Biliary Stent Therapy for Dominant Strictures in Patients Affected by Primary Sclerosing Cholangitis

Bassam Abu-Wasel^a Valerie Keough^b Paul D. Renfrew^c Michele Molinari^a

Departments of ^aSurgery and ^bRadiology, Dalhousie University, Queen Elizabeth II Health Science Center, Halifax, N.S., and ^cDepartment of Surgery, Dalhousie University, The Moncton Hospital, Moncton, N.B., Canada

Key Words

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Abstract

The diagnosis and the treatment of dominant strictures (DS) in patients with primary sclerosing cholangitis (PSC) is challenging and the scientific literature on the subject is quite limited. Only level II and level III evidence is available to guide physicians managing patients with DS and PSC. For the diagnosis, intraductal endoscopic ultrasound is the most sensitive (64%) and specific (95%) test. However, the majority of cases require a combination of several different diagnostic tests, as there is no single investigation that can rule out malignancy in this group of patients. For the treatment, serial endoscopic or percutaneous dilatations provide 1- and 3-year biliary duct patency in 80 and 60% of patients, respectively. Dilatation and stenting are the most common interventions, although the optimal duration of treatment has still not been clearly defined. Bile duct resection and/or bilioenteric bypass are currently indicated only for patients with preserved liver function. For all other patients, benign DS can be treated with endoscopic dilatation with short-term stenting. This approach is effective and safe and does not increase the risk of malignant transformation or compli-

cations for liver transplant candidates. During the last decade, the use of self-expandable metallic stents for benign diseases has become an innovative option. The aim of this article is to review the diagnostic and therapeutic strategies for patients affected by PSC and DS with specific emphasis on the outcomes of patients treated with temporary stents.

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Introduction

Primary sclerosing cholangitis (PSC) is a progressive cholestatic disease with an unpredictable clinical course. Patients can present with fluctuations in serum bilirubin and alkaline phosphatase and periods of cholestasis followed by remissions. Symptoms such as itching, right-upper-quadrant abdominal pain, nausea and generalized weakness can appear over long period of time and sometimes resolve spontaneously. Histologically, PSC manifests with patchy inflammatory infiltrates and fibrosis causing strictures of both the intrahepatic and extrahepatic bile ducts [1]. The hypothesis that PSC is an autoimmune disease is supported by the fact that infiltrates of T lymphocytes are found in the areas of severe inflammation [2, 3]. In western countries, the prevalence of PSC is 20.9 per 100,000 men and 6.3 per 100,000 women [4]

while the incidence is 0.9–1.3 per 100,000 individuals per year [5, 6].

Except for liver transplantation (OLT), no other therapy is able to prolong the survival of PSC patients [7]. Ursodeoxycholic acid [8–11], corticosteroids [12–14], endoscopic or percutaneous dilations of biliary strictures [15, 16] and surgical resection of isolated extrahepatic stenosis [17–19] have all been used to palliate patients with symptomatic PSC, but they do not alter the natural history of the disease.

A localized high-grade stenosis at the time of presentation is the most prominent feature in 15–20% of patients [20, 21]. These dominant strictures (DS) can be located in the intrahepatic ducts but, more frequently, they involve the extrahepatic biliary tree. The exclusion of a malignant stricture is mandatory [22] as the prognosis and the treatment of malignant strictures are quite different from benign strictures. The radiological characteristics of benign DS unfortunately mimic cholangiocarcinomas (CC) and a differential diagnosis is still quite difficult, despite all the recent improvements in modern imaging tests. There is very limited literature on the best diagnostic and treatment modalities for PSC patients with DS [23]. An evidence-based synthesis on the diagnostic and therapeutic options of DS in patients affected by PSC is the main aim of this review, with particular attention being paid to the different stents available for the palliative care of this challenging group of patients.

Diagnosis of PSC

PSC is a chronic and progressive disease of the biliary ducts. Diagnosis of PSC can be obtained by (1) liver biopsy or (2) the identification of typical cholangiographic findings with the concomitant presence of characteristic biochemical abnormalities in the absence of secondary causes of sclerosing cholangitis such as mechanical obstruction or vascular insufficiency [24].

Diagnosis of DS

Functionally, DS are defined as discrete stenoses of the common bile duct (CBD) or the common hepatic duct (CHD) preventing the normal flow of bile into the duodenum [25, 26].

Anatomically, DS are defined as: (1) strictures of the CBD measuring <1.5 mm in diameter or (2) strictures of the CHD with a diameter <1.0 mm within 2 cm from the

Fig. 1. Graphical representation of the intrahepatic and extrahepatic biliary system. DS are defined as stenosis with a diameter smaller or equal to 1.5 mm affecting the CBD and/or stenosis of the CHD with a diameter smaller or equal to 1.0 mm. The CHD is the biliary tract distal to the bifurcation of the right and left biliary systems and proximal to the cystic duct junction.

bifurcation at the hilum [27, 28]. A schematic representation of the anatomical abnormalities of DS is reported in figure 1.

DS of the extrahepatic bile ducts are observed in 10–20% of patients with PSC [27–30]. Diagnostic modalities commonly used to detect DS in these settings are ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), percutaneous transhepatic cholangiography (PTC), endoscopic studies such as endoscopic retrograde cholangiography (ERC) and cholangioscopy in addition to liver function tests, serum tumor markers (e.g. CA 19-9), cytological and bioptic investigations.

At the time of presentation, approximately 75% of DS are benign, whereas 25% are malignant [31] and PSC is the most common risk factor for CC in western countries [32, 33]. Clinical findings suspicious for malignant transformation are: rapid clinical and biochemical deterioration of liver function tests and the presence of worsening jaundice, pruritus, weight loss, marked proximal ductal dilation with distal bile duct tapering and elevated serum levels of CA 19-9 (>100 U/ml) [34, 35].

Symptoms

At the early stage, DS are usually asymptomatic. As the disease progresses, DS often present with an acute exacerbation of jaundice, deterioration of liver function tests

Table 1. Summary of laboratory tests used to discriminate between benign versus malignant DS in patients with PSC

First author [reference] (year)	Number of patients	Diagnostic test	Sensitivity	Specificity	Accuracy	PPV	NPV
Levy [91] (2008)	36	Serum CA 19-9 ≥ 100 ng/ml in patients with PSC	14%	95%	61%	67%	60%
Nakeeb [92] (1996)	34	Bile CEA >30 ng/ml in all patients with DS	72%	84%	n.a.	72%	84%
Levy [91] (2008)	36	Brushings in patients with PSC	29%	100%	71%	100%	67%
Levy [91] (2008)	86	Endoscopic luminal biopsy for all patients with DS	29%	100%	71%	100%	67%
Levy [91] (2008)	36	FISH in patients with PSC	64%	70%	68%	60%	74%
Levy [91] (2008)	36	DIA inpatients with PSC	21%	95%	65%	75%	63%

CEA = Carcinoembryonic antigen; DIA = digital image analysis; n.a. = not applicable; NPV = negative predictive value; PPV = positive predictive value.

and/or cholangitis [33, 35]. In a prospective study, enteric bacteria were detected in the bile of 40% of patients affected by symptomatic DS [36]. Despite in vitro susceptibility, antibiotic treatment was not effective in eradicating bacteria from the bile system, and it has been hypothesized that the state of chronic infection might contribute to the progression of the disease [37].

