Stents in the upper gastrointestinal tract: novel designs and indications

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Stents in the upper gastrointestinal tract: novel designs and indications

Stents in het bovenste deel van het maagdarmkanaal: nieuwe ontwerpen en indicaties

(met een samenvatting in het Nederlands)

Proefschrift

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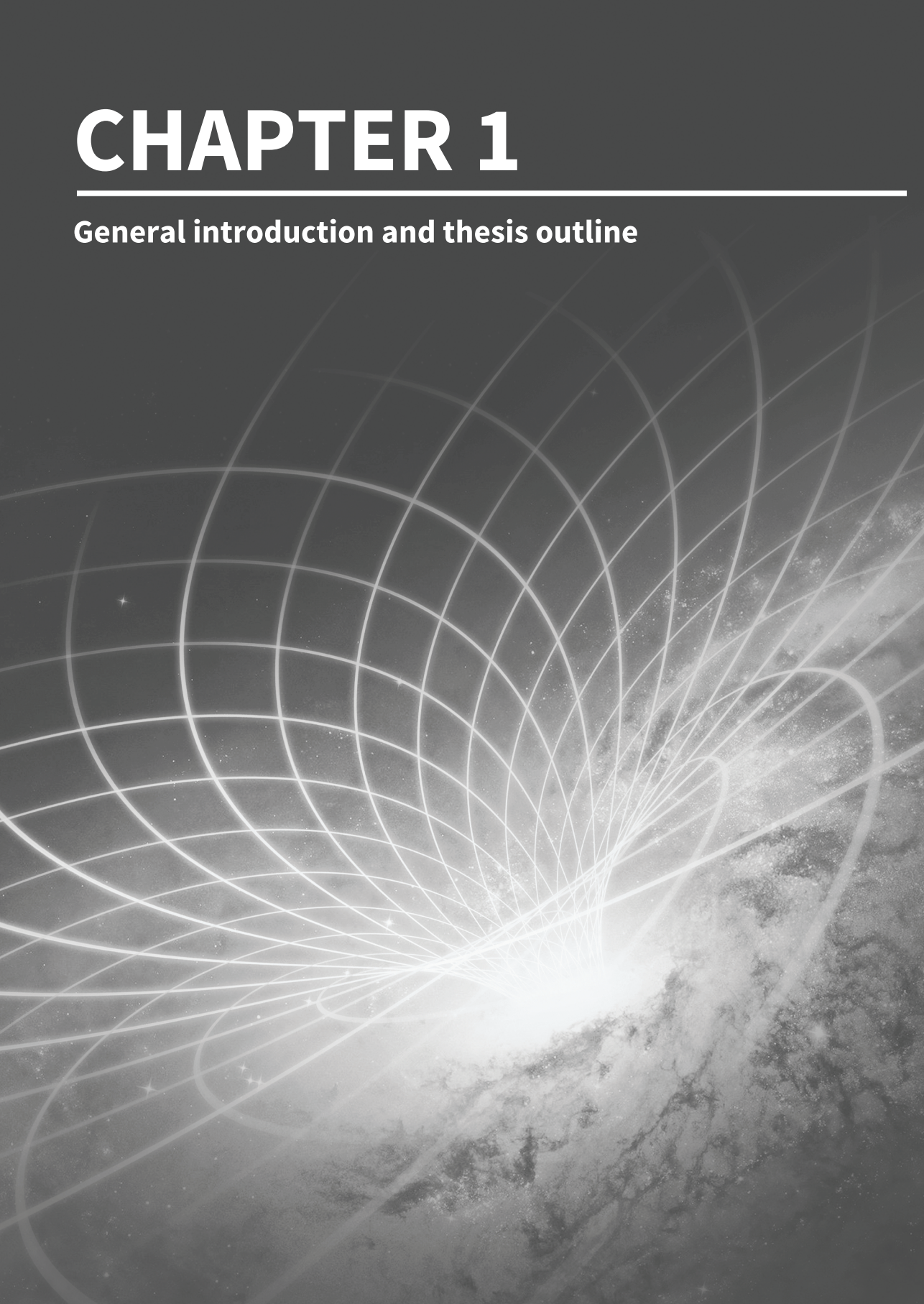
CHAPTER 1

General introduction and thesis outline



The first gastrointestinal endoscopic procedure was performed by Adolf Küssmaul in 1868. Assisted by a professional sword-swallower, he was able to pass a rigid, custom-designed endoscope of 47cm long and 13mm in diameter down to the stomach.[1] Although conflicting statements exist whether Küssmaul was indeed able to adequately visualize the esophagus and stomach, his device is still considered to be the first gastroscope in history. Ever since this first endoscopy of the upper gastrointestinal tract, the procedure has evolved immensely and is nowadays the cornerstone of daily practice in clinical gastroenterology.[2]

Some of the major technical breakthroughs that transformed endoscopy into its current form include the development of the flexible fiber optic endoscope in 1958 and the introduction of electronic endoscopes using video imaging in the 1980s.[3-5] Another important evolution has been the transition of endoscopy from a diagnostic modality alone to an intervention for both diagnostic and therapeutic indications. An important therapeutic endoscopic intervention includes placement of a stent, i.e. a hollow tubular prosthesis, to maintain patency of a hollow organ, especially for treatment of esophageal and biliary strictures. Over the past few decades significant improvements in stent designs have been implemented. A major breakthrough has been the introduction of self-expandable stents as alternative to rigid plastic tubes, for both the esophagus and biliary tract in the late 1980s.[6-8]

The current developments in the field of esophageal and biliary stenting mainly focus on modification and further refinement of stent designs in order to improve clinical outcomes and reduce the rate of stent-related complications. In addition, self-expandable stents are also increasingly used for new indications, such a endoscopic ultrasonography-guided transluminal drainage of fluid collections. For these new indications, self-expandable stents with lumen-apposing capacity were developed.

The general objective of this thesis is to evaluate the clinical efficacy and safety of novel stent designs and indications for use in the upper gastrointestinal tract, including esophageal stents (PART I), biliary stents (PART II) and lumen-apposing metal stents (PART III).

PART I: ESOPHAGEAL STENTS

Patients with an esophageal stricture, either benign or malignant, usually present with dysphagia. Patients with dysphagia are unable to eat a normal diet, which may result in malnutrition, weight loss, aspiration, impaired quality of life and, in case of malignant dysphagia, early mortality.[9,10]

Benign esophageal strictures

Benign esophageal strictures may occur due to a variety of causes, including peptic, corrosive or radiation injury, surgical anastomosis, or esophageal inflammatory disease.[11,12] The mainstay of treatment consists of endoscopic dilation with balloons or bougies. In the majority of patients one to three dilations are sufficient to effectively relieve dysphagia. However, in 30% of patients more sessions are needed because of recurrent stricture formation. The second step in the treatment algorithm of benign strictures is dilation combined with electrocautery incisions or steroid injections.[13-15] This therapeutic option is largely expert based, since randomized studies have not been able to demonstrate an obvious reduction in the number of repeat dilations needed or prolongation of the dysphagia free period.[16-18] Temporary stent placement is the subsequent step in the algorithm, because it offers dilation for a prolonged period of time and it is thought that this ultimately reduces the risk of recurrent stricture formation.[15,19]

Initially self-expandable metal stents (SEMS) and later also self-expandable plastic stents (SEPS) were used. SEMS were uncovered (uSEMS) or partially covered (pcSEMS) with a silicone or polymer coating at the body of the stent, leaving both stent ends uncovered. However, the use of uSEMS and pcSEMS is limited due to tissue ingrowth through the uncovered stent mesh resulting in recurrent dysphagia and difficulties with stent removal.[13] Based on this experience, fully covered (fc) stents were introduced.[20] The main limitation of fcSEMS and fcSEPS is the high rate of stent migration resulting in recurrent dysphagia.[21] In addition, both SEMS and SEPS require repeat endoscopy for stent removal.

Biodegradable (BD) self-expanding stents have been introduced as an alternative to avoid additional endoscopies for stent removal. Most data are available regarding the Ella BD stent, made of an uncovered mesh of polydioxanon, a polymer which gradually degrades within 2-3 months after placement.[22] Experience with BD stents for benign strictures is mainly derived from small, uncontrolled case series.[22-25] Whether patients with benign strictures indeed benefit from BD stent placement, in terms of dysphagia free period and number of repeat endoscopies for dilation, is unknown. Therefore, we performed an international, multicenter randomized study comparing standard dilation and BD stent placement. In **Chapter 2** the results of this study, the DESTINY study, are presented.

Malignant esophageal strictures

Dysphagia due to a malignant stricture is often a late symptom of disease and as a result most patients already have incurable disease at the time of diagnosis.[26] The most commonly performed palliative treatment in these patients consists of placement of a SEMS. Although SEMS placement is known to be both effective and

safe for the palliation of malignant dysphagia, the main drawback of this treatment is the high recurrent dysphagia rate of up to 40%. Similar to SEMS placement for benign indications, the use of pcSEMS is limited due to tissue growth through the uncovered stent mesh, whereas fcSEMS are prone to migrate.[27,28] However, unlike in patients with benign strictures, there is usually no need for stent removal in patients with a malignant stricture due to the limited life expectancy. It has been suggested that the ideal stent design in this patient group is a fcSEMS to preclude tissue ingrowth and provided with specific features to prevent stent migration. Over the last 15 years, several new stent designs and refinements of existing stents have been developed, including flared stent designs, several types of anti-migration flaps and different stent materials.[29-33] In **Chapter 3** we evaluate the clinical efficacy and safety of a novel fcSEMS, the Hanaro Flap stent, designed with specific anti-migration features in an attempt to reduce recurrent dysphagia.

PART II: BILIARY STENTS

Patients with biliary obstruction may present with symptoms of cholestasis, including jaundice, pruritus and malabsorption. To prevent serious complications such as cholangitis and in case of benign strictures secondary biliary cirrhosis, biliary stent placement during endoscopic retrograde cholangiography (ERC) for decompression is recommended.[34, 35]

Before the introduction of biliary SEMS, standard treatment included placement of a plastic endoprosthesis with a luminal diameter of 10Fr (3.3mm).[35,36] The major drawback of these plastic stents is the formation of a bacterial biofilm inside the stent, which may lead to stent obstruction, recurrent jaundice, and occasionally cholangitis. As a result, repeated ERC with stent exchange is in most cases required after approximately 3 months.[35,37] In an attempt to improve stent patency and reduce the number of procedures, SEMS have been introduced as an alternative for plastic stents because of their larger luminal diameter (10mm).[6,35,37,38]

Benign biliary strictures

In patients with a benign biliary stricture (BBS) the use of uSEMS is not desirable due to tissue ingrowth through the stent mesh resulting in a limited long-term stent patency and major difficulties when trying to remove the stent.[39] Therefore, fcSEMS are nowadays preferred for the treatment of BBS.[40] However, since embedding of the stent mesh in the mucosa is unlikely to occur with fcSEMS, stent migration is a frequently encountered problem with migration rates of up to 41%.[40-44] In order to prevent migration, several anti-migration features have been evaluated

with varying results, including stents with anti-migration fins,[40, 44] double pigtail stents for anchoring,[45] and stents with flared ends.[44, 46] In **Chapter 4** we assess the efficacy of a fcSEMS, the Niti-S biliary bumpy stent, with anti-migration features in patients with BBS.

Malignant biliary strictures

Randomized controlled trials have shown that the use of SEMS is superior to plastic stents in patients with malignant extrahepatic bile duct obstruction in terms of recurrent biliary obstruction, number of reinterventions and functional stent time.[47-52] Nonetheless, SEMS placement is not universally accepted as standard treatment due to the high costs of SEMS (€1000) compared to plastic stents (€100). Since patients with malignant extrahepatic bile duct obstruction only have a limited life expectancy, it is thought that the high costs for SEMS might not be offset by a reduction in costs for repeated interventions. Although several studies have investigated costs associated with plastic stent and SEMS placement, results of these studies are inconclusive with regard to the cost-effectiveness of SEMS, particularly in patients with an expected short survival.[50-54] We performed a multicenter randomized controlled trial to evaluate which type of stent, either a plastic stent or SEMS, is superior for the palliation of malignant extrahepatic bile duct obstruction with regard to clinical effects and associated costs. The results of this study, the PLAMET study, are presented in **Chapter 5.**

In studies regarding SEMS placement for palliation of malignant bile duct obstruction, it is often assumed that a longer functional stent time and fewer repeat interventions will result in an improved health-related quality of life (HRQoL). However, none of the studies comparing plastic stents and SEMS for palliation of malignant bile duct obstruction included HRQoL as outcome measure.[47-52] Since HRQoL is an important outcome measure for the evaluation of palliative treatment modalities,[55-58] we evaluated HRQoL in the PLAMET study and report our results in **Chapter 6.**

PART III: LUMEN APPOSING STENTS

The introduction of endoscopic ultrasonography (EUS) in the 1980s resulted in a variety of novel diagnostic and therapeutic procedures.[59] One of the new therapeutic procedures included EUS-guided transluminal drainage. This procedure was initially performed for the treatment of pancreatic fluid collections.[60] Endoscopic drainage entails the creation of a fistulous tract between the upper gastrointestinal tract and the cavity that will be drained, followed by placement of a naso-cystic

catheter or a stent to ensure drainage. The introduction of EUS-guided stent placement enabled prolonged drainage with a decreased risk of perforation or puncture of other organs. Moreover, by using Doppler ultrasound intervening vessels can be identified and avoided at the puncture site, thereby minimizing the bleeding risk.[61-63]

As stated above, plastic double-pigtail stents and naso-cystic catheters were initially used for EUS-guided drainage. However, as with esophageal and biliary stents, their use is limited by the small diameter of the stent lumen (7-10F). Following the successful introduction of SEMS in the biliary tract, biliary SEMS were also introduced for transluminal drainage.[61] However, conventional SEMS for biliary drainage have a tubular design that exhibits limited anchoring capacity in both clinical and experimental settings.[64,65] Therefore, a specifically designed lumen apposing metal stent (LAMS), the Axios stent, has been developed for transluminal drainage.[64,66] The Axios stent is a saddle-shape SEMS with bilateral flanges constructed of braided nitinol and fully covered with silicone. Both ex-vivo benchtop testing and animal studies confirmed the anchoring capacity of the stent with an even distribution of pressure on the luminal walls.[64]

Pancreatic fluid collections

Pancreatic fluid collections (PFCs) may complicate the course of acute and chronic pancreatitis, pancreatic surgery or trauma. They may develop due to disruption of the pancreatic duct with subsequent fluid leakage creating a pancreatic pseudocyst (PP), or as a consequence of maturation of (peri)pancreatic necrosis resulting in walled-off necrosis (WON).[67-69] Until the introduction of endoscopic drainage of PFCs in the late 1980s, treatment options were limited to surgical and percutaneous drainage.[70,71] Nowadays, EUS-guided drainage with placement of double-pigtail plastic stents is an important minimally invasive drainage modality for symptomatic PFCs.[63] The success rate of EUS-guided drainage is highly dependent on the type of PFC drained. Adequate treatment of WON is much more challenging than drainage of PPs as necrosectomy is often required in addition to drainage alone.[72,73]

SEMS and LAMS placement is increasingly performed as alternative for the double-pigtail plastic stents because of the larger diameter of both types of stents. The wider drainage opening is thought to reduce the risk of stent occlusion and associated complications. Furthermore a direct access route is created in case endoscopic necrosectomy is indicated. The first reports on the use of LAMS for EUS-guided PFCs showed promising results with technical and clinical success rates of 100%.[61,66,74-77] However, these data should be critically appraised since all reports have significant limitations such as a small number of patients, the

use of different stent designs, the absence of preset endpoints, lack of long term follow-up and a retrospective design. In an attempt to provide more solid data, we prospectively evaluated the use of the Axios stent for EUS-guided drainage in a large European cohort. In **Chapter 7** we present the results of this study.

Gallbladder

In high-risk surgical patients with cholecystitis, gallbladder drainage is recommended as an alternative treatment to surgery.[78,79] For percutaneous transhepatic gallbladder drainage placement of an external drainage tube is required, which are prone for inadvertent tube dislodgement with the need for repeated procedures and cause discomfort for patients.[80] EUS-guided gallbladder drainage (EUS-GBD) is increasingly performed as alternative and a recent randomized controlled trial showed that this technique, using a naso-biliary drain, is comparable to percutaneous drainage in terms of technical feasibility and clinical efficacy.[66,81] Drawback of the use of naso-biliary drains or pigtail stents is that a fistula tract is required, which has a diameter larger than the diameter of the inserted drain or stent. This may cause air or bile leakage into the peritoneum and associated serious complications. By using SEMS or LAMS the newly formed fistula track can be adequately sealed due to the expansion capacity after placement and thereby reducing the risk of air and bile leakage.

Reports on EUS-GBD using SEMS, especially LAMS, are limited to case reports and small case series without long term follow-up.[66,74,82-84] In **Chapter 8** we report the results of a multicenter, prospective study, in which the feasibility and long term safety of the use of LAMS for EUS-guided gallbladder drainage was evaluated.

In **Chapters 9** and **10** the results of this thesis are summarized and discussed.

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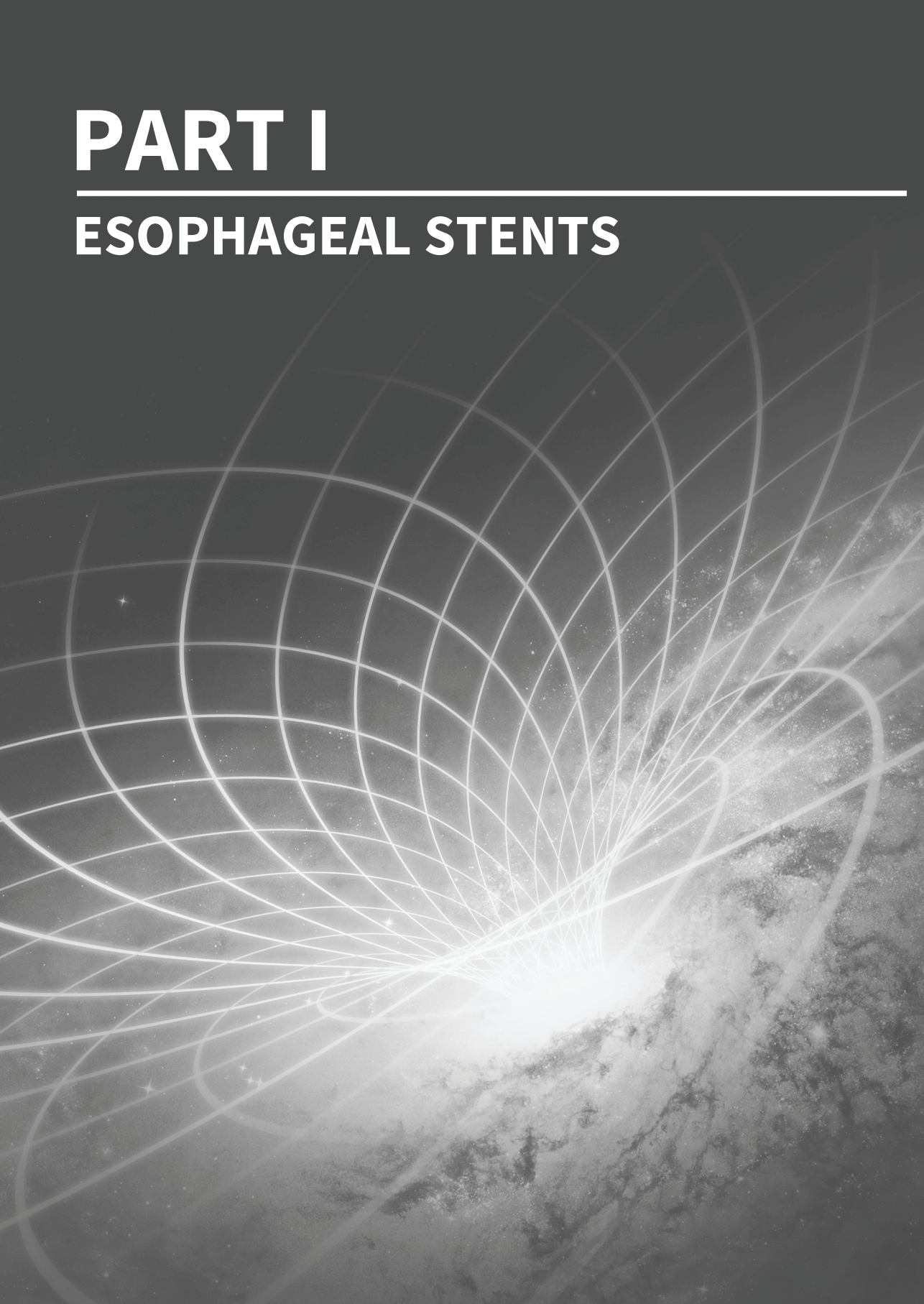
PART I

ESOPHAGEAL STENTS



CHAPTER 2

Dilation or stent placement for refractory benign esophageal strictures: results from a randomized controlled trial

D. Walter on behalf of the Destiny Trial Study Group.

Manuscript in preparation (draft version)

ABSTRACT

Background and aims: Endoscopic dilation is the standard of care for recurrent benign esophageal strictures (BES). Esophageal biodegradable (BD) stent placement is thought to prolong the effect of dilation and to reduce recurrences, without the need for stent removal. The aim of this study was to compare the efficacy and safety of standard dilation and BD stent placement early in the treatment algorithm of recurrent BES.

Methods: Multicenter, randomized study in 8 European centers. Patients treated with 1-5 previous dilations to at least 16mm were included. Dysphagia scores were recorded daily for one month and monthly thereafter. Quality of life (QoL) was assessed using the EQ-5D and visual analogue scale (VAS), and the WHO performance score. Primary study endpoint was the number of endoscopic dilations for recurrent dysphagia within 3 and 6 months post-procedure. Secondary endpoints included time to recurrent dysphagia, time to dilation, number of repeat endoscopies, safety, and quality of life.

Results: A total of 66 patients were included (standard dilation n=34, BD stent n=32) and baseline patient demographics and lesion characteristics were similar between the two groups. After 3 months of follow-up, significantly more endoscopic dilations were performed in the dilation group compared to the BD stent group (median: 1 vs. 0, p<0.001), but the total number of endoscopic procedures in both groups was not significantly different between both groups (p=0.063). There was also no difference in the number of dilations or total number of endoscopic procedures between the treatment groups at 6 and 12 months follow-up. Median time to recurrent dysphagia was 54 days (95% CI 0-116) in the dilation group and 120 days (95% CI 60-181) in the BD stent group (p=0.047). In the dilation group 11 SAEs in 10 patients occurred compared to 21 SAEs in 19 patients in the BD stent group (p=0.014). No difference in quality of life over time was measured.

Conclusion: BD stent placement for recurrent BES is associated with a temporary reduction in the number of repeat dilations and a prolonged time to recurrent dysphagia compared to standard dilation, but significantly more SAEs were observed in patients with a BD stent. Based on these results, it seems too early to recommend placement of a BD stent as treatment of choice in patients with recurrent BES.

INTRODUCTION

Benign esophageal strictures (BES) may occur due to a variety of causes, including peptic, corrosive or radiation injury, surgical anastomosis, post-mucosal resection or esophageal inflammatory disease.[1-3] Dysphagia is the most frequently encountered symptom in these patients, resulting in inability to eat a normal diet, which may lead to malnutrition, weight loss, aspiration and impaired quality of life.[4,5]

The mainstay of treatment for BES is endoscopic dilation with balloon or bougie dilators. Although dilation is safe and effective in relieving dysphagia in the majority of patients, repeated sessions are relatively frequently required because of stricture recurrence.[6-8] Repeat endoscopic treatment is considered a burden to patients and affecting their quality of life, but is also a burden to health care costs.[5,9] Combination therapy of dilation with electrocautery incisions or steroid injections has been proposed to reduce the number of dilations in subgroups of patients BES, but randomized trials were not able to demonstrate a clear reduction in the number of repeated dilations or prolongation of the dysphagia free period.[7,10,11]

In the past decade, temporary stent placement has been introduced as promising step in the treatment algorithm of patients refractory to ongoing dilation. Temporary stent placement will dilate the stricture for a prolonged period of time, which may lead to a reduction of the risk of recurrent stricture formation.[12,13] Initially, partially and fully covered self-expandable plastic and metal stents were used. The main drawback of partially covered stents is tissue ingrowth trough the uncovered stent ends resulting in difficulties with removal, while fully covered stents are more prone to migrate. In addition, for both stent types an additional endoscopy is required for stent removal.[13] To avoid these problems, (uncovered) biodegradable (BD) stents have been suggested as a promising alternative.

Experience with BD stent placement is limited to small case series mainly including patients with refractory strictures with varying results.[14-18] No studies have been performed to evaluate whether BD stent placement earlier in the treatment algorithm could be an effective alternative reducing the risk of recurrent dysphagia symptoms. The aim of this study was to compare the efficacy and safety of standard dilation and BD stent placement early in the treatment algorithm of recurrent BES.

METHODS

We conducted a multicenter randomized trial between January 2012 and January 2015 in eight hospitals in Europe. The study protocol was reviewed and approved by the ethics committees of all participating centers.

Patients

Patients were included if they presented with a recurrent BES due to various causes with a history of at least 1 and maximum of 5 previous endoscopic dilations up to at least 16mm and symptoms of dysphagia for at least solid food (dysphagia score≥2 according to Ogilvie[19], and≤21 according to Dakkak and Bennett[20]). Patients were excluded in case of a life expectancy<2 months, a surgical or interventional procedure in the esophagus within 30 days prior to the study procedure, eosinophilic esophagitis, or motility disorder, previous esophageal stent placement or another dilation method than standard bougie or balloon expansion, coagulopathy, stricture within 1.5 cm of the upper esophageal sphincter, stricture length ≥10cm, active esophageal perforation, leak, fistula, or varices, malignant stricture, stricture within a polypoid lesion, Zenker's diverticulum and inability to pass the delivery system through the stricture.

Randomisation

Permuted block randomization was performed using a centralized computer system with stratification for center and stricture severity (narrow and mild). A mild stricture was defined as a stricture that could be passed by a standard diagnostic endoscope (diameter 9.8mm) and a narrow stricture could not be passed by a standard diagnostic upper endoscope. Patients were randomized in a 1:1 ratio to standard dilation therapy or BD stent placement (SX-ELLA, Ella-CS, Czech Republic). The study had a non-blinded design.

Dilation and stent placement procedure

All endoscopic procedures were performed with patients under sedation according to endoscopists' and centers' preferences. In the standard dilation group, dilation was performed using a balloon or bougie, according to local common practice with the aim to reach a diameter of at least 16mm and a maximum of 18mm. The number of dilations to safely reach a diameter of 16mm was upon the discretion of the treating physician and was performed stepwise when a single session was considered unsafe. The pre-defined diameter of at least 16mm had to be reached within a maximum of 2 weeks. Endoscopy was performed immediately after dilation to check for potential perforations and to confirm efficacy

of the dilation. In the stent group, a BD stent (SX-ELLA, Ella-CS, Czech Republic) was endoscopically placed. All participating endoscopists were experienced in esophageal stent placement and were trained in using the BD stent. Pre-dilation was allowed during the same session. The appropriate stent length (6, 8, or 10cm) was chosen according to the stricture length seen during the initial endoscopy, with the upper and lower end of the stent extending at least 2cm above and below the stricture, respectively. Based upon the initial assessment of the severity of the stricture, an 18mm or 20mm body stent diameter was used for narrow strictures and a 23mm body stent for mild strictures. Endoscopy was performed immediately after stent release to confirm correct positioning and stent expansion across the stricture. After 3 months, a radiographic evaluation was performed to confirm the presence of the gold markers of the BD stent at the site of the stricture. Acid suppression with a proton pump inhibitor was prescribed to all patients according to the standard of care.

In case of recurrent dysphagia within 6 months standard dilation to 16-18mm was performed in both treatment arms. In case of recurrent dysphagia after 6 months, all treatment options were 'open' and treatment was given according to the preference of the endoscopist and the patient.

Study endpoints and follow-up

Primary study endpoint was the number of repeat endoscopic dilations for recurrent dysphagia for at least solid food within 3 and 6 months post-procedure. Secondary endpoints included time to recurrent dysphagia, time to dilation, number of repeat endoscopies, safety, and quality of life. Time to recurrent dysphagia included the number of days between the index procedure and the moment of recurrent dysphagia for at least solid food. Safety was defined as the number of (serious) adverse events with possible or likely relation to the study intervention, as determined by the data safety monitoring board. Serious adverse events included event requiring hospital admission or an endoscopic procedure. Quality of life was assed using the EuroQol (EQ)-5D-5L with the EQ visual analogue scale (EQ-VAS)[21], and the World Health Organization (WHO)performance score.

Patients were contacted by study personnel at 14 days, 1 month, and then monthly until 6 months and thereafter at 12 months after treatment. Patients recorded their dysphagia scores daily for one month and weekly thereafter for one year in a diary.

Sample size and statistical analysis

For sample size calculation, we used the Poisson regression model with a one-sided test, while the Holm–Bonferroni method was used to correct for multiple

comparisons with two primary hypotheses (i.e. 3 and 6 months). We assumed 1 dilation per patient in de BD stent group and 2 dilations per patient in the dilation group at 3 months with an α=0.025, and 2.6 dilations per patient in de BD stent group and 4 dilations per patient in the dilation group at 6 months with α=0.05. This resulted in a total sample size of 60 patients with a power of 0.935. To compensate for a loss to follow-up of 10%, it was decided to include a total of 66 patients.

Normally distributed continuous variables were expressed as means (± SD) and not-normally distributed variables were expressed as medians (IQR and range). Categorical data were presented with percentages. Analysis of the different objectives was performed by using the t-test for analysis of normally distributed continuous data, the Mann-Whitney U test for non-parametric data and the Chi-square test or Fischer's exact test for categorical variables. Time to recurrent dysphagia between groups was compared using Kaplan-Meier and log-ranks tests. The EQ-5D-5L, EQ-VAS, WHO performance score and dysphagia scores were compared using linear mixed model regression analyses and included follow-up time (continuous, per day), treatment group (dilation, BD stent) and the interaction between follow-up and treatment group, corrected for baseline measurements. A p-value of<0.05 was considered to be statistically significant.

