New Clinical Insights into Stents for Malignant Upper Gastrointestinal Disease

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New Clinical Insights into Stents for Malignant Upper Gastrointestinal Disease

Nieuwe klinische inzichten over stents
voor maligne aandoeningen van de bovenste tractus digestivus

Proefschrift

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Chapter 1

General introduction and aims of this thesis

General introduction

Malignant obstructive disease of upper gastrointestinal tract

Malignant obstruction of the upper gastrointestinal (GI) tract is usually a late complication of advanced cancer. According to the location, two separate groups can be distinguished: obstructive disease at the level of the esophagus or cardia, and malignant strictures of the distal stomach and duodenum, the latter also being described as gastric outlet obstruction. Patients suffer from invalidating symptoms related to reduced passage of food and/or liquids. This generally results in anorexia and malnutrition, which is further enhanced by the advanced stage of malignant disease. If patients are not considered for curative therapy, optimal palliation of symptoms is essential in order to improve quality of life. Palliative therapy for obstructive symptoms is one of the most relevant issues and self-expandable metal stents (SEMS) are an accepted treatment modality for this indication.

Palliation of malignant esophageal strictures

Malignant esophageal obstruction is mainly caused by esophageal or cardia cancer, but can also originate from extrinsic compression, for example due to enlarged mediastinal lymph node metastasis or lung cancer. The incidence of esophageal cancer continues to rise. In the Netherlands the incidence increased from around 1200 per year in 2000 to almost 2000 per year in 2010 [1]. Palliative therapy is indicated in the majority of patients because of incurable disease at presentation [2]. Dysphagia is one of the major symptoms to focus on and severity can be classified according to the dysphagia scoring scale (see table 1)[3].

Table 1. Dysphagia Scoring Scale

0	Able to consume a normal diet
1	Dysphagia with certain solid foods
2	Able to swallow semi-solid soft foods
3	Able to swallow liquids only
4	Unable to swallow saliva (complete dysphagia)

Various palliative treatment modalities are available for treating malignant dysphagia, including endoscopic and non-endoscopic techniques [4]. External beam radiation with or without concurrent chemotherapy is the standard approach for unresectable esophageal cancer, aiming for long lasting disease control and alleviation of obstructive symptoms [5, 6]. Alternatively, intraluminal brachytherapy can be applied with localized high

radiation dose [7]. However, major inconveniences are the risk of fistula formation and long time before improvement of dysphagia is expected. In patients with short life expectancy, or in case of failure of radiation, endoscopic therapy is recommended. Nowadays, endoscopic placement of stents is the preferred and most commonly used modality to palliate malignant dysphagia [8]. Other techniques have been described (see table 2), but have been largely abandoned due to significant adverse events and insufficient relief of dysphagia with necessity for repeated interventions [4].

Table 2. Endoscopic techniques for malignant dysphagia

Stent placement
Endoscopic dilation (through the scope balloon or bougie)
Laser therapy (Nd:YAG)
Alcohol injection
Photodynamic therapy
Argon plasma coagulation
Cryospray ablation

SEMS in malignant esophageal strictures

Esophageal stents have been utilized in clinical practice for more than 30 years and self-expandable metal stents (SEMS) are currently by far most commonly used [8]. The majority of SEMS are constructed with a nitinol braiding, increasing its flexibility and reducing esophageal injury [9]. The stent is initially folded in a delivery catheter to accommodate insertion and when deployed, they gradually expand to their final diameter. The main advantages of SEMS therapy are successful endoscopic insertion of the device in almost all cases with rapid (24-48 hours) improvement of dysphagia. However, re-occurrence of obstruction is reported in around one-third of patients, mostly related to tumor ingrowth, overgrowth, SEMS migration or food impaction [10]. Furthermore, other SEMS-related complications can be encountered in the early and late phase after insertion [11].
Various types of SEMS of different manufacturers are currently available on the market [8]. Modifications in design and additional features have claimed to improve stent therapy, but it can be argued whether this really has resulted in better clinical outcome over the past decades. Intensive scientific research, mainly uncontrolled observational studies, has been performed pertaining SEMS therapy in last decades. Covered esophageal SEMS are currently recommended, meaning that a silicone membrane has been attached. In this way tumor ingrowth through the meshes is prevented, as demonstrated in an randomized controlled trial (RCT) published in 2001 [12]. Since then only five RCT's have been conducted to compare different SEMS in malignant dysphagia [13-17]. The available studies suggest that no major differences in efficacy and safety exist between differ-

ent SEMS and up to now there is still insufficient evidence to recommend one particular type of SEMS in the treatment of malignant dysphagia.

Although covering the SEMS is beneficial to prevent ingrowth, the optimal extent of the covering is still unclear. In partially covered SEMS both ends are left uncovered. Extending the covering to the full length of the SEMS could potentially result in less tumor ingrowth through the meshes compared to partially covered SEMS. On the other hand, the disadvantage of a fully covered SEMS might be a higher migration risk. Different kinds of anti-migration features have developed to overcome this problem. These include flare shaped ends, struts or rings to the outer side of the SEMS and internal covering. Moderate clinical efficacy of these features has been described in observational series [18-23]. However, the exact value of these specific features still needs to be established since adequately designed comparative studies are still lacking.

Several adverse events are reported after SEMS placement including severe pain, hemorrhage, perforation, (aspiration) pneumonia, fistula and reflux. Major adverse events occur in approximately 30% after SEMS placement [8]. Little is known about risk factors for the development of adverse events. It was suggested earlier that placement of SEMS for cervical tumors may be limited by patients intolerance and increased risk of adverse events. However, several series have shown similar outcome compared to distal strictures [24, 25]. In addition, some studies have found associations between a higher incidence of adverse events with larger diameter or a specific design of the SEMS [15, 26], but these results have not been confirmed. Hence, it still remains difficult to identify these particular patients who are prone of developing stent-related complications.

The safety of SEMS placement after prior chemo- and/or radiotherapy (CRT) is an important and relevant issue. Nowadays, more patients are treated with CRT with the standard application of neo-adjuvant therapy. In addition, palliative chemotherapy, external radiotherapy and brachytherapy are more frequently used [7, 27]. Furthermore, definitive chemoradiotherapy has been regarded as a curative alternative in patients with an irresectable locally advanced (T4) cancer or in patients who are poor surgical candidates due to co-morbidity [6, 28, 29]. As a consequence, SEMS are inserted in a larger number of patients who have been earlier treated with CRT. Whether previous CRT is associated with a higher risk of adverse events is still uncertain because the available data is limited and discordant. Some studies have reported a higher incidence of adverse events while others have shown similar safety outcomes [30-33]. One limitation is that most studies have included patients who have undergone different CRT regimes. Definitive chemoradiotherapy consists of substantially higher radiation dose and SEMS therapy might be more hazardous in these patients. However, the safety of SEMS in this particular group of patients has not yet been investigated.

Pain is one of the most frequent symptoms in cancer patients and its severity rises in more advanced disease [34, 35]. Adequate treatment of pain should be guaranteed in order to improve quality of life [36]. Knowledge of the risk and intensity of pain, and its

management after esophageal SEMS insertion is limited because it has not yet been properly studied. In studies on esophageal SEMS for malignant disease assessment of pain has never been the primary focus and the reported occurrence of severe pain ranges widely. Therefore, an accurate assessment of pain and its treatment is urgently needed to better inform and manage patients undergoing palliative SEMS placement.

Palliation of malignant gastric outlet obstruction

Malignant gastric outlet obstruction (GOO) comprises strictures of the distal stomach and duodenum. While in Asian countries gastric cancer is the most frequent underlying disease, duodenal compression or ingrowth due to advanced pancreatic head cancer is the predominant cause in the Western world. In patients with pancreatic cancer, gastric outlet obstruction occurs in 15-20% of cases. In the Netherlands, the incidence of pancreatic cancer is steadily climbing with approximately 2200 patients diagnosed in 2010 [1]. Patients with GOO are seriously hampered by symptoms such as nausea, vomiting, inability to eat and loss of weight, causing a significant reduction in patient's quality of life [37]. The most commonly used symptom based classification is the GOO scoring system as shown in table 3 [38].

Table 3. Gastric Outlet Obstruction Scoring system

0	No oral intake
1	Liquids only
2	Soft solids
3	Low-residue or full diet

The primary aim of treatment in patients with an incurable malignancy is to relief symptoms. The traditional procedure to alleviate symptoms caused by GOO is to perform an open or laparoscopic surgical gastrojejunostomy (GJJ). This procedure is associated with a good functional outcome and relieves symptoms in almost all patients [37]. Also, the re-intervention rate in case of re-obstruction is low (2%). The disadvantages of this surgical procedure include significant risks of morbidity and mortality. Furthermore, up to 26% of patients GJJ have delayed gastric emptying, which leads to a prolonged hospital stay after surgery [39-42]. Since the early 1990's endoscopic SEMS placement provides an alternative for the palliative management of GOO.

SEMS in malignant gastric outlet obstruction

The aim of SEMS placement is to achieve anatomical and functional resolution of the malignant stricture. Most SEMS have a braided nitinol construction to enhance flexibility

and are inserted under endoscopic and fluoroscopic guidance. A very high technical success rate over 95% have been demonstrated resulting in a relief of obstructive symptoms within hours to days [38, 43-45]. A downside is the risk of re-obstruction ranging from 10 to 20%, mainly caused by tumor ingrowth through the meshes or overgrowth related to disease progression. In addition, also SEMS migration or food impaction may occur resulting in recurrent obstructive symptoms [38, 43-45]. Consequently, a re-intervention is usually indicated to restore luminal patency.

Currently, SEMS from various manufacturers are available for clinical use. Although all SEMS are built on the same basic fundamentals, each manufacturer produces SEMS with its own unique design and deployment system. The development of duodenal SEMS is ongoing with also introduction of new SEMS. It is highly desirable that the efficacy and safety of newly introduced SEMS is thoroughly investigated before widespread use in clinical practice.