Diagnostic Modalities

Differentiation between malignant and benign DS requires the combination of several diagnostic modalities. Despite the use of complementary tests, the differential diagnosis remains difficult in most cases and very commonly, malignant strictures are detected only at the advanced stage. They are often unresectable, with an overall median survival of only 5 months [37]. For the majority of patients, the diagnosis of benign DS requires the combination of noninvasive and invasive imaging modalities.

Serum Laboratory Tests

Serum laboratory tests are notoriously neither sensitive nor specific enough for the diagnosis of DS [23, 38]. Table 1 summarizes the sensitivity, specificity, accuracy and positive and negative predictive values of the most common laboratory diagnostic tests used in clinical practice.

Noninvasive Imaging Modalities

Ultrasonography

The major limitation of abdominal US is the inability to exclude intrahepatic duct disease: in 23% of cases the diagnosis of PSC is missed on US but confirmed on ERC [39]. On the other hand, abdominal US is significantly more sensitive in detecting extrahepatic DS [37].

CT Scan

Recent reports have shown that CT can detect changes in the bile duct wall after intravenous administration of contrast material [40]. In a prospective study at the University of Padua [39], CT scan findings were compared to magnetic resonance cholangiopancreatography (MRCP) and the sensitivity of CT cholangiography was 94 versus 63% for MRCP. Extrahepatic disease was diagnosed in 69% of cases by CT cholangiography in comparison to 25% with MRCP ($p < 0.05$). These findings were confirmed by a more recent retrospective study that showed that CT cholangiography provided better delineation of the biliary system for the intrahepatic segmental strictures in comparison to MRCP (100 vs. 80%, respectively, $p = 0.03$) [41].

MRCP

MRCP has been extensively used for the diagnosis of PSC [42]. In a prospective case-control study of 34 pa-

Table 2. Summary of noninvasive imaging modalities used to diagnose and discriminate benign versus malignant DS in patients with PSC

First author [reference] (year)	Number of patients	Diagnostic test	Sensitivity	Specificity	Accuracy	PPV	NPV
Majoie [93] (1995)	23	US (intrahepatic DS)	77%	n.a.	n.a.	n.a.	n.a.
Lee [37] (1995)	85	US (extrahepatic DS)	94%	n.a.	n.a.	n.a.	n.a.
Eracleous, [41] (2005)	31	CT (intrahepatic DS)	100%	n.a.	n.a.	n.a.	n.a.
Silverman [94] (1994)	34	MRC	85%	92%	n.a.	85%	n.a.
Moff [43] (2006)	36	MRC (extrahepatic DS)	64%	n.a.	n.a.	n.a.	n.a.
Moff [43] (2006)	36	MRC (intrahepatic DS)	66%	n.a.	n.a.	n.a.	n.a.
Berstad [47] (2006)	66	MRC	77–82%	81–93%	79–86%	86–94%	71–78%

MRC = Magnetic resonance cholangiography; n.a. = not applicable; NPV = negative predictive value; PPV = positive predictive value.

tients, MRCP had a sensitivity of 85–88% and a specificity of 92–97% and a positive predictive value in the range of 85–94% [42]. A recent retrospective study comparing MRCP to ERC has shown that extrahepatic and intrahepatic ductal visualization was excellent in 64 and 66% of cases, respectively, compared to 86 and 74% for ERC [43]. The sensitivity of MRCP ranged from 83 to 91% and specificity ranged from 85 to 96%, respectively.

Table 2 summarizes the sensitivity, specificity, accuracy and positive and negative predictive values of the most commonly used noninvasive imaging modalities to diagnose patients with DS and PSC.

Invasive Diagnostic Tests

Cholangiography

For the majority of cases, the diagnosis of DS is established by MRCP or by ERC and less often by PTC. ERC and PTC provide high-quality images of the biliary tract but both are associated with risks of cholangitis [44], hemorrhage [45], pancreatitis and bowel perforation [46]. For these reasons, MRCP has become more popular as it is noninvasive and with comparable sensitivity (80%)

and specificity (88%). However, MRCP has had inferior performance characteristics in detecting extrahepatic DS when compared to ERC or CT cholangiography [43, 47].

Transpapillary Cholangioscopy

In PSC patients, noninvasive techniques have an overall low sensitivity for the early diagnosis of malignant transformation of DS. Therefore, endoscopic brushings or biopsy should be obtained to exclude CC [48, 49]. In a well-designed prospective observational study from Germany, 53 patients with PSC and DS underwent transpapillary cholangioscopy with endoscopic tissue sampling in addition to ERC [35]. In comparison to ERC alone, cholangioscopy had higher sensitivity (92 vs. 66%, $p = 0.25$), specificity (93 vs. 51%, $p < 0.001$), accuracy (93 vs. 55%, $p < 0.001$), positive predictive value (79 vs. 29%, $p < 0.001$) and negative predictive value (97 vs. 84%, $p < 0.001$).

Intraductal US

In a prospective study from the Mayo Clinics, 86 patients were enrolled to assess the use of advanced molecular and imaging techniques in the presence of indeterminate DS in PSC patients [47]. Intraductal US showed discrete sensitivity (71%), poor specificity (55%), accuracy

Table 3. Summary of invasive imaging modalities used to diagnose and discriminate benign versus malignant DS in patients with PSC

First author [reference] (year)	Number of patients	Diagnostic test	Sensitivity	Specificity	Accuracy	PPV	NPV
Berstad [47] (2006)	66	ERC	85–92%	78–81%	83–86%	86–87%	79–88%
Tischendorf [31] (2006)	53	Transpapillary cholangioscopy	92%	93%	93%	79%	97%
Levy [91] (2008)	36	Intraductal US	64–71%	55–95%	62–82%	53–90%	73–79%

NPV = Negative predictive value; PPV = positive predictive value.

(62%) and positive predictive value (53%), but an acceptable negative predictive value (73%).