RESULTS

Figure 1 shows the trial profile. Baseline patient demographics and lesion characteristics were similar between the two groups (Table 1). Stent placement was successful in all patients in one endoscopic session, while pre-stent placement dilation was performed in 11 patients (34%). In the dilation group the intended dilation diameter was not achieved in one patient (3%), with a maximum diameter of 11mm. In the majority of patients (n=22, 65%) the pre-defined diameter was achieved in one session (median 1; range 1-5). Three patients in the dilation group (9%) and seven patients in the BD stent group (22%) received endoscopic treatment other than standard dilation for (symptoms of) recurrent dysphagia during the first six months of follow-up (Figure 1). Eight patients (12%) died during the study, five patients due to recurrent esophageal cancer, one patient due to recurrent non-seminoma testicular cancer and two patients due to complications of an esophagotracheal fistula.

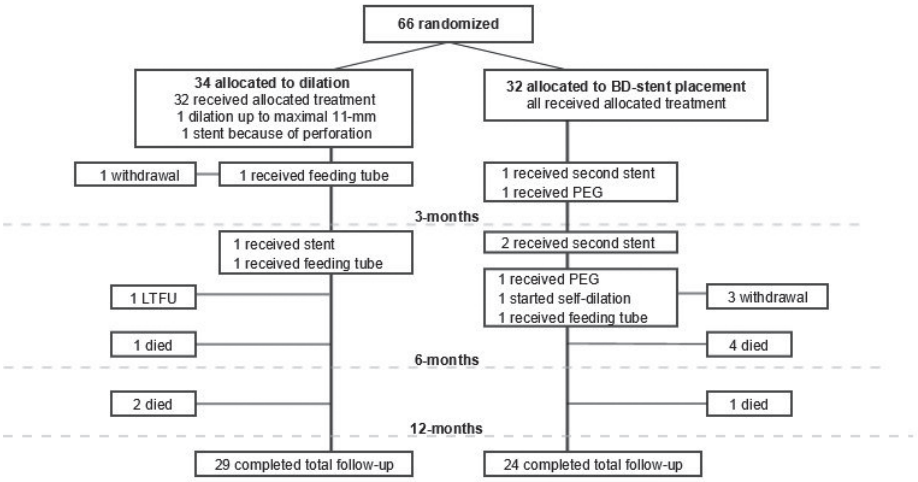


Figure 1 Trial algorithm of the DESTINY study comparing standard dilation and biodegradable (BD) stent placement in patients with a recurrent benign esophageal stricture.

Table 1 Baseline patient and lesion characteristics of 66 patients with a recurrent benign esophageal stricture.

	Dilation N=34 (%)	**BD stent N=32 (%)**
Age, mean (±SD)	62 (12)	62 (9)
Sex, male	26 (77)	21 (66)
Stricture etiology		
Anastomotic	26 (77)	23 (72)
Caustic	2 (6)	1 (3)
Peptic	3 (9)	1 (3)
EMR/ESD	3 (9)	4 (13)
Other	-	3* (9)
Stricture location*		
Proximal	25 (73)	19 (59)
Mid	2 (6)	4 (13)
Distal	7 (21)	9 (28)
Stricture severity		
Mild	9 (27)	11 (34)
Narrow	25 (73)	21 (66)
Tortuosity	1 (3)	2 (6)
Dysphagia score median (IQR)		
Ogilvie	2 (2-2)	2 (2-3)
Dakkak and Bennett	15 (10-21)	15 (10-21)
WHO score, median (IQR)	1 (0-1.25)	1 (0-1)

BD stent=biodegradable stent
EMR=endoscopic mucosal resection
ESD=endoscopic submucosal dissection
*Idiopathic, radiotherapy, combination of EMR and RFA
**Proximal<25 cm, mid 25-30 cm, distal>30cm

Repeat endoscopic dilations

After 3 months of follow-up, significantly more endoscopic dilations were performed in the dilation group compared to the BD stent group (median: 1 vs. 0, p<0.001; Table 2). However, the total number of endoscopic procedures in both groups, including diagnostic or therapeutic endoscopies (i.e. placement of a new stent, feeding tube placement or endoscopic cleaning of food bolus obstruction), was not significantly different between the groups at 3 months (p=0.063; Table2). There was also no difference in the number of dilations or total number of endoscopic procedures between the treatment groups at 6 and 12 months follow-up (Table2).

Table 2 Number of endoscopic dilations and total endoscopic procedures during follow-up in patients with recurrent benign esophageal stricture.

	Median number of procedures (IQR and range)	Dilation N=34	BD stent N= 32	P-value
3- months	Dilations	**1** 1 (0-3/0-11)	**0** (0-0/0-9)	**0.00**
	Total endoscopic procedures	**1** 1 (0-3.25/0-11)	**0** (0-1/0-10)	0.06
6- months	Dilations	**2** (0-4.25/0-13)	**1** (0-3/0-13)	0.29
	Total endoscopic procedures	**2** (0-5/0-13)	**2** (0-4/0-14)	0.76
12-months	Dilations	**3** (0-5/0-19)	**1** (0-5.75/0-22)	0.23
	Total endoscopic procedures	**3** (1-5.25/0-19)	**2** (0-6/0-23)	0.60

BD stent=biodegradable stent
IQR=interquartile range

Recurrent dysphagia

Dysphagia scores improved rapidly in both groups after the index procedure (Figure2). In total, 77% of patients in the standard dilation group experienced recurrent dysphagia (26 of 34 patients), compared to 59% of patients in de BD stent group (19 of 32 patients, p=0.14). The median time to recurrent dysphagia was 54 days (95% CI 0-116) in the dilation group and 120 days (95% CI 60-181) in the BD stent group (p=0.047, Figure3). Four patients in the BD stent group presented with recurrent dysphagia due to food bolus obstruction and in one patient a new stricture was observed at 3cm above the anastomotic site, most likely caused by hyperplastic tissue growth at the proximal stent end.

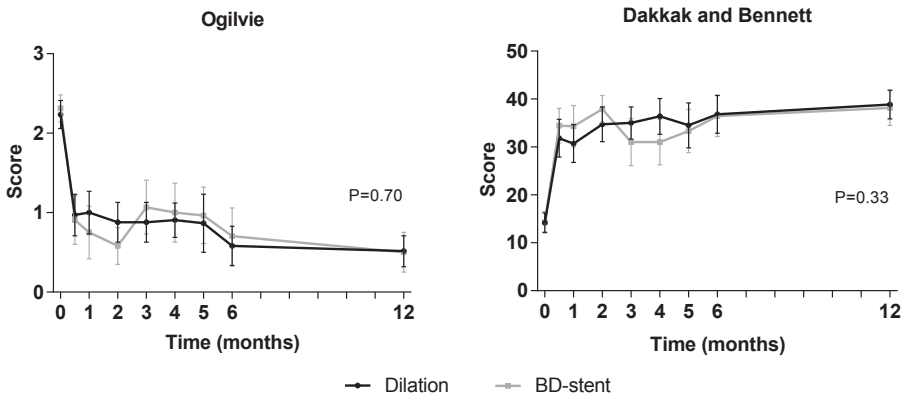


Figure 2 Dysphagia scores measured with the Ogilvie scale (left) and Dakkak-Bennett scale (right). A higher score on the Ogilvie scale represents more dysphagia symptoms, while a higher score on the Dakkak and Bennett scale represents fewer symptoms of dysphagia.

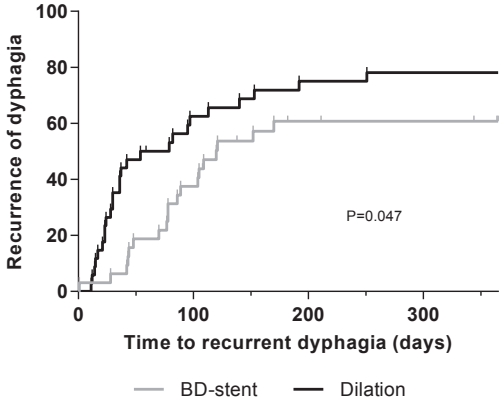


Figure 3 Kaplan-Meier showing time to recurrent dysphagia in patients with a recurrent benign esophageal stricture treated with either standard dilation or biodegradable (BD) stent placement.

Safety

A total of 11 possibly associated SAEs in 10 patients occurred in the dilation group compared to 21 possibly associated SAEs in 19 patients in the BD stent group (p=0.014) (Table 3). The most common SAEs in the BD stent included retrosternal pain (n=9) and abdominal pain, nausea and vomiting (n=5) requiring a (diagnostic) endoscopic intervention or admission. In de dilation group abdominal pain, nausea and vomiting (n=4) was the most common SAE. Two patients in the BD stent group developed an esophago-tracheal fistula, diagnosed 91 and 99 days after initial stent placement, respectively. The fistula was located 2cm above the initial

stricture in one patient and at the site of the initial stricture location in the second patient. Both patients died due to the respiratory insufficiency as a complication of the fistula. Two other patients in the BD stent group presented with dyspnea without evidence for pneumonia, while during endoscopy no signs of a fistula were seen. In both patients the dyspnea improved over time without any treatment. One patient with a BD stent developed a liver abscess which was diagnosed 103 days after initial stent placement and 30 days after dilation for recurrent dysphagia. Surgical resection was performed without any complications. Two patients in the BD stent group presented with severe dysphagia and dehydration symptoms, for which a short hospital stay was required. In the dilation group a perforation was seen in two patients. In one patient, the perforation was seen immediately after the initial dilation session and a fully covered self-expanding metal stent (FCSEMS) was placed. In the second patient, a perforation was seen after FCSEMS placement at day 152 because of frequent recurrence of dysphagia. In this patient the stent was left in situ, a feeding tube was placed and antibiotics were administered.

Table 3 Possible related (serious) adverse events in patients with recurrent benign esophageal strictures treated with standard dilation or a biodegradable (BD) stent.

	Dilation N=32	**BD stent N=21**	**P=value**
Serious adverse events	**10 (29%)***	**19 (59%)***	**0.014**
Pneumonia	2	-	
Infected hematoma anterior of aortic graft	1	-	
Esophageal perforation	2	-	
Esophageal laceration	1	-	
Abdominal pain/nausea/vomiting	4	5	
Retrosternal pain	1	9	
Admission for recurrent dysphagia	-	2	
Esophago-tracheal fistula (resulting in death)	-	2	
Dyspnea without a cause‡	-	2	
Peritonitis with liver abscess	-	1	
Adverse events	**9 (26%)***	**6 (19%)**	0.45
Retrosternal pain	4	3	
(Aspiration) pneumonia	4†	1	
Abdominal pain/nausea/vomiting	2	2	

* More than one complication arose in some patient

‡ No signs for pneumonia, endoscopy performed to make sure stent is in correct position and to exclude fistula formation

† Pneumonia 1 day after dilation in one patient, suggesting aspiration pneumonia. In all other patients more than 7 days between last endoscopic procedure or recurrence of dysphagia and pneumonia

In both patients the perforation resolved without any sequelae. Two patients in the dilation group developed a pneumonia for which hospital admission was required, 48 and 66 days after dilation therapy, respectively. Finally, one patient in the dilation group developed an infected hematoma of an aortic prosthesis 26 days after the dilation procedure. The patient received antibiotics and drainage of the hematoma was performed. Although there was no recurrence of dysphagia, a feeding tube was placed to ensure adequate nutrition. The patient withdrew any further study participation. There was no difference between the groups in the number of AEs (Table3).

Quality of life

No differences in QoL were found on the EQ-5D-5L (p=0.78) and EQ-VAS (p=0.68) over time between the two treatment groups (Figure4). Furthermore, the WHO performance score was not significantly different over time between the two groups (p=0.11).

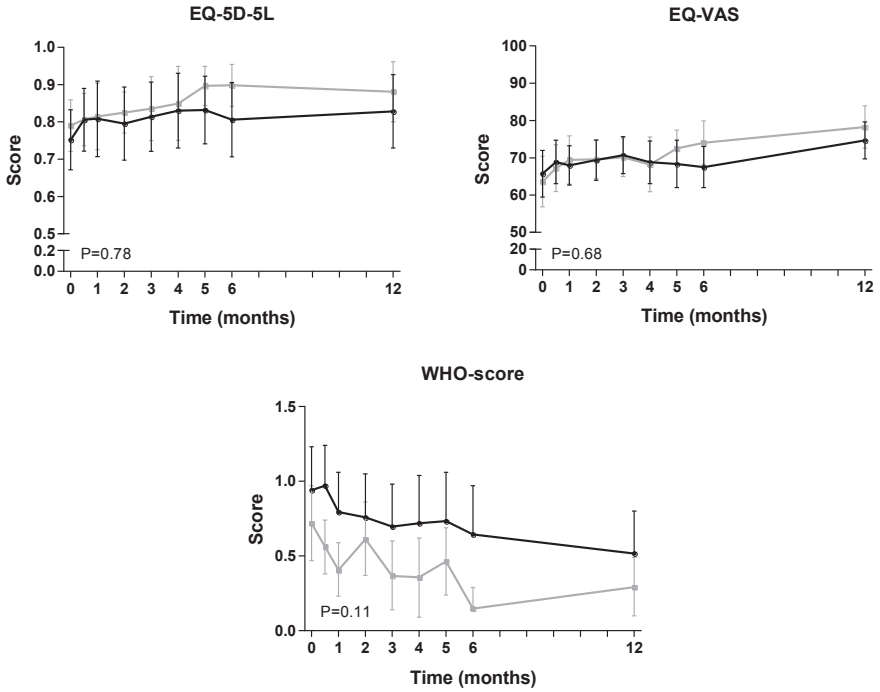


Figure 4 Quality of life measured with the EQ-5D-5L, EQ-visual analogue scale (VAS) and WHO-score in patients with a recurrent benign esophageal stricture treated with standard dilation or biodegradable (BD) stent placement. A higher score on the EQ-5D-5L and EQ-VAS represent a better quality of life, a higher score on the WHO-scale represents a lower quality of life.

DISCUSSION

This multicenter, randomized study compared standard dilation and BD stent placement for the treatment of recurrent BES. We demonstrated that the number of repeat endoscopic dilations after 3 months was significantly higher in the standard dilation group compared to the BD stent group, but no difference was found at the long term. The median time to recurrent dysphagia was significantly longer in the BD stent group compared to the standard dilation group. BD stent placement was associated with more SAEs, including two SAEs leading to death. No differences in quality of life were seen between both treatment groups.

In the late 1990s, biodegradable stent placement for benign esophageal strictures was first reported, with somewhat disappointing results due to inability of the stent to maintain a clinically significant radial force for a prolonged period.[22,23] The development of a commercially available biodegradable stent of polydioxanone, the BD stent (SX-ELLA, Ella-CS, Czech Republic), which maintains a sufficient radial force for 6-8 weeks after implantation and gradually degrades within approximately 3 months, resulted in an increased number of reports on the use of this stent for BES.[15-18] Almost all case series evaluating esophageal BD stent placement included patients with refractory BES, with clinical success rates, defined as patients without recurrent strictures, ranging from 0 to 100% with a mean of 39%.[14] In the current study, our hypothesis was that BD stent placement early in the treatment algorithm would result in a higher clinical success rate. Unfortunately, the clinical success rate of 41% in the BD stent group in our study was similar to the overall reported success rate with BD stents for refractory BES in previous studies. A possible explanation is that we included patients who already had one to five previous dilations in this study, which may be the subgroup that is prone to develop a refractory BES. It may well be that a longer stent dwell time is required for these types of recurrent BES, with a longer period of dilation enabling the underlying inflammation to subside and the stricture to remodel.

The frequency of repeated endoscopic dilations is one the main reasons for the search for an alternative treatment for BES. Frequent and repeated dilations are considered a burden to patients as well as a to health care costs.[5,9] Placement of a BD stent is thought to reduce the number of dilations and we indeed found a significant reduction in the number of dilations in the BD stent group during the first three months after the index procedure. Remarkably, we found no difference in QoL in the first three months of this study, which may be due to the relatively small size of the study. After the first three months, which is approximately the time to degradation of the BD stent, the number of dilations for recurrent dysphagia increased in the BD stent group. As a result, the total number of dilations in both

treatment groups became comparable after 6 months. It is important to note that the total number of endoscopic procedures was not different after 3 months of follow-up due to a substantial number of patients in the BD stent presenting with retrosternal pain, and nausea and vomiting requiring (diagnostic) endoscopy. This type of adverse event has also been reported in previous studies on BD stent placement in the esophagus. The stiffness of the stent and an inflammatory response in the mucosa of the esophagus due to the stent have been postulated as possible explanations for these events.[15,24] In addition, a recent study that investigated the mechanical properties of different esophageal stents showed that BD stents have a relatively high axial force compared to other stent designs, which combined with the stiffness of the stent and the inflammatory reaction, may result in an increased risk of stent-related complications to the esophageal wall. A high axial force of the stent is particularly disadvantageous when the stent is not straight positioned in the esophagus, which is not uncommon due to stricture charactristics.[25] The fact that two patients in our study treated with a BD stent developed an esophago-tracheal fistula suggests that a high local force of the BD stent on the esophageal wall indeed may cause tissue damage leading to a fistula. An esophago-tracheal fistula after BD stent placement for a refractory BES has been reported before. [26] In this regard, it is remarkable that in the few reports on histopathological findings after esophageal BD stent placement, no signs of significant damage to the esophageal wall were reported.[27,28] Theoretically, a stent that is flexible and has a lower axial force may be the preferred stent design for esophageal strictures and may be associated with a lower complication risk. However, to date no other biodegradable stent designs are available. Therefore, the second best option for treatment of recurrent or refractory BES may be the placement of a FCSEMS. However, non-degradable stents have the advantage that an additional endoscopy for stent removal is required in patients with BES.

In the standard dilation group, the number of SAEs was considerably higher compared to literature. For the most commonly reported SAE related to dilation, laceration and/or perforation, the reported rate in literature varies between 0.1 and 3%, compared to 9% (3/32) in our study.[10,13] In the study protocol the decision to perform stepwise dilation was upon the discretion of the treating physician. To minimize the risk for perforation during dilation, the commonly used guideline for dilation of esophageal strictures, the "rule of three", meaning that the maximum dilation diameter should not exceed more than 3 mm per session,[13] was included in the protocol. Important to note, one of the two perforations in the dilation group developed after placement of a FCSEMS because of frequent recurrences in the dilation group. The second perforation developed in a patient with a tortuous and

narrow esophageal stricture, which are known to have a higher risk for perforation.[13]

The strength of this study is the randomized controlled study design with a thorough, long-term follow-up. Only one pilot randomized study including 17 patients with BES comparing BD stent placement with balloon dilation has been performed.[24] It was concluded that BD stent placement was associated with a worse dysphagia score and more adverse events and no difference was seen in number of endoscopic procedures or in quality of life. The difference in dysphagia score was the primary endpoint of this study and it was calculated that 23 patients were required in each arm study to demonstrate a difference in dysphagia score of at least one point. However, due to under-recruitment the study was prematurely closed and after 12 months follow-up only 12 of the 17 included patients could be analysed.[24] A limitation of our study is still the relatively small sample size and the heterogeneity of stricture etiology of the patients included. Due to the relatively low incidence of recurrent BES we decided to include all types of BES strictures and still it took three years to include the intended number of patients in 8 centers. As the pathogenesis of the different types of BES is clearly different, it could well be that some type of strictures will benefit more from (BD) stent placement than others. We did not perform subgroup analyses due the small size of subgroups. Another limitation is the fact that we included patients with one to five previous dilations. It may well that placement of a BD stent directly at first presentation with a BES, at least in a subgroup of patients, may have the greatest impact. We decided to include patients with at least one and a maximum of 5 previous dilations to at least 16 to 18mm to be sure that placement of a stent with a diameter of a minimum diameter of 18mm was justified with a balanced risk of procedure-related complications.

In conclusion, we demonstrate that BD stent placement for recurrent BES is associated with a temporary reduction in the number of repeat dilations and a prolonged time to recurrent dysphagia compared to standard dilation. However, significantly more SAEs were seen in patients with a BD stent. More studies are required to clarify the exact mechanism of this high complication rate and to evaluate whether other stent designs placed for a longer period may have a positive impact on these endpoints in patients with recurrent BES. Based on our results, it seems too early to recommend placement of a BD stent as treatment of choice in patients with recurrent BES.

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CHAPTER 3

A new fully covered metal stent with anti-migration features for treatment of malignant dysphagia

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ABSTRACT

Background and study aims: A new esophageal stent with two anti-migration features was developed to minimize migration. The aim of this study was to evaluate the clinical efficacy and safety of this stent in patients with malignant dysphagia.

Patients and methods: A total of 40 patients with dysphagia due to a malignant obstruction of the esophagus were prospectively enrolled in this cohort study.

Results: Stent placement was technically successful in 39 patients (98%). The median dysphagia-free time after stent placement was 220days (95% confidence interval 94–345 days). Nine patients (23%) experienced recurrent dysphagia due to tissue overgrowth (n = 2), stent fracture (n = 1), and partial (n = 5) or complete (n=1) stent migration. A total of 16 serious adverse events occurred in 14 patients (36%), with hemorrhage (n = 3) and severe nausea or vomiting (n = 3) being the most common causes.

Conclusions: This new stent design was effective for the palliation of malignant dysphagia and had a low rate of recurrent dysphagia. However, despite the anti-migration features, stent migration was still a major cause of recurrent dysphagia. Furthermore, treatment was associated with a high adverse event rate. Dutch Trial Registration (NTR 3313)

INTRODUCTION

Dysphagia is a frequently encountered symptom in patients presenting with esophageal and gastric cardia cancer or, less frequently, obstruction due to extrinsic malignant compression. Due to the late presentation of symptoms, more than 50% of patients already have incurable disease at presentation. For these patients, palliative therapy is the only option to relieve dysphagia.[1] Of the various treatment modalities available, placement of a self-expandable metal stent (SEMS), is still the most commonly performed treatment option worldwide.[2]

Many studies have shown that SEMS placement is both effective and safe for the palliation of malignant dysphagia. However, the main drawback of this treatment is the high rate of recurrent dysphagia (30%–40%), which requires repeat endoscopy.[3,4] The main cause of recurrent dysphagia in partially covered SEMS is tissue ingrowth and overgrowth through the uncovered stent mesh (15%),[5-7] whereas in fully covered (FC) SEMS, the main cause is stent migration (14%).[5,8]

In an attempt to address the high migration rate of FCSEMS and thus reduce the recurrent dysphagia rate, we developed the fully covered Hanaro Flap stent (Esophagus Flap BS–Utrecht design; M.I. Tech, Seoul, South Korea). The stent is designed to resist tissue ingrowth but also to prevent stent migration by the incorporation of two specific anti-migration features – stent-anchoring flaps attached around the stent body and flared stent ends. However, whether these anti-migration features indeed reduce stent migration has yet to be proven.

The aim of this prospective follow-up study was to evaluate the clinical efficacy (with particular focus on recurrent dysphagia due to stent migration) and safety of the Hanaro Flap stent for the palliation of malignant dysphagia.

PATIENTS AND METHODS

Patients

Between June 2011 and October 2012, consecutive patients undergoing stent placement for palliation of malignant dysphagia were enrolled in this prospective multicenter study. Patients were included if they had dysphagia (grade≥2 according to Ogilvie) due to a malignant stricture, defined as a nonoperable malignant obstruction of the esophagus or esophagogastric junction, extrinsic malignant compression, or recurrent malignant dysphagia after esophagectomy. Exclusion criteria included previous stent placement for the same condition, tumor stricture within 2 cm of the upper esophageal sphincter, and tumor length of more than 10 cm. All patients gave informed consent. The study protocol was reviewed and

approved by the Medical Ethics Committees of all four participating centres and registered at the Dutch Trial Registration Site (NTR 3313).

Stent placement

The Hanaro Flap stent is an SEMS constructed of nitinol alloy wire and fully covered with a silicone membrane. The diameter of the stent body is 20mm, with flanges of 26mm at each end (Fig.1). On the body of the stent, three rows of covered anti-migration flaps, with four flaps on each row, are attached. Each flap has a length of 2.5mm and a width of 8.5mm. Lassos at both stent ends allow repositioning after placement or stent retrieval. The stent is available in lengths of 8, 11, and 14cm. A stent measuring at least 4cm longer than the stricture was chosen in the current study to allow for overlap of at least 2cm at the upper and lower border of the stricture. All procedures were performed with the patient under conscious sedation using midazolam or propofol.

Figure 1 Fully covered Hanaro Flap stent (Esophagus Flap BS – Utrecht design; M.I. Tech, Seoul, South Korea), with bilateral flared ends and three rows of anti-migration flaps to prevent migration.

Study end points

The primary end point of the study was recurrent dysphagia, with a particular focus on stent migration as the cause. Secondary end points included technical success of placement, functional outcome (dysphagia score), adverse events, and survival.

Recurrent dysphagia was defined as a dysphagia score of ≥2 after initial successful treatment of dysphagia. Dysphagia was scored according to Ogilvie (grade 0 = ability to eat a normal diet; grade 1 = ability to eat some solids; grade 2 = ability to swallow semisolids only; grade 3 = ability to swallow liquids only; grade 4 = complete dysphagia for liquids). Technical success was defined as successful deployment and placement of the stent at the required location, verified by fluoroscopy and/or endoscopy. A severe adverse event was defined as an event with a

(possible) association to the insertion procedure or to the stent and for which an (endoscopic) intervention or hospitalization was required. Adverse events could be treated conservatively with no need for hospitalization.

Follow-up assessment

Patients were evaluated before stent placement, 14 days after stent placement, and monthly thereafter until death or stent removal. For patients still alive at the end of the study, the minimal duration of follow-up was 6months and the maximum was 12months. Evaluation included dysphagia score and symptoms of retrosternal pain and reflux. In cases of recurrent dysphagia, patients underwent endoscopy.

Statistical analysis

Results were expressed as means (±SD) or medians (range), as appropriate. Dysphagia-free survival and overall survival were calculated according to the Kaplan–Meier method. Cox-regression analysis was performed to calculate hazard ratios (HR) and their corresponding 95% confidence intervals (CI) for predictors of migration and occurrence of adverse events. A P value of<0.05 was considered to be statistically significant. All analyses were performed using SPPS software version 20 (IBM Corp., Armonk, New York, USA).

RESULTS

Patient characteristics

A total of 40 consecutive patients with malignant dysphagia due to esophageal cancer (n=32), extrinsic malignant compression (n=5; 4 lung cancers, 1 metastatic breast cancer), recurrent anastomotic cancer (n=2), and gastric cardia cancer (n=1) were included (Table 1). In four patients (10%), an esophageal-respiratory fistula was present at inclusion.

Outcome and survival

Placement of the Hanaro Flap stent was technically successful in all but one patient (98%). In this patient, the stent collapsed during repositioning using a rat tooth forceps and a second stent was placed inside the first stent. As there was no improvement of dysphagia, both stents were removed the next day and another stent was placed.

At 1month after stent placement, all 39 patients with successful stent placement experienced improvement of the dysphagia score by at least 1 grade. The median

Table 1 Baseline characteristics of 40 patients treated with the fully covered Hanaro Flap stent for the palliation of malignant dysphagia.

Characteristics	N=40
Age, mean±SD, years	68±11
Male, n (%)	29 (73)
Dysphagia score before treatment, n (%)	
Grade 2	4 (10)
Grade 3	18 (45)
Grade 4	18 (45)
Previous radiation and/or chemotherapy, n (%)	
Chemotherapy	5 (12.5)
Radiation	3 (7.5)
Both	18 (45)
None	14 (35)
Stricture location, n (%)	
Proximal	6 (15)
Mid	6 (15)
Distal	28 (70)
Tumor location, n (%)	
Esophagus	32 (80)
Cardia	1 (2.5)
Recurrent anastomotic cancer	2 (5)
Extrinsic compression*	5 (12.5)
Stricture length, mean±SD, cm	5.2±2.1
Stent length, n (%)	
80mm	12 (30)
110mm	22 (55)
140mm	6 (15)

*Ductal carcinoma, small cell carcinoma, non-small cell carcinoma, pulmonary epithelioid hemangioendothelioma, large-cell neuroendocrine carcinoma.

dysphagia score improved, from 3 before stent placement to 1 at 1-month follow up.

A total of 30 patients were followed until death, 4 patients until stent removal, and 6 patients were still alive after a follow-up period of≥6months (range 181–365days). The median survival after stent placement was 76days (95%CI59–93 days). The majority of patients (84%) died as a result of tumor progression. Three patients (10%) died of complications due to (aspiration) pneumonia, one patient (3%) from cardiac arrest, and one patient (3%) from tracheal compression due to tumor growth.

Recurrent dysphagia

The median dysphagia-free time after stent placement was 220 days (95%CI 94–345 days). Nine patients (23%) experienced recurrent dysphagia because of stent migration (n=6; 15%), tissue overgrowth (n=2; 5%), or fracture of the stent (n=1; 3%). Complete stent migration into the stomach was observed in one patient after 39 days, and this stent was removed during endoscopy followed by insertion of a new stent. In the other five patients with stent migration, the stent had migrated 2–6 cm distally after a median of 48 days (range 9–96 days). These stents were endoscopically repositioned. One patient returned twice thereafter with recurrent dysphagia due to partial stent migration, for which the stent was repositioned during repeat endoscopy.

There were no statistically significant predictors of stent migration (Table 2). However, stent migration occurred in 3/6 patients (50%) undergoing ongoing treatment compared with only 3 of 33 patients without ongoing treatment (9%).

Tissue overgrowth was observed in two patients at 44 and 132 days after stent placement, respectively. A second overlapping stent was placed in one patient, and in the other patient the stent was removed and replaced. In one patient, the stent fractured at the level of the stent body 220 days after placement, and the lower part of the stent caused obstruction of the esophagus. A new stent was placed through the fractured stent.

Table 2 Univariate analysis of predictors of stent migration in patients treated with the fully covered Hanaro Flap stent for the palliation of malignant dysphagia.

	Migration n=6 (%)	No migration n=33 (%)	HR	95%CI	P value
Extrinsic compression	1 (16.7)	4 (12.1)	4.4	0.4–42.9	0.21
Previous radiation and/or chemotherapy	4 (66.7)	21 (63.6)	1.2	0.2–6.8	0.80
Ongoing radiation or chemotherapy	3 (50.0)	3 (9.1)	4.5	0.92–22.9	0.06
Stent length					
80mm	1 (16.7)	10 (30.3)	1.0	Reference	
110mm	3 (50.0)	19 (57.6)	0.9	0.1–9.1	0.96
140mm	2 (33.3)	4 (12.1)	2.3	0.2-26.1	0.49
Stricture location					
Proximal	1 (16.7)	5 (15.2)	1.0	Reference	
Mid	1 (16.7)	5 (15.2)	0.4	0.02–6.8	0.53
Distal	4 (66.7)	23 (69.6)	0.3	0.03–2.6	0.26

HR, hazard ratio; CI, confidence interval.