Recurrent obstruction is devastating in patients with incurable disease. In recent years different alterations in SEMS design have been studied in an attempt to lower the re-obstruction rate. As in esophageal stents, covering of the SEMS with a silicone membrane could potentially prevent tumor ingrowth through the gaps of the metal framework. A limited number of studies have been performed using covered SEMS, mainly in an Asian population. Although covered SEMS seem beneficial in preventing ingrowth, they are associated with a higher migration risk compared to uncovered SEMS [46, 47]. For that reason a covered SEMS with effective anti-migration features is eagerly searched for. Several modifications have been suggested, including flare-shaped ends, uncovered ends (i.e. partially covered), internal covering and fixation with clips [46, 48-52]. Unfortunately, significant improvements in clinical outcome have not yet been clearly demonstrated.

Aims

The aim of this thesis is to gain more insight into efficacy and safety of SEMS therapy, including new developments, for malignant upper gastrointestinal strictures.

Outline

The objectives are addressed in several studies presented in this thesis. **Part I** is devoted to SEMS in malignant esophageal dysphagia. In **Chapter 2** we provide a literature overview of the current knowledge of stents in esophageal disease. **Chapter 3** is devoted to an evaluation of palliative esophageal SEMS therapy over a 23 year time period. This not only provides an opportunity to evaluate changes in management over time, but also to discover trends in efficacy and safety. In **Chapter 4** we aimed to identify the optimal length of SEMS covering by comparing partially with fully covered SEMS in the palliative management of malignant dysphagia. In **Chapter 5** we evaluated the clinical outcome of

SEMS therapy in patients who received definitive chemoradiotherapy prior to SEMS placement with primary focus on occurrence of adverse events. **Chapter 6** describes an prospective assessment of pain after palliative SEMS placement. **Part II** focuses on SEMS in malignant gastric outlet obstruction. **Chapter 8** describes the clinical outcome of a new uncovered SEMS in a large series of patients with malignant gastric or duodenal strictures. In **Chapter 7** we aimed to evaluate the efficacy and safety of a newly developed partially covered duodenal SEMS. Finally, **Chapter 9** provides a summary and overall discussion, including a description of the main findings of this thesis and future directions.

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Part I

New clinical insights into stents for malignant esophageal disease

Chapter 2

Esophageal stents for malignant and benign disorders

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Abstract

Endoscopic stent placement is an effective palliative treatment for malignant dysphagia and fistula, leading to rapid symptom relief. However, recurrent dysphagia and other stent-related complications are common for which reason continuously new design modifications are implemented. Although some of these changes facilitate stent placement, complications remain and occur at similar rates. Recently, stents have also been used in benign esophageal disorders. Covered stents have the ability to effectively seal esophageal perforations and leaks, reducing the need for invasive surgery. This benefit does not pertain to patients with refractory benign esophageal strictures, in whom stents have limited long-term effect and are associated with a high complication rate. The initial results of fully covered metal stents in refractory esophageal variceal bleeding are encouraging, but their definite role remains to be further elucidated. This review provides an overview of indications, techniques and management of complications of stents in malignant and benign esophageal disease.

Introduction

Endoscopic stent placement is a minimally invasive procedure that is frequently applied in both malignant and benign esophageal disease. After 30 years, since the first publications in the late 1970s, esophageal stent therapy has evolved into a widely accepted palliative therapeutic procedure to treat malignant esophageal strictures and fistula [1]. Esophageal stenting aims to restore luminal patency and thereby nutritional intake and improve quality of life [2, 3]. Most common disadvantages of stent treatment are recurrent dysphagia and other stent-related complications. In the last decade research has focused on modifying stent design to improve efficacy and safety. In spite of ongoing efforts, stent patency and complication rate have not changed significantly over time [4].
In recent years, stents have also been applied in selected patients with benign esophageal conditions. However, most studies in this area are small and uncontrolled with short follow-up. The optimal indication, stent design and duration of therapy for these conditions thus remain to be determined.
In this review we present an overview of the indications, techniques, and management of complications of stents in malignant and benign esophageal disease and provide an outlook on the future trends and developments.

Esophageal stents in malignant diseases

Esophageal stents are mainly placed in patients with irresectable esophageal carcinoma, who have a short life expectancy, and suffer from marked esophageal stenosis or fistula [5]. Other malignant conditions in which patients are eligible for stent placement are extrinsic esophageal compression or fistula formation as a result of pulmonary cancer, mediastinal cancer or metastatic disease. The main advantages of stent therapy are successful insertion of the device in almost all cases with rapid (24-48 h) improvement of dysphagia. Disadvantages of stent therapy are re-occurrence of dysphagia in up to one-third of patients, and other stent-related complications, including hemorrhage, pain and fistula [6]. Although most stents are placed in the distal or mid esophagus, insertion in the cervical esophagus is considered equally effective [7].
Nowadays, self-expandable metal stents (SEMS) and self-expandable plastic stents (SEPS) are most commonly used in esophageal diseases (Table 1). SEMS consist of a nitinol braiding allowing them to conform to the anatomical angulations. Most SEMS have a partial or full (PC / FC) cover, which prevents tumor ingrowth [8, 9]. Although a FC SEMS prevents tissue ingrowth over the full length of the stent, it is associated with an increased risk of migration [10]. The polyester Polyflex stent is the only available SEPS. It was introduced in 2001 to reduce costs [11].

Table 1. Selected overview of stents currently available in United States, Europe and Asia.

Stent	Manufacturer	Material	Diameter body / flare (mm)	Length (cm)	Covering
Alimaxx-E	Alveolus	Nitinol	18/22	7/10/12	FC with antimigration struts
Esophageal Z-stent	Cook	Stainless steel	18/25	8/10/12/14	PC
Evolution	Cook	Nitinol	20/25	8/10/12.5/15	PC
Flamingo Wallstent	Boston Scientific	Stainless steel	20/30	12/14	PC
Gianturco-Z	Cook	Stainless steel	18/25	8/10/12/14	FC
Niti-S	Taewong Medical	Nitinol	16/20 18/23 20/25	8/10/12/14	FC
Niti-S Double-layered	Taewong Medical	Nitinol	18/26	9/12/15	FC with additional uncovered outer nitinol wires
Niti-S Single-layered	Taewong Medical	Nitinol	18/26	9/12/15	FC
Polyflex	Boston Scientific	Polyester	16/20 18/23 21/28	9/12/15	FC
SX-ELLA	Ella-CS	Nitinol	20/25	8.5/11/13.5/15	FC with antimigration ring
Ultraflex	Boston Scientific	Nitinol	18/23 23/28	10/12/15	PC
Wallflex	Boston Scientific	Nitinol	18/23 23/28	10/12/15	PC / FC

PC Partially covered; FC fully covered

Esophageal stents as palliative treatment for malignant esophageal strictures

Over the last 12 years, only five randomized studies comparing different stents in patients with malignant esophageal strictures were published (Table 2) [12-16]. The first study randomized 100 patients to treatment with one of three SEMS: the PC Ultraflex stent (Boston Scientific, USA), the PC Flamingo Wallstent (Boston Scientific) and the FC SEMS Gianturco Z-stent (Wilson-Cook, Denmark) [12]. The three stents were equally effective in improving dysphagia scores without a significant difference in major complication rate. The second trial randomized 53 patients with a distal esophageal tumor to a PC Flamingo Wallstent (Boston Scientific) or the more flexible PC Ultraflex stent (Boston Scientific) [13]. Clinical outcome was satisfactory in both groups without significant differences in improvement of dysphagia scores and complication rates. A third study randomized 101 patients to a Polyflex (Boston Scientific) or Ultraflex stent (Boston Scientific), showing similar effectiveness in palliation of dysphagia [14]. However, complications, especially late migration, occurred significantly more often after placement of a Polyflex stent. The fourth randomized study with 125 patients evaluated the Ultraflex stent (Boston Scientific), the FC double-layered Niti-S stent (Taewong Medical, Korea), and the Polyflex stent (Boston Scientific) [15]. The Ultraflex and Niti-S stent were equally effective with equal overall complication rates, but recurrent dysphagia occurred more frequently with the Ultraflex stent (52 vs. 31 %), mainly caused by a higher rate of food obstruction. The Polyflex SEPS was associated with high failure of stent placement (17 %) and increased migration risk. Because of a wider diameter of the Polyflex delivery system, insertion is technically more difficult and dilation had to be performed more frequently. Furthermore, SEPS conform less easily to a stricture, making them more susceptible to slipping. Observational series had initially demonstrated effectiveness of SEPS in malignant esophageal obstruction; however, the randomized studies revealed an unacceptable high complication rate [17, 18].

The last trial included 80 patients with malignant esophageal diseases [16]. Patients were randomized to the PC Evolution stent (Cook Medical, Ireland) or the Ultraflex stent (Boston Scientific). The Evolution stent was associated with a significantly lower rate of stent dysfunction (8 vs. 40 %) and major complications (8 vs. 25 %). These data could not be confirmed in another single arm study, which included 44 patients with malignant dysphagia. In this study, the Evolution stent dysfunction rate was much higher (25 %), mainly caused by tumor in- or overgrowth [19].

Table 2. Overview of available randomized trials comparing different type of stents for malignant dysphagia.