Endoscopic Cytology

The majority of malignant DS presents in the perihilar region [50], which is accessible for cytology sampling during ERC. In a prospective Norwegian study of 61 PSC patients, brush cytology performed quite well with excellent sensitivity (100%), specificity (84%), accuracy (88%), positive (68%) and negative predictive values (100%) for the combination of low-grade and high-grade dysplasia or adenocarcinoma [51]. In a more recent prospective study including 36 patients affected by PSC and indeterminate DS [47], brush cytology had a significant lower sensitivity (29%), excellent specificity (100%) and positive predictive value (100%), with comparable accuracy (71%) and negative predictive value (67%).

Endoscopic Intraluminal Biopsy

Endoscopic intraluminal biopsies are obtained from abnormal segments of the bile duct by using fluoroscopic guidance of regular bioptic forceps or during cholangioscopy. For patients affected by PSC, this technique had a 29% sensitivity, 100% specificity, 71% accuracy, 100% positive predictive value and 67% negative predictive value [47].

Fluorescence in situ Hybridization

Fluorescence in situ hybridization (FISH) utilizes fluorescent-labeled DNA probes that bind only to parts of chromosomes with a high degree of sequence similarity, detecting cells with abnormalities indicative of malignancy. In a prospective study, FISH was used to investigate the nature of cytological samples obtained from PSC patients with indeterminate strictures [47]. FISH was 64%

sensitive, 70% specific, 68% accurate and had a 60% positive predictive value and a 74% negative predictive value for the diagnosis of CC [47].

Digital Image Analysis

Digital image analysis is a form of cytological analysis that requires spectrophotometry to quantify cellular constituents [52]. Small foci of tumor cells can be analyzed [53] by computer vision techniques and cell nuclei are classified as diploid, aneuploid or tetraploid. Aneuploid and tetraploid specimens are considered malignant [54]. In a recent study of 36 patients with PSC, DIA had only 21% sensitivity, 95% specificity, 65% accuracy, 75% positive predictive value and 63% negative predictive value for the diagnosis of CC [55].

Table 3 summarizes the sensitivity, specificity, accuracy and positive and negative predictive values of some of the invasive imaging modalities commonly used to diagnose patients with DS and PSC.

Treatments for DS in Patients with PSC

Treatments for DS can be divided into nonoperative and operative. Although operative treatment of benign biliary strictures is effective and provides long-term biliary patency, it is associated with a considerable risk of perioperative morbidity, mortality and important implications for patients who would require OLT in the future. Therefore, nonoperative interventions have become the preferred treatment for patients with benign biliary strictures. Nonoperative therapies are categorized as endoscopic or percutaneous. Endoscopic treatments are associated with very low morbidity and mortality, are usually performed under sedation and most of the time do not

Fig. 2. Examples of plastic stents. **a** Brand-new polymeric temporary stent used for a patient affected by dominant stricture of the distal bile duct. **b** The same type of stent after being removed from the patient several weeks after bile duct dilatation. The stent has

significant deposition of proteinaceous material visible at the proximal and distal ends in addition to inside its lumen (darker parts of the stent). These types of stents require frequent exchange to prevent ascending cholangitis due to clogging of their lumen.

require a hospital stay; they have therefore become the most common interventions for these patients. Percutaneous and radiologically directed treatments are left for patients who fail/who are not candidates for endoscopic therapy as the risk of causing bleeding or intestinal perforation is, to some extent, higher than for endoscopic interventions.

Nonoperative Therapies

Endoscopic Therapy

The main principle of the management of benign biliary strictures is to improve and maintain bile duct patency as well as to prevent recurrent strictures by using the least invasive procedure. Endoscopic interventions have several advantages over operative treatments: they have lower complication rates, they can be performed under sedation instead of general anesthesia and repeated several times if necessary, without altering the biliary anatomy or compromising the possibility of future OLT.

Endoscopic treatments aim at decompressing the biliary tree by dilating the stenotic area so that the physiological bile flow can return to a normal or semi-normal baseline. This can be obtained by utilizing expandable or graduating dilators and by inserting single or multiple biliary stents or, in some circumstances, by the combination of the two modalities. Dilatations can achieve a clinical and biochemical response in approximately 80% of noncirrhotic patients, as shown in retrospective studies [27, 30, 56, 57]. A prospective observational study from Germany evaluated the long-term outcomes of 96 PSC patients who underwent a total of 500 endoscopic dilatations [58]. The actuarial survival free of OLT after the first dilatation of DS was 81% at 5 years and 52% after 10 years

[58]. Despite the biochemical and symptomatic improvement of patients undergoing biliary dilatation with or without stenting, there is still limited literature on the long-term results of endoscopic treatments [59]. Only randomized controlled trials could clarify the exact benefit of endoscopic treatments for DS in PSC patients. One of the limitations is that randomized controlled trials require a significant amount of resources and long-term follow-up, especially for PSC as it is a chronic condition where DS of the biliary system occur over many years [58]. This can be very difficult to accomplish and, therefore, advances in this field are based on limited quality studies.

Nevertheless, the endoscopic approach to benign biliary stricture has continued to evolve and the permutation of possible interventions has expanded significantly with the increasing number of dilators and stents introduced into the available armamentarium [21, 60].

Endoscopic Biliary Stents

The use of biliary stents for benign and malignant diseases has increased considerably over the last decades [61]. With the more frequent demand for biliary interventions, the variety of biliary stents has enlarged and, currently, there are several types of stents available.

In general, biliary stents can be categorized according to the material they are made of (polymers or metal), their expected functional life-span or patency rate (temporary or permanent), size and shape and length [61].

Polymeric Temporary Stents

Plastic stents, also known as temporary stents, were initially the only type available (fig. 2). These stents have

a relatively small lumen that can get easily obstructed by debris and protein deposition. Ascending cholangitis is one of the most common complications associated with plastic stents [62]. Most of the plastic stents have a patency rate limited to 3–4 months and require frequent exchanges [62]. The deposition of intraluminal mucoprotein material is significantly higher in smaller-caliber stents than in larger stents, and in plastic stents versus metallic stents [61, 63]. In vitro studies have shown that luminal occlusion may be directly related to the frictional coefficient of the polymer and the amount of debris deposited in the lumen [63]. Of the different polymers used to create temporary plastic stents, polytetrafluoroethylene (Teflon) seems to be the most promising material in preventing luminal occlusion in comparison to other competing substances such as polyethylene and polyurethane [63]. Modifications of the plastic stents with low-friction coefficient coating, shape of the stents and creation of side holes to improve the bile flow have all been attempted to improve the patency rate but without significant practical advantages [64, 65]. A strategy to enhance the efficacy of plastic stents is the insertion of multiple stents with the intent of stretching the stenotic area and reduce the risk of stent occlusion [66]. Successful outcomes are observed in 62–89% of patients, with very low complication rates suggesting that patients with benign biliary strictures may benefit from using multiple stents. A prospective comparison study with single-stent therapy is still needed to prove clinical superiority [67].