Adverse events

A total of 16 severe adverse events occurred in 14 patients (36%) (Table 3). The most common severe adverse event included hemorrhage in three patients. One patient had tumor growth into the left gastric artery resulting in three episodes of hematemesis, and two patients had one bleeding episode each. All patients were successfully treated with radiation therapy and/or blood transfusion. Severe nausea and/or vomiting requiring admission or feeding tube placement was reported in three patients. A new esophageal-respiratory fistula developed in two patients, after 45 and 166 days, respectively. One patient developed a fistula at the proximal stent end, and in this patient the stent was replaced by another stent type resulting in successful sealing of the fistula. The second patient presented with mediastinitis. An additional stent was placed at the level of contrast leakage. This patient died 2 days after the endoscopy due to septic complications. In one patient with a pre-existing fistula, partial migration of the stent resulted in an unsealed fistula. In this patient, a second Hanaro Flap stent was placed through the first stent, and thereafter a control contrast swallow showed no contrast leakage.

Adverse events, particularly mild retrosternal pain (n=11) and nausea and vomiting (n=4), were seen in 19 of 39 patients (49%). All patients with mild retrosternal

Table 3 Adverse events in patients (n=39) treated with the fully covered Hanaro Flap stent for the palliation of malignant dysphagia.

	Number of events
Total severe adverse events	16 (in 14 patients, 36%)
Severe adverse events,≤7days	10 (in 10 patients, 26%)
Severe pain	2
(Aspiration) pneumonia	2
Severe nausea/vomiting	3
Hemorrhage	2
Tracheal compression	1
Severe adverse events,>7days	6 (in 5 patients, 13%)
Hemorrhage	3
Fistula	2
Migration (resulting in an unsealed fistula)	1
Total adverse events	23 (in 19 patients, 49%)
Mild retrosternal pain	11
Nausea/vomiting	4
Candida esophagitis	2
Other*	6

*Reflux, pneumonia, anemia (during chemotherapy), persistent hiccups, fever of unknown origin, pain due to bone metastasis.

pain experienced this pain for a short period (<7 days), and it was successfully treated with a short course of low-dose analgesics. In the majority of patients, the pain resolved within 24hours after stent placement.

Cox-regression analysis showed that prior radiation therapy and/or chemotherapy was not associated with an increased risk of severe adverse events (P=0.13; HR 2.7, 95%CI0.7–10.0) or adverse events (P=0.23; OR 1.8, 95%CI0.7–4.7).

DISCUSSION

In this prospective, multicenter, follow-up study, the Hanaro Flap stent provided relief of malignant dysphagia in the majority of patients. Although the recurrent dysphagia rate was relatively low, the stent migration rate was not reduced compared with other FCSEMS. This was somewhat surprising because this FCSEMS was specifically designed to reduce migration rates.

The main goal of palliative treatment in patients with inoperable malignant esophageal obstruction is to provide rapid and persistent relief of dysphagia. Although rapid relief of symptoms is achieved in almost all studies that have reported on results of SEMS placement, the occurrence of recurrent dysphagia has largely remained unchanged (i.e. at ~30%–40%).[2,3] Compared with other studies, the 23% rate of recurrent dysphagia in the current study was relatively low.

It is known that stent migration is the main cause of recurrent dysphagia when FCSEMS are placed in the esophagus.[3] To prevent migration, several anti-migration features have been reported. However, results have been mixed: bilateral flared ends (5%–14% migration),[9,10] anti-migration struts (36%),[11] or a double layered mesh (0–12%).[5,10,12] The migration rate of 15% in the current study is comparable to the rate for FCSEMS that have bilateral flared ends as their only anti-migration feature, suggesting that the flaps of the Hanaro Flap stent are of only limited value for the prevention of migration. However, it is important to note that migration was only partial in 5/6 patients in the current study, with a downward migration of a few centimeters seen during endoscopy. Nonetheless, all patients with migration had symptoms of recurrent dysphagia. In contrast, the majority of reported stent migrations with other SEMS were into the stomach.[5,9,11] In the current study, management of partial migration included endoscopic repositioning, which is relatively easy to perform and associated with lower costs than placement of a new stent. It is possible that increasing the number of flaps might result in prevention of partial migration.

Placement of the Hanaro Flap stent was associated with a high adverse event rate. Severe adverse events were reported in 36% of patients, which is in the

upper range when compared with rates of 18%–36% with other FCSEMS.[3,4,9] An interesting finding was the occurrence of severe nausea and/or vomiting in three patients, as this is a not commonly reported adverse event after esophageal SEMS placement. Hirdes et al. recently reported frequent nausea and/or vomiting in a study in which single-dose brachytherapy was combined with biodegradable stent placement for dysphagia due to esophageal cancer.[13] The high axial force of the biodegradable stent was proposed to be a causative factor due to its negative effect on esophageal motility. However, this is unlikely to be the cause in the current study because recent in vitro testing showed that the Hanaro esophageal stent only has a moderate to low axial force.[14] Another explanation might be that severe nausea and/or vomiting was caused by impaired esophageal motility due to the malignant process. All three patients had undergone radiation therapy and two had also received chemotherapy before stent placement. Radiation therapy may induce esophageal damage in the form of necrosis and fibrosis, and concomitant chemotherapy could enhance this effect resulting in impaired esophageal motility.

A negative effect of radiation therapy and/or chemotherapy prior to stent placement has also been reported in previous studies on SEMS placement in the esophagus. It has been suggested that it increases the risk of (severe) adverse events, although this was not confirmed in all studies.[15] Although no association between prior radiation therapy and/or chemotherapy and occurrence of (severe) adverse events was found, it should be taken into account, particularly when comparing these results with other studies, that a relatively high percentage of patients (64%) had undergone radiation therapy and/or chemotherapy in the current study,

Retrosternal pain was recorded in a significant number of patients (33%) in the current study and is also a commonly encountered adverse event after stent placement in other studies, with incidence rates ranging from 10% to 34%.[2,4,9,11,]12 Nonetheless, a strict definition of retrosternal pain is not always used across studies; for example, in some studies only pain requiring admission or (high dose) opiates was reported, whereas in the current study, any retrosternal pain that required any form of pain medication was recorded as an adverse event; this might explain the high overall rate of retrosternal pain in 13 of 39 patients (33%). Furthermore, the thorough prospective follow-up schedule with specific attention to symptoms such as retrosternal pain and reflux may have also contributed to this high adverse event rate. Symptoms such as retrosternal pain are probably less frequently encountered in studies in which adverse events are collected retrospectively.

It is also possible that stent characteristics (e.g. anti-migration flaps) contributed to the occurrence of adverse events. Only a randomized study comparing the fully covered Hanaro stent with and without flaps will give a definitive answer as to

whether the flaps induce adverse events. However, as the flaps are small in size (2.5•8.5mm) and flexible, we think that they are unlikely to be the cause of adverse events.

The prospective follow-up schedule is one of the strengths of this study, particularly the first follow-up visit 2 weeks after stent placement, which is likely to be important with regard to the recording of procedure-related adverse events. The main limitations of the study are the lack of randomization and a control group. Moreover, there are differences in definitions of adverse events, follow-up schedule, and patient characteristics between reported studies. To overcome these limitations in future studies, we recently started an initiative to define end points for studies investigating stents in the gastrointestinal tract.

In conclusion, this study demonstrated that the Hanaro Flap stent is effective for the palliation of malignant dysphagia with a low recurrent dysphagia rate. However, despite the anti-migration features, stent migration was still a major cause of recurrent dysphagia. It is unclear whether the relatively high rate of adverse events was the result of the selected patient population and thorough follow-up or a result of stent characteristics.

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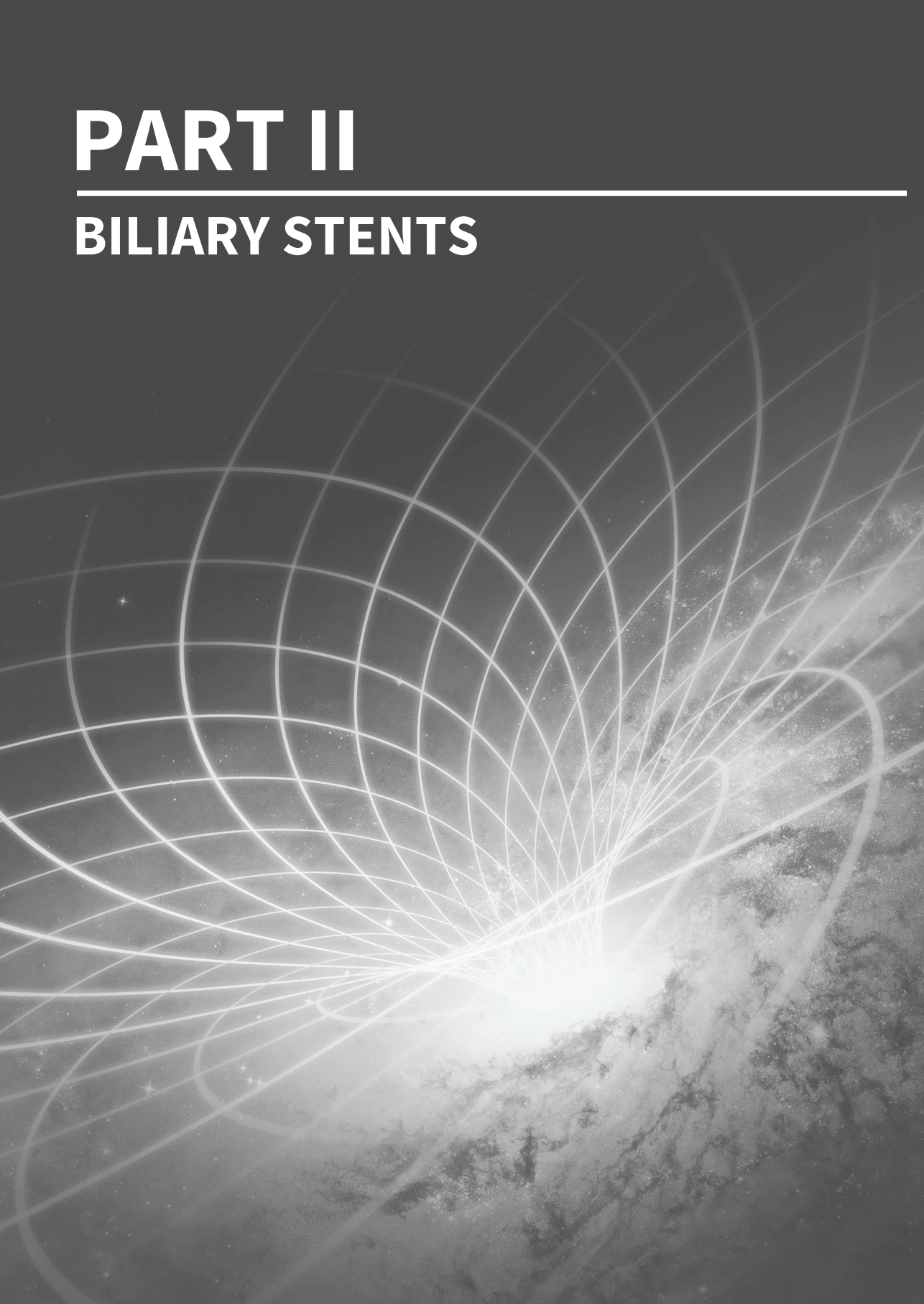
PART II

BILIARY STENTS



CHAPTER 4

A fully covered self-expandable metal stent with anti-migration features for benign biliary strictures: a prospective, multicenter cohort study

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ABSTRACT

Background: Self-expandable metal stents (SEMS) are increasingly used for the treatment of benign biliary strictures (BBS). A new fully covered (FC) SEMS with flared ends and high conformability was designed to prevent migration of the stent.

Objective: To evaluate the efficacy of a novel FCSEMS with anti-migration features.

Design: Prospective cohort study

Setting: Five hospitals in the Netherlands and Belgium.

Patients: Consecutive patients with BBS.

Intervention: FCSEMS placement for 3 months.

Main Outcome Measurements: Initial and long term clinical success, stent migration rate and safety.

Results: Thirty-eight patients (24 men, mean age 53 ± 16 years) were included. Stent placement was technically successful in 37 patients (97%). Two patients died due to an unrelated cause before stent removal and no data on these patients was available on stricture resolution. Initial clinical success was achieved in 28 of 35 patients (80%). During follow-up after stent removal, 6 of 28 patients (21%) developed a recurrent stricture. Overall, the long term clinical success rate was 63% (22 of 35 patients). Stent migration occurred in 11 of 35 patients (31%), including five symptomatic (14%) and six asymptomatic migrations (17%). In total, 11 serious adverse events occurred in 10 patients (29%), with cholangitis (n=5) being most common.

Limitations: Non-randomized study design.

Conclusions: Good initial clinical success was achieved after placement of this novel FCSEMS, but stricture recurrence was in the upper range compared to other FCSEMS. Stent migration seems not different from other FCSEMS with a flared design.

INTRODUCTION

Benign biliary strictures (BBS) may develop as a result of a variety of causes, of which chronic pancreatitis and post-surgical bile duct injuries, either following cholecystectomy or on the anastomotic site after liver transplantation, are most frequently encountered.[1] To prevent the occurrence of serious complications due to these strictures, including jaundice, cholangitis and secondary biliary cirrhosis, biliary decompression is recommended.[2]

Endoscopic therapy with placement of multiple plastic stents has evolved as first choice treatment modality for biliary dilation. Treatment consists of sequential stenting with increasing numbers of plastic stents during a one-year period with 3-monthly stent exchanges to preclude stent obstruction. With this approach, stricture resolution is achieved in 80-89% of patients with post-surgical strictures[3-6] and in 31-92% of patients with chronic pancreatitis.[4,5,7,8]

Major drawback of this therapy is the need for frequent stent exchanges to prevent or manage stent occlusion, even if multiple stents are placed.[8,9] In an attempt to improve stent patency and reduce the number of procedures required, self-expandable metal stents (SEMS) have been introduced as an alternative for plastic stents because of their larger luminal diameter. It has already been demonstrated that SEMS have a longer stent patency compared to plastic stents in patients with malignant biliary strictures.[10] Uncovered SEMS for benign strictures are not desirable due to tissue ingrowth through the stent mesh resulting in a limited long-term stent patency and difficulties with removal over time.[11-14] Therefore, fully covered (FC) SEMS are increasingly preferred to treat benign strictures.

The advantage of FCSEMS is the possibility of easy stent removal in case of adequate dilation of the stricture or in case of stent dysfunction. However, as embedding of the stent mesh in the mucosa is unlikely to occur, stent migration is a frequently encountered problem with migration rates up to 41%.[15-19] In order to prevent migration, several anti-migration features have been tested with varying results, including stents with anti-migration fins,[18,19] double pigtail stents for anchoring[20] and stents with flared ends.[18,21]

Moon et al. recently reported excellent results for the prevention of migration using the Niti-S bumpy type stent (Taewoong Medical, Seoul, South Korea) in patients with benign pancreatic duct strictures.[21] The Niti-S bumpy type stent is fully covered and has two anti-migration features, including a high conformability at the middle part of the stent and flared stent ends at both sides. Until now, no data are available on the use of this stent for strictures in the biliary tract. Therefore, the aim of our study was to prospectively assess the efficacy of this FCSEMS with anti-migration features in patients with BBS.

PATIENTS AND METHODS

Patients

Between August 2010 and April 2013, consecutive patients with BBS were enrolled in this prospective, multicenter study in two tertiary referral hospitals and three general hospitals in the Netherlands and Belgium. Inclusion criteria for enrolment were (1) clinical symptoms of biliary obstruction and/or an extrahepatic biliary stricture seen during ERCP, (2) a benign etiology of the extrahepatic bile duct stricture, as confirmed with a computed tomography (CT) scan and/or endoscopic ultrasonography (EUS), (3) age 18 years or older, and (4) stent placement feasible during ERCP. Exclusion criteria were (1) a peripheral or hilar biliary stricture, (2) a stricture due to primary sclerosing cholangitis, (3) previous metal stent placement and (4) a history of surgical hepatico-jejunostomy, choledocho-jejunostomy or choledocho-duodenostomy. All patients provided written informed consent. The study was approved by the Medical Ethics Committees of all participating centers and registered at the Dutch Trial Registration (NTR 1910).

Niti-S biliary bumpy stent

The Niti-S biliary bumpy stent (Taewoong Medical, Seoul, South Korea) is a SEMS constructed of nitinol wire with bilateral flared ends. The flared ends are covered with silicone whereas the body of the stent is covered with a polytetrafluoroethylene (PTFE) membrane. At the body of the stent the cell sizes are irregular, resulting in different segmental radial forces and a high conformability. The combination of the high conformability and the flared ends are proposed to reduce the risk of stent migration. On the proximal stent end a removal string is attached. The stent is available in 4-, 6-, 8-, 10- and 12-cm lengths. For this study stents with a diameter of 10-mm were used.

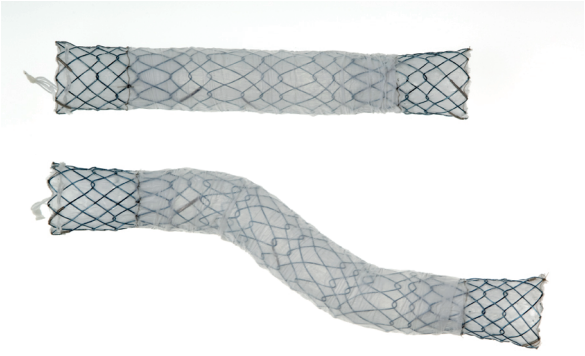

Figure 1 FC Niti-S biliary bumpy stent.

Stent placement and removal

Stent placement was performed during ERCP under conscious sedation with midazolam or propofol, monitored anesthesia care, or general anesthesia. Following biliary cannulation, stricture location and length were determined with fluoroscopy and the appropriate stent length was determined. The stent was placed across the stricture with approximately 1-cm of the stent exposed to the duodenal lumen.

Removal was performed with rat-tooth forceps by grasping the distal end of the stent after a 3-month dwell time. The effect of dilation on the biliary stricture was assessed by fluoroscopy immediately after stent removal. In case of a persisting stricture a new stent (plastic or metal) was placed at the discretion of the treating physician.

Follow-up assessment

Patients were evaluated just prior to stent placement and removal, 14 days after stent placement and removal and subsequently at 3-month intervals for one year. Evaluation included assessment of clinical symptoms and biochemical markers of biliary obstruction. In case of recurrent biliary obstruction, patients underwent a new endoscopic procedure.

Definition of endpoints

Primary endpoint of the study was initial clinical success and secondary endpoints included technical success of stent placement and removal, stent migration rate, long term clinical success and safety.

Initial clinical success was defined as resolution of the stricture during control fluoroscopy immediately after stent removal. Technical success was defined as accurate positioning and deployment of the stent along the entire length of the stricture with easy free flow of contrast fluid through the stent to the duodenum. Stent migration was defined as either proximal or distal, and divided into symptomatic and asymptomatic migrations. Symptomatic migration included migration resulting in complications and/or a persistent stricture. Asymptomatic migration included migration without complications and with stricture resolution. Long term clinical success was defined as initial clinical success without the need for repeat stent placement for stricture recurrence during study follow up. Safety was defined as the number of early (<7 days) and late (≥7 days) serious adverse events.

Statistical analysis

Continuous variables were reported as mean (standard deviation) and median (interquartile range (IQR) or range), as appropriate. Categorical variables were reported in terms of frequency counts and proportions. Success rates between

different subgroups were analyzed using χ^2 or Fisher exact testing, whenever appropriate. A p-value of <0.05 was considered statistically significant. All analyses were performed using SPPS software version 20 (SPSS Inc, Chicago, Ill). The study is descriptive by design and therefore no formal power calculation was performed.

RESULTS

In total, 38 patients with BBS were included in the study (Table1). The most common stricture cause was chronic pancreatitis (n=24), followed by post-surgical stricture formation (n=7), papillary stenosis (n=4), severe acute pancreatitis (n=1), post-chemotherapy (n=1) and post-cholelithiasis (n=1). The median duration of disease was 179 days (IQR 55-353 days). Thirty patients (79%) were previously treated with (multiple) plastic stents and had undergone a mean of 2 replacements (ranging from 1-7) before inclusion. Two patients were assigned as lost to follow up, both died due to an unrelated cause (pancreatic carcinoma and severe renal failure) in the period between stent placement and removal, and those patients were not included in analysis on clinical success and safety.

Table 1 Clinical baseline characteristics of 38 patients with benign biliary strictures.

Characteristics	**N=38**
Age, y, mean (± SD)	53 (16)
Male, n (%)	24 (63)
Stricture etiology, n (%)	
Chronic pancreatitis	24 (63)
Post-surgical	7 (18)
Iatrogenic ampullary stenosis	4 (11)
Other*	3 (8)
Prior common bile duct stenting, n (%)	30 (79)
Length of the stricture, cm (mean (range)	3.0 (0.5-5)
Location of stricture, n (%)	
Distal common bile duct	30 (79)
Mid common bile duct	8 (21)

* other include severe acute pancreatitis, post-chemotherapy, post-cholelithiasis

Technical success

Stent placement was technically successful in 37 of 38 patients (98%). In 1 patient the stent did not cover the entire length of the stricture due to inward migration following deployment. A plastic stent was therefore placed through the FCSEMS

to cover the complete stricture. Due to severe abdominal pain both stents had to be removed 5 days after placement and were replaced with another type FCSEMS. In 3 patients (8%), stent deployment progressed slowly after the sheath had been fully removed and balloon dilation of the stent was required in one of them to achieve adequate deployment of the stent.

Clinical success

Stricture resolution was achieved in 28 of 35 patients, resulting in an initial clinical success rate of 80%. In 6 of 7 patients with a persisting stricture, the stent dwell time was less than the intended 3-month period due to stent migration (n=5) and early removal due to suspicion of cholecystitis (n=1). One patient with a persisting stricture was diagnosed with pancreatic cancer at the time of stent removal.

During a median follow-up of 265 days (IQR 93-285) after stent removal or migration, 6 of 28 patients (21%) developed recurrent stricturing. None of the patients with asymptomatic migration developed recurrent stricture. The median time to stricture recurrence was 135 days (IQR 20-206 days). Therefore, long term clinical success was achieved in 22 of 35 patients (63%).

Initial clinical success was similar in patients with BBS due to chronic pancreatitis and post-surgical strictures (17/24 (71%) vs. 5/7 (71%), p=0.98). The long term clinical success seemed higher in patients with post-surgical stricture, although this difference was not statistically significant (5/7 (71%) vs. 13/24 (54%), p=0.42). In patients with symptomatic stent migration the initial success was significantly lower compared to patients with asymptomatic or no migration (0/5 (0%) vs. 28/33 (85%), p<0.005). In addition, final success was significantly lower in the stent migration group (0/5 (0%) vs. 22/33 (67%), p=0.005). The clinical success rate in patients previously treated with (multiple) plastic stents was similar to patients without previous treatment, both for the initial success (24/28 (86%) vs. 4/7 (57%), p=0.13) and the final success rate (19/28 (68%) vs. 3/7 (43%), p=0.38).

Stent removal was successfully performed in 28 patients after a median stent dwell time of 97 days (range 1-355 days). In 8 patients no stent removal was performed since the stent had completely migrated.

Stent migration

Stent migration occurred in 11 of 35 patients (31%), including five symptomatic (14%) and six asymptomatic migrations (17%) (Table2.). Of the five patients with symptomatic migration, three presented with cholangitis before scheduled stent removal (median 68 days, range 8-68), including one patient with a partial distal stent migration and two patients with complete distal migration. All three patients

Table 2 Migration of the Niti-S biliary bumpy stent in 35 patients with a benign biliary stricture.

	N=35
Total migration	**11 (31)**
Symptomatic	**5 (14)**
Distal	5 (14)
Partial	1
Complete	4
Asymptomatic	**6 (17)**
Proximal	1 (3)
Distal	5 (14)
Partial	1
Complete	4

underwent secondary stent placement with either a plastic stent or SEMS. In the other two patients complete distal stent migration was seen during the scheduled ERCP for stent removal and fluoroscopy showed a persisting stricture for which plastic stents were placed.

All asymptomatic migrations were detected during the scheduled ERCP for stent removal, including one proximal migration, one partial distal migration and four complete distal migrations. None of these six patients experienced any symptoms due to stent migration and fluoroscopy showed no persisting stricture.

Safety

A total of 11 serious adverse events (SAEs) occurred in 10 patients (29%) (Table3). The most common SAE included cholangitis in 5 patients, due to stent migration (n=3) and stent occlusion (n=2). In the two patients with cholangitis due to stent occlusion the stent was longer in situ than the intended 3-month period. One patient postponed the scheduled stent removal and presented with cholangitis 141 days after stent placement. In the other patient, known with thrombosis of the superior mesenteric and splenic vein, stent removal was postponed because of bleeding duodenal varices. This was managed conservatively, but resulted in delayed stent removal. This patient presented with cholangitis 155 days after stent placement. One patient with pre-existing cholelithiasis was diagnosed with cholecystitis 4 days after stent placement. Since imaging showed numerous gallstones this was thought to be the cause of cholecystitis and the FCSEMS was left in place and cholecystectomy was performed. Another patient developed severe abdominal pain a few hours after stent placement. Since there was a high clinical suspicion of cholecystitis with the FCSEMS as potential cause of occlusion of the cystic duct, the FCSEMS was exchanged for two plastic stents. However, after further imaging

this patient was diagnosed with recently developed portal vein thrombosis as cause of the symptoms which was presumed not to be related to the procedure.

Table 3 Serious adverse events in 35 patients treated with the Niti-S biliary bumpy stent for a benign biliary stricture.

Characteristics	11 in 10 patients (29%)
<7 days	5 in 5 patients (14%)
Flare up of chronic pancreatitis	1
Post-ERCP pancreatitis	1
Cholecystitis	1
Portal vein thrombosis	1
Post ERCP fever	1
≥7 days	6 in 5 patients (14%)
Cholangitis	5
Stent occlusion	2
Stent migration	3
Bleeding of duodenal varices	1

DISCUSSION

This prospective, multicenter follow-up study is the first report on the clinical efficacy of this novel FCSEMS for the treatment of BBS. Although we demonstrated a good initial clinical success with this stent, stricture recurrence was seen in a considerable number of patients. Furthermore, despite the proposed anti-migration features of this FCSEMS, the stent migration rate in this study was still significant.

Following the successful introduction of SEMS for the treatment of malignant biliary strictures, SEMS are also increasingly being used for the treatment of BBS.[10,14] In the first reports on SEMS for BBS, uncovered SEMS were used without the intent of removal. Although the short term results were promising, hyperplastic tissue ingrowth through the stent mesh caused stent obstruction on the long-term in up to 100% of patients.[11-14] To overcome the problem of tissue ingrowth, temporary placement of partially covered SEMS was introduced as an alternative treatment.[22,23] Although no problems were encountered during a 4- to 5-month stent dwell time, tissue ingrowth through the uncovered portion of the stent not only resulted in difficulties with stent removal but also led to newly induced strictures at the former site of the uncovered proximal portion of the stent.[23] The use of FCSEMS almost completely eliminates the problem of tissue ingrowth, but is hampered by the risk of stent migration in up to 41% of patients due to a lack of embedding of FCSEMS in the wall of the common bile duct.[15-19]

In an attempt to reduce the risk of stent migration, this novel FCSEMS was designed with flared ends at both stent ends and a high conformability at the middle part of the stent. Moon et al. used this type stent for the treatment of 32 patients with benign pancreatic duct strictures and reported no migrations and a 100% stricture resolution rate after a 3-month stent dwell time. However, control fluoroscopy showed (asymptomatic) de novo pancreatic-duct strictures on the proximal stent end in five patients (16%).[21] Poley et al. also reported a low migration rate in a study using FCSEMS with flared ends for the treatment of BBS (3%). Nonetheless, higher migration rates have also been reported with this stent design (10.5-33%).[18,24,25] In a study by Park et al., reporting a migration rate of 33%, no differentiation was made between symptomatic and asymptomatic migrations. Based on the limited information on the migrations in that study, it seems that only 3 of the 7 reported migrations were symptomatic, resulting in a corrected migration rate of 14%.[18] In our present study, we observed a comparable total migration rate with this novel FCSEMS of 31%, with symptomatic migration in 14% of patients. This latter means more precisely that in half of all patients with stent migration the stricture had completely resolved and that none of these patients developed recurrent strictures during the follow-up period. This suggests that migration of the stent in those patients might have occurred because the stricture was optimally dilated. Other studies have also reported stricture resolution in a significant proportion of patients with stent migration.[11,16,22,25-27]

Stent migration may also lead to complications, such as cholangitis, in patients without stricture resolution.[15,28] Cholangitis due to stent migration occurred in three patients (8%) in our study and all patients required additional stenting. Combined with two cases of cholangitis due to stent obstruction, the incidence of cholangitis (13%) is comparable to other series reporting on FCSEMS, with cholangitis rates varying between 5% and 14%.[1,18,24,26] No complications were observed due to the stent design, such as formation of de novo strictures or difficulties when removing the stent.

The initial clinical success rate, defined as stricture resolution at the moment of stent removal, using FCSEMS for BBS has been reported to exeed 80% in most studies (range 60% to 95%).[16-20,24,26,27,29] The lowest stricture resolution rates (60-67%) have been reported in patients with BBS due to pancreatitis,[17,19,24,27] which is in line with results obtained with progressive plastic stenting.[3-5,7,8] We found a comparable initial clinical success rate of 80%, with only a slightly lower success rate (71%) in patients with strictures due to chronic pancreatitis. In addition, previous treatment of the stricture has been reported to negatively influence treatment success.[23] It can be imagined that patients with previously failed plastic stent therapy have more refractory strictures and are therefore also more difficult

to treat with SEMS. However, in our study, a high percentage of patients (79%) had previously been treated with plastic stents, but no association was found between previous stent placement and treatment failure.