Author [reference]	Year	Stent type (n)	Technical success	Improvement in dysphagia score (mean)	Recurrent dysphagia	Major complica-tions
Siersema [12]	2001	Ultraflex (34)	97 %	3.3 to 0.7	26 %	24 %
		Flamingo (33)	100 %	3.2 to 0.5	33 %	18 %
		Gianturco-Z (33)	100 %	3.2 to 0.7	24 %	36 %
Sabharwal [13]	2003	Flamingo (22)	100 %	2.7 to 0.9	6.4 %	13.6 %
		Ultraflex (33)	100 %	2.7 to 1.0	9.6 %	16 %
Conio [14]	2007	Polyflex (47)	98 %	±2.8 to 1.2	44 % [a]	8.7 % [a]
		Ultraflex (54)	100 %	±2.8 to 1.2	33 %	5.5 %
Verschuur [15]	2008	Ultraflex (42)	100 %	3 to 0 [b]	52 % [c]	21 %
		Niti-S (42)	95 %	3 to 0 [b]	31 %	12 %
		Polyflex (41)	83 % [c]	3 to 1 [b]	37 %	20 %
Van Heel [16] [d]	2012	Ultraflex (40)	100 %	3.0 to 0.5	40 %	25 %
		Evolution (40)	100 %	3.0 to 0.5	8 % [c]	8 % [c]

[a] Mulivariate analysis showed a significantly higher complication and recurrent dysphagia rate (OR 2.3, 95 CI 1.2-2.4)
[b] Dysphagia scores reported in median
[c] $p<0.05$
[d] 91 % with malignant dysphagia and 9 % with malignant esophago-respiratory fistula

Stent innovations include anti-reflux and anti-migration features. The anti-reflux features were particularly developed for stents bridging the lower esophageal sphincter. This was generally done by attaching a valve to the distal end of the stent, inhibiting backflow from gastric contents into the esophagus. Theoretically, this should prevent reflux symptoms, esophagitis, and possibly aspiration. Although some studies have indicated that anti-reflux stents reduced gastro-esophageal reflux, a recent meta-analysis could not identify a significant difference in symptoms and complications associated with reflux and in quality of life [8]. Therefore, the use of anti-reflux stents has largely been abandoned.

Antimigration features include uncovering of distinct areas of the metal mesh and a wider diameter of the stent flares, as well as addition of struts, or rings to the outer side of the stent serving as anchoring devices. Both the Alimaxx-E (Alveolus, USA) equipped with outer antimigration struts, and the SX-ELLA (Ella-CS, Czech Republic) with a flip-flop

antimigration ring fall in the latter category. Several studies, however, have shown that, in spite of these design modifications, these stents frequently dislocate [10, 20, 21]. In addition, the SX-Ella stent has been associated with a considerable number of major complications, such as hemorrhage, fistula formation, and severe pain, which likely relate to excessive pressure of the anti-migration ring. The Niti-S stent has a dog-bone shape to prevent migration and is available in two designs, a fully covered single-layered SEMS and a double layered version with a FC inner polyurethane layer and an outer uncovered nitinol mesh to attach the stent to the esophageal wall. Several studies have reported good clinical efficacy and acceptable migration rates (up to 12 %) with both types Niti-S stents [15, 22-24]. In one study, the double-layered version was associated with a significantly lower combined recurrent dysphagia and complication rate than the single layer version (12 vs. 58%) [23]. However, the high complication rate of the single-layered Niti-S stent used in that study was not confirmed in a recent large single arm study [22]. The FC Wallflex stent (Boston Scientific) is characterized by two migration-resistant features: distinct shouldering at both sides and internal covering. This stent has so far only been evaluated in one study for the treatment of malignant strictures [25]. Although the risk of migration was low (9 %), major complications were commonly seen (30 %), which might be related to the relatively high radial force of the Wallflex stent.

In summary, the available studies suggest that no major differences in efficacy and safety exist between different stents. However, there is still insufficient evidence to recommend one type of SEMS in the treatment of malignant dysphagia. Specific features reduce migration rates of FC SEMS; however, they can also induce traumatic injury and lead to major adverse events.

Stent placement as palliative treatment for malignant esophageal fistula

Fistulas usually result from infiltration of esophageal cancer to the respiratory tract or pleural cavity. Additionally, lung and mediastinal cancers can penetrate to the esophagus, also creating fistulas. Multiple series have reported on the use of covered SEMS to seal off fistulas, with closure rates ranging between 73 and 100 % [26-33]. At the same time, it is also crucial that pleural and mediastinal fluid collections are drained aggressively. Both PC and FC SEMS can be used as long as the covering completely seals the fistula. Unfortunately, randomized studies to recommend a specific type of SEMS are lacking. The largest non-comparative series to date reports on 61 patients with esophago-respiratory fistulas treated with covered SEMS [33]. Ten patients also required a tracheobronchial stent to seal the fistula. Complete sealing of the fistula was achieved in 49 patients (80 %) and re-intervention was effective in the majority of 17 patients in whom the fistula had re-opened. Based on these data, and in the absence of effective alternative treatments, SEMS is considered the treatment of choice in malignant fistulas.

Stents after chemo-radiotherapy.

Stents are also effective at providing symptom relief in patients with a malignant esophageal stricture after chemo- and/or radiotherapy. However, it still remains controversial whether stent placement is more hazardous in these patients [34, 35]. Some studies reported a higher incidence of complications, while others found that previous chemoradiotherapy did not affect the safety of stent treatment. These contradictory results could be related to differences in radiation dose. Recent studies show that both prior radiation and chemoradiotherapy with a relatively high radiation dose of 50.4 Gy increases the risk of stent-associated complications, predominantly esophagorespiratory fistula and pneumonia [36, 37]. It has been hypothesized that a biodegradable stent, which gradually dissolves and loses its radial force in 3 months, may avoid late injury when used in combination with radiotherapy. This has been evaluated in a study in which patients were palliated with concurrent brachytherapy and a biodegradable ELLA-CS stent [38]. Although effective in restoring luminal patency, the study was terminated prematurely because of an unacceptable high rate of stent-related major complications, in particular severe pain and vomiting.

Stent placement as a bridge to surgery

Neoadjuvant chemoradiotherapy is increasingly being used to improve long-term outcome after esophagectomy [39]. Stent insertion before neoadjuvant therapy is an interesting new concept in the management of resectable esophageal malignancy. A stent could serve as a bridge to surgery while a patient undergoes neoadjuvant therapy, and improve nutritional status by ensuring oral solid intake without the need for nasoenteral or percutaneous feeding tubes. Because esophagectomy is scheduled shortly after termination of neoadjuvant therapy, late stent-related complications can be averted. This approach has been evaluated in several studies, using different types of stents and various neoadjuvant regimes [40-44]. Stents were either extracted prior to esphagectomy or removed during surgery. They appear effective in improving dysphagia and maintaining nutrition. However, complications, although rare, may occur. These include esophageal perforation requiring urgent surgery, and stent migration. The latter has in case series been reported to result in small bowel perforation or obstruction. Furthermore, in one study, the number of patients proceeding to curative resection was surprisingly low due to progression or discovery of metastatic disease [44]. These findings indicate that more studies are needed to determine the role of stents during neoadjuvant therapy before implementing such use in regular practice. These studies should also clarify concerns about the possible spreading of viable tumor cells in the circulation after stent placement.

Stent-related complications

Recurrent dysphagia

Recurrent dysphagia remains a problem after stent insertion and occurs in almost one-third of patients. Endoscopic re-intervention is successful in most cases [6, 45]. In cases of tumor over- or ingrowth, insertion of a second stent is effective to restore luminal patency (Fig. 1). This can also be considered in cases of stent migration. However, we believe that either endoscopic repositioning or exchanging for a new stent is preferable. Obstruction due to impacted food can easily be managed by endoscopic stent clearance. Another rare late complication is spontaneous stent fracture with collapse. The stent-in-stent technique seems safe and effective in these situations and can also be used to facilitate removal of the fractured SEMS [46, 47].

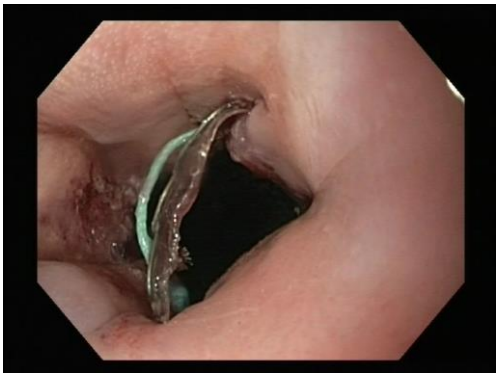
Fistula formation

Esophago-respiratory fistulas are mostly seen several months after stent indwell. Due to the radial force and resulting pressure necrosis, which is most extreme at the level of the flares, it is usually seen next to the proximal or distal margin of the stent. In these cases, placement of an additional covered SEMS is an effective method.

Retrosternal pain

Another complication is the development of retrosternal pain after stent insertion. In our experience, this occurs more frequently than the reported rate of 13 % [48]. In our institution, we found a 60 % rate of moderate to severe pain in a prospective assessment of 50 patients after esophageal SEMS insertion for malignant stenosis (submitted for publication). Pain lasted for an average of 10 days and 91 % of patients required analgesics, with good effect in all patients without the need for stent removal in any of them.

Figure 1. Semicircular overgrowth of hyperplastic and tumoral tissue at the proximal end of a fully covered SEMS.



Esophageal stents in benign esophageal disease

The use of esophageal stents has recently expanded towards the management of benign refractory or recurrent esophageal strictures and perforations. Although indications for the use of esophageal stents in this particular field are expanding, several potential drawbacks must be taken into consideration, including the chance of recurrent stricture formation, high migration rates, bleeding risk, risk of fistula formation, and traumatic stent removal [49].