Dilatation and Plastic Stent Placement versus Dilatation only

In clinical practice, the choice of treatment is based more on the institution preference and expertise rather than on good evidence, because the interpretation of the current literature is somewhat difficult due to the heterogeneity of the studies and patients' characteristics.

There is some general agreement that for the majority of patients with benign DS, more than one endoscopic intervention is needed to keep the bile duct patent [56, 59]. In the past, endoscopic biliary dilatation was often followed by the insertion of one or more plastic stents to maintain the patency of the bile duct. These studies have shown that the insertion of biliary plastic stents can successfully treat benign biliary strictures, but these patients have a relatively high risk of developing ascending cholangitis (up to 50%) [26, 27, 47]. Short-term stenting may be a valuable strategy to avoid occlusion considering that 81% of patients with plastic stents left for only 1–2 weeks remained asymptomatic in a retrospective cohort study

[27]. Improvement of clinical and biochemical parameters was observed in 83% of cases and the rates of being reintervention-free after 1 and 3 years were 80 and 60%, respectively [27].

In more recent years, the practice of inserting stents after a successful dilatation has been further challenged by several other studies.

In a prospective study of 106 patients with PSC treated with ursodeoxycholic acid, Stiehl et al. [26] performed interval ERC and documented the occurrence of benign DS in 49%. Common bile duct stenoses were dilated up to 24 French, whereas stenoses of the intrahepatic ducts (up to 2 cm proximally to the bifurcation) were dilated up to 18–24 French. Balloon dilatations were repeated at 4-week intervals until satisfactory dilatation was obtained. Only 5 individuals (10%) required temporary stents and underwent a mean of 4.5 dilatations over 5 years. Similar to the results reported by van den Hazel et al. [44], patients affected by DS had a 5-year survival of 70% that was higher than what was predicted by using the Mayo Clinic survival model for PSC patients not treated by dilatation or stenting [56]. It is still unclear whether ursodeoxycholic acid alone or in combination with aggressive endoscopic therapy was responsible for the improved survival [27].

Another retrospective study compared 2 groups of PSC patients with DS treated with balloon dilation alone, and balloon dilation plus stenting [59]. Stent placement did not achieve any additional benefit and was associated with more complications due to infections [59]. Unfortunately, there are no randomized controlled trials to determine whether stent therapy following dilation is superior to dilation alone.

In summary, the current literature suggests that balloon dilatation with or without the placement of one or more plastic stents is safe and effective [68], but it is still unclear if sustained symptomatic relief and resolution of the stricture are achieved during long-term follow-up [68]. Although there are no randomized controlled trials comparing best supportive therapy to endoscopic management of DS in PSC patients, most of the observational studies have shown that dilatation with or without stenting provides better outcomes than what was predicted by the Mayo risk score [57].

Self-Expandable Metallic Stents

Patients treated with endoscopic biliary dilatation or plastic stent insertion usually require several interventions to achieve satisfactory results [69]. Suboptimal stricture resolution and the development of cholangitis due to

stent occlusion are the most significant drawbacks of this approach.

Self-Expandable Metallic Stents (SEMS) were initially developed for the palliation of malignant biliary strictures because of their larger diameter and lower risk of obstruction (fig. 3). Their larger diameters and their radial expansion make SEMS a very attractive alternative for the management of benign biliary strictures as, theoretically, they provide a continuous centrifugal dilatation that might result in a higher likelihood of resolution of the stenosis. However, these qualities are counterbalanced by the fact that bare SEMS can induce tissue hyperplasia and tissue embedment with subsequent occlusion and tissue ingrowth that precludes their safe removal when no longer needed. Because of these characteristics, a new generation of fully or partially covered SEMS has been developed. These covered stents prevent tissue embedment by the presence of a silicone coating. In addition, silicone makes these stents very smooth, reducing the friction between the stent and the biliary duct so that endoscopic removal can occur without major problems. This important feature makes them more suitable for the management of benign strictures.

Types of Stents. Metal stents can be classified on the basis of their composition, mainly stainless steel or nitinol. Nitinol has become the most common material used for SEMS as it is biocompatible, elastic and maintains a shape memory. Nitinol is the result of the fusion of 55% nickel and 45% titanium. The strong intermetallic bonds between nickel and titanium have a very low reaction rate, thus preventing immunological responses and corrosion [70].

Initially, SEMS featured an uncovered design. Because early studies had shown tissue overgrowth in patients with both benign and malignant diseases, their patency rate was inferior to the expectations. In addition, noncovered SEMS could not be removed even after a short period of time as they had the tendency to become embedded in the bile duct wall. These limitations led to the development of covered SEMS. Covered SEMS have a metallic skeleton and are surrounded by a biocompatible, synthetic layer which is resistant to the effects of bile, gastric and pancreatic secretions [71].

Outcomes of Uncovered SEMS. The current literature on the use of SEMS for benign biliary strictures is very limited. Even more so is the evidence of their use in PSC patients with DS.

Foerster et al. [72] deployed uncovered SEMS in 7 patients with benign bile duct stenosis or bilioduodenal fistulas who failed dilatation and plastic stent placement.

Fig. 3. Examples of SEMS. **a** Uncovered SEMS: this type of metallic stent does not have any covering layer to prevent tissue ingrowth between the metallic wires. **b** Partially covered SEMS: there is a layer covering the main metallic frame. This layer is usually made of Teflon, making the stent smooth and preventing the stent from becoming embedded in the bile duct after being deployed. The proximal and distal ends of the stent are not covered by Teflon. **c** Fully covered SEMS: in this type of metallic stent, the entire length of the stent is covered by a layer of Teflon. One of the advantages of fully covered SEMS is that the stent can be removed endoscopically whenever necessary. In addition, the Teflon layer prevents ingrowth of the bile duct in the space between the metallic wires, increasing the long-term patency rate of these stents.

There were no stent occlusions after a short mean follow-up of only 8 months, but endoscopic stent removal was not feasible. O'Brien et al. [73] evaluated the interaction between uncovered SEMS and the bile duct by performing a choledoscopic examination at 1 year in patients who had had stents placed for benign conditions. The study showed for the first time that there was a complete epithelization of the metal stent in all subjects. Median patency was 35 months (range 7–72 months) but with symptomatic stent occlusion occurring in 62% of patients at a certain point. Because of these findings, the use of uncovered SEMS for benign biliary stenosis has been abandoned.