Although the initial clinical success rate in our study was comparable to other studies, the stricture recurrence rate of 21% is in the upper range when compared to recurrence rates varying from 5 to 25% in other studies.[16-18,20,26,27,29,30] Stricture recurrence after initial resolution could imply that the stricture has been dilated properly but the remodelling process was not yet completed, suggesting that a shorter stent dwell time might result in higher recurrence rates. However, high stricture recurrences rates have been reported in studies with both shorter (2 months)[28,30] and longer stent dwell time (4-6 months).[17,18]

Total stent dwell time varies considerably between reports on SEMS for the treatment of BBS (from 2 to 6 months) and mostly there is no rationale mentioned for the length of stent dwell time. Recently, two studies have shown that a longer stent dwell time may improve initial clinical outcome.[24,25] Poley et al. performed a study to evaluate safety of stent removal of a FCSEMS with a proximal lasso that enables inside-out removal. Stent removal was performed after 2 months and in case of a persisting stricturing a new stent was placed. After 2 months, stricture resolution was only achieved in 30% of patients, while after a second FCSEMS placement success was achieved in 65% of patients.[24] Kalaheh et al. retrospectively analysed 133 patients who received a FCSEMS for the treatment of BBS and found a stent dwell time>3 months to be a predictor for stricture resolution.[25] On the other hand, a longer stent dwell time may result in more complications. Two of three patients in our study with a longer stent dwell time (>4 months) developed cholangitis as a result of stent occlusion. Therefore, the optimal stent dwell time remains to be determined.

An important limitation of our study is the absence of a control group treated with either plastic stents or another type of FCSEMS. Therefore, we compared our results with those of other case series. Due to substantial differences in study design, type of stent used, stent dwell time and stricture cause between studies no definite conclusions can be drawn on the efficacy of this stent compared to other stents. Furthermore, we also included patients with different types of strictures, with the number of separate stricture types being small. Nonetheless, the overall sample size of our study was in the upper range compared to most other published series. The strength of our study is its prospective nature with substantial follow up after stent removal to allow accurate evaluation of stricture recurrence. As a result we were able to provide information on the stricture recurrence rate.

In conclusion, this study shows that the use of this novel FCSEMS for the treatment of patients with BBS resulted in a good initial clinical success rate. The occur-

rence of stent migration was comparable with other FCSEMS with a flared design. Stricture recurrence after initial successful treatment with this novel FCSEMS is in the upper range compared to other FCSEMS. However, it is questionable whether this is really due to the design of the stent since other factors, such as stent dwell time and patient characteristics, might play a role in stricture recurrence as well. It is therefore recommended that future studies will compare various endoscopic treatment strategies in order to ensure progress in the optimal treatment of patients with BBS.

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CHAPTER 5

Cost efficacy of metal stents for palliation of extrahepatic bile duct obstruction in a randomized controlled trial

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ABSTRACT

Background and aims: Endoscopic stents are placed for palliation of extra-hepatic bile duct obstruction. Although self-expandable metals stents (SEMS) remain patent longer than plastic stents, they are more expensive. We aimed to evaluate which type of stent (plastic, uncovered [uSEMS], or partially covered [pcSEMS]), is most effective and assessed costs.

Methods: We performed a multi-center randomized trial in 219 patients at 18 hospitals in the Netherlands from February 2008 through February 2013. Patients were randomly assigned for placement of a plastic stent (n=73), uSEMS (n=75), or pcSEMS (n=71) during endoscopic retrograde cholangiopancreatography. Patients were followed for up to one year. Researchers were not blinded to groups. The main study endpoints included functional stent time and costs.

Results: The mean functional stent times were 172 days for plastic stents, 288 days for uSEMS, and 299 days for pcSEMS (P<.005 for uSEMS and pSEMS vs plastic). Initial placement of plastic stents (€1,042) cost significantly less than of SEMS (€1,973) (P=.001). However, the total cost per patient at the end of the follow-up period did not differ significantly between plastic stents (€7,320) and SEMS (€6,932) (P=.61). Furthermore, in patients with a short survival times (≤3 months) or metastatic disease, total cost per patient did not differ between plastic stents and SEMS. No differences in costs were found between pcSEMS and uSEMS.

Conclusion: Although placement of SEMS (uncovered or partially covered) for palliation of extra-hepatic bile duct obstruction is initially more expensive than placement of plastic stents, SEMS have longer functional time. Total costs after one year do not differ significantly with stent type. Dutch Clinical Trial Registration no: NTR1361

INTRODUCTION

Extrahepatic bile duct obstruction is a common complication in patients with pancreatic adenocarcinoma, cholangiocarcinoma or malignant lymphadenopathy. The majority of patients have already metastatic or locally advanced disease at the time of diagnosis and therefore only 10-20% of patients are eligible for curative surgical resection.[1, 2] For all other patients, treatment consists of palliative placement with a plastic or self-expandable metal stent (SEMS) to relieve symptoms of jaundice, pruritus, malabsorption and cholangitis.[3-5]

Randomized controlled studies have shown that SEMS are superior to plastic stents in terms of recurrent biliary obstruction, number of reinterventions and functional stent time.[6-11] Nonetheless, SEMS placement is not universally accepted as standard treatment. High costs of SEMS and the uncertainty that these high costs might not be offset by a reduction in costs for reinterventions are the main reasons for reluctance, especially in patients with a short survival. Although several studies have investigated costs associated with plastic and SEMS placement, results of these studies are inconclusive on the cost-effectiveness of SEMS use, particularly in patients with an expected short survival.[9-13] Most studies suggest that SEMS are only cost-effective in patients with a long survival, i.e. longer than 4-6 months. Based on these results, the use of SEMS is often reserved for patients with a prolonged survival expectancy whereas plastic stents are used in patients with a limited survival expectancy (<3 months).[14-16] Besides tumour size and presence of (hepatic) metastasis, there are no criteria that reliably predict survival.[9, 10, 15, 17, 18] Furthermore, all but one study compared plastic stents with uncovered SEMS (uSEMS)[11] while partially covered SEMS (pcSEMS) and fully covered SEMS are increasingly being used.[19] As a result, to date there are no strong recommendations regarding stent choice for the palliation of malignant extrahepatic bile duct obstruction.

The aim of this study was to evaluate which type of stent, either a plastic stent of SEMS, is superior for the palliation of malignant extrahepatic bile duct obstruction with regard to clinical effects and associated costs, both in patients with a short and long survival. For this, we compared the three most commonly used stent types (plastic, uSEMS and pcSEMS) in a multicentre randomized controlled trial, with a full cost comparison using detailed information on health care use.

PATIENTS AND METHODS

We conducted a multicentre randomized trial between February 2008 and February 2013 in 3 tertiary referral centres and 15 general hospitals. The study protocol was reviewed and approved by the ethics committees of all participating centres and registered at the Dutch Trial Registration (NTR1361).

Patients

Patients were included if they presented with an increased serum bilirubin level (≥30 mmol/L) and/or clinical symptoms of obstructive jaundice due to an inoperable obstructive malignancy at the level of the extrahepatic common bile duct. A patient was considered to be inoperable if the tumor was locally irresectable, distant metastases were present or when the patient was in a poor medical condition. Exclusion criteria included a malignancy involving the intrahepatic bile ducts or duodenum, a known history of cholecystitis (unless cholecystectomy had been performed), a history of surgery to the bile duct and a World Health Organization (WHO) performance score of 4 (100% of time in bed). Written informed consent was obtained before randomisation.

Randomisation

Patients were randomized for endoscopic placement of a plastic stent, uSEMS or pcSEMS during ERCP. The randomisation process was conducted before the start of the ERCP using a web based randomisation program with stratification for centre of inclusion and for primary stent placement or stent placement for a first episode of stent dysfunction (i.e. a second stent). Patients included for primary stent placement could be included again in the study in case of a first period of stent dysfunction. No blinding was performed.

Stent placement procedure

All endoscopic procedures were performed in patients under conscious sedation with midazolam or propofol (with or without fentanyl). After successful bile duct cannulation and guidewire placement across the stricture, retrograde cholangiography was performed to visualize the stricture. If no stricture was visualized or intrahepatic involvement was seen, the patient was excluded. If the stricture comprised an extrahepatic stricture without hilar involvement, the assigned type of stent was placed. For plastic stents this included a 10Fr polyurethane stent (Boston ScientificCorporation, Natick, MA, USA) or a 10Fr polyethylene stent (Cook, Inc., Winston-Salem, NC, USA) in lengths of 5 to 10cm. For both types of SEMS a 10-mm Wallstent™ RX (Boston Scientific Corporation) either uncovered or with a

partial permalume cover in lengths of 4-, 6-, or 8-cm was used. Stent types were randomized in a 1:1:1 fashion. Stent length was chosen according to the stricture location and length. Sphincterotomy was performed at the discretion of the endoscopist. In case of failed stent placement, stent insertion was conducted during an additional attempt, either with ERCP, percutaneous transhepatic cholangiography (PTC) or using a combined approach (rendez-vous).

Follow-up and end-points

Study endpoints included functional stent time, proportion of patients with stent dysfunction, cause of stent dysfunction, patient survival, serious adverse events (SAEs) and costs. Functional stent time was defined as the time from stent placement to stent dysfunction, patients' death or one-year follow-up if no stent dysfunction occurred. Stent dysfunction was defined as the presence of symptoms of obstructive jaundice or cholangitis in combination with confirmation of stent obstruction or migration during ERCP. SAEs were divided in short term (<7days) and long term (≥7days) events. Cost evaluation included costs for initial stent placement (including secondary procedures in case of initial failure), costs for total initial treatment (initial stent placement and hospitalisation), follow-up costs (diagnostics, treatment and hospitalisation for stent dysfunction and complications) and endoscopic costs (costs for initial stent placement and costs for additional endoscopic procedures during follow-up)

Patients were prospectively followed by home visits or telephone calls by study personnel at 14 days, 1 month, and then monthly until 6 months and 2-montly thereafter until a maximum of one year after treatment. Patients received a diary in which symptoms of obstructive jaundice were scored every day for 1 month and every week thereafter. In case of symptoms of obstructive jaundice, patients were evaluated in the hospital and ERCP was performed, if permitted by the patients' clinical condition. Further treatment was at the discretion of the treating physician and included stent replacement, additional stent placement or stent cleaning. Patients with a first episode of stent dysfunction were eligible to be re-included in the study in the stent dysfunction stratum. The volume of health care use, including all diagnostic and therapeutic procedures and hospital admissions, was listed in standardized case record forms during all follow-up moments and hospital visits.

Sample size and statistical analysis

For the sample size, we calculated that 80 patients were required in each stent group if the hazard ratio for stent dysfunction was at least 0.5 for the comparison of the two treatment groups (plastic vs. uSEMS and plastic vs. pcSEMS) with α=0.05

and β=0.8, considering a stent failure rate of 30-50% for plastic stents, 15-35% for uSEMS and 10-20% for pSEMS.[7-11, 20]

Comparison between the groups was performed with Student t-test or Mann-Whitney test for continuous variables and the χ^2-test or Fisher's exact test for categorical variables. Functional stent time and survival were calculated according to the Kaplan-Meier method and the 3 groups were compared by the log-rank test and Cox-regression analysis. No p-value adjustment was performed for multiple comparisons.

For each patient, real medical costs were calculated by multiplying volume of care (units of healthcare utilization reported in the case record forms) with their corresponding unit prices. For the most important cost item, stent placement during ERCP, the unit price was determined using the micro-costing method, which is based on a detailed inventory and measuring of all the resources used.[21] All other unit prices were determined using proxy charges of real costs, based on Dutch consumer price indices and the Dutch Health Authority.[22, 23] Reference prices are listed in Appendix 1. Since costs per patient are typically highly skewed, we used non-parametric bootstrapping techniques to calculate the mean costs per patient and to derive a p-value for the differences in distribution of costs.[24] Discounting was not relevant because of the limited time horizon per patient. All statistical analyses were performed using an intention-to-treat approach and with SPPS software version 20 (SPSS Inc, Chicago, Ill). All co-authors had full access to the study data and reviewed and approved the final manuscript.

RESULTS

A total of 240 patients were enrolled in the study, 188 patients with a first stent placement and 52 patients with a stent placement after a first episode of stent dysfunction. Eight patients were included in both strata. Twenty-one patients were excluded after the ERCP procedure (involvement of intrahepatic ducts n=7, no stenosis n=4, withdrawal of informed consent n=4, duodenal involvement n=2, benign stricture n=2, surgical candidate n=1, previous surgery of bile duct n=1), resulting in a final inclusion of 219 patients (Figure 1). Patient characteristics per stratum are listed in Table 1. Pancreatic cancer was the most common stricture cause in both strata. However, in patients with primary stent placement this proportion was significantly higher compared to patients with a second stent placement (87% vs. 67 %, p=0.004). Furthermore, the mean bilirubin level was significantly higher in patients with a primary stent placement (187 mmol/L vs. 56 mmol/L, p<0.005). No difference was observed between the three different stent groups in both strata.

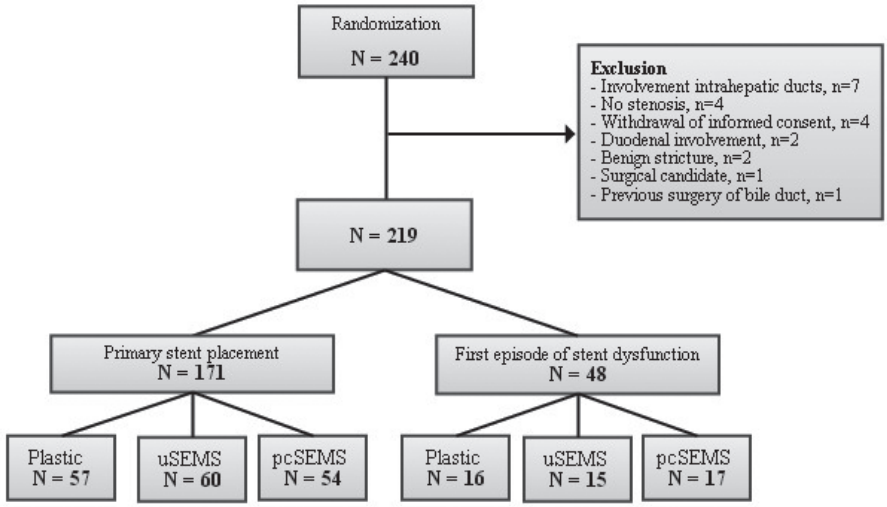

Figure 1 Flow chart showing the patients' course during the study.

Table 1 Patient characteristics of 219 patients with malignant extrahepatic bile duct obstruction.

	Primary stent placement N=171	Second stent placement N=48	P value
Male gender (%)	80 (47)	28 (58)	0.16
Mean age (years) (SD)	73 (13)	71 (10)	0.07
Tumour cause (%)			**0.004**
Pancreas	148 (87)	33 (69)	
Other	23 (13)	15 (31)	
Metastatic disease (%)			0.14
Yes	83 (49)	31 (65)	
No	87 (51)	17 (35)	
Median bilirubin level* (µmol/L)(IQR)	187 (122-254)	56 (52-97)	**<0.001**
Reason for inoperability (%)			0.37
Local irresectable	80 (47)	22 (46)	
Poor clinical condition	32 (18)	6 (12)	
Metastatic disease	49 (29)	14 (30)	
Combination	10 (6)	6 (12)	
Mean WHO score (SD)	1.4 (0.9)	1.3 (0.9)	0.36
Histological diagnosis (%)			0.11
Yes	39 (23)	18 (38)	
No	132 (77)	30 (62)	

* normal value<21 µmol/L WHO score=World Health Organization (WHO) performance score

Stent placement

Stent placement during the first ERCP was successful in 174 of 219 patients (79%). Stent placement was unsuccessful in 44 of 171 patients (26%) with a primary stent placement and in one of 48 patients (2%) with a first episode of stent dysfunction. The main reason for failure was inability of cannulation of the common bile duct (31 of 45 patients = 69%). There was no difference in initial failure between the different stent groups (plastic; 25% vs. uSEMS; 19% vs. pcSEMS; 18%, p=0.57). Failure was higher in general hospitals (23%) compared to tertiary referral centres (14%), although this difference was not significant (p=0.12).

Finally, successful stent placement was achieved in 204 of 219 patients (91%), during ERCP (n=179), PTC (n=14) or rendez-vous (n=11). Fifteen patients (9%) were not treated with a stent, but were treated conservatively (n=9), with a PTC drain (n=4) or underwent palliative gastrojejunostomy (n=2).

Overall median length of hospital stay after stent placement was 4 days (IQR 2-6), with a significant difference between patients with successful stent placement (median 3 days, IQR 2-6) and patients with initial failure (median 8 days, IQR 5-12; p<0.05).

Patient survival

After 1-year follow-up, 182 of 219 patients died (83%), 30 patients (14%) were still alive and 7 patients (3%) were lost to follow-up. Overall median survival was 109 days (95% CI 85-133), with no difference in survival between the different stent types (Figure 2a). Survival was significantly shorter for patients with metastatic disease compared to patients without metastasis (80 days, 95% CI 62-98 vs. 172 days, 95% CI 105-239, p=0.001) (Figure2b). Median survival in patients with placement of a second stent was significantly longer (171 days, 95% CI 118-224) compared to patients with primary stent placement (89 days, 95% CI 66-112), p=0.031), (Figure2c). At 3 months, 47% of patients with primary stent placement were still alive compared to 77% in the group of patients with a second stent (p<0.001).

Stent dysfunction and functional stent time

During a mean follow-up of 131 days (IQR 34-209), stent dysfunction was observed in 42 of 171 patients (25%) with primary stent placement; 23 in the plastic stent group (40%), 10 in the uSEMS group (17%) and 9 in the pcSEMS group (17%) (p=0.003). Mean functional stent time was 172 days (95% CI 126-219), 268 days (95% CI 219-317) and 286 days (95% CI 240-332), respectively (p=0.001) (Figure 3a). Patients with SEMS had a significantly lower hazard (uSEMS: HR 0.33, 95% CI 0.16-0.69 and pcSEMS: HR 0.32, 95% CI 0.15-0.69) for developing stent

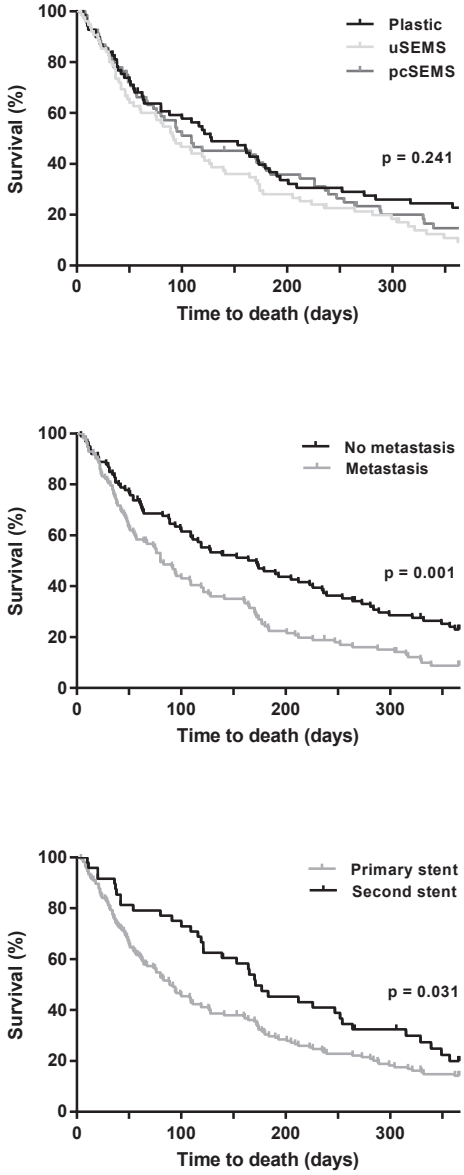

Figure 2 Patient survival after stent placement for palliation of malignant extrahepatic bile duct obstruction using the Kaplan-Meier method by (A) stent type, (B) presence of metastasis and (C) primary or second stent placement.

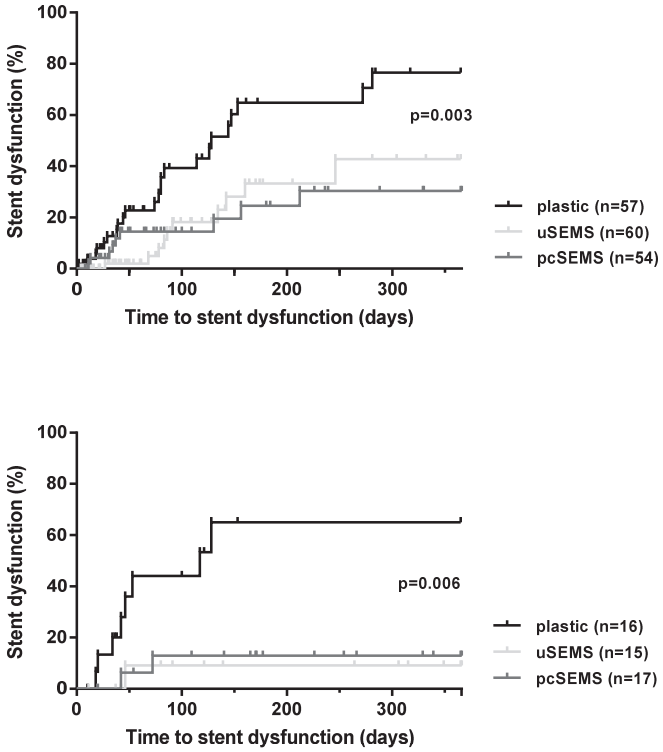

Figure 3 Functional stent time after stent placement for palliation of malignant extrahepatic bile duct obstruction using the Kaplan-Meier method for (A) patients with primary stent placement and (B) patients with a second stent.

dysfunction before death or end of study compared to patients with a plastic stent. Mean number of reinterventions was 0.65 for patients in the plastic stent group, 0.28 in the uSEMS group and 0.27 in the pcSEMS group (p=0.002).

Eleven of 48 patients (23%) with stent placement after a first episode of stent dysfunction developed stent dysfunction; 8 in the plastic stent group (50%), 1 in the uSEMS group (7%) and 2 in the pcSEMS group (12%) (p=0.006) during a mean follow-up time of 193 days (IQR 93-325). Mean functional stent time was 170 days (95% CI 85-255), 367 days (95% CI 282-391) and 326 days (95% CI 274-378), respectively (p=0.002) (Figure3b). In this subgroup, patients with SEMS also had a significantly lower hazard, uSEMS (HR 0.10, 95% CI 0.01-0.082) and pcSEMS (HR 0.15, 95% CI 0.03-0.70), for developing stent dysfunction compared to patients with a plastic stent. Mean number of reinterventions was 0.69 for patients in the plastic stent group, 0.07 for the uSEMS group and 0.10 in the pcSEMS group (p=0.003).

In both strata no significant differences were found in functional stent time and risk of stent dysfunction between uSEMS and pcSEMS. One quarter of patients with stent dysfunction presented with cholangitis (13 of 53 patients); 5 in the plastic stent group, 5 in the uSEMS group and 3 in the pcSEMS group (p=0.147). Mechanisms of stent dysfunction are shown in table2.

Table 2 Mechanism of stent dysfunction per stent type.

	Plastic N=73	uSEMS N=75	pcSEMS N=71
Debris	24	3	5
Migration	5	1	0
Ingrowth	0	6	0
Overgrowth	0	1	2
Other/unknown	2*	0	4**
Total	**31(42%)**	**11 (15%)**	**11 (15%)**

* Combination of debris and migration (n=2)
** No ERCP performed due to poor clinical condition of the patient (n=2), haemobilia (n=1), failed ERCP due to duodenal stenosis (n=1)

Serious adverse events

Short term SAEs were seen in 5 patients in the plastic stent group (7%), in 5 patients in the uSEMS group (7%) and in 3 patients in the pcSEMS group (3%) (p=0.76) (Table3). In all three groups 10 long term SAEs occurred (p=0.99). Chole-

Table 3 Serious adverse events after stent placement for malignant extrahepatic bile duct obstruction.

	Plastic N=73	uSEMS N=75	pcSEMS N=71
Short term SAE	**5 (7%)**	**5 (7%)**	**3 (4%)**
Post procedural fever	3	1	2
Post ERCP-pancreatitis	-	1	-
Other*	2	3	1
Long term SAE	**10 (14%)**	**10 (13%)**	**10 (14%)**
Cholecystitis	1	-	1
Pancreatitis	1	-	-
Gastric outlet obstruction	3	3	3
Other *	5	7	6

*Pneumonia (2), pulmonary embolism (2), cardiac arrest (1), urosepsis (1)
** Includes hospital admissions for dehydration (3), pneumonia (2), portal vein thrombosis (2), unkown fever (1), spontaneous bacterial peritonitis(1), leakage of PTC drain (1), retroperitoneal bleeding after celiac plexus neurolysis (1), collum fracture (1), cardiac arrest (1), rectal blood loss (1), hematemesis (1), deep vein thrombosis (1), pulmonary embolism (1), severe ascites (1).

cystitis was reported in two patients, in one patient with a plastic stent and in one patient with a pcSEMS. Pancreatitis was only reported in one patient with a plastic stent. Gastric outlet obstruction requiring surgery or stent placement was the most common long term complication (n=9; 30%).

Costs

Costs for the initial stent placement were significant higher for both SEMS types compared to plastic stents in both patients with primary stent placement (€2011 and €1933 vs. €1092, p=0.001, figure 4a) and patients with stent placement for a first episode of stent failure (€1967, €1997 vs. €871, p=0.001, figure 4b). Costs for the whole initial treatment were not statistically significant different between patients with a plastic stent, uSEMS and pcSEMS in patients with primary stent placement (€4282 vs. €5076 vs. €4599, p=0.44, figure 4a) as well as in patient with secondary stent placement (€3556 vs. €3545 vs. €3849, p=0.88, figure 4b).

During follow-up, in patients with primary stent placement mean costs for diagnostic and treatment for stent dysfunction were significantly higher in patients with a plastic stent (€790) compared to patients with uSEMS (€375, p=0.04) and pcSEMS (€151, p=0.002). In patients with a second stent placement costs for stent dysfunction were also significantly higher in the plastic stent group (€966) compared to uSEMS (€52, p=0.03) and pcSEMS (€207, p=0.007). Costs for hospitalisation during follow-up were not statistically different between the stent groups in both strata (Fig4a and b).

Mean total costs per patient for the total treatment were not significantly different between the three different stent types in both patients with primary stent placement and patients with a second stent.

Costs in patients with successful initial stent placement

Costs for initial stent placement were not different from the costs of one ERCP, as shown in Table 1 in the Appendix. Costs for hospitalization were also not significantly different between the groups (p=0.26). Costs for the whole initial treatment were higher in the SEMS group (€2614) compared to the plastic stent group (€2225), although this difference was not significantly different (p=0.06). There was no significant difference between uSEMS and pcSEMS. Mean total costs, including follow-up, were not significantly different between the three different stent types (€6906 for plastic stents, €7039 for uSEMS and €5801 for pcSEMS; p=0.28)

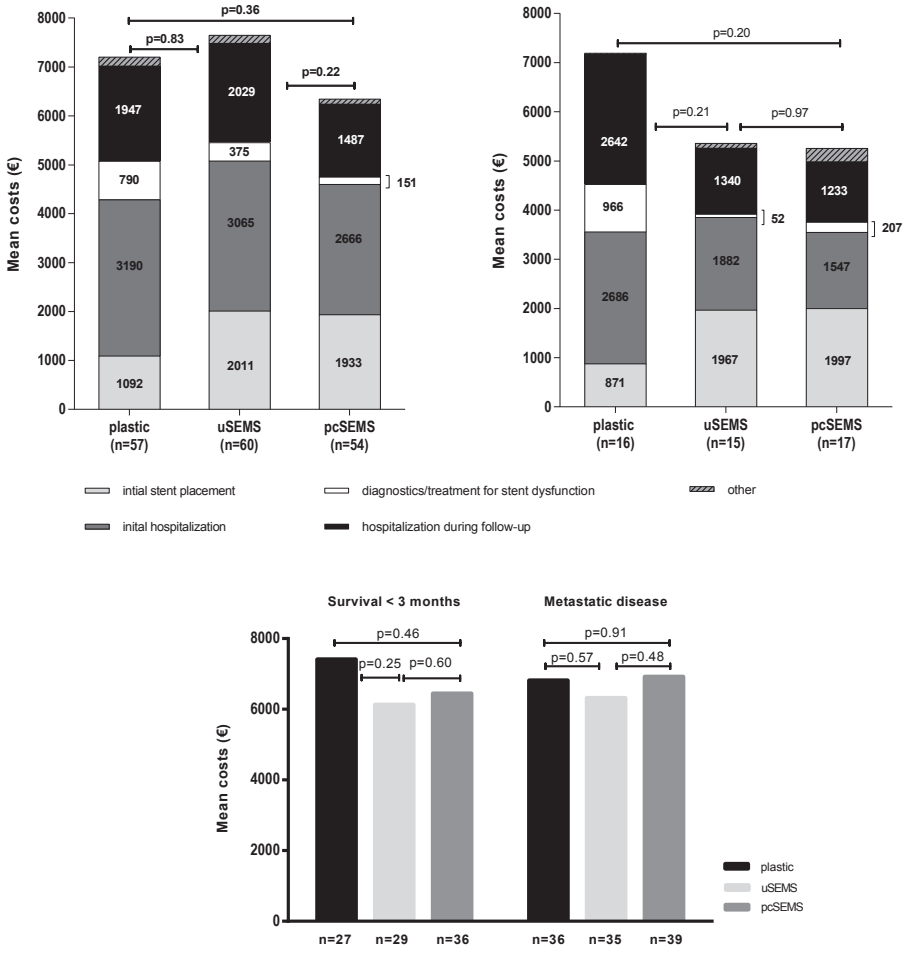

Figure 4 Mean costs during follow-up (per patient in euro (€)) for palliation of malignant extrahepatic bile duct obstruction. (A) Primary stent placement. (B) Second stent placement. (C) Short survival (<3months) and metastatic disease.

Costs in short survivors

For patients with a short survival (≤3 months) and patients with metastatic disease, we found no difference in total costs between plastic stents and SEMS (Fig4c). In patients with successful initial stent placement, total costs were also not different between plastic stents and SEMS in patients with a short survival (€6555 vs. €5719; p=0.4) or metastatic disease (€6593 vs. €6179; p=0.69). In all subgroups there were also no differences in costs between pcSEMS and uSEMS placement.

Endoscopic costs

Mean costs per patient for the endoscopy department, i.e. only ERCP-related costs, were not different in the overall study population. In patients with a primary stent placement, mean costs were €1724 for plastic stents, €2081 for uSEMS and €2021 for pcSEMS (p=0.20). Mean costs in patients with a second stent were €1733, €2205 and €2019 (p=0.19), respectively.

However, costs for the endoscopy department were significantly higher for SEMS compared to plastic stents in patients with a short survival (<3 months) (€1255 vs. €1796, p=0.006), patients with metastatic disease (€1542 vs. €1987, p=0.012) and patients with successful initial stent placement (€1769 vs. €2201, p=0.018). There were no differences in costs between uSEMS and pcSEMS placement.