Benign esophageal strictures

For centuries, the mainstay of therapy for benign esophageal stenosis has been dilation therapy, using either wire-guided polyvinyl (Savary) or balloon dilators [50, 51]. The efficacy varies depending on the etiology and complexity of the stricture. Clinical response for anastomotic, caustic, peptic, and radiation-induced strictures has been reported in, respectively, 92, 84, 81 and 58 % of patients [52]. Alternative therapies, such as steroid injection and incisional therapy, can be attempted in strictures unresponsive to conventional endoscopic dilation [53]. However, particularly patients with complex strictures have a considerable risk of persistent or recurrent dysphagia. The concept of stent therapy relies on continuous dilation for a period of at least 6 weeks, which should result in sustained luminal patency after removal. Different types of stents have been evaluated for this purpose, including SEMS, SEPS, and, most recently, biodegradable stents. Overall, stents led to sustained improvement of dysphagia in close to 50 % of patients [54]. However, clinical response varied widely between published series. This could be explained by differences in type and duration of prior dilation treatment, etiology, and length of the stricture, degree of inflammation contributing to the stricture, and indwelling time of the stent. The type of stent design and physical properties may also affect outcome, but comparative studies are lacking. Furthermore, definitions of clinical success vary among studies precluding accurate comparison between endoscopic interventions. Obviously, another important aspect of stent therapy in benign esophageal disease is safety. The use of uncovered and PC SEMS was hampered by the occurrence of serious adverse events, mainly formation of new stenosis due to ingrowth of hyperplastic tissue through the uncovered meshes of the stent [55, 56]. Longer indwelling time increased the risk of complications, such as perforation, fistula, stent fracture, and esophageal avulsion [57]. FC SEMS may be associated with fewer major adverse events after stent extraction. In a retrospective study evaluating 329 stent extractions in 214 patients with benign esophageal disease, removal of PC SEMS was associated with more complications compared to FC SEMS (25 vs. 4 %) [58]. These data suggest a preference for FC SEMS, but this should be balanced against the higher risk of stent migration. Several small, uncontrolled series have reported a 33-48 % migration rate of FC SEMS [25, 59, 60]. Whether this was due to

complete stricture resolution remained unclear. The sparse available data indicate that dysphagia frequently recurs after stent removal and already becomes apparent after 2 weeks [25]. Overall, it is evident that the efficacy of FC SEMS for benign esophageal strictures is still unsatisfactory. Nevertheless, it is our policy to attempt stent therapy in patients with refractory benign strictures, also because alternative therapies are usually impracticable. Anchoring the proximal flare of the SEMS to the esophageal wall using hemoclips, sutures, umbilical tape, or an over-the-scope-clip is a promising new endoscopic technique to prevent migration and could be an option to improve outcome of stent therapy [61-64]. Complications of stent extraction, particular for PC SEMS, can be prevented by extraction of the stent within 6 weeks or using the stent- in-stent technique [65]. Removal of FC SEMS is often easy and less traumatic, and in our experience the indwelling time of these stents can be extended up to 3 months. Further research with adequate long-term follow-up is warranted to determine the true role of FC SEMS in benign refractory strictures.

SEPS and biodegradable stents in benign refractory strictures

Placement of a SEPS has also been evaluated in benign esophageal strictures. The long-term efficacy of SEPS, in terms of relief of dysphagia, ranged from 0 to 80 % [66-71]. The material of the fully covered Polyflex stent gives less rise to hyperplastic tissue in- and overgrowth. However, migration is frequently encountered. In the largest prospective study, migration was observed in 22 % of 40 patients with refractory benign strictures, which is comparable to malignant disease [66]. Polyflex stents were particularly associated with frequent complications, such as severe chest pain, bleeding, perforation, reflux, food impaction, and fistula formation [66]. These serious drawbacks were confirmed in other retrospective series with high migration and complication rates (respectively 7-66 and 6-28 %) [67-71]. These results are worrisome and make current SEPS less suitable for benign refractory strictures.

Biodegradable stents do not require removal, and only a few series have evaluated these stents in benign refractory strictures. Results of initial series demonstrated good clinical outcome, but these studies were hampered by short follow-up [72, 73]. These results were not confirmed by the only study with adequate longer-term follow-up, which revealed low efficacy of the biodegradable ELLA-CS stent [74]. Recurrent dysphagia occurred in 21 of 28 patients (75 %) after a median of 90 days, caused by recurrent stricture formation (n = 15), stent migration (n = 3) and food impaction (n = 3). In patients who failed after initial stent insertion, sustained clinical success could also not be achieved with sequential stenting with a second or even third biodegradable stent. These results are disappointing, both in terms of persistent stricture relief as well as complication rates. Although the concept of biodegradable stenting for benign esophageal strictures is

appealing, biodegradable stents cannot be recommended over extractable SEMS at this moment.

Drug-eluting stents

Local drug delivery via drug-eluting stents (DES) has been developed for the use in interventional cardiology to prevent vascular re-stenosis, and has recently also been investigated in gastrointestinal diseases, mainly in malignant biliary obstruction [75]. Paclitaxel is the most commonly applied drug due to its antiproliferative, antiangiogenic, and apoptotic properties. Theoretically, the continuous release of paclitaxel could result in a reduced stent-induced tissue reaction. This could be an attractive stent feature for benign esophageal strictures, as it can prevent secondary strictures and severe stent embedment. Whereas human studies are not yet available, one animal study compared the use of DES with non-DES in the esophagus of dogs [76]. DES was associated with less granulation tissue formation, proliferation, and fibrosis without stent migration. These results are encouraging and warrant further research. Before human application, future studies should also focus on the potential systemic side effects of paclitaxel, although toxic plasma levels are not expected from local delivery.

Esophageal perforations and leaks

Spontaneous or iatrogenic esophageal perforations are life-threatening events, associated with high morbidity and mortality [77]. Prompt intervention is of pivotal importance in the management of these patients. Surgical treatment has traditionally been advocated, but is associated with poor outcome [78]. Placement of covered stents that seal the perforation has evolved into a promising less-invasive treatment modality. This should be combined with aggressive drainage of pleural and mediastinal fluid collections and broad-spectrum antibiotics. The low incidence of esophageal perforations hampers a randomized trial between surgical and endoscopic treatment ever being performed. Thus, evidence is largely based upon case series. A recent systematic review evaluated various stents in a pooled analysis of 267 patients with esophageal ruptures and anastomotic leaks [79]. Clinical success, in terms of a healed perforation after stent removal, was achieved in 85 % without any difference between the three stent designs. Stent-related complications were seen in 34 % and were caused by migration and tissue in- and overgrowth. As expected, migration occurred more frequently in SEPS and FC SEMS than in PC SEMS. Endoscopic re-intervention, with stent repositioning and exchanging for a wider-diameter stent, was required in 25 % of patients and was least needed in the PC SEMS group. Additionally, procedure-related adverse events occurred in 3 % of patients and included bleeding and enlargement of the leak due to stent misplacement. Occurrence of the latter complication emphasizes that a stent should not be deployed without

endoscopic or radiologic confirmation of proper guide-wire positioning. Overall mortality rate was 13 %, which is lower than reported for surgical intervention. Although this comparison should be interpreted with caution, it is our strong opinion that stent therapy should be considered as first treatment option in esophageal perforations and leaks because of the high clinical efficacy and its minimally invasive nature. It is still unclear which stent type is preferred in these conditions, because all three stents have their specific advantages and disadvantages. No firm guidelines regarding the optimal duration of stent therapy are available. We recommend removal of the stent within 6 weeks, particularly when a PC SEMS has been placed [65]. Usually, this is sufficient for the esophageal wall to heal. In case a FC SEMS has been inserted, the indwell time of the stent can be extended.

Refractory esophageal variceal bleeding

Placement of SEMS is an interesting new therapeutic intervention to control refractory esophageal variceal bleeding after failed endoscopic therapy. The efficacy and safety of the especially designed SX-ELLA Danis stent (Ella-CS), has so far been addressed in four case series [80-83]. It is an extractable fully covered SEMS that can be deployed in the lower esophagus over a guidewire using an inflated distal balloon for adequate positioning. Hemostasis was reached in 77-100 % of patients. Stent migration has been reported in up to 25 %, but endoscopic repositioning is generally feasible. Stents can be left in place for 2 weeks, allowing liver function to improve. It appears that these SEMS are easily removable with a relatively low risk of complications despite the presence of portal hypertension. Therefore, they can serve as a bridge to more definite therapy, such as band ligation, transjugular intrahepatic portosystemic shunt (TIPS), or liver transplantation. They can also serve as a definitive treatment in patients with limited life expectancy and those (currently) unsuitable for TIPS or transplantation [84]. Overall, these data suggest that stent therapy can be used effectively in patients with esophageal variceal bleeding refractory to conventional endoscopic treatment. Further studies are needed to establish their definite role.

Conclusion

Stent therapy is an effective treatment modality in various esophageal conditions. Currently, SEMS placement is the preferred option in palliative treatment of malignant dysphagia and fistula. It has been shown that covered SEMS are preferred over rigid plastic tubes and SEPS in malignant disease. However, recurrent obstruction and other adverse events are still frequently encountered, necessitating further improvements in stent designs. Novel developments, such as new types of covering and anti-reflux or anti-migration features, have not (yet) resulted in improvement of outcome. Importantly, the

management of esophageal cancer is changing with increased use of chemo- and/or radiotherapy. There is growing evidence that these modalities, especially radiation, have a negative influence on the outcome of stent therapy. On the other hand, some studies indicate that temporary stents could be beneficial in certain circumstances, for instance as a bridge to surgery when stents are combined with neoadjuvant therapy. Although these concepts are interesting, larger studies are needed before incorporating them in regular practice. In contrast to malignant disease, the available data on stent therapy in benign conditions are limited and largely originate from uncontrolled series. Refractory benign esophageal strictures have been treated with different types of stents, including SEMS, SEPS, and biodegradable stents. In contrast to esophageal perforations and leaks, stent therapy for benign esophageal strictures is still disappointing, since less than 50 % of patients respond favourably and the risk of complications is substantial. Improvements in stent design and also randomized trials, comparing different stent designs and modalities, are warranted.

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Chapter 3

Twenty years of self-expandable metal stents placement for malignant esophageal strictures: a retrospective observational study

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Submitted

Chapter 4

A randomized study comparing a fully and a partially covered self expandable metal stent for the palliation of malignant esophageal strictures

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Submitted

Chapter 5

Safety of stent placement in recurrent or persistent esophageal cancer after definitive chemoradiotherapy: a case series

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Introduction

The prognosis of patients with esophageal cancer is dismal. More than 50% of patients are diagnosed with incurable disease due to metastasis or locally advanced disease at time of presentation [1]. In recent years, definitive chemoradiotherapy (CRT) has proven to be a curative alternative in patients both with an unresectable locally advanced (T4) carcinoma as well as in patients who are unfit for surgery due to co-morbidity [2-4]. However, failure of treatment is frequently observed on the long-term, with a 5-year survival of around 25% [3, 4].