Outcomes of Partially Covered SEMS. Partially covered SEMS (PCSEMS) were introduced in an effort to prolong the duration of patency in patients with malignant biliary obstructions [74].

The advantages of PCSEMS are:

- (1) increased patency rate due to the fact that the covering layer prevents tissue ingrowths in the stent wall;
- (2) they can be removed endoscopically when placed across the papilla because of the smooth surface provided by the covering layer [75, 76].

Recent studies have shown that PCSEMS can be used to stent and dilate benign biliary strictures but that their patency rate decreases over time. In a recent study, only 37% of PCSEMS used for the management of benign biliary duct strictures remained patent at 36 months [71]. In another study, 90% of benign biliary strictures were successfully treated with PCSEMS, but their migration occurred in 14% of cases [77]. Migration of SEMS is a complex issue as endoscopic retrieval is often impossible and patients require surgical intervention. In a follow-up study, Mahajan et al. [78] further analyzed the long-term response after a mean follow-up of 2.5 years and found that sustained stricture resolution was observed in only 60% of cases.

Outcomes of Fully Covered SEMS. Fully covered SEMS (FCSEMS) were developed to overcome the limitations of PCSEMS. Sauer et al. [79] reported their 8-year experience with SEMS in 121 patients with benign biliary strictures. This retrospective study compared the treatment results between FCSEMS and PCSEMS. FCSEMS were used in 45% of the patients while PCSEMS were deployed in the remaining 55%. The mean time of stent treatment was 165 days with a mean follow-up after stent removal of 735 days. Overall stricture resolution was achieved in 63% of patients, but the clinical success decreased to 50% for chronic pancreatitis compared to 71% for all the other conditions. A 20% complication rate was observed during or immediately after stent placement, while the complication rate was 12% during stent removal. Stent migration occurred in 16% of cases. Besides stent migration, the other most common flaws of fully covered SEMS were: intestinal reflux, tissue hyperplasia, pancreatitis and cholecystitis. Although most cases of pancreatitis were mild, FCSEMS had a higher rate of acute pancreatitis than plastic stents (7.3 vs. 1.3%). One of the possible reasons for the increased risk of pancreatitis is that FCSEMS might occlude the pancreatic duct due to their larger diameter and constant centrifugal pressure on the surrounding structures [80]. Acute cholecystitis and cholangitis can also occur more frequently than when plastic stents are used. This is due to the fact that covered SEMS occlude the cystic duct and prevent the gallbladder to drain in the common bile duct. This predisposes the development of infections in the gallbladder or in the excluded bile segment when covered SEMS are deployed at the hepatic hilum [81]. The reported rate of cholecystitis after the deployment of covered SEMS ranges between 2.9 and 12% [82, 83].

In more recent years, FCSEMS have undergone some important design changes. Flared ends and anchoring flaps have been added to minimize the risk of migration,

and flared ends and distal loops were added to facilitate their removal during endoscopy with the use of grasping forceps or snares.

Park et al. [84] compared two types of fully covered SEMS in 43 patients with benign biliary strictures. One type of stent had four anchoring flaps at the proximal end with flared distal end, and the other with flared end at both proximal and distal parts but without anchoring flaps. After a median period of 6 months, no patients in the anchoring flap group had stent migration while 33% of patients in the flared end group experienced that problem ($p = 0.004$). The removal rate of the fully covered SEMS was 100% in both groups without any complication. Immediate improvement of biliary strictures was seen in 91% of patients who received anchoring flap stents and 88% in the flared end group. Unfortunately, during the median follow-up period of 4 months following stent removal or migration, 16% had recurrence of the stricture.

Recently, a retrievable, Teflon, fully covered SEMS with a ball-type wire mesh at the distal end was designed to prevent stent migration and intestinal reflux [85]. This new stent also has a loop that allows it to be pulled inside-out more easily during removal. Researchers from the Netherlands are currently conducting a prospective study assessing a new type of FCSEMS with a proximal retrieval lasso for the treatment of benign biliary strictures [69].

Even if the data on the treatment of benign biliary strictures using FCSEMS are encouraging, the risks of migration, infection, pancreatitis and the inability to remove the stents have not been completely resolved. Comparative data on the efficacy of using biliary dilatation with single or multiple plastic stents versus covered SEMS for benign biliary strictures is lacking and prospective studies are needed. Besides this, the cost of SEMS represents a major limiting factor for their routine use in benign biliary strictures, and the cost-effectiveness ratio between the use of plastic stents and SEMS has not yet been assessed.

Percutaneous Transhepatic Therapies

Percutaneous transhepatic dilatations and/or stenting produce clinical and biochemical improvements similar to endoscopic therapy [86]. This approach is only indicated for symptomatic patients who have failed endoscopic management, in order to avoid potential serious side effects, and it decreases the quality of life due to the discomfort of external stents.

Surgical Interventions

The most important consideration to guide physicians in their decisions regarding the treatment of PSC patients

Table 4. Overview of the technical and clinical success of different biliary stents used for the treatment of extrahepatic benign biliary stenosis

Indications for biliary duct stent insertion in extrahepatic benign bile duct strictures	Single plastic stent		Uncovered SEMS		Multiple plastic stents	
	technical success	clinical success	technical success	clinical success	technical success	clinical success
All indications	94%	61%	98%	62%	97%	87%
Postoperative benign biliary stenosis	86%	64%	97%	59%	100%	87%
Chronic pancreatitis	100%	36%	100%	80%	n.a.	n.a.
Biliary stricture after OLT	97%	81%	100%	50%	88%	89%

n.a. = Not applicable.

with DS should be the potential impact on future OLT. OLT is the best treatment option for patients with PSC with liver decompensation with an overall 5-year survival of 70–85% [51, 55]. Although OLT provides the best survival, the number of available grafts is insufficient to match the number of potential candidates [87] and it is performed only when PSC is associated with liver failure.

The management of DS in PSC should be at centers where it is possible to have a multidisciplinary approach to the problem. In the past, DS were mainly managed surgically, but with the advancement of nonoperative modalities, the trend has shifted towards endoscopic techniques as they offer the advantage of being less invasive, can be performed in outpatient settings and repeated whenever necessary [88].

Early management of DS should aim at improving the symptoms and the quality of life of these patients without jeopardizing the possibility of future OLT. Nowadays, resection or bypass surgery should only be performed on a small and selected group of patients who have DS in the extrahepatic duct without signs of cirrhosis [89].