DISCUSSION

This multicentre, randomized study is the first study comparing three different stent types for the palliation of malignant extrahepatic bile duct obstruction. We found that total medical costs are not different between patients treated with a plastic stent or with SEMS, even in patients with a survival shorter than three months. In addition, we confirm previous findings showing that SEMS are superior to plastic stents with regard to functional stent time and stent dysfunction.

Ever since the introduction of SEMS for the palliation of malignant biliary obstruction in 1989, the costs of SEMS have been a subject of debate.[25, 26] Placement of SEMS, approximately 10 times the price of a plastic stent, will only be cost-effective when the high initial costs are offset by a reduction in costs during follow-up. There is convincing evidence that for patients with a relatively long survival after stent placement, i.e. longer than 4-6 months, total health care costs of SEMS placement compare favourably with plastic stent placement.[7-12, 27, 28] For patients with an expected survival of only 3-4 months or those with metastatic disease, plastic stents are generally recommended as the most "economical" option. However, this recommendation is largely based on decision analysis studies and only supported by two randomized clinical studies. [9, 10, 12, 13] In our study, total treatment costs for patients with a short survival and those with metastatic disease were not different between plastic stents and SEMS. In fact, we found that the costs difference for initial stent placement were already outweighed when costs of hospitalisation after stent placement were included in the initial treatment costs.

The median duration of hospital stay after stent placement in our study was 4 days and costs for hospitalization comprised 60% of the total costs of the initial treatment. Interestingly, only two other studies included costs for hospital stay

after stent placement in their cost analysis.[6, 9] Lammer et al. reported a relatively long hospital stay after stent placement, with a mean of 10 and 21 days for SEMS and plastic stents, respectively. It is not surprising that these authors concluded that hospital stay was the main cost driver of the initial treatment. However, stent placement in this study was performed using a percutaneous approach and can therefore not directly be compared to the endoscopic setting.[6] Prat et al. included a fixed duration of two days of hospital admission for all patients in their cost calculation, irrespective of the actual duration of admission.[9] The use of such a standard price for the initial treatment has actually been used in all previously performed randomized studies.[7-11] As a result, none of these previously published studies have taken into account costs associated with failure of stent placement and hospital stay and therefore unlikely reflect real healthcare costs. We included all healthcare costs associated with the treatment and found that stent costs are only a minor contributor to the total health care costs. This may hold even more strongly in countries were costs for hospital stay are higher than in our study, such as the United States.

We only achieved successful stent placement during the first ERCP in 78% of patients, compared to a technical success rates of 88-100% in other studies.[6-11, 29] However, in all those studies patients were only included in the study if successful cannulation of the common bile duct was established. If we would have included only patients after successful cannulation of the common bile duct, as was done in other studies, our technical success rate would also have been 93%.

In order to provide a detailed and complete overview of all costs associated with stent placement for palliation of malignant extrahepatic bile duct obstruction, we included the costs of all intramural health care use in our calculation. However, local reimbursement policies ultimately determine which costs have the highest impact. For example, in the Netherlands, the costs for the type of stent used are most important for an endoscopy department as these costs put the main pressure on the budget. We therefore also performed a sub-analysis with only the costs for the endoscopy department. We found no cost differences between plastic stents and SEMS in the overall study population. However, subgroup analysis revealed that costs for the endoscopy department were significantly higher for SEMS in patients with a short survival, metastatic disease and in patients with successful initial stent placement. Beside differences in reimbursement policies, prices of unit costs may also vary considerably between countries. In an attempt to make a more generalizable cost analysis, decision analysis studies using cost ratios rather than unit costs have been conducted.[11-13, 15] Based on these decision models, it has been concluded that SEMS placement is cost-effective when SEMS costs are less than half the costs of an ERCP.[12] In our setting, the costs of SEMS comprise 48% of

the costs of the ERCP and indeed we found that SEMS are a cost-effective option. Nonetheless, in a study by Yoon et al., it was demonstrated that SEMS placement can also be cost-effective when SEMS are four times the price of an ERCP.[27]

At the time that we started this study, pcSEMS were increasingly used as alternative for uSEMS to prevent recurrent biliary obstruction due to tissue ingrowth through the stent meshes. Although we indeed found no cases of tissue ingrowth through the mesh of pcSEMS in our study, in other studies tissue ingrowth through the uncovered stent ends has been reported as cause of stent failure.[30, 31] In order to completely overcome the problem of tissue ingrowth, fully covered SEMS (fcSEMS) have been developed. These stents became only available during the course of this study. A recent meta-analysis has however not shown a clear benefit for either type of stent, i.e. uSEMS, pcSEMS or fcSEMS, in terms of functional stent time or survival. However, the most common causes of stent dysfunction differ considerably between these types of stents, with tissue ingrowth being the predominant cause of stent dysfunction for uSEMS and migration for fcSEMS.[19, 20, 30-33] In an attempt to further reduce stent dysfunction and prolong stent patency modifications of the SEMS design are continuously being developed, such as a fcSEMS with anti-migration features.[34] If the efficacy of SEMS will indeed be further increased, this will even more strengthen the recommendation of using the more expensive SEMS for palliation of extrahepatic bile duct obstruction with SEMS.

The median survival of 109 days in our study is in the lower range compared to the median survival of 108-149 days in other studies comparing plastic stents and SEMS.[6, 7, 9-11] This can probably be explained by the high percentage of patients with metastatic disease in our study (52%) compared to other studies (27-39%).[6, 10, 11] Metastatic disease is known to have an adverse effect on survival, which was also observed in our study. Interestingly, we also found a significant difference in survival between patients with primary stent placement and those receiving a second stent (142 vs. 199 days). It is remarkable that the latter group had a longer survival, since these patients already had a prior period of stent placement. The significant lower bilirubin level at baseline could implicate less aggressive disease in this group of patients. However, it could possibly also be explained by less diagnostic delay in these patients.

The strength of this study is the randomized controlled study design with a comparison of three commonly used stents. Only one previous study compared plastic stents with covered SEMS and in none of the other studies plastic stents were compared with both uSEMS and pcSEMS. Furthermore, it is the largest study in which plastic and metal stents for the treatment of malignant extrahepatic bile duct strictures were compared. Regarding the cost analysis we thoroughly collected all items that contribute to the use of health care starting at the time of

treatment but also during follow-up. As this was a multicentre study involving 18 centres, comprising approximately 20% of all Dutch hospitals, the results of this study likely reflect the quality of endoscopic palliative care of patients with extrahepatic bile duct obstruction of the entire country and not just of one centre. A limitation of the study is that the power calculation was based on clinical outcome of stent placement and not on cost differences. Furthermore, as is true for all cost studies and discussed above, it is to some extent difficult to translate these results to countries with other costs and reimbursement systems.

In conclusion, this study shows that placement of SEMS is cost-effective for the palliation of malignant extrahepatic bile duct obstruction. The clinical outcome of SEMS placement is superior compared to plastic stent placement and although initial costs for stent placement are higher for SEMS, total costs are not different between both stent types. Furthermore, in patients with a short survival total treatment costs are also not higher for SEMS. Since the clinical outcome with SEMS is favorable and total costs are not different, we recommended SEMS placement for palliation of extrahepatic bile duct obstruction in all patients.

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CHAPTER 6

Higher quality of life after metal stent placement compared to plastic stent placement for malignant extrahepatic bile duct obstruction: a randomized controlled trial

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ABSTRACT

Background: For palliation of extrahepatic bile duct obstruction self-expandable metals stents (SEMSs) are superior to plastic stents in terms of stent patency and occurrence of stent dysfunction. We assessed health-related quality of life (HRQoL) after stent placement to investigate whether this also results in a difference in HRQoL between patients treated with a plastic stent or SEMS.

Patients and methods: Randomized multicenter trial with 219 patients randomized to plastic stent (n=73) or SEMS (uncovered (n=75) and covered (n=71); n=146) placement. HRQoL was assessed with two general questionnaires (EQ-5D-5L and QLQ-C30) and one disease specific questionnaire (PAN-26). Questionnaires were filled out before treatment, at 14 days, and then monthly until 6 months thereafter. Scores were analyzed using linear mixed model regression and included all patients with baseline and at least one follow-up measurement.

Results: HRQoL data was available in 140 of 219 patients (64%), 71 patients (32%) declined participation and in 8 patients (4%) only baseline questionnaires were available. Baseline characteristics were the same for patients with a plastic stent or SEMS. On the QLQ-C30, the interaction between follow-up time and type of stent was significantly different on two of five functional scales (physical functioning (p=0.004) and emotional functioning (p=0.01)) in favor of patients with a SEMS. In addition, patients with SEMS reported significantly less frequent symptoms of fatigue (p=0.01), loss of appetite (p=0.02) and nausea and vomiting (0.04) over time. The EQ-VAS score decreased in time in both treatment groups, indicating a statistically significant decrease in HRQoL over time

Conclusion: In patients with inoperable malignant extrahepatic bile duct obstruction metal stent placement results in better scores for general- and disease-specific HRQoL over time compared to plastic stent placement.

INTRODUCTION

The majority of patients with malignant extrahepatic bile duct obstruction already have metastatic or locally advanced disease at the time of diagnosis.[1,2] Treatment of these patients is focusing on palliation of symptoms due to bile duct obstruction, such as jaundice, pruritus, malabsorption and cholangitis. The palliative treatment of choice for recanalization of the obstructed bile duct is placement of a biliary stent, either a plastic or a self-expandable metal stent (SEMS).[3]

Randomized trials have not shown any survival benefit for either type of stent, but SEMS are clearly superior in terms of functional stent time and occurrence of stent related complications.[4-9] Remarkably, it is unknown whether this also translates into an improved health-related quality of life (HRQoL) in patients with SEMS. None of the studies comparing plastic stents and SEMS included HRQoL as outcome measure, while preservation of HRQoL should be an important goal of palliative treatment. Especially when there is no difference in overall survival between therapeutic options, it has been suggested that HRQoL should be the main outcome measurement to evaluate efficacy of palliative treatment modalities.[10-14]

In the present study we assessed HRQoL repeatedly after stent placement to investigate the difference in HRQoL of patients treated with a plastic stent or SEMS for the palliation of extrahepatic bile duct obstruction.

METHODS

This multicenter randomized controlled trial (PLAMET-trial) was conducted between February 2008 and February 2013 in 3 tertiary referral centers and 15 general hospitals. The study protocol was reviewed and approved by the ethics committees of all participating centers and registered at the Dutch Trial Registration (NTR1361). The results on clinical outcome (functional stent time, survival, adverse events) and costs of this trial have been reported recently.[9]

Patients

Patients were included if they presented with an increased serum bilirubin level (≥30 μmol/L) and/or clinical symptoms of obstructive jaundice due to an inoperable obstructive malignancy at the level of the extrahepatic common bile duct. Exclusion criteria included a malignancy involving the intrahepatic bile ducts or duodenum, known history of cholecystitis (unless cholecystectomy had been performed), previous surgery of the bile ducts and a World Health Organization

(WHO) performance score of 4 (100% of time in bed). Written informed consent was obtained from each patient before randomization.

Randomization

Randomization was conducted before the start of the ERCP using a web-based randomization program with stratification for center of inclusion and for primary stent placement or stent placement after a first episode of stent dysfunction. Patients included for primary stent placement could be included again in the study in case of a first period of stent dysfunction. Blinding was not performed. Patients were randomized to treatment with a plastic stent, an uncovered SEMS (uSEMS) or a partially covered SEMS (pcSEMS) in a 1:1:1 ratio. Plastic stents included a 10Fr polyurethane stent (Boston Scientific Corporation, Natick, Mass, USA) or a 10Fr polyethylene stent (Cook, Inc., Winston-Salem, NC, USA). Both SEMS types included the 10-mm Wallstent™ RX (Boston Scientific Corporation, Natick, Mass, USA), either uncovered or with a partial permalume cover.

Stent placement procedure

Stent placement was performed during ERCP with patients under conscious sedation with midazolam or propofol. In case no stricture was visualized or when hilar involvement was seen, patients were excluded. The length of the stent was chosen according to the stricture localization and stricture length. Endoscopic sphincterotomy was performed at the discretion of the endoscopist. In case of failed stent placement, stent insertion was in most cases conducted during an additional attempt, either with ERCP, percutaneous transhepatic cholangiography (PTC) or a combined approach (rendez-vous).

Quality of life

Quality of life was assessed using the oncology-specific EORTC QLQ-C30,[15] the pancreatic cancer-specific EORTC QLQ-PAN26[16] and the EuroQol (EQ)-5D-5L including the EQ visual analogue scale (EQ-VAS).[17] The QLQ-C30 incorporates five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and, nausea and vomiting), a global health scale and various single symptom items. The QLQ-PAN26 incorporates seven symptom scales (pancreatic pain, digestive symptoms, altered bowel habit, hepatic symptoms, body image, sexuality, and satisfaction with health care) and various single symptom items. The scoring for the QLQ-C30 and QLQ-PAN26 consists of answer categories ranging from 'not at all' (scored as 1) to 'very much' (scored as 4). Scores on the items for the global health scale ranged from 1 ('very poor') to 7 ('excellent'). In the

functional scales, a high score means better functioning, whereas in the symptoms scales a higher score means more or more severe symptoms.

The EQ-5D-5L assesses 5 dimensions (mobility, self-care, daily activities, pain/discomfort, and anxiety/depression) and for each dimension patients can mark one of three levels of severity. The EQ-VAS is a vertical visual analogue scale on which patients are asked to rate their overall health state and varying between 'worst imaginable health state' and 'best imaginable health state'.

Patients were asked to fill out all questionnaires at baseline, 14 days after treatment and monthly thereafter until 6 months or death. Questionnaires were filled out during home visits or during follow-up phone calls with assistance of trained study personnel.

Statistical analysis

The HRQoL was one of the secondary endpoints of the PLAMET trial.[9] Primary endpoint of the study included functional stent time. Sample size calculation showed that 80 patients were required in each stent group to achieve a hazard for stent dysfunction of at least 0.5 between two treatment groups (plastic vs. uSEMS and plastic vs. pcSEMS) with α=0.05 and β=0.8. Analyses were performed according to the intention-to-treat principle. All patients with data at baseline and at least one follow-up measurement were included in the analyses. The two SEMS groups (uSEMS and pcSEMS) were combined in the analyses. Categorical variables were analyzed using Fisher's exact test and continuous variables with the t-test or Mann-Whitney U test, as appropriate. Survival was calculated according to the Kaplan-Meier method and compared with the log-rank test.

For the QLQ-C30 and QLQ-PAN26 questionnaires, scoring algorithms produced by the EORTC Quality of Life Study Group were used.[18] For the EQ-5D-5L the score was classified into a health status profile and linked to an index score based on empirical preferences for health status from a Dutch general population sample.[17,19]

The HRQoL scores per stent group were displayed in graphs using the mean scores with the 95% confidence interval. We compared HRQoL scores using linear mixed model regression analyses and included follow-up time (continuous, per day), stent type (plastic, SEMS) and the interaction between follow-up and stent type, corrected for baseline HRQoL measurements. For the hepatic symptom scale (i.e. symptoms of jaundice and pruritus) on the QLQ-PAN26 questionnaire, separate analyses were performed for short-term effects (≤30-days after inclusion) and long-term effects (>30-days after inclusion).

All analyses were performed using SPPS software version 20 (SPSS Inc, Chicago, Ill). A p-value less than 0.05 was considered significant.

RESULTS

Baseline characteristics

A total of 240 patients were enrolled in the study, of which 21 were excluded after the ERCP had been performed. Reasons for exclusion were involvement of intrahepatic ducts (n=7), no stenosis (n=4), withdrawal of informed consent (n=4), duodenal involvement (n=2), benign stricture (n=2), surgical candidate (n=1) and previous surgery of the bile duct (n=1). The remaining 219 patients were randomized to receive a plastic stent (n=73) or SEMS (uncovered (n=75) or covered (n=71); n=146). Baseline questionnaires and at least one follow-up measurement were available in 140 of 219 patients (64%), 71 patients (32%) declined participation in the HRQoL sub-study and in 8 patients (4%) only baseline questionnaires were available. Baseline characteristics of the patients that completed HRQoL questionnaires were similar for patients with a plastic stent and SEMS (Table 1). HRQoL data, predominantly from the period just before death, was missing in 13% of patients. In the patient group without available HRQoL data patients had

Table 1 Baseline characteristics of patients that completed HRQoL questionnaires.*

	(n=140)		
	Plastic N=40	**SEMS N=100**	**P**
Male gender	18 (45)	51 (51)	0.57
Age, mean (SD)	72 (11)	72 (11)	0.96
Stent type	NA		
uSEMS		49 (49)	
pcSEMS		51 (51)	
Stratum			0.67
First stent placement	31 (78)	72 (72)	
Second stent placement	9 (22)	28 (28)	
Tumor etiology			0.80
Pancreas	32 (80)	83 (83)	
Other	8 (20)	17 (17)	
Metastatic disease	23 (58)	60 (60)	0.85
Bilirubin, µmol/L, mean(SD)	175 (110)	178 (119)	0.87
WHO score, mean(SD)	1.4 (1.0)	1.4 (0.9)	0.85
Histologic diagnosis	9 (23)	26 (26)	0.83
Survival, median (95% CI)	127 (48-205)	121 (57-185)	0.56

* Patients with baseline questionnaire and at least one follow-up questionnaire.
WHO=World Health Organization
Values are displayed as number and percentage except if stated otherwise

more often received a first stent (86% vs 74%, p=0.04) and had less frequently metastatic disease (39% vs. 59%, p=0.01) compared to patients with HRQoL data.

General health

Overall, HRQoL on the functional scales of the EORTC QLQ-C30 questionnaire was higher in patients with a SEMS compared to patients with a plastic stent (Figure1). The interaction between follow-up time and type of stent was statistically significant on two functional scales (physical functioning (p=0.01) and emotional functioning (p=0.01)). On all scales, the HRQoL of the SEMS group remained stable over time and decreased in the plastic stent group (Table2). The general HRQoL of all patients in our study was considerably lower compared to the HRQoL of the general population on all functional scales (Figure1). The EQ-VAS score decreased in time in both treatment groups, indicating a statistically significant decrease in HRQoL over time (Figure2).

Symptom scales and single items

Patients with SEMS reported significantly less frequent symptoms of fatigue (p=0.01), loss of appetite (p=0.02) and nausea and vomiting (0.04) over time. The severity of symptoms remained stable in the SEMS group and increased in the plastic stent group (Table2). On all other general symptom and single item scales no difference in scores between stent groups was found over time.

QLQ-PAN26 questionnaire

A reduction of hepatic symptoms, i.e. jaundice and pruritus, was seen after stent placement in both groups, with no difference in hepatic symptoms during the first month of follow-up between patients with a plastic stent and SEMS (Figure3). A statistically significant increase of digestive symptoms over time was observed in both groups, with a stronger increase of digestive symptoms in the plastic stent group (p=0.003).

DISCUSSION

This multicenter randomized clinical trial is the first study comparing HRQoL between patients treated with a plastic stent or SEMS for palliation of malignant extrahepatic bile duct obstruction over time. We demonstrated that patients with a SEMS scored significantly better on both general and disease specific HRQoL questionnaires over time. In the plastic stent group, the HRQoL deteriorated over time on most scales, while HRQoL remained stable in patients with a SEMS.

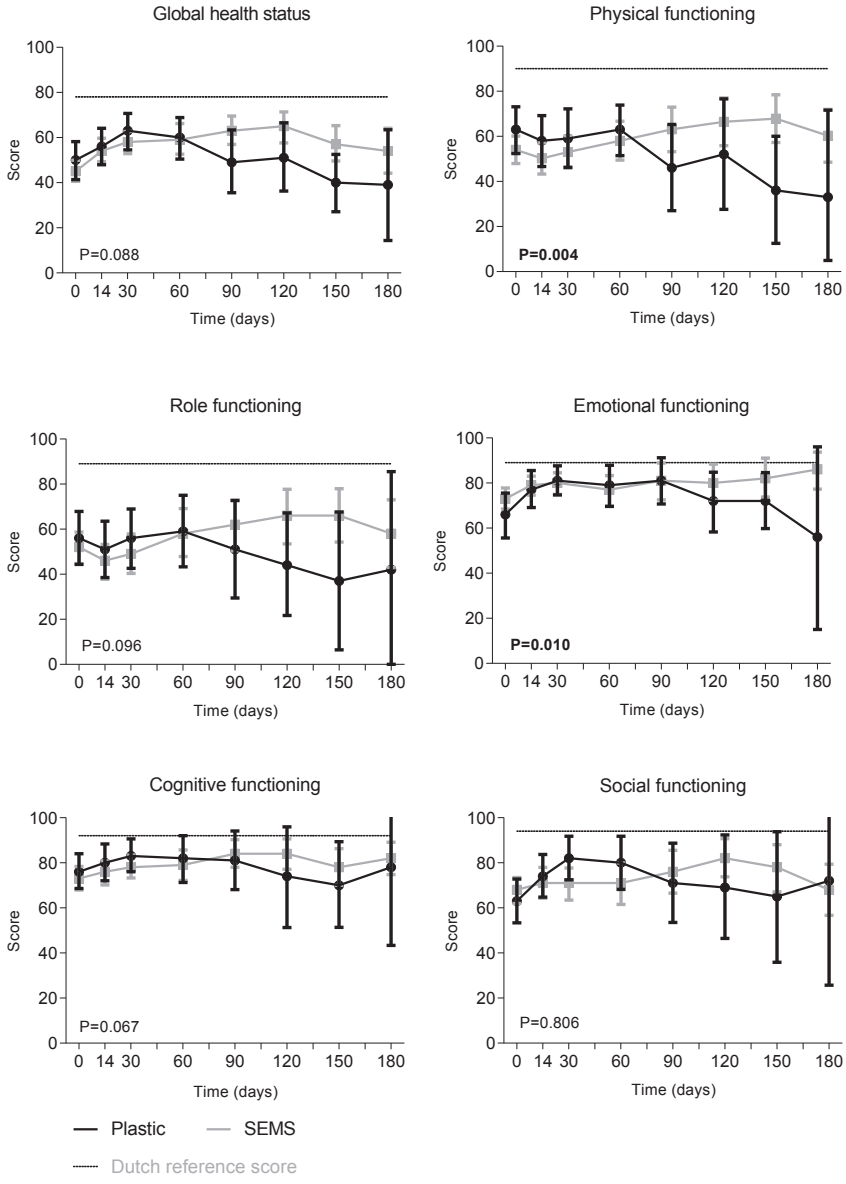

Figure 1 Global health status and functional scales of the EORTC QLQ-C30 measure after treatment with a plastic stent (n=40) or SEMS (n=100) for malignant extrahepatic bile duct obstruction. Graphs show the mean scores with 95% CI of the scales during 6-months follow-up. Higher scores represent a higher level of functioning. Reference scores (dashed line) of a general Dutch population (n=1731) are given.[23] P-value is shown for plastic vs. SEMS over time.

Table 2 Changes in QoL score during follow-up after plastic stent or SEMS placement for malignant extrahepatic bile duct obstruction.

	Scale	Baseline measure (mean)	Change in HRQoL score (per 0.5 year follow-up (95% CI))				p-value
			PLASTIC		SEMS		
EQ-5D	EQ-5D utility	0.6	0.1	(-0.1, 0.4)	0.1	(-0.1, 0.2)	0.61
	Visual analogue scale	53	-25	(-39, -11)*	-11	(-19, -3)*	0.08
	Global health	47	-21	(-37, -4)*	-4	(-13, 6)	0.09
Functional	Physical	56	-35	(-52, -17)*	-5	(-15, 5)	0.01
	Role	53	-23	(-47, 3)	2	(-12, 16)	0.01
	Emotional	71	-19	(-34, -4)*	4	(-5, 13)	0.01
	Cognitive	74	-18	(-34, -2)*	-0.3	(-10, 9)	0.07
	Social	66	-14	(-37, -10)	-11	(-23, 3)	0.81
Symptom	Fatigue	58	26	(5, 47)*	-7	(-19, 5)	0.01
	Nausea and vomiting	25	25	(7, 43)*	4	(-6, 14)	0.04
	Pain	35	9	(-12, 29)	4	(-8, 16)	0.70
Single items	Dyspnea	21	5	(-16, 26)	1	(-11, 12)	0.70
	Insomnia	43	-4	(-27, 18)	-14	(-26, -1)*	0.48
	Appetite loss	55	50	(23, 76)	13	(-3, 28)	0.02
	Constipation	22	-2	(-22, 19)	-8	(-20, 4)	0.58
	Diarrhea	21	22	(2, 42)	2	(-9, 14)	0.10
	Financial difficulties	6	-0.3	(-12, 12)	-0.8	(-8, 6)	0.94
PAN-26	Pancreatic pain	40	5	(-11, 20)	10	(1, 19)*	0.56
	Digestive symptoms	49	58	(35, 80)*	17	(3, 30)*	0.01
	Hepatic symptoms<30 days#	49	-9	(-24, 6)	-22	(-31, -13)*	0.13
	Hepatic symptoms≥30 days¶		13	(-2, 27)	3	(-6, 11)	0.24
	Altered bowel habit	33	4	(-16, 24)	3	(-9, 14)	0.91
	Body Image	26	42	(20, 63)*	-2	(-14, 11)	0.01
	Satisfaction with health care	25	-14	(-36, 8)	7	(-6, 21)	0.11

* Significant values (P<0.05)
# Change in HRQol for 30 days of follow-up
¶ Change in HRQoL in 5 months of follow-up
EQ-5D and functional scale: higher scores represent a higher level of functioning
Symptom, single item and PAN-26: Higher scores represent more complaints.

Endoscopic stent placement is the treatment of choice for palliation of symptoms due to malignant extrahepatic bile duct obstruction.[3] Stent placement results in restoration of bile flow and as a consequence in relief of symptoms due to biliary obstruction. It is known that stent dysfunction is observed more frequently and faster with plastic stents than with more expensive SEMS, whereas survival is not affected by type of stent.[4-9] However, limited data are available with regard

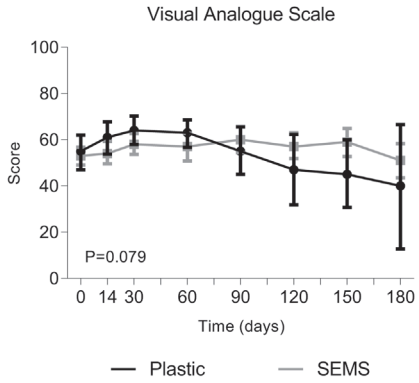

Figure 2 Visual analogue scale scores of the EQ-5D-5L questionnaire after treatment with a plastic stent (n=40) or SEMS (n=100) for malignant extrahepatic bile duct obstruction. Graph shows the mean score with 95% CI of the scale during 6-months follow-up. Higher scores represent a better self-rated health.

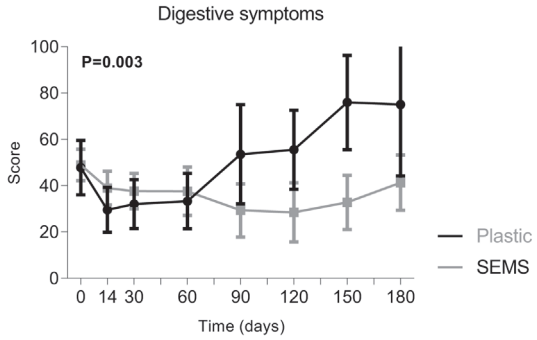

Figure 3 Symptom scales of the EORTC QLQ-PAN26 questionnaire after treatment with a plastic stent (n=40) or SEMS (n=100) for malignant extrahepatic bile duct obstruction. Graphs show the mean scores with 95% CI of the scales during 6-months follow-up. Higher scores represent more complaints.

to the impact of stent placement on HRQoL, while the patients' functional status should be an important outcome measure in a palliative treatment setting.[11,13,14]

Only three small non-randomized studies have been performed assessing the impact of plastic stent placement on HRQoL in patients with malignant extraheptic bile duct obstruction. The HRQoL at baseline was compared with HRQoL at one- to three- months after plastic stent placement and it was concluded in all three studies that HRQoL improved in this first period after stent placement.[20-22] In the study by Abraham et al., baseline HRQoL scores were lower when compared to

a general US reference population.[22] This is in line with our findings that on all functional scales HRQoL was considerably lower than in a healthy Dutch reference population.[23] Luman et al. did not perform a direct comparison with a reference population, but functional scales scores of the QLQ-C30 were comparable to the low scores found in our study.[21] In contrast, in the study by Ballinger et al. the majority of patients rated their physical health before stent placement as good to very good. However, in the latter study the scores were not compared to a reference group.[20]

To date no studies have evaluated long term HRQoL after stent placement or compared HRQoL between patients treated with a plastic stent or SEMS. Since patients with a SEMS less frequently present with symptoms due to stent dysfunction, it is generally assumed that this also translates in a better HRQoL in these patients.[6,24] This is the first study showing that patients with incurable extrahepatic biliary obstruction treated with SEMS placement indeed experience a better HRQoL over time. Both general and disease specific HRQoL remained more or less stable over time in patients with SEMS, while HRQoL deteriorated in patients with a plastic stent. Patients treated with a SEMS scored better on physical and emotional functioning over time. Furthermore, they were less tired and reported less frequent symptoms of appetite loss, and nausea and vomiting. However, the higher HRQoL scores may not only be due to a lower stent dysfunction rate in the SEMS group. The fact that patients were not blinded for the type of stent used could have influenced the results to some extent.

We experienced that physicians were sometimes reluctant in including patients in the study due to the burden of completing HRQoL questionnaires during the last period of life. We therefore decided that participating in the HRQoL substudy was non-compulsory for study inclusion, since HRQoL was a secondary study endpoint. Considering the relatively high percentage of patients that declined participating in the HRQoL sub study (32%), it seems likely that completing the HRQoL questionnaires was also by the patients experienced as a considerable burden. A potential consequence of suboptional completion of the questionnaires is the occurrence of non-random selection bias. In this case, we would have expected that patients who declined participation would be the ones with an inferior health status. Surprisingly, survival and WHO score were in fact comparable in both groups while the proportion of patients with metastatic disease was even higher in patients that indeed participated.

Missing data is another frequently encountered problem in HRQoL studies in patients with advanced stage disease since patients are often unable to complete questionnaires due to their deteriorating health status.[22,25,26] We also observed a high proportion of missing questionnaires (13%) and this was seen most fre-

quently just before the patient deceased, indicating that the missing data were nonrandom. As a result, HRQoL scores at the end of follow up might have been too optimistic.[25] However, nonrandom missing data occurred in both treatment arms in our study and therefore for comparison of HRQoL between the groups this will not be of major concern.