Endoscopic stent placement is effective as a palliative measure to manage malignant esophageal obstruction [5, 6]. Several studies have evaluated the outcome of esophageal stent placement in patients who had undergone chemo- and/or radiotherapy [7-14]. Some have reported a higher incidence of complications, whereas others have stated that stent placement is as safe as in patients without such treatment. These contradictory results could be related to different radiation dose regimes. Definitive CRT consists of a substantially higher radiation dose compared with standard radiotherapy. We assumed that this higher radiation dose is responsible for an increased risk of complications after stent placement. However, this assumption has not been thoroughly examined in the limited number of studies that are available regarding this topic. Therefore, we assessed the safety and efficacy of esophageal stent placement in 13 patients who had previously received definitive CRT with curative intent.

Patients and methods

Patients

Patients were identified from the esophageal cancer database of our clinic, which serves a tertiary referral function. All patients identified from 2006 until 2011 were enrolled if endoscopic stent placement was performed for esophageal obstruction resulting from esophageal carcinoma and if the patient had previously been treated with definitive CRT with curative intent. All patients suffered from dysphagia grade 2 (ability to eat semisolids only) or higher. Recurrence or persistence of esophageal cancer was confirmed by both endoscopy and histological examination of biopsy specimens.

Endoscopic stent placement

All procedures were performed with the patient under conscious sedation. The lesion was inspected with a standard or pediatric video endoscope, and the location and length of the stenosis were determined. Dilation of the stenosis was carried out if indicated to allow passage of the endoscope. A stent of at least 2 to 4 cm longer than the malignant stricture was used, which allowed it to extend at least 1 to 2 cm above and below the

proximal and distal margins of the tumor. The stent was advanced over a guidewire and deployed under fluoroscopic or endoscopic view.

Assessment of clinical success and complications

Medical records and endoscopy reports of all patients were reviewed. Data on previous CRT (including indication and dosage regime), stent placement, clinical success, complications, reinterventions and survival were collected. Technical success of stent placement was defined as adequate deployment and positioning of the stent at the site of the stricture. Clinical success was defined as an improvement of at least 1 grade in dysphagia score after the procedure. Dysphagia score consisted of five grades: 0, able to eat a normal diet; 1, able to eat some solid food; 2, able to eat semisolids only; 3, able to swallow liquids only; 4, complete dysphagia [15]. Major complications were defined as life-threatening complications and severe pain. Minor complications were defined as non-life- threatening complications.

Results

Clinical characteristics

A total of 13 patients were identified who underwent esophageal stent placement after previous definitive CRT (Table 1). Seven patients with unresectable cancer were diagnosed with an invasive (T4) tumor. Severe co-morbidity prohibited curative operation in 4 patients with a T3 (n=2) or T2 (n=2) tumor, whereas 2 patients (T3 and Tx) were unwilling to undergo operation. Twelve patients were treated with concomitant CRT, whereas 1 patient received sequential therapy with curative intent because of the risk of developing a tracheosophageal fistula. The chemotherapeutic regime consisted of 6 times weekly carboplatin (AUC 2) and paclitaxel (50 mg/m^2). The intended external radiation dose was 50.4 Gy, divided in 28 fractions, given 5 times a week. One patient received a lower radiation dosage of 41.4 Gy because of pulmonary dysfunction in combination with 5 chemotherapeutic cycles because of severe candidal esophagitis. This was followed by intraluminal brachytherapy with a total dose of 6 Gy. CRT was discontinued prematurely in a second patient because of pneumonia and deterioration of the physical condition. Before stent placement, the median dysphagia score was 3 (range, 2–4). In all patients a significant esophageal stricture was demonstrated endoscopically without evidence of a fistula.

Table 1. Baseline characteristics of patients

Characteristics	No.
No. patients	13
Sex (M/F)	9/4
Mean age, years (range)	67 (51-82)
Reason for CRT	
Invasive (T4) cancer	7
Contra-indications for operation	4
Unwillingness to operation	2
Location of obstruction	
Proximal esophagus	1
Mid-esophagus	5
Distal esophagus	7
Histology	
Squamous cell carcinoma	8
Adenocarcinoma	5
Radiotherapy	
Total radiation dose (Gy), median (range)	50.4 (41.4-50.4)
No. of fractions, median (range)	28 (18-28)
Chemotherapy	
Carboplatin / Paclitaxel	13
Dysphagia score before stent	
2	1
3	9
4	3
End of CRT to stent insertion (days), median (range)	375 (28-837)

Stent placement and clinical efficacy

Thirteen stents were successfully inserted in 13 patients. Eleven esophageal self expandable metal stents (SEMS), including the Ultraflex stent (Boston Scientific, Natick, Mass) (n=5), Evolution stent (Cook Medical, Winston-Salem, NC) (n=3), Niti-S stent (Taewoong, Seoul) (n=1), Alimaxx-E stent (Alveolus, Charlotte, NC) (n=1), SX-Ella stent (Ella-CS, Hradec Kralove, Czech Republic) (n=1), and 2 plastic Polyflex stents (Boston Scientific) were used. Eight stents were partially covered, whereas 5 were fully covered. The median length of the stent was 10 cm (range, 8.5-15 cm). Endoscopic dilation of the stricture, either with Savary bougies or balloon dilation was carried out in 6 of 13 patients before stent placement. Clinical success was achieved in all 13 (100%) patients after stent placement.

Morbidity and mortality after stent placement

Nine complications occurred in 8 (62%) patients after stent insertion, including 8 major and 1 minor complication (Table 2).

Table 2. Complications and recurrent dysphagia after stent placement

No. of patients	13
Total complications	9 in 8 patients (62%)
Major complications	8 in 7 patients (54%)
Hemorrhage	1
Tracheosophageal fistula	2
Pneumonia	4
Severe retrosternal pain	1
Minor complications	1 (8%)
Mild retrosternal pain	1
Recurrent dysphagia	4 in 3 patients (23%)
Stent migration	1
Tumor overgrowth	2
Food impaction	1

Within 1 month after stent placement, 4 major complications were observed. These included pneumonia (n=3) and severe retrosternal pain (n=1) after a median of 8 days (range, 1-22 days). One of the 3 patients who experienced pneumonia died because of severe respiratory insufficiency 11 days after the procedure. The others were treated with antibiotics with good outcome. One patient experienced severe retrosternal pain directly after the endoscopic procedure. In this patient a pinpoint stricture was first treated with Savary dilation to 9 mm, after which a stent was placed. Removal of the stent after 6 days resulted in complete pain relief. Afterwards, enteral feeding was guaranteed by a percutaneous radiologic gastrostomy. Four major complications occurred more than 1 month after initial stent placement. One patient experienced pneumonia at 39 days after initial stent placement. This complication was preceded by the placement of second stent 3 days earlier because of tumor overgrowth. Antibiotic therapy was successful in this case. One patient had a fatal massive GI hemorrhage 257 days after stent placement. The bleeding focus remained unknown because diagnostic evaluation could not be completed before death. This patient had a T4 tumor with invasion of the aorta before CRT commenced. In two patients a trachea-esophageal fistula occurred during follow-up. Both patients had esophageal cancer with invasion to the left bronchus before CRT was commenced. Th first patient was successfully treated after 141 days with a second fully covered esophageal metal stent. The other patient had already received a second stent after 336 days because of tumor overgrowth (see below). The fistula was effectively managed 231 days later with a third fully covered stent. One minor complication was demonstrated: mild retrosternal pain after 1 day, which was managed effectively with acetaminophen and low dose narcotic analgesics.

During follow-up a total of 4 events of recurrent dysphagia occurred in 3 patients (Table 2). In 1 patient 2 episodes were noted. One episode was related to stent migration 57 days after stent placement, for which, after endoscopic removal of the migrated stent, a second stent was inserted. The second episode was because of food bolus impaction, which was managed by cleaning of the stent. Tissue overgrowth was observed at the proximal end of the stent in 2 patients, 36 and 336 days, respectively, after stent placement. A second stent was placed subsequently, resulting in improvement of dysphagia in both cases. At the time of analysis 1 patient was still alive. The median survival for the 12 patients was 135 days (range, 20–591 days) after stent placement. The patients' characteristics and outcomes are summarized in Table 3.

Discussion

Esophageal stent placement for malignant dysphagia after chemo- and/or radiotherapy has been reported and is considered to be effective. Whether stent placement in these patients is associated with a higher risk of complications is still controversial [7-14]. We assumed that these conflicting results could be explained by different levels of radiation exposure. Definitive chemoradiotherapy delivers a high total radiation dose with curative potential in esophageal cancer. In the present case series we assessed the outcome of stent placement in 13 patients with persistent or recurrent esophageal cancer after previous definitive CRT. We have demonstrated that although stent patency is high, major complications, mainly pulmonary infections and fistula formation, occur in 54% of patients.

It has been shown that stent placement offers rapid relief of dysphagia in malignant esophageal disease [6, 16]. Alternative treatment options, such as brachytherapy and external beam radiation, are also capable of improving dysphagia in malignant obstruction, but they are known to have limited effect on tumor reduction in case of prior exposure to radiation. Our results demonstrate that in these patients stent placement provides adequate palliation of symptoms. Recurrent dysphagia occurred in 23% of patients and repeated endoscopic intervention led to resolution of dysphagia in all cases. These results are similar to the efficacy reported in patients without chemoradiotherapy [16-18]. In patients without prior definitive chemoradiotherapy, an overall major complications incidence of 23 to 37% after stent placement is reported [16, 19, 20]. With a major complication rate of 54 % (7 of 13 patients), our study supports the concept that esophageal stent placement after prior definitive CRT is associated with a high risk of life-threatening complications. Obviously, this has to be taken into consideration when treatment options are weighed, and needs to be discussed with the patient. Although 2 complications were associated with fatal outcome, all other adverse events could be managed successfully.