Conclusion

Despite the significant advances in several diagnostic modalities used to differentiate benign from malignant DS in patients with PSC, there is no single test that can be considered the gold standard. Combining several modalities with the clinical characteristics of each patient is therefore recommended.

OLT is the treatment of choice for patients with PSC associated with liver decompensation. In this group of patients, endoscopic or percutaneous dilatation with or without stenting provides symptomatic relief and pre-

vents rapid hepatic deterioration. Dilatation with stenting is a valid strategy to stabilize patients and to bridge their condition until organ replacement is indicated.

Symptomatic noncirrhotic PSC patients with DS can be treated both endoscopically and surgically. Repeated endoscopic dilations of DS can improve survival compared to best supportive care as predicted by the Mayo risk score [57].

A recent systematic review [90] of the evidence on the use of stents for benign extrahepatic biliary strictures has shown that technical success was achieved in 98.9% of cases with the deployment of uncovered SEMS, 94.8% with the deployment of single plastic stents and 94% with multiple plastic stents (table 4).

The overall clinical success rate was 94.3% when multiple plastic stents were inserted in the bile duct across the stricture, 79.5% when uncovered SEMS were used and 59.6% when single plastic stents were employed. Complication rates were higher for uncovered SEMS (39.5%) than for single (36%) and multiple plastic stents (20.3%). In view of these findings, the use of multiple plastic stents appears the best endoscopic intervention for patients with benign dominant extrahepatic biliary strictures.

Patients who fail nonoperative techniques and those with DS suspicious for malignancy are best managed by resection. In the last decades, the use of a multidisciplinary approach for PSC patients has improved their survival, but the management of indeterminate DS remains a clinical challenge and high-quality prospective studies are needed.

References

- Lee YM, Kaplan MM: Primary sclerosing cholangitis. *N Engl J Med* 1995;332:924–933.
- Nakanuma Y, Hirai N, Kono N, Ohta G: Histological and ultrastructural examination of the intrahepatic biliary tree in primary sclerosing cholangitis. *Liver* 1986;6:317–325.
- Broome U, Grunewald J, Scheynius A, et al: Preferential V beta3 usage by hepatic T lymphocytes in patients with primary sclerosing cholangitis. *J Hepatol* 1997;26:527–534.
- Bambha K, Kim WR, Talwalkar J, et al: Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United States community. *Gastroenterology* 2003;125:1364–1369.
- Boberg KM, Aadland E, Jahnsen J, et al: Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. *Scand J Gastroenterol* 1998;33:99–103.
- Kingham JG, Kochar N, Gravenor MB: Incidence, clinical patterns, and outcomes of primary sclerosing cholangitis in South Wales, United Kingdom. *Gastroenterology* 2004;126:1929–1930.
- Smith T, Befeler AS: High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Curr Gastroenterol Rep* 2007;9:54–59.
- Charatcharoenwitthaya P, Lindor KD: Primary sclerosing cholangitis: diagnosis and management. *Curr Gastroenterol Rep* 2006;8:75–82.
- Fickert P, Wagner M, Marschall HU, et al: 24-norUrsodeoxycholic acid is superior to ursodeoxycholic acid in the treatment of sclerosing cholangitis in Mdr2 (Abcb4) knockout mice. *Gastroenterology* 2006;130:465–481.
- Beuers U, Spengler U, Kruijs W, et al: Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: a placebo-controlled trial. *Hepatology* 1992;16:707–714.
- Lindor KD: Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. *N Engl J Med* 1997;336:691–695.
- van Hoogstraten HJ, Vleggaar FP, Boland GJ, et al: Budesonide or prednisone in combination with ursodeoxycholic acid in primary sclerosing cholangitis: a randomized double-blind pilot study. Belgian-Dutch PSC Study Group. *Am J Gastroenterol* 2000;95:2015–2022.
- Vacca M, Krawczyk M, Petruzzelli M, et al: Current treatments of primary sclerosing cholangitis. *Curr Med Chem* 2007;14:2081–2094.
- Ishibashi H, Komori A, Shimoda S, Gershwin ME: Guidelines for therapy of autoimmune liver disease. *Semin Liver Dis* 2007;27:214–226.
- Stiehl A: Primary sclerosing cholangitis: the role of endoscopic therapy. *Semin Liver Dis* 2006;26:62–68.
- Stiehl A, Rost D: Endoscopic treatment of dominant stenoses in patients with primary sclerosing cholangitis. *Clin Rev Allergy Immunol* 2005;28:159–165.
- Yamamoto T, Hirohashi K, Kubo S, et al: Surgery for segmental primary sclerosing cholangitis. *Hepatogastroenterology* 2004;51:668–671.