To minimize the number of missing data and to obtain a high participation rate, a thoughtful selection should be made of all available instruments to measure HRQoL in an effort to minimize the burden to the patient. We used both validated generic and disease-specific questionnaires, a common combination in studies on HRQoL.[14] For disease-specific health we used the validated EORTC pancreatic module (PAN-26), since we expected that the majority of patients in the study would be stented for incurable pancreatic cancer. In addition to the EORTC-QLQ-C30 questionnaire to measure generic health, we also used the EQ-5D-5L. Since the latter questionnaire could be completed in only a few minutes,[17] compared to the approximately twelve minutes required for the QLQ-C30 and PAN-26,[16] we expected that using this second generic questionnaire would not be of a significant additional burden to the patient.

The main strength of this study is the randomized design with comparison of the two most frequently used stent types for biliary decompression. This is the first study evaluating the long term effect of biliary stent placement on HRQoL and the first study comparing HRQoL between patients with a plastic stent or SEMS. Furthermore, we used validated questionnaires for both general health and disease specific HRQoL. Limitations of the study included lack of blinding and the nonrandom selection of patients that completed HRQoL questionnaires. Nonetheless, the patients who completed the questionnaires were well balanced between the plastic stent and SEMS groups.

In conclusion, this randomized controlled trial shows that SEMS placement in patients with incurable malignant extrahepatic bile duct obstruction results in better scores on several aspects of both general- and disease-specific HRQoL over time compared to plastic stent placement. In patients with a SEMS HRQoL remained stable over time, while HRQoL deteriorated over time in patients with a plastic stent.

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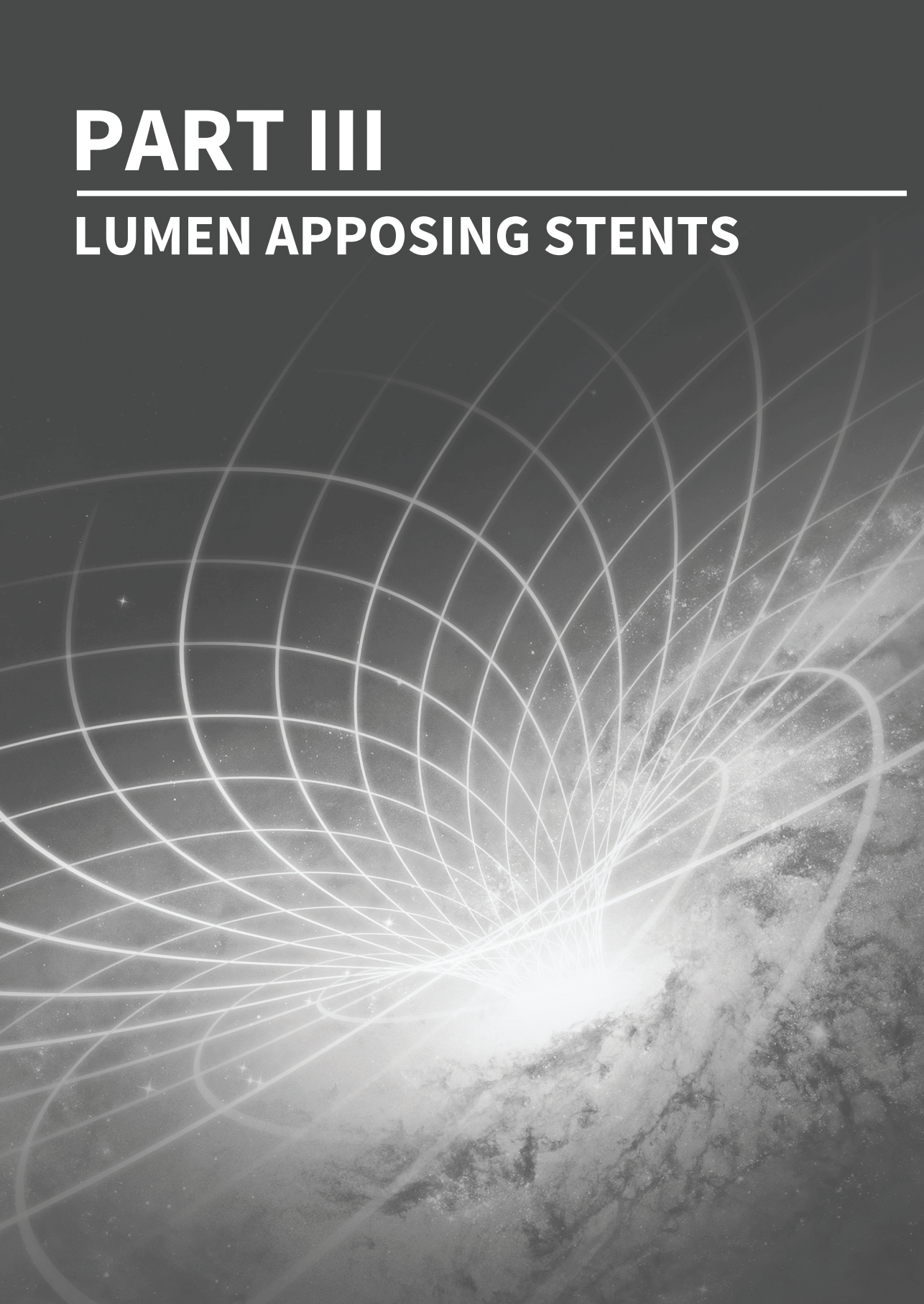
PART III

LUMEN APPOSING STENTS



CHAPTER 7

A novel lumen-apposing metal stent for endoscopic ultrasound-guided drainage of pancreatic fluid collections: a prospective cohort study

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ABSTRACT

Background and study aims: A novel large-diameter, lumen-apposing, self-expandable metal stent with bilateral flanges was recently developed for endoscopic ultrasound (EUS)-guided transmural drainage of symptomatic pancreatic fluid collections (PFCs). The aim of this study was to evaluate the efficacy and safety of this stent in a large cohort.

Patients and methods: Patients with a PFC undergoing EUS-guided drainage with this novel stent were prospectively enrolled in this multicenter cohort study.

Results: There were 61 patients: 46 patients (75%) with walled-off necrosis (WON) and 15 (25%) patients with a pancreatic pseudocyst (PP). Stent placement was technically successful in 60 patients (98%, 95%CI 95-100%). Clinical success, defined as resolution of clinical symptoms in combination with a decrease of PFC size to ≤2 cm on imaging, was achieved in 93% (95%CI 77-100%) of patients with a PP and in 81% of patients with WON (95%CI 69-94%). Treatment failure occurred in nine patients (16%, 95%CI 6-26%), including four patients who required surgical intervention. Stent removal was performed in 82% of patients after a median of 32 days (range 2-178) and was rated as easy in all but one patient. In 10 patients, endoscopic stent removal was not performed because of stent migration (n=3), stent dislodgement during necrosectomy (n=3), stent removal during surgery (n=2), or refusal by the patient (n=2). In total, five major complications were reported (9%, 95%CI 2-16%), including PFC infection (n=4) and perforation (n=1).

Conclusion: EUS-guided drainage using this novel stent is feasible and the clinical results obtained are promising with a low major complication rate.

INTRODUCTION

Endoscopic ultrasonography (EUS)-guided transmural drainage with placement of double-pigtail plastic stents is the recommended drainage modality for symptomatic pancreatic fluid collections (PFCs).[1-3] Clinical success rates largely depend on the type of PFC, with higher success rates reported for pancreatic pseudocysts (PP, 82-100%) compared to walled-off necrosis (WON; 53-100%).[1,4] However, the efficacy of drainage is limited due to the small diameter (7-10 Fr) of the double-pigtail plastic stents. Therefore, multiple pigtail stents are placed to ensure a wider drainage opening. The risk of stent occlusion with secondary infection of the collection is high, in particular when the PFC contains large pieces of necrotic debris. Furthermore, if access to the collection is required for endoscopic transmural necrosectomy, balloon dilation of the tract is required to allow introduction of the endoscope in the collection.[1]

To overcome these limitations, placement of a self-expanding metal stent (SEMS) may be an alternative to plastic pigtail stents. The main advantage of a SEMS is its larger luminal diameter (≥10mm), which potentially results in longer stent patency, faster PFC resolution, a reduced need for endoscopic re-interventions, and a lasting access route for necrosectomy.

The use of different types of SEMSs has been reported in case reports and small case series. Most of these SEMSs were tubular stents designed for transluminal drainage, such as bile duct drainage.[5-10] When used for transmural drainage, these SEMS have some limitations, including a high risk of stent migration. Therefore, a novel large-diameter SEMS with bilateral flanges, the Axios stent (Xlumena Inc., Mountain View, CA, has been designed especially for transmural drainage. Until now, only three small studies have reported on the use of this new stent and demonstrated high technical success rates (89%-100%) and high clinical success rates (93%-100%) in patients with successful stent placement.[11-13] In this paper, we report the experience with the Axios stent for drainage of PFCs from a larger cohort study.

PATIENTS AND METHODS

Patients

From May 2011 to November 2012, all patients with a symptomatic PFC who underwent Axios stent placement in 15 European centers were prospectively enrolled in a web-based database. The decision to place an Axios stent placement was at the discretion of the treating physician and there were no specific inclusion

or exclusion criteria. PFCs were classified according to the revised 2012 Atlanta Classification[14] as pancreatic pseudocyst (PP) or WON. The protocol was approved by the Medical Ethical Committee and all patients gave informed consent prior to Axios stent placement.

Axios stent

The Axios stent is a SEMS constructed of braided nitinol that is fully covered with silicone (Fig.1). The stent design, with wide flanges on both ends, provides anchoring within the PFC and even distribution of pressure on the luminal walls. The stent is delivered through a 10.5-Fr catheter, which is Luer-locked to the inlet port of the endoscope instrumentation channel to provide controlled deployment of the stent. The stent is CE-marked for drainage of PFCs. For this study, stents with a length of 10mm in between the flanges and luminal diameters of 10mm and 15mm were used.

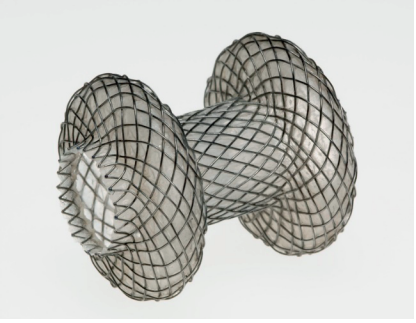

Figure 1 The Axios-stent, which has wide flanges on both ends to provide anchorage.

Procedure

Drainage was performed under conscious sedation, monitored anesthesia care or general anesthesia. Prophylactic antibiotics were administered at the discretion of the endoscopist. Under linear EUS-guidance, the collection was punctured from the stomach or duodenum using a 19-gauge EUS-FNA needle or the NAVIX access device (Xlumena Inc). A 0.035-inch guide wire was passed through the needle or the NAVIX access device and coiled in the PFC. The fistula tract was then dilated using a cystostome or the NAVIX access device. Further balloon dilation was performed at the discretion of the endoscopist. The delivery catheter was placed over the wire and the distal end of the stent was deployed in the PFC lumen under fluoroscopic and/or EUS-guidance, while the proximal stent end was deployed under fluoroscopic and/or endoscopic view. The use of endoscopic intervention,

including necrosectomy and placement of a nasocystic drain, was dictated by the clinical course of the patient (i.e. persisting fever).

Definition of endpoints

Study endpoints included technical success, clinical success and safety. Technical success was defined as satisfactory access and drainage of the PFC following placement of the Axios stent. Clinical success was defined as resolution of clinical symptoms in combination with a decrease of PFC size to≤2 cm on imaging without the need for an additional endoscopic or percutaneous stent or drain placement, or surgery. Safety was defined as the number of minor and major procedure-related complications. Procedure related major complications (i.e. bleeding, PFC infection, perforation, stent migration) included complications requiring admission, endoscopic or surgical intervention. PFC infection was defined as any new septic event that occurred after the initial endoscopic drainage, as proven by new-onset fever and/or positive blood cultures. Perforation was defined as free intraperitoneal air on imaging studies in association with peritoneal signs. Stent migration was defined as adverse event if an intervention was required to retrieve the stent either from within the PFC or the enteral lumen. Procedure related minor complications included complications not requiring admission or endoscopic intervention.

Statistical analysis

SPSS (version 20.0) statistical software was used for data analysis. Continuous variables were reported by using means (standard deviation) and medians (range), as appropriate. Categorical variables were reported in terms of frequency counts and proportions. Logistic regression analysis was performed to calculate odds ratios (OR) and their corresponding 95% confidence intervals (CI) for predictors of clinical success.

RESULTS

Patients

In total, 61 patients were included in 15 centers with a median of 3 patients per center (range 1-12) (Table 1). Data on four patients (6.6%) were limited to the technical procedure and these patients were excluded from further analysis. Two patients with WON and one patients with PP were lost to follow up after transfer to the referring hospitals and one patient with WON died due to an unrelated cause (myocardial infarction) 116 days after stent placement.

Table 1 Characteristics of 61 patients with pancreatic fluid collections**.**

Characteristic	N=61
Age, mean (SD)	55 ± 14
Male sex, no. (%)	38 (62)
Etiology of pancreatitis, no. (%)	
Gallstone disease	19 (31)
Alcoholic	22 (36)
Idiopathic	9 (15)
Post-surgical	6 (10)
Other*	5 (8)
Indication for drainage, no. (%)	
Pain	19 (31)
Infection	16 (26)
Enlargement	9 (15)
Gastric outlet/bile duct obstruction	8 (13)
Combination of complaints	5 (8)
Missing	4 (7)
Type of PFC no. (%)	
PP	15 (25)
WON	46 (75)

*Other include: drugs, trauma, post-ERCP, unkown, pancreas divisum
PP pancreatic pseudocyst
WON walled-off necrosis

Technical success

Stent placement was technically successful in 60 patients (98%, 95%CI 95-100%). In one patient, the entire stent was fully deployed inside the PFC and two plastic pigtail stents were placed to achieve adequate drainage. During repeat endoscopy, the Axios stent could successfully be removed from the PFC. In another patient, the entire stent was deployed in the PFC, but the stent could be repositioned correctly. In two patients, the stent did not deploy properly and a new stent was placed. Details on PFC characteristics and the endoscopic procedures are shown in Table2 and Fig.2.

Clinical success

Clinical success was achieved in 13 of 14 patients (93%, 95%CI 77-100%) with PP and in 35 of 43 patients with WON (81%, 95%CI 69-94%) (p=0.31). Mean time to confirmed resolution of the PFC was 38 ± 35 days (median 29 days; range 1-136). In none of the patients with PP additional endoscopic intervention was required to achieve clinical success, whereas in patients with WON additional necrosectomy

Table 2 Characteristics of 61 patients with pancreatic fluid collections (PFCs) and drainage procedure

Characteristic	N=61
Technical success, no. (%)	60 (98)
Location of PFC, no. (%)	
Body	35 (57)
Tail	11 (18)
Head	7 (12)
Neck	4 (7)
Entire pancreas	2 (3)
Peripancreatic	2 (3)
PFC dimension, cm (median (range))	9 (4-20)
PFC infected, no. (%)	
Yes	33 (54)
No	28 (46)
Bulging, no. (%)	
Yes	41 (67)
No	20 (33)
Drainage site, no. (%)	
Gastric	58 (95.1)
Cardia	8 (13.1)
Body	40 (65.6)
Antrum	10 (16.4)
Duodenum	3 (4.9)
Dilation of tract before placement, no. (%)	
No	34 (55.7)
Yes	27 (44.3)
Stent size, no. (%)	
10x10mm	22 (36.1)
10x15mm	39 (63.9)
Anaesthesia, no. (%)	
Conscious sedation	30 (49.2)
Monitored anesthesial care	18 (29.5)
General anesthesia	13 (21.3)

and/or irrigation was performed in 43% (15 of 35 patients) of patients: 7 patients (20%) required one intervention and 8 patients (23%) more than one intervention. Univariate logistic regression showed no association between clinical success and infection of the PFC (OR 0.50, 95% CI, 0.11-2.23), PFC size (OR 0.99, 95%CI 0.98-1.01) and PFC etiology (gallstone vs. alcohol, OR 7.14, 95%CI 0.75-67.98, gallstone vs. other OR 0.53, 95%CI 0.33-8.35).

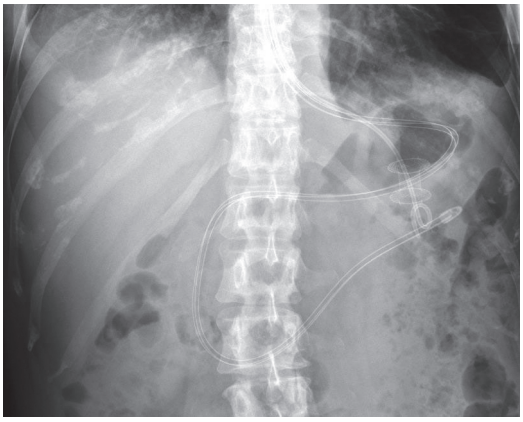

Figure 2 Abdominal X-ray showing a 10-mm transgastric Axios stent in position for the drainage of an area walled-off necrosis and a nasocystic irrigation tube that has been passed through the lumen of the Axios stent because of lack of clinical improvement. A nasoenteral feeding tube was placed to ensure adequate intake is also seen.

Nine patients (16%, 95%CI 6-26%) had treatment failure, including four patients requiring surgical intervention, one patient with PP (perforation (n=1)) and three patients with WON (persistent infection (n=1), retroperitoneal abscess (n=1) and paracolic necrotic cavity (n=1)). The other reasons for treatment failure included placement of plastic pigtail stents because of Axios stent dislodgement during necrosectomy (n=3), nasocystic tube placement for irrigation (n=1) and additional Axios stent placement to obtain a more convenient route of approach to perform necrosectomy (n=1).

Stent removal

Endoscopic stent removal was performed in 47 of 57 patients (82%) after a median of 32 days (range 2-178). Stent removal was successful in all patients using a snare or rat-tooth forceps. In 11 of these 47 patients (23%), hyperplastic tissue in- or overgrowth of the stent was observed, but stent removal was uneventful (Fig.3). In 10 patients, no endoscopic stent removal was performed because of migration of the stent (n=3), stent dislodgement during necrosectomy (n=3), removal during surgery (n=2) or refusal by the patient (n=2). Stent migration was observed during control abdominal ultrasound (n=2) or upper endoscopy (n=1), 65, 86 and 216 days after stent placement, respectively. On further imaging (abdominal X-ray, abdominal ultrasound and upper endoscopy) these stents could no longer be visualized. None of these patients experienced symptoms due to stent migration.

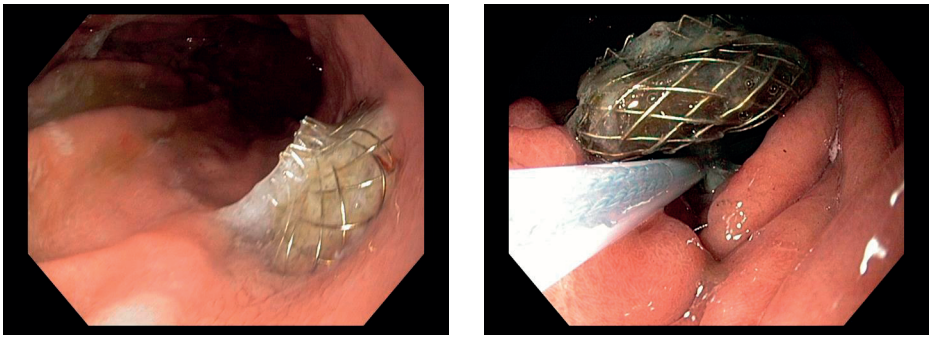

Figure 3 Endoscopic views showing: **(a)** hyperplastic tissue overgrowth at the gastric end of a stent that had been in position for 75 days; **(b)** safe removal of the stent using a snare, after a first attempt at removal using a rat-tooth forceps had failed because of unraveling of the nitinol wires.

Complications

Major complications were seen in five of 57 patients (9%, 95%CI 2-16%), including PFC infection (n=4) and perforation (n=1). PFC infection included new onset infections in patients with WON, which was in three patients caused by occlusion of the stent by necrotic debris. All four patients were successfully treated with endoscopic necrosectomy in combination with antibiotics and/or nasocystic drainage. One patient with a 6 x 8-cm pseudocyst presented with fever and peritoneal signs a few hours after stent placement and imaging showed free air in the abdominal cavity. During surgery it appeared that the proximal flange of the Axios stent was still positioned in the stomach but the distal flange was completely detached from the PP and facing the peritoneal cavity. Sixteen minor complications occurred in 14 patients (25%, 95%CI 14-36%), including self-limiting device related bleeding (n=4), transient fever of unknown origin (n=3), stent migration (n=3), stent dislodgement (n=3) and food contents in the PFC (n=3).

DISCUSSION

This multicenter prospective cohort study is the largest series reporting on the use of SEMS for EUS-guided drainage of PFCs. We demonstrated that EUS-guided placement of the Axios stent for transmural drainage was feasible, with a technical success rate of 98% and a clinical success rate of 93% for PP and 81% for WON. Furthermore, placement was found to be safe, with a major complication rate below 10%.

The large luminal diameter (≥10 mm) of SEMS is thought to facilitate effective drainage, resulting in higher clinical success rates and faster PFC resolution. For

patients with WON, the clinical success rate of drainage with SEMS (81%) in our study is in the upper range when compared to the reported success rate of drainage with plastic pigtail stents (53-100%),[1-4] while the success rate with SEMS for PPs (93%) may be similar when compared to plastic pigtail stents (82-100%).[1,4] The already high success rate for PP drainage with plastic stents is due to the fact that fluid from PP can easily flow through and alongside plastic pigtails. However, while in most reported studies at least one additional intervention was required to achieve PP resolution,[4] we found that with SEMS no additional interventions were required to achieve clinical success. If this reduction can be confirmed in a randomized trial comparing SEMS with plastic stents, the use of more expensive SEMS may be justified for drainage of PP. In patients with WON, only in 15 of 35 patients (43%) additional necrosectomy and/or irrigation procedure was required to achieve resolution. In 7 of 15 patients (47%) only one intervention was required, while the remaining patients required more than one intervention. This suggests that using SEMS may also result in a reduction in the number of procedures for the treatment of WON; however limited data have been published on the exact number of repeat interventions to achieve resolution of WON.

In the first reports on the use of SEMS for transmural drainage of PFCs, stents with a tubular design were used, including stents intended for a biliary, tracheal or esophageal indication. In an effort to prevent SEMS migration, double-pigtail stents were placed in or alongside the SEMS as anchoring device. Nonetheless, stent migration was still reported in 6-10% of patients.[5,8] Stents that were partially covered have also been used to prevent migration of the stent. The mechanistic idea here is that tissue ingrowth at both stent ends will reduce migration. Barresi et al. report that partially covered stents indeed effectively prevent stent migration, but in one patient surgery was required to remove a stent that was fully embedded in the stomach wall.[15] To improve result of transmural drainage, novel SEMS designs have been developed such as the Axios and NAGI stent (Taewoong Medical). The Axios stent was designed in a saddle shape with large bilateral flanges to achieve firm anchoring. Despite this anchoring design, stent migration and stent dislodgement have been reported with this device.[11,12] Migration to the stomach was reported in one patient (7%), in whom the cystgastrostomy tract had been dilated up to 15 mm before placement of a 10 mm stent.[11] In another study, both spontaneous migration, with no clinical consequences for the patient, as well as stent dislodgement were reported.[12] We also observed spontaneous stent migration and stent dislodgement, each in 3 patients (5%). Although migration was not associated with any adverse consequences, SEMS migration may cause severe complications such as perforation or obstruction in the gastrointestinal tract. In addition, the anchoring design could also not prevent that the stent became

completely detached from the PP in one patient a few hours after placement. In our opinion, further refinements in stent design are therefore required to improve the anchoring capacity and in that way reduce the risk of stent migration and dislodgement.

The current study has several strengths and limitations. First, this is the largest prospective study on EUS-guided SEMS placement for transmural drainage of PFCs published to date. Furthermore, we used clear and predefined definitions for classification of PFCs and study endpoints. A limitation of the study was the lack of a control group treated with plastic pigtail stents or other types of SEMS. Therefore, definite conclusions on efficacy of the device cannot be drawn. Furthermore, no standardized time points for follow-up were defined in the study protocol and repeat endoscopy was performed at the discretion of the endoscopist. Patients were followed until resolution of the PFC and therefore no data are available with regard to long-term complication or recurrence rates. Finally, the indication for placing an Axios was at the discretion of the physician with no predefined criteria and as a result selection bias of the study population is possible. However, the high percentage of WON cases might indicate that not only easy cases were treated with the Axios stent.

In conclusion, this study shows that EUS-guided drainage using the Axios is feasible and the obtained clinical results seem promising. However, before SEMS placement is widely adopted randomized controlled studies are required to confirm these results and to compare them with alternative treatment modalities for PFC both for long-term results and cost-effectiveness.

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CHAPTER 8

EUS-guided gallbladder drainage with a lumen apposing metal stent; a prospective long-term evaluation

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MESSAGE

Endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) has been introduced as alternative to percutaneous transhepatic gallbladder drainage for the treatment of acute cholecystitis in high-risk surgical patients. Lumen apposing metal stents (LAMS) have been developed to adequately seal the newly formed fistula track and ensure anchoring of both lumina. This study is the first multicenter prospective study on the use of a LAMS for EUS-guided gallbladder drainage in high-risk surgical patients with acute cholecystitis. We demonstrated that EUS-GBD is an elegant and safe procedure in experienced hands with a high technical (90%) and clinical success (96%) rate.

IN MORE DETAIL

Endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) has been shown to be comparable to percutaneous gallbladder drainage (PTGBD) in terms of technical feasibility and clinical efficacy for the treatment of acute cholecystitis in high-risk surgical patients.[1] However, a potential serious complication of this technique is air or bile leakage into the peritoneal cavity, since insertion of a drain or plastic stent requires a fistula tract with a diameter larger than the diameter of the inserted drain or stent. Therefore, a specifically designed lumen apposing metal stents (LAMS) has been developed for transenteric drainage and successfully tested in animal models.[2,3] Preliminary clinical experience with LAMSs for drainage of peri-pancreatic fluid collections (PFC) appears to be consistent with anchoring features tested in animal models.(4-6) However, reports on the use of LAMSs for gallbladder drainage is limited to case reports and small case series without long term follow-up. [3,5,7-12]

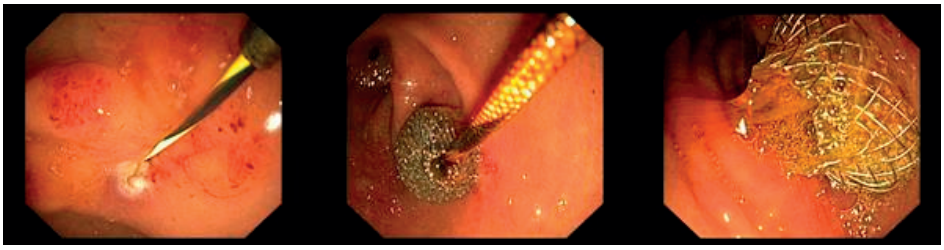

Figure 1 Successful transgastric EUS-guided gallbladder drainage using a lumen-apposing metal stent

We performed a multicenter, prospective study to determine the feasibility and safety of the use of LAMS for EUS-GBD in high-risk surgical patients with acute cholecystitis. A total of 30 patients were included. Technical success was achieved in 27 of 30 patients (90%) (Fig. 1) and clinical success in 26 of 27 patients (96%). Two of 27 patients (7%) developed recurrent cholecystitis due to LAMS obstruction. Successful LAMS removal was performed in 15 of 30 patients (50%) after a mean of 91 days (SD ± 24 days). In 15 patients (50%) no LAMS removal was performed because of death (n=5), significant tissue overgrowth (n=2) or other causes (n=8). Mean follow-up was 298 days (SD ±82 days) for all patients and 364 days (SD ±82 days) for the patients alive at the end of the study. A total of 15 SAEs (50%) were reported, including 4 that were possibly stent- or procedure-related (13%). Overall mortality was 23% (7/30), with 30-day mortality of 17% (5/30).

METHODS AND RESULTS

See '**Details online'** section

COMMENTS

This study is the first multicenter prospective study on the use of a LAMS for EUS-GBD in high-risk surgical patients with acute cholecystitis. To date, EUS-GBD using a LAMS has been described in 8 reports including 30 patients, reporting an overall technical success rate of 93%. [3,5,7-12] This high success rate is most likely an overestimation since the majority of reports included retrospective small case series and case reports, which are prone to publication bias. Technical failures were only reported by de la Serna-Higuera et al. who retrospectively evaluated EUS-GBD in 13 patients using the same LAMS as was used in the present study.[7] These authors reported a technical success rate of 85%, with two technical failures.[7] In addition, in four patients a second fully covered tubular SEMS was inserted through the LAMS to ensure stent patency and stability, resulting in difficulties with stent placement in 6 of 13 patients (46%) in this study.[13] In our study technical failures occurred in 3 of 30 patients (10%) and technical problems with LAMS deployment in another 2 of 30 patients (7%), resulting in an overall technical difficulties rate of 17%. However, in all three patients with technical failures, successful endoscopic drainage was ultimately achieved during the same procedure with placement of an additional stent.

In order to improve technical success, refinements of the current LAMS and accessories may improve the results of EUS-GBD. The evolution of the LAMS used in the present study is a new delivery system with electrocautery on the tip, which allows puncture and release of the stent in a single-step procedure, thus decreasing the number of accessories to be exchanged and consequently potentially reducing the frequency of complications. This newly developed device (Hot Axios, Xlumena, Mountain View, CA) has already successfully been utilized for both gallbladder and PFCs drainage.[12,14] Furthermore, since the procedure is challenging, even in experienced hands, a learning curve should be anticipated. Because of these considerations, it is our opinion that EUS-GBD should currently only be performed in high volume experienced centers.

It is known that a mature fistula tract is formed in the porcine model following LAMS placement after a period of 4-5 weeks.[2] In order to minimize the risk of recurrent cholecystitis and bile leakage, we decided to leave the LAMS in place for a period of three months. A drawback was that we experienced significant tissue overgrowth in three patients (10%) at the time of LAMS removal that precluded removal in two patients(Fig. 2). Although a more significant tissue reaction can be expected after a longer stent dwell time, we hypothesize that stent location, either gastric of duodenal, might also influence the degree of tissue overgrowth. The retroperitoneal location of the duodenum results in a more stable tract to the gallbladder as compared to the stomach, in which more peristaltic movements might result in a more pronounced tissue reaction.