Pneumonia was 1 of the major complications observed most often and was unrelated to the presence of a tracheosophageal fistula. In all cases these events occurred within 1

Table 3. Characteristics and clinical outcome of patients after stent placement with prior chemoradiotherapy

No	Sex/ Age	Location esopha-gus	T-stage pre-CRT (invasion)	RTX (Gy)	CTX	Interval (days) £	Stent (Covering)	Complications or recurrent dysphagia (days after stent)	Survival (days)
1	M/64	Distal	4 (aorta)	50,4	C/P	375	Evolution (PC)	Gastrointestinal bleeding (257)	257
2	F/68	Mid	4 (left bronchus)	50,4	C/P	34	Niti-S (FC)	Tumor over-growth (336¶), tracheosophage-al fistula (567¶)	591
3	M/74	Distal	3	50,4	C/P	435	Polyflex (FC)	Mild chest pain (1), stent migra-tion (57), food impaction (126)	154
4	M/54	Mid	4 (aorta and left bron-chus)	50,4	C/P	28	Alimaxx-E (FC)	Tracheosopha-geal fistula (141¶)	183
5	M/51	Distal	4 (VPI)	50,4	C/P	221	Ultraflex (PC)	Pneumonia (11)	20
6	F/82	Distal	3	50,4	C/P	408	SX-Ella (FC)		335
7	F/60	Mid	2	50,4	C/P	837	Polyflex (FC)	Pneumonia (22)	22
8	M/65	Distal	4 (aorta and pleura)	45*	C/P*	42	Ultraflex (PC)		55
9	M/54	Distal	4 (aorta and left lung)	50,4	C/P	410	Ultraflex (PC)		251
10	M/79	Distal	3	50,4	C/P	556	Ultraflex (PC)		86
11	F/70	Mid	2	41,4*	C/P*	413	Ultraflex (PC)		116
12	M/72	Prox	4	50,0	C/P▲	321	Evolution (PC)	Pneumonia (5), tumor over-growth (36¶), pneumonia (3†)	55
13	M/69	Mid	x	50,4	C/P	63	Evolution (PC)	Severe chest pain (6)	Alive

C/P, Carboplatin/Paclitaxel; CRT, chemoradiotherapy; CTX, Chemotherapy; FC, fully covered; PC, partially covered; RTX, Radiotherapy; VPI, Vena Pulmonalis Inferior
¶ Additional stent was placed; * CTX and RTX not completed; ▲ Sequential CRT; † After second stent placement; £ Time between CRT and stent placement

month after endoscopic stent placement. Aspiration pneumonia is a common complication, which has been described up to 14% of cases after stent placement [5, 7, 16, 21, 22]. It has been suggested that patients are more prone to aspiration due to increased reflux after overlapping the gastroesophageal sphincter [23, 24]. However, in only 1 of 3 patients who experienced pneumonia, the stent traversed the lower sphincter. Thus, it is likely that not only reflux, but also other factors such introduction of bacteria into the respiratory tract during the endoscopic procedure, and enhanced susceptibility because

of pulmonary toxicity induced by radiotherapy and chemotherapy, are responsible for the increased risk of pneumonia [25-27].

Formation of a fistula usually develops as a late complication after esophageal stenting for malignant obstruction [7, 16, 18-20]. In our study, a relatively high rate of fistula formation was encountered. The life expectancy of these patients was relatively long, and fistulas occurred late after stent placement. Interestingly, fistulas were exclusively demonstrated in patients with locally invasive disease (T4) before CRT. Two patients had a tracheosophageal fistula. In both patients tumor invasion into the left bronchus was established before CRT was commenced. In 1 of these patients the fistula was demonstrated nearly 2 years after stent placement, which suggests that progression of esophageal cancer may also be a contributing factor. Nevertheless, because the fistula occurred while a stent is in place, we considered the event to be a major complication. In both cases endoscopic placement of a second stent to overlap the fistula was successful. Additionally, development of a fistula to the aorta was suspected in a third patient who presented with an acute massive GI hemorrhage. In this patient, CRT was indicated because of T4 esophageal cancer with aortic invasion. The association of fistula and esophageal T4 tumors with prior exposure to CRT has previously been described after stent insertion [13, 28]. As a result of radiation-induced or chemotherapy-induced esophageal injury, the esophageal wall is susceptible to significant pressure necrosis caused by expansion of the stent. The deleterious effects of radiotherapy are known to be dose dependent. Thus, it is likely that exposure to definitive CRT is responsible for an increased risk of fistula formation, especially in patients with T4 cancer. Four patients with established T4 cancer did not develop a fistula during follow-up. However, mean survival after stent placement was evidently shorter in these cases: 95 versus 344 days. These data also suggest that those patients who survive longer have a higher risk of fistula formation.

There are potential shortcomings of this analysis. First of all, because of the retrospective nature, the number of complications, especially minor complications that did not require hospitalization or repeated intervention, could have been underestimated. Second, different types of stents were used in our patients. Inasmuch as only a limited number of each stent was used, no inference can be made about whether a particular stent may actually perform better or worse results compared with the overall result.

In conclusion, stent placement is highly effective in the resolution of dysphagia in patients with earlier definitive CRT. Importantly, recurrent dysphagia can be effectively treated with repeated endoscopic intervention. However, these favorable results come at a certain cost. First, these patients seem to be susceptible to the development of pulmonary infections early after stent placement. Second, the risk of formation of a fistula is relatively high and is mainly seen after long-term follow-up in patients with invasive (T4) cancer.

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Chapter 6

Early pain detection and management after esophageal metal stent placement in incurable cancer patients: a prospective observational cohort study

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Abstract

Background and study aims: Studies on esophageal self-expandable metal stents (SEMS) studies mainly focus on efficacy and recurrent dysphagia. Retrosternal pain has been described in up to 14% of the patients, however prospective daily pain assessment has not yet been performed. We conducted a prospective study to evaluate the occurrence and management of pain after esophageal SEMS deployment.

Patients and methods: A total of 65 patients who underwent SEMS placement for incurable malignant esophageal stenosis were included. Patients used a diary to record intensity of pain twice daily for 2 weeks, according to the Numeric Rating Scale (NRS). A pain score ≥ 4 was used to determine whether patients experienced significant pain. If pain occurred, acetaminophen was used and in case of ongoing pain, an opiate was prescribed. Dose, duration and kind of analgesic were noted.

Results: The rate of significant pain increased from 0% at baseline to 60% on Day 1 ($p<0.001$), followed by 37% and 25% on Days 7 and 14, respectively. The rate of analgesics use increased from 20% at baseline to 78% on Day 1 ($p<0.001$), followed by 72% and 62% on Days 7 and 14, respectively. The use of opiates increased from 14% at baseline to 42% on Day 1 ($p<0.001$). No variables associated with SEMS related pain were found.

Conclusions: Two-thirds of patients experience significant pain after esophageal SEMS insertion and analgesics, including opiates, are frequently required. Patients need to be informed and preventive prescription of analgesia should be considered in order to improve quality of life.

Introduction

Esophageal cancer is the eighth most common cancer worldwide [1], with more than 400,000 deaths per year [2]. Despite recent advances in the treatment of esophageal cancer, 50% of patients still have incurable disease at the time of presentation because of metastasis or locally advanced disease [3]. Dysphagia is a devastating symptom of incurable obstructive esophageal cancer with a major impact on patient's quality of life. Options for treating dysphagia include self-expandable metal stent (SEMS) placement, external beam radiation and brachytherapy [4-6].

Although brachytherapy has shown to provide better long-term relief of dysphagia, SEMS placement leads to more rapid improvement [7]. Furthermore, endoscopic stent placement is also an effective palliative measure to manage malignant esophageal fistula [5]. The aim of stenting is to restore luminal patency and thereby maintain nutritional intake and improve quality of life [5]. SEMS are the most commonly used stents and different types of stents are available. Palliative stent insertion has been shown to result in significant improvement in all scales of quality of life, except for pain [8]. Pain is one of the most common symptoms in cancer patients. Its intensity increases as the disease advances, with a reported prevalence of 64% in patients with metastatic or advanced stage disease [9, 10].

A great variety of measures are available to assess cancer pain. One of the most commonly used pain rating scale is the Numerical Rating Scale (NRS). The NRS is a 11 point scale where the end points are the extremes of no pain and worst pain. The NRS is well accepted by patients [11, 12]. The 'cut-off' point for experiencing significant pain is when a pain score of 4 or higher is noted. It has been shown that at that level, pain has a major impact on daily functioning [13, 14]. Undertreatment of pain is associated with significant functional impairments, poor sleep, increased depression and anxiety and impaired quality of life [15]. In studies reporting on the outcome of esophageal stenting, but in which post-procedural pain management was not the primary focus of the study, 3,6% of patients develop severe retrosternal pain and 14,1% develop mild retrosternal pain after esophageal SEMS insertion [16-27]. However, in our experience, in daily practice, the rate is much higher. For that reason, we conducted a prospective study to systematically evaluate the occurrence and management of pain in a large cohort of consecutive patients after esophageal SEMS deployment.

Patients and methods

Patients

Between March 2011 and December 2013, consecutive patients who were treated with an esophageal SEMS for a malignant esophageal or cardiac stricture or concomitant fistula were enrolled in this study. Patients were included if they suffered from dysphagia, at

least grade 2 (ability to eat semisolids only) or symptoms compatible with esophageal fistula. Patients with extrinsic malignant compressions or after esophageal resection with gastric tube reconstruction were also eligible for inclusion. Exclusion criteria were inability to fill out a pain diary or inability to undergo an upper endoscopy.

Endoscopic stent placement

Esophageal stent placement was performed under conscious sedation using midazolam and/or fentanyl. The lesion was inspected with a standard or paediatric video endoscope to determine location and length of the stenosis and/or malignant fistula. The length of the SEMS was chosen based on the stricture length plus a minimum of 2 cm at each side. SEMSs of various manufacturers were allowed and selection was based on availability and physician discretion. The SEMS was advanced over a guidewire until it passed the distal end of the stenosis, and then it was deployed under endoscopic guidance and in some cases also under fluoroscopic guidance. After the procedure, patients stayed in the endoscopy department for 2 to 3 hours for observation. Thereafter, they returned home or to the ward.

