.7%)	4 (100%)	
Age of hepatic transplantation (years)	56.5 (8.4) (46.5;69.9)	49.5 (10.6) (41.1;64)	0,311
MELD.	13.6 (10) (6;30.1)	22.7 (14.8) (6;40)	0,335
Months between TH and stenosis development	11.2 (21.1) (1;54)	5.8 (7) (0;16)	0,58
Type Liver Donor			
SME	6 (100%)	4 (100%)	1
Organ Type			
Total Liver	6 (100%)	4 (100%)	1
Organ age (years)	61.7 (20.6) (33;89)	70.5 (20.9) (45;89)	0,532
Transplantation Characteristics			
Cold ischemia time	7.8 (1.5) (5.6;9.6)	6.3 (0.2) (6.1;6.5)	0,06
Time of Intervention	7.8 (1.8) (6.1;11.1)	7 (1.2) (5.9;8.4)	0,442
Combined Transplantation			
None	6 (100%)	4 (100%)	1
T0 liver function tests			
PAL	243.7 (180.3) (67;544)	391.8 (238.9) (132;616)	0,337
ALAT	64.8 (12.1) (52;83)	175.2 (224.1) (33;505)	0,397
ASAT	45.3 (15.6) (20;62)	83.8 (96.4) (28;228)	0,485

Tot Bili	10 (5.1) (5;19)	77.8 (124.9) (12;265)	0,357
Dir Bili	6.5 (5) (3;16)	62 (105.4) (7;220)	0,37
GGT	216.3 (76.9) (111;306)	800.5 (600.6) (292;1554)	0,147
T0 bili-IRM Characteristics of the stenosis			
Stenosis lenght	4 (0.8) (3;5)	8.5 (3) (4;10)	0,053
Stenosis diameter	1.8 (2.4) (0;5)	0.2 (0.5) (0;1)	0,296
Distance of stenosis by the confluence of I.H. bile ducts	23.5 (7.4) (15;33)	24.2 (5.1) (18;30)	0,873
Intra-hepatic bile ducts dilatation	0.2 (0.5) (0;1)	1 (0) (1;1)	0,058
Size of left IH bile duct	6.6 (3.5) (3.7;11.5)	9.2 (2.5) (6;12)	0,267
Size of right IH bile duct	5.2 (3.2) (2.5;9.1)	6.3 (2.8) (4.2;10.4)	0,638
Size of middle IH bile duct	4.2 (2.3) (2.8;6.8)	5.4 (1.4) (3.7;7)	0,467
Stones	0.2 (0.5) (0;1)	0 (0) (0;0)	0,391
			mean (SD) (min;max)

Table 8: Univariate analysis ofrisk factors for absence of normalization of liver function tests

Liver function tests n=13(on 14 patient with 1 year metallic stenting and 1 year of follow up)			
Covariate	**Absence of normalization (n=2)**	**Normalization (n=11)**	**p-value**
Recipient variables			
Age (years)	57.5 (9.2) (51;64)	54.1 (8.8) (41;70)	0,694
Gender F	0 (0%)	3 (27.3%)	1
Gender M	2 (100%)	8 (72.7%)	

Age of hepatic transplantation (years)	57.6 (9) (51.3;64)	53.7 (9) (41.1;69.9)	0,644
MELD.	8 (2.8) (6;9.9)	18.7 (11.7) (6;40)	0,027
Months between TH and stenosis development	0.5 (0.7) (0;1)	8.6 (15.7) (0;54)	0,117
Type Liver Donor			
SME	2 (100%)	11 (100%)	1
Organ Type			
Total Liver	2 (100%)	10 (90.9%)	1
Organ age (years)	83 (4.2) (80;86)	54.5 (22.3) (23;89)	0,003
Transplantation Characteristics			
Cold ischemia time	7 (1.1) (6.2;7.7)	7.4 (2.3) (4.1;12.3)	0,709
Time of Intervention	6.6 (1) (5.9;7.3)	7.2 (1.7) (4.7;11.1)	0,547
Combined Transplantation			
None	2 (100%)	10 (90.9%)	1
T0 Function liver tests			
PAL	495.5 (170.4) (375;616)	348 (310.2) (67;1077)	0,421
ALAT	89.5 (53) (52;127)	119.3 (143) (33;505)	0,634
ASAT	41 (8.5) (35;47)	69 (61.9) (20;228)	0,201
Tot Bili	13 (1.4) (12;14)	74.1 (114.2) (5;304)	0,125
Dir Bili	7.5 (0.7) (7;8)	54 (83.6) (3;220)	0,112
GGT	660 (500.6) (306;1014)	468.5 (447.6) (111;1554)	0,685