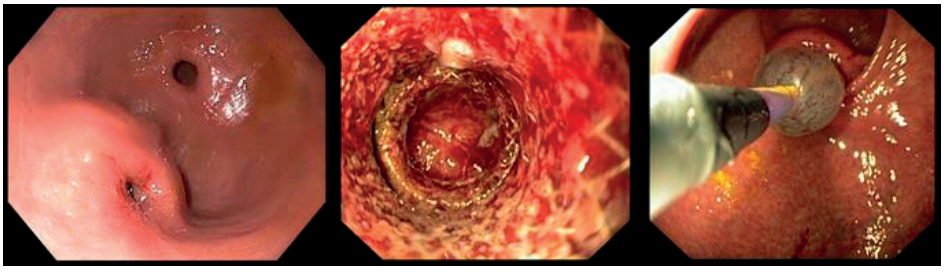

Figure 2 (A) Significant tissue overgrowth of a lumen-apposing metal stent (LAMS) by gastric mucosa after a stent dwell time of 125 days. (B) The LAMS is dilated up to 10 mm with a balloon and, (C) can be entered and removed inside-out with rath-tooth forceps

Ultimately, in half of the patients in our study no LAMS removal was performed, mainly due to a poor clinical condition of the patient and/or patients' refusal. In none of these patients LAMS-related complications were observed during a mean stent dwell time of 364 days. Long-term stenting without stent-related complications, even up to 3 years, has also been reported in other studies on EUS-GBD

using SEMS.[7, 15-17] In light of these results, leaving stents, either SEMS or LAMS, permanently in place may likely be considered as an alternative treatment option, which avoids the risks and discomfort associated with a repeat procedure for stent removal. Furthermore, although gallbladder drainage is most often intended as a bridge to elective surgery, none of the patients in our study turned out to be eligible for elective cholecystectomy mainly due to their ongoing high surgical risk. In order to reduce the risk of recurrent cholecystitis in these patients, permanent drainage is desirable. The advantage of EUS-GBD compared to PTGBD is that long-term stenting does not require an external drainage catheter, which likely may increase patients' comfort and quality of life.[15]

Safety was closely monitored in our study and all serious adverse events were reviewed by an independent data safety monitoring board. The 30-day mortality in our study was 17%, which is comparable to the 30-day mortality or in-hospital death of 15.4% after PTGBD. In addition, the 7% stent- or procedure-related mortality observed in our study is comparable to that of PTGBD (around 4%). However, the rate of non-fatal SAEs (n=9, 30%) is substantially higher than reported for PTGBD (15%).[18] One explanation for this high complication rate could be the relatively poor clinical condition of patients in our study. None of the patients in our study was eligible for elective cholecystectomy, as compared to more than 40% in studies with patients treated with PTGBD.[18] Another reason might be our thorough and long-term follow-up with special focus on all types of complications, compared to a great variety of complication registrations in PTGBD studies.[18] Noteworthy, stent migration was not observed in our study, while this has been reported in up to 7% after EUS-guided drainage of pancreatic fluid collections using both SEMS and LAMS.[6,19]

In conclusion, we think that EUS-GBD using LAMS is an elegant procedure in high risk surgical patients with acute cholecystitis when performed by an experienced endoscopist. However, large comparative studies are needed to confirm these promising results, to optimize the technical procedure and to address remaining questions, such as optimal stent dwell time and preferred route of access.

DETAILS ONLINE

Methodological description

Patient inclusion

- Age≥18 years

- Diagnosis of acute cholecystitis according to the Tokyo Guidelines (clinical signs, laboratory findings, and imaging findings)
- High surgical risk, defined as (1) ASA score > III, (2) APACHE II score ≥ 12, (3) onset of symptoms≥7 days before first presentation, (4) advanced malignancy, and (5) deemed unsuitable for surgery for any other reason based on surgical consultation.
- Written informed consent

Patient exclusion
- Altered anatomy of the upper gastrointestinal tract due to surgery of the oesophagus, stomach or duodenum
- Pancreatitis
- Liver cirrhosis, portal hypertension and/or gastric varices
- Abnormal coagulation (INR>1.5 and not correctable and/or platelets <50.000/mm^3)
- Previous drainage of the gallbladder
- Pregnancy

IRB/registration
Study protocol was reviewed and approved by the IRB of all participating centers. Registration at the Dutch Trial Registration (www.trialregister.nl) under number (NTR 3633).

Main outcomes
- Safety, defined as the number of (possible) stent- or procedure-related severe adverse event (SAEs), e.g. bile leakage with development of peritonitis, significant bleeding, or a non-scheduled endoscopic/surgical intervention due to an adverse event.
- A Data Safety Monitoring Board (DSMB) was installed to review all SAEs and to determine whether these were (possibly) associated with the stent or the procedure.
- Technical success of LAMS placement, defined as successful access to the gallbladder followed by adequate transmural LAMS deployment
- Technical success of LAMS removal was defined as successful removal at oesophago-gastroduodenoscopy (EGD) of the LAMS using a polypectomy snare or rat-tooth forceps in a single session.
- Clinical success, defined as resolution of clinical parameters of acute cholecystitis within 96 hours. Clinical parameters assessed were abdominal pain scored

by the patients on a 10-point visual analogue scale, body temperature, white blood cell count and serum C-reactive protein concentration.
- Recurrence of cholecystitis, defined as recurrence of acute cholecystitis according to Tokyo Guidelines after complete clinical response, either before or after LAMS removal.

Study approach
- Consecutive patients with acute cholecystitis and an indication for gallbladder drainage at high surgical risk were included in the study.
- Written informed consent was obtained from each enrolled patient before the procedure.
- EUS-guided gallbladder drainage using LAMS
- Daily follow-up until resolution of cholecystitis (pain score, temperature, WBC and C-reactive protein)
- LAMS removal after 3-months
- 3-monthly follow-up, total follow-up one year

Device and technique
- LAMS (Axios; Xlumena, Mountain View, CA); constructed of braided nitinol and fully covered with silicone. Wide flanges on both ends provide anchoring of the gallbladder and gut lumens with an even distribution of pressure on the luminal walls. The diameter of the flanges is approximately twice the diameter of the lumen. Delivery through a 10.5F catheter, which is luer-locked to the endoscope instrumentation channel inlet port to provide controlled deployment of the stent, CE-marked and FDA-approved for drainage of peripancreatic fluid collections.
- Technique:
- Drainage under conscious sedation (midazolam and fentanyl), monitored anesthesia care (propofol), or endoscopist-administered propofol sedation, depending on institutional standard sedation practices and patient status.
- All patients were on antibiotics.
- Visualization of gallbladder and determination of optimal site, stomach or duodenum, for puncture using linear-array EUS.
- Gallbladder puncture using 19-gauge EUS-FNA needle, passing 0.035-inch guide wire through the needle and coiling in gallbladder.
- Dilation of fistula tract using a cystostome or balloon dilator.
- Placement of a delivery catheter over the guidewire, deployment of the distal end of the stent in the gallbladder lumen under fluoroscopic and/or EUS-guid-

ance; deployment of proximal stent end using a combination of fluoroscopic and endoscopic view and EUS guidance, depending on endoscopist preference

Sample size calculation

- Sequential testing safety model was used to calculate the minimum number of patients needed to demonstrate that EUS-guided drainage using a LAMS is not unsafe.(18;19) If the safety boundary in the model (stent- or procedure-related SAEs≥25% of patients) was not crossed after inclusion of 14 patients we were allowed to conclude that the procedure is not unsafe, taking into account a risk of 11% of stent- or procedure-related SAEs in patients receiving PTGBD.(3)
- We estimated that a sample size of 23 patients was required to demonstrate a clinically relevant 20% difference in recurrence of cholecystitis during one year of follow-up using a two-sided α of 0.05 with a power of 0.80. We estimated a recurrent cholecytitis rate of 25% after PTGBD based on the literature. (20-27)
- To compensate for a potential loss to follow-up of 10%, we aimed to include 30 patients in the study.

Data analysis

- An interim analysis was performed after each (possibly) stent- or procedure-related SAE and a DSMB meeting was scheduled after every three SAEs.
- SPSS 20.0.0 (SPSS, Inc, Chicago, IL, USA); Continuous variables were reported by using means (standard deviation) and medians (range), as appropriate. Categorical variables were reported in terms of frequency counts and proportions.

Details of results

Patient characteristics

	N=30 (100%)
Mean age, years (range)	85 (68-97)
Male gender (%)	11 (37)
Indication EUS-GBD (%)	
ASA score≥3	13 (44)
APACHE score≥12	3 (10)
Symptoms≥7 days	2 (7)
Advanced malignancy	2 (7)
Combination	5 (16)
Expert opinion	5 (16)
Calculous cholecystitis (%)	22 (87)
Median time since onset symptoms, days (range)	2 (1-28)

Procedural characteristics and clinical outcome of EUS-GBD using a lumen-apposing metal stent (LAMS).

	N=30 (100%)
Technical success	27 (90)
Anaesthesia	
Consious sedation	26 (97)
Monitored anesthesia care	4 (3)
Puncture site	
Stomach	11 (37)
Duodenum	19 (63)
LAMS size	
10 x 10 mm	13 (43)
10 x 15 mm	17 (57)
Median total scope time, min (range)	15 (13-110)
Stent removal	15 (50)
Time to stent removal, days (±SD)	91 (24)
Reason for no stent removal	
Death before scheduled removal	5 (33)
Poor clinical condition	3 (20)
Refusal by the patient	3 (20)
Significant tissue overgrowth	2 (13)
Ongoing cholecystolithiasis	1 (7)
Polypoid lesion in the gallbladder	1 (7)
Stent dwell time for stents left in situ (±SD)	364 67
Clinical success	26/27 (96%)
Recurrent cholecystitis	2/27 (7%)

Overview of all SAEs and review decision of the DSMB

	Outcome	DSMB
1 (Aspiration) pneumonia	Death	**Procedure-related**
2 Pancreatic cancer/infection	Death	**Possible stent-/procedure-related**
3 Urosepsis	Death	Not related
4 Pancreatic cancer	Death	Not related
5 Myocardial infarction	Death	Not related
6 Cholangiosepsis	Death	Not related
7 Colorectal cancer	Death	Not related
8 Melena/ thrombus in gallbladder	Resolved	**Stent-related**
9 Jaundice (hemobilia)	Resolved	**Stent-related**
10 Cholangitis (gallstones)	Resolved	Not related
11 Cholangitis (malignant)	Resolved	Not related
12 Acute (biliary) pancreatitis	Resolved	Not related
13 Ischemic stroke	Sequelae	Not related
14 Pneumonia	Resolved	Not related
15 Hip fracture	Sequelae	Not related

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CHAPTER 9

Summary and discussion

Endoscopy is nowadays the cornerstone of daily clinical practice in gastroenterology, with stent placement as one of the most important endoscopic therapeutic interventions.[1] A major breakthrough in this field has been the introduction of self-expandable metal stents (SEMS) for both the esophagus and biliary tract in the late 1980s.[2,3] To further improve clinical outcome and reduce the rate of stent-related complications, ongoing modifications and further refinements of stent designs take place. In addition, novel SEMS with lumen-apposing capacity are increasingly being used for new indications, such as endoscopic ultrasonography (EUS)-guided transluminal drainage of fluid collections.

The general objective of this thesis was to evaluate the clinical efficacy and safety of novel stent designs and indications in the upper gastrointestinal tract, including esophageal stents, biliary stents and lumen-apposing metal stents (LAMS).

PART I: ESOPHAGEAL STENTS

Benign esophageal strictures

Endoscopic dilation is the standard of care for patients with recurrent benign esophageal strictures (BES) and is known to be effective in relieving dysphagia. However, in a subgroup of patients repeated endoscopic sessions are required because of stricture recurrences.[4,5] Biodegradable (BD) stent placement is thought to prolong the effect of dilation and so to reduce recurrences, without the need of stent removal.[6-8] In **Chapter 2** we compare standard dilation with BD stent placement for the treatment of recurrent BES in an international, multicenter randomized study, the DESTINY study. A total of 66 patients was included and randomized to standard dilation (n=34) or BD stent placement (n=32). After 3 months of follow-up, significantly more endoscopic dilations were performed in the dilation group compared to the BD stent group (median: 1 vs. 0, $p<0.001$). However, the total number of endoscopic procedures in both groups was not significantly different between the groups after 3 months ($p=0.063$). There was also no difference in the number of dilations or total number of endoscopic procedures between the treatment groups at 6 and 12 months of follow-up. The median time to recurrent dysphagia was significantly shorter in the dilation group (54 days) compared to the BD stent group (120 days, $p=0.047$). The number of possibly related SAEs was statistically significant higher in the BD stent group (21 in 19 patients) compared to the dilation group (11 in 10 patients, $p=0.014$). No differences in quality of life were seen over time on any of the scales.

In our study we found that BD stent placement was associated with a significant reduction in the number of dilations during the first three months after the index

procedure. However, the total number of endoscopic procedures was not different after 3 months of follow-up due to a substantial number of patients in the BD stent presenting with retrosternal pain, and nausea and vomiting requiring (diagnostic) endoscopy. In other studies on BD stent placement in the esophagus these types of adverse events have also been reported and it is thought that the stiffness of the stent might play a role in this.[9-11] The flexibility of a stent is related to the axial force, i.e. the force required to keep a stent straight, and it is has recently been shown that a BD stent has a high axial force and therefore theoretically may exert a high force to the esophageal wall.[9] The fact that two patients in our study treated with a BD stent developed an esophagotracheal fistula suggests that the high axial force of the BD stent indeed causes some tissue damage to the esophageal wall. Another theory is that the complications are the result of an inflammatory response of the mucosa to the stent material.[11] However, an increased inflammatory reaction has never been shown in histopathological specimens after BD stent placement.[12,13]

Since the theory of prolonged esophageal dilation due to stent placement still seems appealing, we think it is important to compare standard dilation with different types of esophageal stents to evaluate which type of stent is preferred for this indication. Therefore, we initiated an international, randomized, multicenter study comparing standard dilation with placement of the fully covered (fc) WallFlex stent (Boston Scientific, Natick, MA). Although the mechanical properties of this SEMS might not be perfect, i.e. the axial force is still considerable, this stent is one of the most commonly used SEMS for malignant esophageal strictures with primarily positive experiences reported.[14] In addition, promising results were recently reported using this stent for the treatment of benign refractory post-surgical esophageal strictures in three patients.[15] However, a drawback of the use of a SEMS is the need for stent removal, which requires an additional endoscopy in all patients.

In our study we found that BD stent placement was associated with a temporary reduction in the number of repeat dilations. Recurrence of the primary stricture after initial treatment success could imply that the stricture was properly dilated, but that remodelling of the stricture was not yet completed.[16] This would suggest that a longer stent dwell time might result in a lower recurrence rate. Considering the high complication rate during the dwell time of the BD stent, a longer stent dwell time might not be desirable, aside from the fact that there are currently no esophageal BD stents available with a longer degradation time. A longer stent dwell time with a fcSEMS is also associated with an potentially increased risk of stent migration or tissue overgrowth.[17,18] The optimal stent dwell time in patients with a benign esophageal stricture is an issue to be resolved.

In our study we included patients with already one to five previous dilations. It could be hypothesized that stent placement in patients with a first episode of dysphagia might result in a higher clinical success rate. However, since there is a considerable subgroup of patients that already benefit from one dilation, direct stent placement should ideally only be performed in patients at high risk for recurrent strictures, i.e. patients with a complex stricture.[4,5] Another option is to perform stent placement at an even earlier stage, for example direct after esophagectomy or endoscopic mucosal resection, to prevent stricture formation. In an animal study evaluating BD stent placement direct after esophageal endoscopic mucosal resection it was found that the time to stricture formation was significant longer in the BD stent group, but no differences in incidence of stricture formation were found.[12]

Malignant esophageal strictures

Placement of a SEMS is the most commonly performed therapeutic intervention for palliation of malignant dysphagia. Although SEMS placement is known to be both effective and safe, a major drawback of this therapy is the high rate of recurrent dysphagia (30% to 40%) due to tissue ingrowth or stent migration.[17,18] In **Chapter 3,** we describe the results of a multicenter, prospective study evaluating a new fcSEMS, the Hanaro Flap stent (M.I. Tech, Seoul, South Korea), designed to resist tissue ingrowth as well as to prevent stent migration by the incorporation of two specific anti-migration features, i.e. stent-anchoring flaps attached around the stent body and flared stent ends. In total, 40 patients with malignant dysphagia were included in the study. Nine patients (23%) experienced recurrent dysphagia. The cause of recurrent dysphagia included partial or complete stent migration in six patients (15%), tissue overgrowth in two patients (5%) and fracture of the stent in one patient (3%). Serious adverse events occurred in 36% of patients and adverse events in almost half of the patients (49%). The majority of events included retrosternal pain (n=13) and nausea and vomiting (n=7).

The overall recurrent dysphagia rate with this novel fcSEMS was relatively low (23%) compared to other fcSEMS (30-40%).[17,18] Nonetheless, stent migration was still the most common cause of recurrent dysphagia (15%) despite the anti-migration features of the stent. This migration rate is comparable to the rate for fcSEMS that have bilateral flared ends as their only anti-migration feature, suggesting that the flaps of the Hanaro Flap stent are only of limited value for the prevention of migration.[19,20] It is important to note that migration was only partial in 5 of 6 patients in our study and could be treated with endoscopic repositioning, which is relatively easy to perform and associated with lower costs than placement of a new stent. However, the number of (serious) adverse events was relatively high

compared to other studies with fcSEMS.[17,18,21,22] Since there was no control group it is unclear whether this is the result of a selected patient population, thorough follow-up or the result of stent characteristics. In order to be able to draw firm conclusions on a new stent design, it is important that new stents will be evaluated in randomized trials and compared to a commonly used stent. We therefore initiated the 'WAVE-study', a multicenter randomized study comparing the commonly used fc Wallflex stent (Boston Scientific, Natick, MA) to a novel fcSEMS, the Egis stent (S&G Biotech Inc, Seoul, Korea), which is thought to reduce both the incidence of recurrent dysphagia as well as the complication rate. This new stent is constructed from knitted nitinol, instead of braided nitinol used in most other available esophageal SEMS, which is thought to result in a low axial force. The axial force is the force required to recover to a straight position after bending and so the force exerted to the luminal wall when the stent is positioned in a curve.[14,23] It is hypothesized that a low axial force results in a lower complication rate due to less esophageal wall damage and due to a better adaption to the local esophageal anatomy in a lower risk of migration. The radial force of the stent, which is the force required to bend the stent, is probably also an important stent characteristic. It is suggested that a relatively high radial force is preferred to maintain luminal patency of the stent in a stricture and to ensure proper fixation of the stent to the esophageal wall, preventing migration. This would suggest, that the ideal stent design should have a low axial force and a high radial force.[14] However, although it is important to be aware of the mechanical properties of a new stent, it is not yet possible to completely explain or predict clinical findings based on these characteristics since many other variables also play a role in the behaviour of the stent in the esophagus.

As alternative for SEMS placement, single-dose brachytherapy is also a commonly performed therapy for the palliation of malignant dysphagia.[24-26] Brachytherapy is known to provide long-term relief of dysphagia but there is a lag time of approximately 3 months between treatment and relief of symptoms. It is therefore recommended to perform brachytherapy only in patients with a relatively good prognosis.[27] The combination of SEMS placement and single-dose brachytherapy could in theory result in both an immediate and sustained relief of dysphagia. Randomized trials have indeed shown that this combination therapy resulted in a prolonged dysphagia free survival.[28,29] In addition, there was no increased risk of esophago-tracheal fistula formation, which has previously been reported as severe complication after this combination therapy.[30] Further innovations include combining both treatments into one therapy, i.e. irradiation stents.[31,32] The first trial with a SEMS loaded with ^{125}I seeds demonstrated a prolonged survival and better relief of dysphagia compared to conventional SEMS. However, no differ-

ence was found in the dysphagia recurrence rate.[33] Further studies are needed to confirm these promising results.

PART II: BILIARY STENTS

Benign biliary strictures

SEMS are increasingly used for the treatment of benign biliary strictures (BBS) as alternative for sequential stenting with an increasing number of plastic stents.[34,35] However, stent migration is a frequently encountered problem when using fcSEMS since embedding of the stent mesh in the mucosa is unlikely to occur. Although several anti-migration features for fcSEMS have been developed, migration is still a challenging problem with migration rates up to 40%.[36-39] In **Chapter 4** we evaluated a novel fcSEMS, the Niti-S bumpy type stent (Taewoong Medical, Seoul, South Korea), especially designed to prevent migration due to the flared ends and high conformability. We performed a prospective cohort study in five hospitals in the Netherlands and Belgium including 38 patients with a BBS. Stent placement was technically successful in 37 patients (97%). Initial clinical success, defined as resolution of the stricture during control fluoroscopy immediately after stent removal, was achieved in 28 of 35 patients (80%). During follow-up after stent removal, 6 of 28 patients (21%) developed a recurrent stricture after a median of 135 days. Overall, the long-term clinical success rate was 63% (22 of 35 patients). Stent migration occurred in 11 of 35 patients (31%), including five symptomatic (14%) and six asymptomatic migrations (17%). In total, 11 serious adverse events occurred in 10 patients (29%), with cholangitis (n=5) being most common.

The initial clinical success rate of 80% in our study, defined as stricture resolution at the moment of stent removal, is comparable to other studies using fcSEMS for BBS (range 60% to 95%). However, the stricture recurrence rate of 21% is in the upper range when compared to recurrence rates varying from 5 to 25% in other studies.[36-38,40-45] Stricture recurrence after initial resolution could imply that the stricture has been dilated properly but the remodelling process was not yet completed, suggesting that a longer stent dwell time might result in lower recurrence rates. Though, high stricture recurrences rates have also been reported in studies with a longer stent dwell time (4-6 months) compared to 3 months dwell time in our study.[38,41] Therefore, the optimal stent dwell time remains to be determined.

Despite the proposed anti-migration features of this fcSEMS, the stent migration rate of 31% in our study was high compared to migration rates ranging from 3% to 33% with other fcSEMS with flared ends.[41,42,46] In only half of the patients in

our study stent migration was symptomatic, suggesting that migration in these patients might have occurred because the stricture was optimally dilated. Other studies have also reported stricture resolution and no stricture recurrence in a significant proportion of patients with stent migration.[37,43,44,47,48]

An important limitation of almost all studies on fcSEMS placement for BBS is the absence of a control group treated with either plastic stents or another type of fcSEMS. Therefore, results are often compared with other case series. Due to substantial differences in study design, patient characteristics, stent dwell time, and stricture cause between studies, no definite conclusions can be drawn on the efficacy and safety of the novel stents evaluated. Nonetheless, the overall opinion seems to be that FCSESM placement for BBS is not an optimal treatment strategy due to the ongoing risk of migration despite several proposed anti-migration features for fcSEMS.

Placement of a biodegradable (BD) self-expandable biliary stents has been introduced as alternative treatment option for BBS.[49,50] In theory, a BD stent has the advantage of long-term dilation without the need of stent removal. In the past few years several types of BD stents have been evaluated in the biliary tract in animal studies with promising results.[51,52] However, until now there is only limited data from clinical studies. One case series reported successful treatment of two patients with an intrahepatic post-surgical biliary strictures with a follow-up of two years.[53] More recently, preliminary results were presented regarding BD stent placement in 10 patients with fibrotic pancreatic duct strictures due to chronic pancreatitis. It was concluded that stent placement was technically feasible, the stent completely degraded and stricture resolution was achieved in 86% of patients without stricture recurrence after one year.[54] These results seem promising and warrant further investigation, preferably in a randomized setting in comparison to progressive plastic stenting, which is still the standard of care.

Malignant biliary strictures

Endoscopic stent placement is the procedure of choice for palliation of extrahepatic bile duct obstruction and randomized controlled trials have shown that SEMS are associated with a longer stent patency compared to plastic stents.[55-60] However, SEMS are not universally accepted as standard treatment since data is inconclusive on whether or not the high initial costs of SEMS are offset by a reduction in costs for repeat interventions.[61,62] Furthermore, it is unknown whether the use of SEMS translates into an improved health-related quality of life (HRQoL), an important outcome measure to evaluate efficacy of palliative treatment.[63]

To evaluate which type of stent, either a plastic stent or SEMS, is superior for the palliation of malignant extrahepatic bile duct obstruction with regard to both

clinical effects, associated costs and HRQoL we conducted a multi-center randomized trial at 18 hospitals in the Netherlands and Belgium, the PLAMET study. A total of 219 patients were included and randomly assigned for placement of a plastic stent, uncovered SEMS (uSEMS), or partially covered SEMS (pcSEMS) during endoscopic retrograde cholangiography (ERC). In **Chapter 5,** we report the outcomes regarding clinical effects and associated costs. Stent dysfunction was observed significantly more often in the plastic stent group (42%) compared to the uSEMS (15%) and pcSEMS (15%) groups. Furthermore, the mean functional stent time was significantly longer in patients with an uSEMS (288 days) and pcSEMS (299 days) compared to plastic stents (172 days). There was no difference in survival between the different stent types. The costs for initial placement of plastic stents (€1,042) were significantly lower than for SEMS (€1,973). However, total costs per patient at the end of the follow-up period were not significantly different between plastic stents (€7,320) and SEMS (€6,932). Furthermore, in patients with a short survival (≤3 months) or metastatic disease, total cost per patient were also not different between plastic stents and SEMS. We found no differences in costs between patients with pcSEMS and uSEMS.

The costs of SEMS have been subject of debate ever since the introduction of SEMS in the 1980s.[2,64] There is convincing evidence that for patients with a relatively long survival after stent placement, i.e. longer than 4-6 months, total health care costs of SEMS placement compare favourably with plastic stent placement.[55-61,65] For patients with an expected survival of only 3-4 months or those with metastatic disease, plastic stents are generally recommended as the most "economical" option. However, this recommendation is largely based on decision analysis studies and only supported by two randomized clinical studies.[59,61,62,65] In our study, total treatment costs for patients with a short survival and those with metastatic disease were not different between plastic stents and SEMS. In fact, we found that the costs difference for initial stent placement were already outweighed when costs of hospitalisation after stent placement were included in the initial treatment costs. Interestingly, only two other studies included costs for hospital stay after stent placement in their cost analysis and all other randomized trials used a standard price for initial treatment, irrespective whether stent placement was successful or not.[55,58] As a result, none of these previously published studies reflects real healthcare costs. We included all healthcare costs associated with the treatment and found that stent costs are only a minor contributor to the total health care costs. However, as is true for all cost studies, it is difficult to translate our results to countries with other costs and reimbursement systems.

In **Chapter 6,** we assessed HRQoL of patients included in the PLAMET study. Data on HRQoL were available in 140 of 219 patients (64%), 71 patients (32%)

declined participation and in 8 patients (4%) only baseline questionnaires were available. HRQoL was assessed with two general questionnaires and one disease specific questionnaire. We found that patients treated with a SEMS scored better on physical and emotional functioning over time compared to patients with a plastic stent. In addition, patients with SEMS reported significantly less frequent symptoms of fatigue, appetite los, and nausea and vomiting. The HRQoL measured with self-rating on a visual analoge scale decreased in time in both treatment groups, indicating a statistically significant decrease in HRQoL over time.

Although it is generally assumed that less frequent stent dysfunction in patients with SEMS will translate in a better HRQoL, to date there are no studies evaluating long term HRQoL after stent placement or comparing HRQoL between patients treated with a plastic stent or SEMS. We performed the first study showing that patients with incurable extrahepatic biliary obstruction treated with SEMS placement indeed experience a better HRQoL over time. Both general and disease specific HRQoL remained more or less stable over time in patients with SEMS, while HRQoL deteriorated in patients with a plastic stent. A limitation of the study, which is possibly influencing the results, is the fact that patients were not blinded for the type of stent used. Furthermore, since we experienced that physicians were sometimes reluctant to include patients in the study due to the burden of completing HRQoL we decided that participating in the HRQoL sub-study was non-compulsory for inclusion in the PLAMET study. Considering the relatively high percentage of patients that declined participating in the HRQoL sub-study (32%), it seems likely that completing HRQoL questionnaires was also seen by the patients themselves as a considerable burden. To minimize the burden for patients, we think a thoughtful selection should be made of all available instruments to measure HRQoL.

Based on the results of the PLAMET study, showing that SEMS are superior to plastic stents in terms of functional stent time, number of repeat interventions, HRQoL and absence of a difference in terms of costs and survival, we strongly recommend SEMS placement as the preferred treatment for palliation of extrahepatic bile duct obstruction. With this conclusion, the next question arises, namely which type of SEMS should be used. In the PLAMET study we found no differences between uSEMS and pcSEMS, except for the cause of stent dysfunction, i.e. mainly tissue ingrowth for uSEMS and stent obstruction due to debris in the pcSEMS group. In recent years, fcSEMS have been developed to completely overcome the problem of tissue ingrowth and thereby to reduce stent dysfunction. However, a recent meta-analysis has not shown a clear benefit for either type of stent, i.e. uSEMS, pcSEMS or fcSEMS, in terms of functional stent time or survival.[66] As expected, the causes of stent dysfunction differed between the different types of stents, with tissue ingrowth being the predominant cause of stent dysfunction for uSEMS and migra-

tion for fcSEMS. To further reduce stent dysfunction, modifications of SEMS design are continuously being developed, mainly focussing on anti-migration features for fcSEMS.[67,68] Beside antimigration features such as flared stent ends and anchoring flaps, there is increasing emphasis on improving the flexibility of the stent in order to prevent migration. It is thought that SEMS with a low axial force, are less prone to migrate and have a lower complication risk due to a high conformability of the stent.[14,23] Some small, non-randomized reports indeed suggest lower migration and complication rates with SEMS with a low axial force.[68,69] We are currently performing a feasibility study with a highly flexible laser-cut fcSEMS with flared ends, the X-Suit NIR biliary stent (Medinol Ltd., Tel Aviv, Israel), to evaluate safety and migration. If the results of this feasibility study are promising, a randomized controlled trial will be performed with this stent.