Pain assessment

All patients completed a pain diary at baseline and every day for 2 weeks after esophageal SEMS placement. They recorded the severity of pain twice daily using the numerical rating scale (NRS). This scale consists of a series of numbers from 0 to 10, with zero represeting no pain and 10 representing an extreme level of the worst imaginable pain. The daily highest pain score was noted and used for analysis. Patients were followed up by phone 7 days and 14 days after SEMS placement to collect the daily NRS scores. A pain score ≥ 4 was used to determine whether patients experienced significant pain. Pain scores were also classified as mild, moderate, or severe pain, representing a pain intensity of 1 to 3, 4 to 6 and 7 to 10, respectively.

Analgetic regimen

We have used the 3-step ladder for cancer pain relief in adults according to the World Health Organization (WHO). If pain occurs, acetaminophen (1000 mg) was started 3 to 4 times daily. The second step of prescribing mild opioids was routinely skipped. If acetaminophen did not provide adequate pain relief (NRS≥4), strong opioids were started, either transdermal fentanyl (Fentanyl, Bipharma, Hameln, Germany) or long-acting oxycontin (Oxycodon, Mudipharma Pharmaceuticals B.V., Hoevelaken, The Netherlands). In case of breakthrough pain, patients received short-acting oxynorm (Oxycodon, Mudipharma Pharmaceuticals B.V., Hoevelaken, The Netherlands) given a maximum of 6 times a day. Dosage was modified according to the reported NRS score collected on Day 7 and 14 after SEMS placement. Furthermore, patients were instructed to call in case of significant pain at any moment, and dosage was re-evaluated accordingly. Dosage of strong

opioids was increased with the intent of achieving adequate pain relief (NRS<4). The type and dosage of pain medication were recorded at baseline and after 1 and 2 weeks. In order to compare dosages of different opioids, daily dosages of fentanyl and oxycontin were converted to an equivalent dosage of morphine.

Statistical analysis

Patient demographics and clinical characteristics were presented using descriptive statistics. Overall survival after stent placement was calculated using the Kaplan-Meier method. Pain scores and proportion of patients with pain score ≥4 were compared between different time points using the paired T-test and McNemar's test, respectively. Also proportion of patients using analgesics between different time points were analyzed using the McNemar's test's. Pain score ≥ 4 over time at different time points after day 0 was analyzed using logistic regression with repeated measurement to account for correlation between measurements within a patient (SAS 9.4, PROC GENMOD). To assess the effect of covariates on pain over time, we considered time as linear factor and in time we assessed the following covariates: gender, age, degree of dysphagia, histology, tumor location, previous treatment with chemotherapy or radiotherapy and stent type. Factors with a P<0.20 in the univariable analysis were entered into a multivariable stepwise regression model. A P value <0.05 was considered statistically significant. All calculations were done using the SPSS 21 statistical software package (SPSS, Chicago, Illinois, USA) and SAS 9.4.

Results

Patient and stent characteristics

Sixty-five patients were treated with a SEMS for a malignant stricture of the esophagus (N=58) or gastric tube (N=7), including 6 patients with a concomitant fistula. Table 1 shows the clinical characteristics of these patients. Endoscopic SEMS insertion was technically successful in all patients. Five types of stents were used: partially covered Ultraflex stents (Boston Scientific, Natick, Mass, United States), partially covered Evolution stents (Cook Medical, Bloomington, IN, United States), fully covered Hanaro stents (M.I. Tech, Korea) and partially as well as fully covered Wallflex stents (Boston Scientific, Natick, Mass, United States). Median length was 10 cm and median diameter was 18 mm. None of the patients underwent dilation to facilitate SEMS placement. Median survival after stent placement was 10 weeks (95% CI: 5.6 – 14.3, Kaplan-Meier survival curve, Fig. 1).

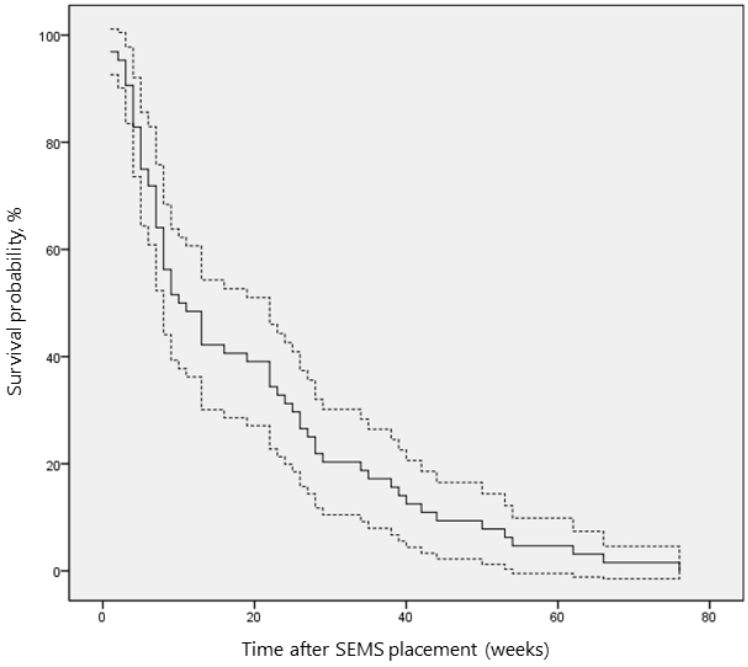
Table 1. Baseline characteristics of 65 patients.

Characteristics	No.
Sex (male/female)	50 / 15
Median age, y (range)	66 (39-89)
Histology	
Adenocarcinoma	37 (57%)
Squamous cell carcinoma	26 (40%)
Other	2 (3%)
Location	
Proximal esophagus	4 (6%)
Mid esophagus	20 (31%)
Distal esophagus	34 (52%)
Gastric tube after esophageal resection	7 (11%)
Indication SEMS insertion	
Stenosis	59 (91%)
Stenosis with fistula	6 (9%)
Dysphagia score	
Grade 2 (able to eat semi-solid foods)	5 (9%)
Grade 3 (able to swallow liquids only)	41 (60%)
Grade 4 (unable to swallow anything)	19 (31%)
Type of SEMS	
Boston Ultraflex (pc[1]) (small body)	18 (28%)
Cook Evolution (pc[1]) (wide body)	14 (21%)
M.I. Tech Hanaro stent (fc[2]) (small body)	9 (14%)
Boston Wallflex (fc[2]) (small body)	10 (15%)
Boston Wallflex (pc[1]) (small body)	14 (22%)
Pre-treatment	46 (71%)
Chemotherapy	16 (25%)
Radiotherapy	3 (4%)
Chemo/radiotherapy	23 (34%)
Brachytherapy	5 (8%)

[1]Partially covered

[2]Fully covered

Figure 1 Kaplan-Meier curve (bold line) and 95% pointwise confidence limits (dashed lines) for the survival function after SEMS placement.



Pain

A pain diary was filled out as requested by all 65 patients. Two patients died 1 week after SEMS insertion and therefore, pain scores of the second week were not available. At baseline, none of the patients experienced significant pain (i.e. pain score ≥ 4) with a median pain score of 0. On the first day after SEMS insertion, 39 patients (60%) reported significant pain ($p<0.001$). On Days 7 and 14, significant pain was observed in 24 (37%) and 16 patients (25%), respectively (Fig. 2). The highest pain score was noted on Day 1, with a median pain score of 5 (range 0-10). Median pain scores were 3 (range 0-8) on Day 7 and 1 (range 0-8) on Day 14. Univariable logistic regression analysis is shown in table 2. No significant differences were found in occurrence of significant pain after SEMS placement over time.

Figure 2 Percentage of patients experiencing significant pain during the first 14 days after esophageal SEMS insertion (pain score ≥ 4).

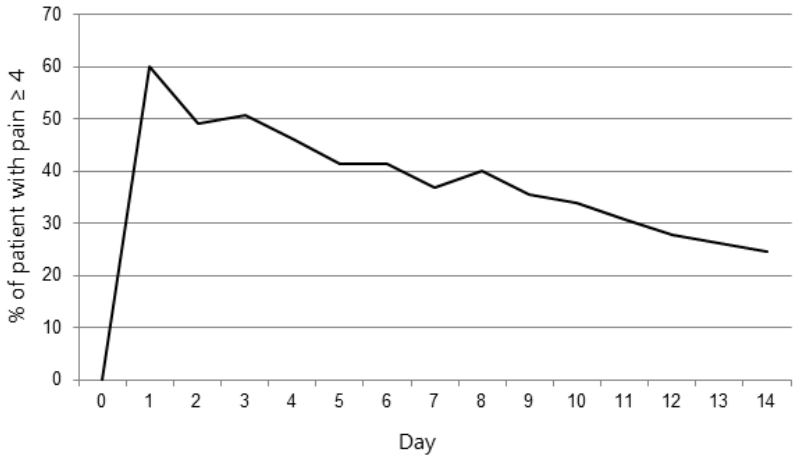


Table 2. Univariable analysis on the development of a pain score ≥ 4 after SEMS placement.[1]

Covariate		Univariable analysis	
		OR (95% CI)	P value
Gender	Female vs. male	0.97 (0.87-1.08)	0.53
Histology	Squamous cell carcinoma vs. aden bocarcinoma	0.93 (0.79-1.09)	0.39
Prior radiotherapy	No vs. yes	1.09 (0.99-1.19)	0.06
Prior chemotherapy	No vs. yes	0.98 (0.89-1.07)	0.65
Dysphagia	Grade: 4 vs. 2-3	1.06 (0.96-1.16)	0.24
Tumor location	Distal vs. proximal/mid	0.97 (0.88-1.07)	0.52
Type of stent	Hanaroo vs. Ultraflex Wallflex vs. Ultraflex	0.91 (0.79-1.05) 0.97 (0.87-1.08)	0.21 0.60

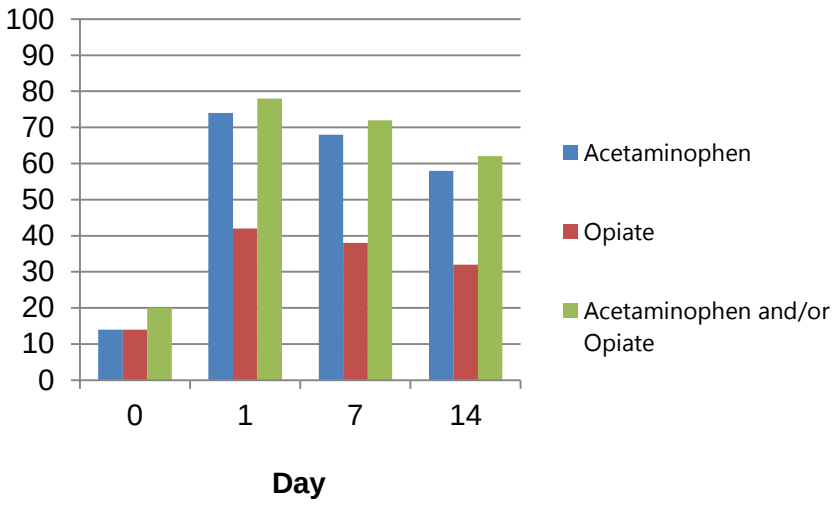
[1]Odds ratio (OR) represents the relative difference in pain decrease per day between groups.