T0 bili-IRM Characteristics of the stenosis			
Stenosis lenght	7 (4.2) (4;10)	9 (8.4) (3;27)	0,673
Stenosis diameter	3 (2.8) (1;5)	0.3 (0.8) (0;2)	0,401
Distance of stenosis by the confluence of I.H. bile ducts	27 (4.2) (24;30)	21.6 (6.7) (14;33)	0,27
Intra-hepatic bile ducts dilatation	0.5 (0.7) (0;1)	0.7 (0.5) (0;1)	0,744
Size of left IH bile duct	7.8 (1.6) (6.7;9)	8.6 (3.8) (3.7;12.6)	0,701
Size of rightIH bile duct	6.1 (0.6) (5.7;6.5)	6.4 (3.7) (2.5;11.1)	0,834
Stones	0 (0) (0;0)	0.1 (0.4) (0;1)	0,356
			mean (SD) (min;max)

The surgical treatment.

The surgical treatment was necessary in 5 patients after endoscopic failure: 2 duct-to-duct biliary reconstruction and 3 Roux-en-Y hepatico-jejunostomy (R-Y)had been performed.

The first type of intervention was proposed for a long CBD, cause of an "S" shape.

A Roux-en-Y hepatico-jejunostomy was realized for the 3 early stenosis (mean 4,3 months). In 2 cases were done after many ERCP performed in a few time for continuous stent migration. 1 patient of this group, operated of hepatico-jejunostomy, underwent 6 months later to a left hepatectomy for stenosis of the left intra-hepatic bile duct with repetitive acute cholangitis. The patient died 3 weeks later for post-operative complications aggravated by sepsis. The third underwent surgery for stricture recurrence 20 months after the end of the endoscopic treatment.

3 patients have at least 1 year follow up (mean 19 months), 2 duct to duct reconstructions and 1 R-Y. The liver function tests were normalised in all of them. A MRCP was realised in the patient underwent R-Y reconstruction and the intra hepatic bile ducts were not dilated. No others treatment were necessary in the 2 remaining cases.

Matching between MRCP and ERCP measures.

MRCP was done in 47 of 55 patients after a variable time between 1 and 54 months (mean 8.1 months) after hepatic transplantation.

In 2 patients the measurements could not be done because of artifacts.

MRCP failed to identify the stenosis in 2 patients of 45. There were no false negative cases. The sensitivity and the specificity in our series in detecting biliary stenosis were 95% and 100% respectively.

The evaluation of stenosis length, diameter and distance from biliary convergence were done in 45 patients. In 32 patients the measurements were done on MRCP images, however in the remaining 13 patients were done on Coronal T2 weighted images because the MRCP images were man-made.

Four parameters were compared between MRCP and the ERCP cholangiography: presence of stenosis, the length, the diameter and the distance of the stenosis from the bottom of the hepatic biliary confluence. The measurement have been taken on the first Bili-MRCP and the first ERCP. We defined the measures congruent if the mismatch between the MRCP and ERCP was less than 3 mm. For the diameter the congruence was of the 84% (27/32), with a size overestimated by the ERCP in the 93.75%. The length matched in 50% (16/32), overestimated by the MRCP in the 78.12%. The distance from the confluence matched in 26 %(7/26), overestimated by the ERCP in the 76.92% . *Table 9-10*

Table 9 T0 MRCP parameters analyzed and results in the population underwent to endoscopy

Covariate	
Stenosis lenght	10.4 (6.5) (2;27)
Stenosis diameter	0.6 (1) (0;5)
Distance of stenosis by the confluence of I.H. bile ducts	23.4 (7) (11;37)
Intra-hepatic bile ducts dilatation	85%
Left intra-hepatic bile duct dilatation	82.4%
Right intra-hepatic bile duct dilatation	52.9%
Size of proximal CBD in mm	
6	5.9%
7	11.8%
9	14.7%
10	26.5%
11	8.8%
12	11.8%
13	2.9%
14	8.8%
15	5.9%
16	2.9%
Size of left IH bile duct	7.4 (3) (3.1;16)
Size of rightIH bile duct	6.1 (2.5) (2.5;12.3)
Size of middle IH bile duct	5 (1.3) (2.8;7.3)
Stone	4(11.4%)
	mean (sd) (min;max)