Besides stent modifications, combination treatment modalities of SEMS placement with endoscopic ablation therapy are increasingly performed to improve stent patency.[70] Most important endoscopic ablation therapies include photodynamic therapy (PDT) and radiofrequency ablation (RFA). PDT involves intravenous administration of a photosensitizer which accumulates in the neoplastic cells followed by exposure of this tissue to a light with the appropriate photo activating wave length. As a result, ischemia, apoptosis and necrosis of tumor tissue is induces.[70] PDT therapy in combination with SEMS placement has mainly been studied in patients with cholangiocarcinoma and has shown promising results with an increased survival and improved biliary drainage. A drawback of this therapy is the risk of development of phototoxicity of the skin as complication.[71-73]

Endoscopic intraductal RFA is another promising technique using a catheter that induces thermal injury and subsequent localized necrosis. This therapy can be applied prior to SEMS placement as well as for treatment of SEMS occlusion secondary to tumor ingrowth.[70,74] Several case reports have demonstrated that RFA prior to SEMS placement is technically feasible and safe. In addition, results regarding survival and stent patency suggest improved outcomes for this combination therapy, but no direct comparisons between RFA plus stenting and stenting alone have been performed.[75-79] The scarce data on the use of RFA for occluded SEMS shows that the technique is feasible with good results for short-term efficacy and safety.[80-82] However, before a more widespread use of this technique is advocated, it is important to evaluate the effect of direct application of radiofrequency energy on the SEMS and whether or not this will lead to complications.

PART III: LUMEN APPOSING STENTS

Endoscopic transluminal drainage, in particular of pancreatic fluid collections (PFCs), is increasingly performed since the introduction of endoscopic ultrasonography (EUS). Initially, a naso-cystic catheter or plastic double-pigtail stents were used for drainage.[83,84] More recently, SEMS have become popular to use because of their larger luminal diameter of 10mm compared to 3.3mm for plastic stents. However, the tubular design of conventional (biliary) SEMS exhibits limited anchoring capacity.[85] Therefore, specifically designed lumen apposing metal stent (LAMS) have recently been developed for transluminal drainage.[86]

Pancreatic fluid collections

After the introduction of LAMS, a few case reports and case series were published with promising results regarding EUS-guided drainage of PFCs.[87-90] However, due to the use of different terminology, inclusion of small numbers of patients, and publication bias no firm conclusions regarding the use of LAMS for this indication can be drawn. We therefore initiated an international multicenter study (**Chapter 7** to evaluate EUS-guided PFC drainage using a LAMS, the Axios stent (Xlumena Inc., Mountain View, CA). In total, 61 patients from 15 European centers were prospectively enrolled in the study. Technical success of stent placement was high (98%) and clinical success was achieved in 93% of patients with a pancreatic pseudocyst (PP) and in 81% of patients with walled-off necrosis (WON). In three patients, stent migration was observed during abdominal ultrasound (n=2) or upper endoscopy (n=1). None of these patients, however, experienced symptoms due to stent migration. In total, five major complications were reported (9%), including PFC infection (n=4) and perforation (n=1). Based on these results, we concluded that EUS-guided drainage using this novel LAMS was feasible and the obtained clinical results are promising with a low major complication rate.

For patients with WON, the clinical success rate of drainage (81%) in our study was in the upper range when compared to the reported success rates of drainage with plastic pigtail stents (53-100%), while the success rate for PPs (93%) was similar when compared to plastic pigtail stents (82-100%).[84,91] The high success rate for PP drainage with plastic stents is due to the fact that fluid from PP can easily flow through and alongside plastic pigtails. However, when using plastic stents at least one additional intervention is usually required to achieve clinical success in contrast to no additional interventions in our study.[91] In patients with WON, comprising solid necrotic tissue, additional necrosectomy and/or irrigation procedures were required to achieve resolution in 43% of patients using LAMS, with only one intervention in half of those patients. Whether there is indeed a true

reduction in number of reinterventions needed due to the larger luminal diameter of the stents should be confirmed in a randomized trial comparing LAMS with plastic stents, since only limited data have been published on the exact number of repeat interventions to achieve resolution of PFCs or WONs. Despite the anchoring design of LAMS, we observed spontaneous stent migration and stent dislodgement, all without any adverse consequences. However, LAMS migration may cause severe complications such as perforation or obstruction in the gastrointestinal tract. Therefore, further refinements in stent design are required to improve the anchoring capacity and so to reduce the risk of stent migration and dislodgement.

Our results are comparable to another recently published prospective case series using the Axios stent[88] and a large retrospective case series using a slightly different type of LAMS.[92] The main conclusion from all case series is that LAMS placement is technically feasible and safe and that clinical outcomes seem promising. To further evaluate the clinical advantage of LAMS, randomized trials are required. The first randomized trial on EUS-guided PFC drainage, mainly PPs, compared multiple plastic stents with placement of a modified fcSEMS.[93] No differences were reported in terms of technical feasibility, efficacy, and safety. In addition, the procedure time was significantly shorter in the fcSEMS group and it was stated that this might result in less adverse events, less patient discomfort and fewer radiation exposure. Since the costs for SEMS and LAMS are significantly higher than plastic stents, the additional value of these stents should not remain limited to a shortened procedure time alone to be cost-effective. Based on the preliminary results of case series, the higher initial costs might be offset by a reduction in the number of repeat interventions needed. For this evaluation, it is important to differentiate between drainage of PP and WON, since in general WON drainage is associated with a higher number of repeat interventions.[91]

The optimal stent dwell time of LAMS for EUS-guided PFC drainage is another important issue still to be addressed. The large diameter of the stent could potentially allow for a fast drainage of PFCs and consequently a short stent dwell time. A shorter stent dwell time might reduce the number of stent related adverse events, such as severe tissue overgrowth precluding removal and stent migration. On the other hand, recurrence of the PFC might be a risk in case of early stent removal. However, a recent prospective cohort study evaluating early LAMS removal in patients with PPs, demonstrated that only those patients with a pancreatic ductal leak or disconnection of the pancreatic duct were at high risk for recurrence of the PP.[94]

Gallbladder

Early laparoscopic cholecystectomy is considered the optimal treatment for acute cholecystitis in the majority of patients.[95] However, in high risk surgical patients drainage of the gallbladder is recommended.[96, 97] Following the promising results of EUS-guided drainage of PFCs, EUS-guided gallbladder drainage (EUS-GBD) has been introduced as alternative to percutaneous transhepatic gallbladder drainage.[87,98] Reports on the use of LAMSs for gallbladder drainage are limited to case reports and case series without long-term follow-up.[87,90,99-101] In **Chapter 8**, we performed an international, prospective multicenter study including 30 patients to determine the feasibility and safety of the use of a LAMS, the Axios stent (Xlumena Inc., Mountain View, CA) for EUS-GBD in acute cholecystitis. Technical success was achieved in 90% of patients and clinical success was achieved in 96% of patients. Two patients (7%) developed recurrent cholecystitis due to LAMS obstruction within two weeks after stent placement. Successful LAMS removal was performed in half of the patients after a mean of 91 days. In the other half of patients no LAMS removal was performed because of death (n=5), significant tissue overgrowth (n=2) or other reasons (n=8). A total of 15 serious adverse events (50%) were reported, including 4 that were possibly stent- or procedure-related (13%). We concluded that EUS-GBD using LAMS is an elegant procedure in high risk surgical patients with acute cholecystitis when performed by an experienced endoscopist.

We reported technical failures in 3 of 30 patients (10%) and technical problems with LAMS deployment in another 2 of 30 patients (7%), resulting in an overall rate of technical difficulties of 17%. In only one previous study on EUS-GBD using LAMS technical failures were reported, with difficulties with stent placement in 6 of 13 patients (46%).[90] In order to improve technical success, refinements of the current LAMS and accessories may improve the results of EUS-GBD. The evolution of the LAMS used in both our studies, the Axios stent, is a new delivery system with electrocautery on the tip, which allows puncture and release of the stent in a single-step procedure, thus decreasing the number of accessories to be exchanged and consequently potentially reducing the frequency of complications. This newly developed device (Hot Axios, Xlumena, Mountain View, CA) has already successfully been utilized for both gallbladder and PFCs drainage.[102,103] The development of realistic ex-vivo animal models for training of EUS-guided drainage may also contribute to higher technical success rates.[104]

As with EUS-guided PFC drainage, the optimal stent dwell time is an important issue to be addressed for gallbladder drainage. In order to minimize the risk of recurrent cholecystitis and bile leakage, we decided to leave the LAMS in place for a period of three months. A drawback was that we experienced significant tissue overgrowth in three patients (10%) at the time of LAMS removal that precluded

removal in two patients. We hypothesize that stent location, either gastric of duodenal, might also influence the degree of tissue overgrowth. The retroperitoneal location of the duodenum might result in a more stable tract to the gallbladder as compared to the stomach, in which more peristaltic movements might result in a more pronounced tissue reaction.

Ultimately, in half of the patients in our study no LAMS removal was performed, mainly due to a poor clinical condition of the patient and/or patients' refusal. Furthermore, although gallbladder drainage is most often intended as a bridge to elective surgery, none of the patients in our study turned out to be eligible for elective cholecystectomy mainly due to their ongoing high surgical risk. For these patients requiring long-term drainage, EUS-GBD seems more appealing than percutaneous gallbladder which requires an external drainage catheter affecting patients' comfort and quality of life.[97] A recent relatively large retrospective study in 73 patients showed that EUS-GBD using fcSEMS was associated with fewer adverse events (4 vs. 17, p=0.013), decreased need for repeat gallbladder drainage (4 vs. 23, p=0.001) and a shorter post-procedure hospital stay (8 vs 16, p=0.046) compared to percutaneous drainage.[105] Randomized studies are needed to confirm the promising results of EUS-GBD using LAMS and to demonstrate if this treatment is of additional value compared to percutaneous drainage.

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CHAPTER 10

Summary in Dutch (Nederlandse samenvatting)

Endoscopie is tegenwoordig niet meer weg te denken uit de dagelijkse zorg voor patiënten met maag-, darm- en leverziekten.[1] Het plaatsen van een stent is een van de belangrijkste therapeutische endoscopische handelingen. Een grote doorbraak op dit gebied is de ontwikkeling van zelf-ontplooibare metalen stents (‘*self-expandable metal stents’, SEMS*) voor de slokdarm en de galwegen in de jaren ‘80.[2-4] Sindsdien zijn er continu aanpassingen en verfijningen doorgevoerd aan het stent ontwerp om de klinische uitkomsten van behandeling met een SEMS te verbeteren en het aantal complicaties te doen verminderen. Daarnaast is er recent een heel nieuw type SEMS ontwikkeld die gebruikt kan worden voor het endoscopisch echografie (*‘endoscopic ultrasonography’, EUS)* geleid, transluminaal draineren van vochtcollecties. Deze stent is speciaal ontworpen om twee lumina bij elkaar te houden (*‘lumen apposing metal stents’, LAMS*).

Het doel van dit proefschrift was het evalueren van het klinische effect en de veiligheid van verschillende type nieuwe stents en indicaties voor gebruik in het bovenste deel van het maagdarmkanaal, zoals slokdarm stents, stents voor de galwegen en zogenoemde LAMS.

DEEL I: SLOKDARM STENTS

Zowel patiënten met een benigne als maligne stenose van de slokdarm presenteren zich meestal met voedselpassageklachten, ook wel dysfagie genoemd. Ten gevolge van dysfagie kunnen er problemen ontstaan zoals ondervoeding, gewichtsverlies, voedselaspiratie, een afgenomen kwaliteit van leven, en in het geval van een maligne stenose, vroegtijdig overlijden.[5,6]

Benigne slokdarmstenose

De standaard behandeling van een benigne slokdarmstenose bestaat uit endoscopische dilatatie, welke erg effectief is met betrekking tot verlichting van dysfagie klachten. In een aanzienlijke subgroep van patiënten is het echter noodzakelijk om herhaaldelijk te dilateren vanwege een steeds terugkerende stenose.[7] Door het plaatsen van een stent zal er voor een langdurigere periode dilatatie plaatsvinden en er wordt aangenomen dat zodoende het aantal recidieven kan worden verminderd.[8] Het gebruik van een biologisch afbreekbare (‘*biodegradable’, BD*) stent zorgt er voor dat er geen verwijdering van de stent hoeft plaats te vinden.

In **Hoofdstuk 2** vergelijken we standaard dilatatie met het plaatsen van een BD stent bij patiënten met een terugkerende benigne slokdarmstenose in een internationale, multicentrische, gerandomiseerde studie, de DESTINY studie. In totaal werden er 66 patiënten geïncludeerd en gerandomiseerd voor standaard

endoscopische dilatatie (n=34) of BD stent plaatsing (n=32). Na een periode van 3 maanden waren er significant meer endoscopisch dilatataties verricht in de dilatatie groep in vergelijking met de BD stent groep (mediaan 1 vs. 0, p<0.001). Het totaal aantal endoscopische procedures in beide groepen was op dat moment echter niet significant verschillend (p=0.063). Ook werd er geen verschil gezien in het aantal dilatataties of het totaal aantal endoscopische procedures tussen de behandelgroepen na 6 en 12 maanden. De mediane duur tot terugkeer van dysfagie was significant korter in de dilatatie groep (54 dagen) in vergelijking tot de BD stent groep (120 dagen, p=0.047). Het aantal mogelijk geassocieerde ernstige complicaties was significant hoger in de BD stent groep (21 in 19 patiënten) dan in de dilatatie groep (11 in 10 patiënten, p=0.014). Er werd geen verschil gezien in de kwaliteit van leven over tijd tussen beide groepen.

Samenvattend gaat het plaatsen van een BD stent bij patiënten met een terugkerende benigne slokdarmstenose gepaard met een tijdelijke afname van het aantal herhaalde dilatataties en een langere duur tot terugkeer van dysfagie klachten in vergelijking met standaard dilatatie. In de BD stent groep werden echter significant meer ernstige complicaties gezien. Gebaseerd op deze resultaten is het niet gerechtvaardigd om het plaatsen van een BD stent aan te bevelen als eerste keuze behandeling van patiënten met een terugkerende benigne slokdarmstenose.

Kwaadaardige slokdarmstenose

Het plaatsen van een SEMS die volledig bekleed is met een kunststof omhulsel, een volledig gecoverde (*'fully covered', fc*) SEMS, is de meest uitgevoerde behandeling ter palliatie van maligne dysfagie.[9] De behandeling is effectief en veilig, maar een belangrijk nadeel is dat bij 30 tot 40% van de patiënten terugkeer van dysfagie klachten optreedt ten gevolge van weefsel overgroei of uitzakken, migratie, van de SEMS.[10]

In **Hoofdstuk 3** beschrijven we de resultaten van een multicentrische, prospectieve studie waarin we een nieuwe fcSEMS onderzoeken, de Hanaro Flap stent. Deze stent is ontworpen om weefsel ingroei tegen te gaan en tevens om migratie te voorkomen door twee specifieke anti-migratie eigenschappen; weerhaakjes op het middenstuk van de stent en wijd uitlopende stent uiteinden. In totaal werden 40 patiënten met maligne dysfagie in de studie geïncludeerd en negen patiënten (23%) kregen opnieuw dysfagie klachten. De oorzaak van de terugkerende dysfagie klachten was het gedeeltelijk- of volledig migreren van de stent bij zes patiënten (15%), weefsel overgroei bij twee patiënten (5%) en het breken van de stent bij één patiënt (3%). Ernstige complicaties traden op bij 36% van de patiënten en milde complicaties bij bijna de helft van de patiënten (49%). Het

merendeel van de complicaties betrof retrosternale pijn (n=13) en misselijkheid en braken (n=7).

De conclusie van deze studie was dat het percentage patiënten met terugkerende dysfagie klachten met deze nieuwe fcSEMS relatief laag was ten opzichte van andere fcSEMS. Echter, migratie van de stent was de meest voorkomende oorzaak van terugkerende dysfagie ondanks de specifieke anti-migratie eigenschappen van de stent. Het aantal (ernstige) complicaties was relatief hoog in vergelijking met de resultaten van andere studies met fcSEMS.

DEEL II: GALWEG STENTS

Patiënten met een galwegstenose presenteren zich vaak met klachten van cholestase, zoals geelzucht, jeuk en malabsorptie. Ter voorkoming van ernstige complicaties, zoals cholangitis en, in het geval van een benigne stenose, secundaire biliaire cirrose, wordt geadviseerd galafvloed te bewerkstelligen door het plaatsen van een galwegstent middels endoscopische retrograde cholangiografie (ERC).[11,12]

Benigne galwegstenose

Het plaatsen van een fcSEMS wordt steeds vaker uitgevoerd ter behandeling van een benigne galwegstenose als alternatief voor sequentieel behandelen met een toenemend aantal parallel geplaatste plastic stents.[11,13] Migratie van de stent is echter een veel voorkomend probleem bij het gebruik van fcSEMS omdat de stent zich niet vasthecht aan de omgevende mucosa. Hoewel er al verschillende anti-migratie eigenschappen voor fcSEMS zijn ontwikkeld, is stent migratie nog steeds een veelvoorkomend probleem.[14-17]

In **Hoofdstuk 4** evalueren we een nieuw type fcSEMS, de Niti-S bumpy type stent, speciaal ontwikkeld om migratie te voorkomen door een soepel en makkelijk vervormbaar ontwerp met wijd uitlopende stent uiteinden. We hebben een prospectieve cohort studie uitgevoerd in vijf ziekenhuizen in Nederland en België waarbij 38 patiënten werden geïncludeerd met een benigne galwegstenose. Het plaatsen van de stent was technisch succesvol in 37 patiënten (97%). Het initiële klinische succes, gedefinieerd als het verstreken zijn van de stenose bij controle fluoroscopie direct na stent verwijdering, werd bereikt bij 28 van de 35 patiënten (80%). Gedurende de periode na verwijdering van de stent ontwikkelden 6 van de 28 patiënten, na een mediaan van 135 dagen, opnieuw een stenose. Concluderend werd er op de lange termijn bij 63% van de patiënten (22 van de 35 patiënten) klinisch succes bereikt. Stent migratie vond plaats bij 11 van de 35 patiënten (31%), waarvan vijf symptomatische (14%) en zes asymptomatische migraties (17%). In

totaal traden er 11 ernstige complicaties plaats in 10 patiënten (29%), waarvan cholangitis (n=5) de meest voorkomende was.

Samenvattend is het initiële klinische succes van 80% in onze studie vergelijkbaar met resultaten in andere studies waarin fcSEMS worden gebruikt voor de behandeling van een benigne galwegstenose (variërend van 60 tot 90%). Het percentage patiënten waarbij de stenose recidiveert na initieel klinisch succes is met 21% echter relatief hoog in vergelijking met recidief percentages variërend van 5 tot 25% in andere studies. Ondanks de veronderstelde anti-migratie eigenschappen van de onderzochte fcSEMS was het stent migratiepercentage van 31% in onze studie hoog in vergelijking tot migratie percentages van 3 tot 33% met andere fcSEMS met wijd uitlopende stent uiteinden.

Maligne galwegstenose

Het endoscopisch plaatsen van een stent is de eerste keuze palliatieve behandeling bij patiënten met een maligne extrahepatische galwegstenose. Gerandomiseerde studies hebben laten zien dat het plaatsen van een SEMS gepaard gaat met een langere functionele stent tijd in vergelijking met plastic stents.[18-23] Het gebruik van SEMS is echter nog niet algemeen geaccepteerd als standaard behandeling, omdat er onduidelijkheid bestaat of de hoge kosten die gepaard gaan met het plaatsen van een SEMS wel worden gecompenseerd door een afname van de kosten voor herhaalde endoscopisch ingrepen door de langere functionele stenttijd. Bovendien is het onbekend of het plaatsen van een SEMS zich ook vertaald in een verbeterde, gezondheid gerelateerde, kwaliteit van de leven (‘*health related quality of life’, HRQoL*), een belangrijke uitkomstmaat om palliatieve behandelingen te evalueren.[24,25]

Om te onderzoeken welk type stent, een plastic stent of SEMS, superieur is voor de palliatie van een maligne extrahepatische galwegstenose met betrekking tot klinische uitkomsten, geassocieerde kosten en de HRQoL, hebben we een multicentrische gerandomiseerde studie uitgevoerd in 18 ziekenhuizen in Nederland en België, de PLAMET studie. In totaal werden 219 patiënten in de studie geïncludeerd en gerandomiseerd voor het plaatsen van een plastic stent, een niet gecoverde (‘*uncovered’, u*) SEMS of een partieel gecoverde (‘*partieel covered’, pc*) SEMS tijdens ERC.

In **Hoofdstuk 5** beschrijven we de uitkomsten met betrekking tot de klinische resultaten en de daarbij behorende kosten. Stent dysfunctie werd significant vaker gezien in de groep patiënten met een plastic stent (42%) dan in de groep patiënten met een uSEMS (15%) en een pcSEMS (15%). Verder zagen we dat de gemiddelde functionele stent tijd significant langer was bij patiënten met een uSEMS (288 dagen) en een pcSEMS (299 dagen) dan in patiënten met een plastic

stent (172 dagen). Er was geen verschil in de overleving van patiënten tussen de verschillende typen stents. De initiële kosten voor het plaatsen van een plastic stent (€1,042) waren significant lager dan de kosten voor beide typen SEMS (€1,973). De totale kosten per patiënt aan het einde van de studie periode waren echter niet significant verschillend tussen patiënten met een plastic stent (€7,320) of SEMS (€6,932). Bovendien zagen we ook geen verschil in totale kosten tussen de verschillende typen stents bij patiënten met een relatief korte overleving (≤3 maanden) of patiënten met gemetastaseerde ziekte. Tot slot was er op geen enkel punt een verschil in kosten tussen uSEMS en pcSEMS.

In **Hoofdstuk 6** hebben we de HRQoL geëvalueerd van patiënten die deelnamen aan de PLAMET studie. Er waren gegevens beschikbaar over de HRQoL van 140 van de 219 patiënten (64%), 71 patiënten (32%) zagen af van deelname en van 8 patiënten (4%) waren alleen gegevens beschikbaar van aanvang van de studie. De HRQoL werd geëvalueerd met twee algemene vragenlijsten en één ziekte specifieke vragenlijst. We vonden dat patiënten die behandeld waren met een SEMS beter scoorden op het fysieke en emotionele vlak gedurende de studieduur in vergelijking tot patiënten met een plastic stent. Tevens rapporteerden patiënten met een SEMS significant minder vaak symptomen van vermoeidheid, slechte eetlust, misselijkheid en braken. Het cijfer dat patiënten zelf gaven aan hun HR-QoL, gemeten op een visueel analoge schaal, daalde in beide groepen significant naarmate de tijd vorderde.

De PLAMET studie laat zien dat een SEMS superieur is ten opzichte van een plastic stent wat betreft de functionele stent tijd, het aantal herhaalde endoscopieën en de kwaliteit van leven en dat er geen verschil is op het gebied van kosten en overleving. Gebaseerd op deze resultaten pleiten wij er voor dat het plaatsen van een SEMS de behandeling van eerste keus is voor een maligne extrahepatische galwegstenose.

DEEL III: 'LUMEN APPOSING' STENTS

Endoscopische transluminale drainage, in het bijzonder van vochtcollecties in het pancreas (*'pancreatic fluid collections', PFCs*), wordt steeds vaker uitgevoerd sinds de introductie van endo-echografie (*'endoscopic ultrasonography', EUS*).[26,27] Aanvankelijk werd er een naso-cystische sonde of plastic dubbele 'pigtail' stents gebruikt voor drainage. Sinds kort worden SEMS gebruikt vanwege een grotere diameter van het stent lumen, namelijk 10mm in vergelijking tot 3.3mm van plastic stents.[28] Het buisvormige ontwerp van conventionele (galweg) SEMS heeft echter weinig capaciteit om de twee lumina waartussen gedraineerd wordt stevig bij

elkaar te houden. Om die reden zijn er speciale stents ontwikkeld die twee lumina bij elkaar kunnen houden *('lumen apposing metal stent', LAMS)*.[29]

Vochtcollecties in het pancreas

Na de introductie van LAMS zijn er een aantal case reports en case series gepubliceerd die veelbelovende resultaten lieten zien met betrekking tot EUS-geleide drainage van PFCs.[30-33] Door verschillen in gebruikte terminologie, kleine aantallen patiënten en publicatie bias, kunnen er echter geen conclusies worden getrokken over het gebruik van LAMS voor deze indicatie. Om die reden hebben wij het initiatief genomen om een internationale, prospectieve, multicentrische studie op te zetten (**Hoofdstuk 7)** om EUS-geleide drainage van PFCs door middel van een LAMS, de Axios stent, te evalueren.

In totaal werden 61 patiënten uit 15 Europese centra geïncludeerd in de studie. Het technisch succes van stent plaatsing was hoog (98%) en klinisch succes werd behaald bij 93% van de patiënten met een pancreas pseudocyste (PP) en bij 81% van de patiënten met een necrotische collectie *('walled-off necrosis', WON*). Bij drie patiënten werd er migratie van de stent gezien bij echografie van de buik (n=2) of gastroscopie (n=1). Geen van deze patiënten had echter klachten bemerkt door het migreren van de stent. In totaal werden er vijf ernstige complicaties gezien (9%), waaronder infectie van de PFC (n=4) en een perforatie (n=1). Gebaseerd op deze getallen, hebben wij geconcludeerd dat EUS-geleide drainage door middel van een LAMS mogelijk is, de behaalde resultaten veelbelovend zijn en gepaard gaat met een laag complicatie risico.

Galblaas

Vroege laparoscopische cholecystectomie wordt gezien als de optimale behandeling voor een acute cholecystitis bij de meerderheid van de patiënten.[34] Bij patiënten met een hoog operatie risico wordt er echter aanbevolen om de galblaas te draineren.[35] In navolging van de veelbelovende resultaten van EUS-geleide drainage van PFCs, heeft EUS-geleid draineren van de galblaas nu ook haar intrede gedaan als alternatief voor percutane transhepatische galblaasdrainage.[36] Het gebruik van LAMS voor EUS-geleide galblaas drainage (EUS-GBD) is tot nu toe slechts beschreven in case reports en in case series zonder een langdurig vervolg van de patiënten.[30,37,38]

In **Hoofdstuk 8** hebben we een internationale, prospectieve, multicentrische studie uitgevoerd bij 30 patiënten om de haalbaarheid en veiligheid te evalueren van het gebruik van LAMS voor EUS-GBD van acute cholecystitis bij patiënten met een hoog operatie risico. Het technisch succesvol plaatsen slaagde bij 90% van de patiënten en klinisch succes werd behaald bij 96% van de patiënten. Twee

patiënten ontwikkelden opnieuw een cholecystitis binnen twee weken door verstopping van de LAMS. De LAMS werd succesvol verwijderd bij de helft van de patiënten na een gemiddelde periode van 91 dagen. Bij de andere helft van de patiënten werd de LAMS niet verwijderd vanwege overlijden (n=5), weefsel groei over de stent (n=2) en een aantal andere redenen (n=8). In totaal werden er 15 ernstige complicaties geregistreerd, waarvan er vier mogelijk ten gevolge van de stent of de procedure waren ontstaan (13%). Wij concludeerden dat EUS-GBD door middel van een LAMS een elegante procedure is bij patiënten met een acute cholecystitis en een hoog operatie risico, indien dit wordt uitgevoerd door een ervaren endoscopist.

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Walter D, Teoh AY, Itoi T, Pérez-Miranda M, Larghi A, Sanchez-Yague A, Siersema PD, Vleggaar FP. EUS-guided gallbladder drainage with a lumen apposing metal stent; a prospective long-term evaluation. Gut. 2015; 0; 1-3 [Epub ahead of print]

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LIST OF ORAL PRESENTATIONS

2012 United European Gastroenterology Week - Amsterdam
- A novel large-diameter metal stent, the Axios stent, for endoscopic ultrasonography guided drainage of peripancreatic fluid collections: a multicenter experience (***Oral Free Paper Prize***)

2013 Voorjaarsvergadering NVGE - Veldhoven
- A new fully covered metal stent (HANARO-ECT stent) for the treatment of malignant esophageal strictures: a prospective follow-up study
- A fully covered self-expandable metal stent, Niti-S, for benign biliary strictures: a prospective multi-center follow-up study
- Placement of a fully covered metal stent (AXIOS) for EUS-guided drainage of peripancreactic fluid collections; a prospective European cohort study

2013 Najaarsvergadering NVGE - Veldhoven
- Cost concerns should not affect the choice for plastic or metal stent for unresectable malignant common bile duct obstruction: a randomized controlled trial

2013 United European Gastroenterology Week - Berlin
- Cost concerns should not affect the choice for plastic or metal stent for unresectable malignant common bile duct obstruction: a randomized controlled trial (***Oral Free Paper Prize***)

2014 Voorjaarsvergadering NVGE - Veldhoven
- EUS-guided drainage with a large diameter metal stent is a safe treatment for acute cholecystitis in high risk patients
- Quality of life after stent placement for palliation of common bile duct obstruction: a randomized controlled trial comparing plastic and metal stents

2014 Digestive Disease Week - Chicago

- Metal stent placement is cost-effective for palliation of malignant common bile duct obstruction: randomized controlled trial
- Quality of life after stent placement for palliation of common bile duct obstruction: a randomized controlled trial comparing plastic and metal stents
- EUS-guided drainage with a large diameter metal stent is a safe treatment for acute cholecystitis in high-risk surgical patients

2014 United European Gastroenterology Week - Vienna

- Quality of life after stent placement for palliation of common bile duct obstruction: a randomized controlled trial comparing plastic and metal stents (***Oral Free Paper Prize***)

2015 Voorjaarsvergadering NVGE - Veldhoven

- A randomized comparison of degradable esophageal stent versus dilation therapy for patients with recurrent benign esophageal strictures: 6-month results (***President Select session***)

2015 United European Gastroenterology Week - Barcelona

- A randomized trial comparing biodegradable stent placement and endoscopic dilation for recurrent benign esophageal strictures

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Daisy Walter was born on the 23th of June 1986 in Gouda. After graduation from secondary school (Emmauscollege, Rotterdam) in 2004, she started her study at the medical school of Utrecht University. During her study she performed her Gynaecology internship in South-Africa (Tygerberg Hospital, Stellenbosch). In 2010 she performed a research internship on platelet function in chronic kidney disease at the department of Hematology of the University Medical Center Utrecht and the Meander Medical Center Amersfoort. In May 2011 she received her medical degree and started her PhD-studies at the Department of Gastroenterology and Hepatology of the University Medical Center Utrecht under supervision of Prof. dr. P.D. Siersema and dr. F.P. Vleggaar on stents in the upper gastrointestinal tract, as reported in this thesis. In 2012, 2013 and 2014 she received an Oral Free Paper Prize during the European Gastroenterology Week. In May 2014 she started with the first part (Internal Medicine) of her residency program of Gastroenterology and Hepatology at the Meander Medical Center Amersfoort under supervision of Dr. R. Fijnheer.