- Hirai I, Ishiyama S, Fuse A, et al: Primary sclerosing cholangitis successfully treated by resection of the confluence of the hepatic duct. *J Hepatobiliary Pancreat Surg* 2001;8:169–173.
- Ahrendt SA, Pitt HA, Kalloo AN, et al: Primary sclerosing cholangitis: resect, dilate, or transplant? *Ann Surg* 1998;227:412–423.
- Van Laethem JL, Deviere J, Bourgeois N, et al: Cholangiographic findings in deteriorating primary sclerosing cholangitis. *Endoscopy* 1995;27:223–228.
- Bjornsson E, Lindqvist-Ottosson J, Asztely M, Olsson R: Dominant strictures in patients with primary sclerosing cholangitis. *Am J Gastroenterol* 2004;99:502–508.
- Gossard AA, Angulo P, Lindor KD: Secondary sclerosing cholangitis: a comparison to primary sclerosing cholangitis. *Am J Gastroenterol* 2005;100:1330–1333.
- Olsson R, Boberg KM, de Muckadell OS, et al: High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. *Gastroenterology* 2005;129:1464–1472.
- LaRusso NF, Shneider BL, Black D, et al: Primary sclerosing cholangitis: summary of a workshop. *Hepatology* 2006;44:746–764.
- Ponsioen CY, Lam K, van Milligen de Wit AW, et al: Four years' experience with short-term stenting in primary sclerosing cholangitis. *Am J Gastroenterol* 1999;94:2403–2407.
- Stiehl A, Rudolph G, Kloters-Plachky P, et al: Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. *J Hepatol* 2002;36:151–156.
- van Milligen de Wit AW, van Bracht J, Rauws EA, et al: Endoscopic stent therapy for dominant extrahepatic bile duct strictures in primary sclerosing cholangitis. *Gastrointest Endosc* 1996;44:293–299.
- Olsson RG, Asztely MS: Prognostic value of cholangiography in primary sclerosing cholangitis. *Eur J Gastroenterol Hepatol* 1995;7:251–254.
- MacCarty RL, LaRusso NF, Wiesner RH, Ludwig J: Primary sclerosing cholangitis: findings on cholangiography and pancreatography. *Radiology* 1983;149:39–44.
- May GR, Bender CE, LaRusso NF, Wiesner RH: Nonoperative dilatation of dominant strictures in primary sclerosing cholangitis. *AJR Am J Roentgenol* 1985;145:1061–1064.
- Tischendorf JJ, Kruger M, Trautwein C, et al: Cholangioscopic characterization of dominant bile duct stenoses in patients with primary sclerosing cholangitis. *Endoscopy* 2006;38:665–669.
- Bergquist A, Broome U: Hepatobiliary and extra-hepatic malignancies in primary sclerosing cholangitis. *Best Pract Res Clin Gastroenterol* 2001;15:643–656.
- Farrant JM, Hayllar KM, Wilkinson ML, et al: Natural history and prognostic variables in primary sclerosing cholangitis. *Gastroenterology* 1991;100:1710–1717.
- Kaya M, de Groen PC, Angulo P, et al: Treatment of cholangiocarcinoma complicating primary sclerosing cholangitis: the Mayo Clinic experience. *Am J Gastroenterol* 2001;96:1164–1169.
- Rosen CB, Nagorney DM, Wiesner RH, et al: Cholangiocarcinoma complicating primary sclerosing cholangitis. *Ann Surg* 1991;213:21–25.
- Pohl J, Ring A, Stremmel W, Stiehl A: The role of dominant stenoses in bacterial infections of bile ducts in primary sclerosing cholangitis. *Eur J Gastroenterol Hepatol* 2006;18:69–74.
- Lee JG, Schutz SM, England RE, et al: Endoscopic therapy of sclerosing cholangitis. *Hepatology* 1995;21:661–667.
- Bjornsson E, Boberg KM, Cullen S, et al: Patients with small duct primary sclerosing cholangitis have a favourable long term prognosis. *Gut* 2002;51:731–735.
- Macchi V, Floreani A, Marchesi P, et al: Imaging of primary sclerosing cholangitis: preliminary results by two new non-invasive techniques. *Dig Liver Dis* 2004;36:614–621.
- Schulte SJ, Baron RL, Teeffey SA, et al: CT of the extrahepatic bile ducts: wall thickness and contrast enhancement in normal and abnormal ducts. *AJR Am J Roentgenol* 1990;154:79–85.
- Eracleous E, Genagrits M, Papanikolaou N, et al: Complementary role of helical CT cholangiography to MR cholangiography in the evaluation of biliary function and kinetics. *Eur Radiol* 2005;15:2130–2139.
- Silverman W: Complication rate of endoscopic retrograde cholangiopancreatography (ERCP) in patients with primary sclerosing cholangitis (PSC): is it safe? *Gastroenterology* 1994;106:A359.
- Moff SL, Kamel IR, Eustace J, et al: Diagnosis of primary sclerosing cholangitis: a blinded comparative study using magnetic resonance cholangiography and endoscopic retrograde cholangiography. *Gastrointest Endosc* 2006;64:219–223.
- van den Hazel SJ, Wolfhagen EH, van Buuren HR, et al: Prospective risk assessment of endoscopic retrograde cholangiography in patients with primary sclerosing cholangitis. Dutch PSC Study Group. *Endoscopy* 2000;32:779–782.
- Harbin WP, Mueller PR, Ferrucci JT Jr: Transhepatic cholangiography: complications and use patterns of the fine-needle technique: a multi-institutional survey. *Radiology* 1980;135:15–22.
- Cohen SA, Siegel JH, Kasmin FE: Complications of diagnostic and therapeutic ERCP. *Abdom Imaging* 1996;21:385–394.