<u>Table 10 T0 ERCP parameters analyzed and results in the population underwent to endoscopy</u>

Covariate	
Stenosis lenght	6.4 (2;20)
Stenosis diameter	3.2 (1;7)
Distance of stenosis by the confluence of I.H. bile ducts	26 (12;45)
Intra-hepatic bile ducts dilatation	31%
Dilatation of proximal extra-hepatic CBD	40.5%
	mean (min;max)

5. Discussion

Here we report the longest continuous full covered metallic stenting treatment for ABS series in the literature[34]with minimum follow-up of 12 months, to evaluate the long terms outcome and the usefulness of surgery in case of endoscopic failure. The benefit and outcome of the endoscopic treatment are reported. We show that this procedure is feasible, safe and the rate of technical endoscopic success is really high. Furthermore, we investigated how patient's characteristics, type of organ, surgical technique and diagnostic path could influence the success of the treatment and the overall survival.

The ERCP joined the diagnostic with therapeutic side, evaluating the type and the characteristic of lesion. Moreover, it provide the possibility to adapt the treatment with balloon, plastic and metallic stent. The advantages of the endoscopic procedure is strictly linked to the morbidity, mortality and the rate of success of this procedure compared to the other possible treatment: the surgery. Sutcliffe et all. evidenced that, after hepatico-jejunostomy, a normal graft function in 8/44 patients (18%), improved in 16/44 (36%), but remained abnormal in 20/44 (45%)[35]really far from the result of the endoscopic treatment.

As far as we know, our study is among the largest cohort series of patient treated with fully covered metallic stent (Kahaleh et al. 34pt, Tarantino et al. 39pt)and the one with the longest period of continuous stenting (Poley et al. 5.5 months) and follow-up (Tarantino et al. 22.1 months group treated with self-expandable metal stent insertion after treatment failure of conventional plastic stent insertion)[34]. Although the number of ERCP for patient is lightly higher, because of replacement of the stent after 6 months, the outcome, considered as absence of subsequent interventional procedures, is really encouraging.

Among the risk factors evaluated for the occurrence of ABS, only the sex appears to be significantly different in two cohorts of patients . For sure, in the last 15 years, the knowledge about the risk factors depending on organ, patient and surgery technical factors has improved. That could have reduced the impact of them on the development of the stenosis.

In our series, as reported in literature, most of the frequent factors considered cause of ABS in the past, such as: type of organ, warm and cold ischemic time, are actually not associated with higher risk of developing a stenosis[12] .

The analysis of the risk factors of recurrence is also interesting. In our center there is an easy access to MRCP to diagnose and to follow-up the patient after the end of the treatment. The comparison of the measurements confirmed the importance of length of the stenosis and the dilatation of intra hepatic bile duct, so the severity of the initial stricture, is still predictive of ABS recurrence[9]. In particular we have noticed that when the stenosis is longer, the risk of recurrence is higher. As expected, the normalization of the liver function tests, occurred more frequently in case of younger liver.

In case of recurrence of the stenosis, surgical treatment is often considered as the definitive and lasting operative therapeutic option. When it has been realised after endoscopy the result is good but it is still burdened by important comorbidity if compared to endoscopy. Davidson et all. noticed that the complication rate post-CDJ was minor in those who underwent a failed nonsurgical approach than those proceeding straight to surgery and analysing our series we evidenced the same[36]. About the type of operation in literature the Biliary-enteric anastomosis is preferred. In our series the duct-to-duct biliary reconstruction was favored in case of long CBD. In this case, some stenosis were associated to a "S" shape of the common bile duct , cause of a "syphon effect". This type of stenosis contraindicates the endoscopy as it implies technical difficulties and, also in case of resolution of the stenosis, the "syphon effect" could be the cause of the final failure of the treatment. When the operation is realized many months after the transplantation, the vascularization is considered good and adapted to support a new anastomosis. However the dissection of the hepatic hilum is laborious and the risk to damage the hepatic artery is important. Biliary-enteric anastomosis is a safe, effective, therapy for biliary strictures. The duct-to-duct anastomosis, done at the time of liver transplantation, is left. That reduces the risks of an important dissection of the hepatic hilum. The research of the common bile duct is done with the "needle test" and, proximally to the stenosis, a latero-lateral anastomosis is performed. That improves vascularization. This anastomosis saves the anatomic way to access the BD for an endoscopic second look, if necessary, and part of the bile could still pass thought the stenosis.