- 47 Berstad AE, Aabakken L, Smith HJ, et al: Diagnostic accuracy of magnetic resonance and endoscopic retrograde cholangiography in primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2006;4:514–520.
- 48 Ponsioen CY, Vrouwenraets SM, van Milligen de Wit AW, et al: Value of brush cytology for dominant strictures in primary sclerosing cholangitis. *Endoscopy* 1999;31:305–309.
- 49 Boberg KM, Jepsen P, Clausen OP, et al: Diagnostic benefit of biliary brush cytology in cholangiocarcinoma in primary sclerosing cholangitis. *J Hepatol* 2006;45:568–574.
- 50 Ahrendt SA, Pitt HA, Nakeeb A, et al: Diagnosis and management of cholangiocarcinoma in primary sclerosing cholangitis. *J Gastrointest Surg* 1999;3:357–367.
- 51 Vera A, Moledina S, Gunson B, et al: Risk factors for recurrence of primary sclerosing cholangitis of liver allograft. *Lancet* 2002;360:1943–1944.
- 52 Sebo TJ: Digital image analysis. *Mayo Clin Proc* 1995;70:81–82.
- 53 Persons DL, Takai K, Gibney DJ, et al: Comparison of fluorescence in situ hybridization with flow cytometry and static image analysis in ploidy analysis of paraffin-embedded prostate adenocarcinoma. *Hum Pathol* 1994;25:678–683.
- 54 Moreno Luna LE, Kipp B, Halling KC, et al: Advanced cytologic techniques for the detection of malignant pancreatobiliary strictures. *Gastroenterology* 2006;131:1064–1072.
- 55 Graziadei IW, Wiesner RH, Marotta PJ, et al: Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. *Hepatology* 1999;30:1121–1127.
- 56 Dickson ER, Murtaugh PA, Wiesner RH, et al: Primary sclerosing cholangitis: refinement and validation of survival models. *Gastroenterology* 1992;103:1893–1901.
- 57 Baluyut AR, Sherman S, Lehman GA, et al: Impact of endoscopic therapy on the survival of patients with primary sclerosing cholangitis. *Gastrointest Endosc* 2001;53:308–312.
- 58 Gotthardt DN, Rudolph G, Kloters-Plachky P, et al: Endoscopic dilation of dominant stenoses in primary sclerosing cholangitis: outcome after long-term treatment. *Gastrointest Endosc* 2010;71:527–534.
- 59 Kaya M, Petersen BT, Angulo P, et al: Balloon dilation compared to stenting of dominant strictures in primary sclerosing cholangitis. *Am J Gastroenterol* 2001;96:1059–1066.
- 60 Angulo P, Lindor KD: Primary sclerosing cholangitis: emerging new promising therapies. *J Clin Gastroenterol* 2000;31:271–273.
- 61 Raijman I: Biliary and pancreatic stents. *Gastrointest Endosc Clin N Am* 2003;13:561–592.
- 62 Khashab MA, Kim K, Hutfless S, et al: Predictors of early stent occlusion among plastic biliary stents. *Dig Dis Sci* 2012;57:2446–2450.
- 63 van Berkel AM, van Marle J, van Veen H, et al: A scanning electron microscopic study of biliary stent materials. *Gastrointest Endosc* 2000;51:19–22.
- 64 Costamagna G, Mutignani M, Rotondano G, et al: Hydrophilic hydromer-coated polyurethane stents versus uncoated stents in malignant biliary obstruction: a randomized trial. *Gastrointest Endosc* 2000;51:8–11.
- 65 Nakamura S, Ohara H, Yamada T, et al: Efficacy of plastic tube stents without side holes for middle and lower biliary strictures. *J Clin Gastroenterol* 2002;34:77–80.
- 66 Costamagna G, Pandolfi M, Mutignani M, et al: Long-term results of endoscopic management of postoperative bile duct strictures with increasing numbers of stents. *Gastrointest Endosc* 2001;54:162–168.
- 67 Draganov P, Hoffman B, Marsh W, et al: Long-term outcome in patients with benign biliary strictures treated endoscopically with multiple stents. *Gastrointest Endosc* 2002;55:680–686.
- 68 Perri V, Familiari P, Tringali A, et al: Plastic biliary stents for benign biliary diseases. *Gastrointest Endosc Clin N Am* 2011;21:405–433.
- 69 Pausawasadi N, Soontornmanokul T, Rerknimitr R: Role of fully covered self-expandable metal stent for treatment of benign biliary strictures and bile leaks. *Korean J Radiol* 2012;13(suppl 1):S67–S73.
- 70 Srinivasan I, Kahaleh M: Biliary stents in the millennium. *Adv Ther* 2011;28:960–972.
- 71 Cantu P, Hookey LC, Morales A, et al: The treatment of patients with symptomatic common bile duct stenosis secondary to chronic pancreatitis using partially covered metal stents: a pilot study. *Endoscopy* 2005;37:735–739.
- 72 Foerster EC, Hoepffner N, Domschke W: Bridging of benign choledochal stenoses by endoscopic retrograde implantation of mesh stents. *Endoscopy* 1991;23:133–135.
- 73 O'Brien SM, Hatfield AR, Craig PI, Williams SP: A 5-year follow-up of self-expanding metal stents in the endoscopic management of patients with benign bile duct strictures. *Eur J Gastroenterol Hepatol* 1998;10:141–145.
- 74 Dumonceau JM, Nicaise N, Deviere J: The ultraflex diamond stent for benign biliary obstruction. *Gastrointest Endosc Clin N Am* 1999;9:541–545.
- 75 Kahaleh M, Tokar J, Le T, Yeaton P: Removal of self-expandable metallic Wallstents. *Gastrointest Endosc* 2004;60:640–644.
- 76 Shin HP, Kim MH, Jung SW, et al: Endoscopic removal of biliary self-expandable metallic stents: a prospective study. *Endoscopy* 2006;38:1250–1255.
- 77 Kahaleh M, Behm B, Clarke BW, et al: Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm? (with video). *Gastrointest Endosc* 2008;67:446–454.
- 78 Mahajan A, Ho H, Sauer B, et al: Temporary placement of fully covered self-expandable metal stents in benign biliary strictures: mid-term evaluation (with video). *Gastrointest Endosc* 2009;70:303–309.
- 79 Sauer BG, Regan KA, Srinivasan I, Shami VM, Rehan ME, Ellen K: Temporary placement of covered self-expandable metal stents (CSEMS) in benign biliary strictures (BBS): eight years of experience. *Gastrointest Endosc* 2010;71:110–111.
- 80 Cote GA, Kumar N, Ansstas M, et al: Risk of post-ERCP pancreatitis with placement of self-expandable metallic stents. *Gastrointest Endosc* 2010;72:748–754.
- 81 Ho H, Mahajan A, Gosain S, et al: Management of complications associated with partially covered biliary metal stents. *Dig Dis Sci* 2010;55:516–522.
- 82 Bezzi M, Zolovkins A, Cantisani V, et al: New ePTFE/FEP-covered stent in the palliative treatment of malignant biliary obstruction. *J Vasc Interv Radiol* 2002;13:581–589.
- 83 Hausegger KA, Thurnher S, Bodendorfer G, et al: Treatment of malignant biliary obstruction with polyurethane-covered Wallstents. *AJR Am J Roentgenol* 1998;170:403–408.
- 84 Park do H, Lee SS, Lee TH, et al: Anchoring flap versus flared end, fully covered self-expandable metal stents to prevent migration in patients with benign biliary strictures: a multicenter, prospective, comparative pilot study (with videos). *Gastrointest Endosc* 2011;73:64–70.
- 85 Hwang JC, Kim JH, Yoo BM, et al: Temporary placement of a newly designed, fully covered, self-expandable metal stent for refractory bile leaks. *Gut Liver* 2011;5:96–99.
- 86 Skolkin MD, Alspaugh JP, Casarella WJ, et al: Sclerosing cholangitis: palliation with percutaneous cholangioplasty. *Radiology* 1989;170:199–206.
- 87 UNOS: <http://www.unos.org> (accessed February 29, 2008).
- 88 Ahrendt SA: Surgical approaches to strictures in primary sclerosing cholangitis. *J Gastrointest Surg* 2008;12:423–425.
- 89 Tsai S, Pawlik TM: Primary sclerosing cholangitis: the role of extrahepatic biliary resection. *Adv Surg* 2009;43:175–188.
- 90 van Boeckel PG, Vleggaar FP, Siersema PD: Plastic or metal stents for benign extrahepatic biliary strictures: a systematic review. *BMC Gastroenterol* 2009;9:96.
- 91 Levy MJ, Baron TH, Clayton AC, et al: Prospective evaluation of advanced molecular markers and imaging techniques in patients with indeterminate bile duct strictures. *Am J Gastroenterol* 2008;103:1263–1273.
- 92 Nakeeb A, Lipsett PA, Lillemoe KD, et al: Biliary carcinoembryonic antigen levels are a marker for cholangiocarcinoma. *Am J Surg* 1996;171:147–152.
- 93 Majoie CB, Smits NJ, Phoa SS, et al: Primary sclerosing cholangitis: sonographic findings. *Abdom Imaging* 1995;20:109–112.
- 94 Silverman WB, Kaw M, Rabinovitz M, Schade RR, Bates BL: Complication rate of endoscopic retrograde cholangiopancreatography (ERCP) in patients with primary sclerosing cholangitis (PSC): is it safe? *Gastroenterology* 1994;106:359.