In our series both intervention were realized and with similar results. The patient died due to a complication of the second operation, a left hepatectomy, not the Roux-en-Y hepatico-jejunostomy.

In our study, MRCP demonstrates a high sensitivity and specificity (95% and 100% respectively) in identifying biliary stenosis. The sensitivity and specificity found in literature confirms our experience. For L. H. Katzb et al. of the MRCP sensitivity and specificity is respectively 94.4% and 88.9%, PPV and PPN values, 94.4% and 89.9%, respectively. MRCP correctly diagnosed all anastomotic strictures with a sensitivity of 100%[37]. Beltra´n et al. evaluated the diagnostic accuracy of MRCP after T-tube removal in liver transplant recipients with late biliary complications. The sensitivity in that study was 93%, and specificity, 97.6%, with a PPV of 96.3% and NPV, 95.2%; the global diagnostic accuracy was 95.6% [38].

MRCP is also an accurate method for measuring the length of the stenosis, the diameter and the distance from the biliary convergence with results comparable with ERCP. The tendency of the MRCP to slightly overestimate the length of the stenosis and underestimate its distance from the biliary convergence, when compared to ERCP, can be explained by the fact that MRCP presents an imaging of the biliary tree in its physiologic state owing to the inherent contrast provided by the bile. Otherwise, in ERCP the biliary tree is imaged by direct injection of contrast material that increases the interior pressure. Furthermore, in our study, the measurement of the stenosis diameter by ERCP was done after deploying the prosthesis in cases treated endoscopically, adding an average of 2 mm to the stenosis diameter.

In addition MRCP can evaluate the whole biliary tree giving information if there are either bile dilatation, biloma, endoluminal debris or calculi, bile ducts irregularity (could suggest ischemia or recurrent PSC in some cases) but also can evaluate the liver and the surrounding structures.

The limitations of MRCP are its low spatial resolution, the presence of motion artefacts degrading the images and the presence of ascites or collections (including biloma) in the liver hilum degrading the images. When MRCP images cannot be analysed or acquired, analysis of coronal T2 weighted imaged may be of value.

Our study has several limitations. This is a retrospective study with potential recall bias. The numbers of patient enrolled is still limited, and is really difficult to compare this population with others centers. We noticed that no differences are evidenced between the two populations with more or less than 1 year follow up. This observation allowed us to think that the results, at the end of the follow up, will be comparable. Despite the follow up is quite long, that is not enough to consider the expectancy of life of this patient. It is necessary to compare our protocol, of 1 year consecutive stenting with others. The decision to operate on the patient, that could be evident in certain cases, is difficult to take in patients already stented and with late recurrence where, probably, a new endoscopic treatment could be proposed. This decision tree has to consider the risk factors of re-stenosis after endoscopic treatment. It is evident the importance to define these risk factors to create a decision chart with pre-established criteria from which the cases were selected for surgery. At the moment we cannot rule out this bias in medical decision. No significant changing in clinical management and process for surgery decision have been evidenced.

6. Conclusion

Our aim was to describe the complete treatment of anastomotic strictures, and to evaluate long-term outcomes, at least 1 year, for patients who underwent 1 year continuous FCSEMS. Successful long-term results have been obtained in 93% of cases treated by endoscopy and 100% of cases treated by endoscopy followed by surgery. However one of the five patients underwent surgery died after the treatment. Highest advantages in endoscopic treatment were observed in patients with small stenosis length and without dilatation of the Intra hepatic bile ducts. It is still necessary to work on the correct therapeutic decision tree including predictor factors as found in our study for evaluating risk benefit of the procedure. The MRCP is an accurate method of imaging the biliary tree in transplanted patients with suspected biliary complications. It should be the imaging modality of choice reserving direct cholangiography for therapeutic procedures. The ERCP cholangiography and MRCP are comparable for the diagnosis of stenosis but the possibility to match the measurements still needs to be studied in depth.

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