Analgesics

At baseline, 13 patients (20%) were using analgesics, either acetaminophen and/or opiates. On the first day after SEMS insertion, any kind of analgesic use significantly increased to 78% ($P<0.001$) and declined to 72% and 62% on Days 7 and 14, respectively. Fourteen patients (22%) did not require any analgesic drug during 2 weeks of follow up. In 23 patients (35%), adequate pain relief was achieved with use of acetaminophen only. Irrespective of use of opioids, the number of patients using acetaminophen, significantly increased after stent placement from 13.8% at baseline to 73.8% on Day 1 ($P<0.001$) and decreased during follow-up from 67.7% on Day 7 to 58.5% on Day 14.

Because of insufficient pain relief with acetaminophen, 18 patients (28%) started opiates on the first day after stent placement, with a mean daily morphine dose of 43.2 mg. During follow up, dosage decreased to a mean dosage of 39.3 mg on Day 7 and 32.0 mg on Day 14. Only 1 patient started opiates 1 week after stenting, using morphine 40 mg daily, without dosage modification during the second week. Nine patients (14%) were already using opiates at baseline, with a mean daily morphine dosage of 74.7 mg. In these 9 patients, dosage increased to 98.7 mg, 132.0 mg and 145.4 mg on Days 1, 7 and 14, respectively. Overall, the percentage of patients using any form of opiate significantly increased after stent placement from 13.8% at baseline to 41.5% on Day 1 ($P<0.001$). Proportions of patients using acetaminophen, opiates and a combination are shown in Fig. 3.

Figure 3. Percentage of patients using analgesics before and during first 2 weeks after SEMS placement.



Adverse events

During the 2-week study period, a total of 12 adverse events (AEs) in 11 patients were recorded. Distal migration of the stent was observed in 6 patients, with a median of 3.5 days after stent insertion. All were managed endoscopically. In 2 patients the stent was removed, after which a new metal stent was deployed. In the remaining 4 cases the stent was repositioned using a grasping forceps. Food impaction inside the stent occurred in 1 patient 3 days after stent placement and was treated by endoscopic cleaning. Pulmonary complications were encountered in three patients, including aspiration pneumonia (n=2, after a median of 3 days) and symptomatic tracheal compression directly after esophageal stent insertion. The latter was managed by placing an tracheal stent. One patient developed mediastinal air and para-esophageal fluid collections on CT-scan after 8 days, suspected of an esophageal perforation. This patient was managed conservatively with antibiotics and survived the 2-week follow-up. One patient due to a probable upper gastrointestinal bleeding and another patient died due to progressive disease.

Discussion

Metal stenting is one of the most widely used palliative treatment modalities for malignant dysphagia and fistula, mainly because of a favourable and rapid clinical response. However, stent-related AEs are not infrequently encountered. In this prospective study, we have shown that 60% of patients develop significant pain immediately after SEMS insertion. Although post-procedural pain gradually diminishes over time, 25% of patients still report significant pain after 2 weeks, despite analgesic therapy.

A key domain of palliative care is the focus on optimizing comfort by reducing invalidating symptoms. Pain is one of the most essential symptoms because of its huge impact on daily functioning and quality of life [13, 14]. Therefore, it is of utmost importance that pain be recognized early and adequately treated [28].

Considering our findings, we believe that pain after SEMS placement has been largely underestimated in previous reports and perhaps also in clinical practice. In literature, incidences of up to 14% have been described, however post-procedural pain management was not the primary focus in these studies [16-27]. In fact, this is the first study evaluating pain experience in a prospective fashion using daily registration. An important finding of our study is the high incidence and intensity of pain on Day 1 after stent placement, accompanied by a high consumption of analgesics. This is probably related to the instant expansion of the SEMS after deployment. Strong radial and axial forces induce stretching of the malignant process, but also cause pressure that damages the surrounding esophageal wall. The esophagus eventually seems to conform to the fully expanded SEMS. This might explain why severity of pain and also need of analgesic therapy gradually decreases over time. One of the aims of our study was to identify patient- or stent-related factors that might predict to the development of pain, after SEMS

placement. A previous in vitro study has shown various in radial and axial force patterns among esophageal SEMS [29]. It is assumed that SEMS with a higher axial force cause more retrosternal pain due to high pressure and damage to the esophageal wall. This assumption was supported by 2 reports on the Wallflex stent, a SEMS with a high axial force, demonstrating a relatively high incidence of retrosternal pain and pressure ulceration [17, 30]. Considering radial forces, it seems that 2 different pressure profiles can be distinguished [29]. The first group (e.g. Evolution and Wallflex) is associated with a relatively low initial radial force with gradual decline during expansion, while the second group (e.g. Ultraflex and Hanaro) demonstrates an initial high radial force followed by a rapid decline during expansion. The features of the second group could potentially induce more pain due to immediate forceful dilation of the stricture. However, in our current study, we were not able to find a relation between type of stent and pain experience, especially not when stents were grouped according to their pressure profile. This might be related to the limited number of each type of stent that was used, and probably also influenced by other stent- and patient-related factors. However, several factors were tested using regression analysis, but none appeared to be predictive of the occurrence and length of significant post-procedural pain. In particular, we didn't find any effect of previous treatment with chemotherapy and/or radiation on pain. These results are in line with other studies, showing similar incidences of chest pain in patients with and without prior treatment. However, these findings should still be interpreted with caution, considering the limited number of patients and potential under-registration of post-procedural pain in other studies.

Approximately 40% of the patients were in need of opioids and in most of them, opioid therapy could not be discontinued. We did observe a decline in daily dosage in patients who started opioids directly after SEMS placement. These issues are extremely relevant for patients as they are in need of optimal palliative care. For that reason, physicians should discuss the possible occurrence of post-procedural pain with patients prior to SEMS placement. In our opinion, preemptive opioid therapy is not indicated, but opioids should be started if sufficient relief cannot be achieved with acetaminophen. A specialized oncology nurse can be recommended to closely monitor and guide these patients, especially shortly after SEMS placement.

There are some limitations of our study that should be acknowledged. Scoring pain intensity using the NRS is a subjective measure and comparing one patient's pain with another's should be done with caution. Pain perception is based on (mal)adaptive behavioral patterns, psychological and social factors, which were not addressed in our study. On the other hand, objective diagnostic tests assessing pain intensity are not available and besides individual analgesic need, the NRS scale is, in our opinion, the most appropriate rating tool at this time.

In conclusion, SEMS for malignant esophageal disease results in moderate to severe pain in 60% of patients immediately after stent placement and approximately 75% of patients

require some form of analgesic therapy. Patients need to be informed about this very common side effect and a proactive management is needed in order to prevent post-procedural pain.

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Part II

New clinical insights into stents for malignant gastric outlet obstruction

Chapter 7

Endoscopic treatment of malignant gastric and duodenal strictures: a prospective, multicenter study

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Gastrointest Endosc. 2014;79:66-75

Abstract

Background: Malignant gastric outlet obstruction is often treated by stent placement.

Objective: To investigate the outcomes of stent placement in the palliative treatment of malignant neoplasms.

Design: Prospective, observational, multicenter registry.

Setting: Six tertiary care centers in 5 countries.

Patients: A total of 108 adult patients with malignant gastric outlet obstruction.

Interventions: Placement of an uncovered, self-expandable, metal duodenal stent.

Main outcome measurements: The primary endpoint was stent patency at 14 days after stent implantation. Secondary endpoints included stent patency at 1, 2, 3, and 6 months, gastric outlet obstruction scoring system (GOOSS) scores at 14 days and 1, 2, 3, and 6 months after stent deployment, technical success, adverse events, and patient survival (ie,, confirmed duration of the implant).

Results: Technical success was achieved in 99.1% of stent placements. Stent patency at 14 days was 94.6%. Kaplan-Meier estimates of stent patency were 92.9% at 1 month, 86.2% at 2 months, 81.9% at 3 months, and 63.4% at 6 months. At 14 days, GOOSS scores increased by a median of 1 point. The overall GI adverse event rate was 32.4%; however, the stent-related adverse event rate was 19.4%. The median implant duration was 47 days (range 0-195 days).

Limitations: Observational study, no control group.

Conclusions: Duodenal stent placement resulted in prompt relief of malignant gastric outlet obstruction and improved GOOSS scores (ClinicalTrials.gov Identifier NCT00991614).

Introduction

Gastric outlet obstruction can occur in conjunction with several different malignant conditions intrinsic or extrinsic to the GI system; however, the resultant gastroduodenal stricture or obstruction manifests with the same constellation of clinical signs and symptoms. Historically, patients with malignant gastroduodenal obstruction have been treated by a variety of open surgical interventions intended to restore continuity and function of the GI tract. These methods include open surgical resection of the tumor and surrounding GI structures, surgical bypass of the obstruction, and decompressive gastrostomy (with or without feeding tube placement) [1]. Some patients are not candidates for open surgical treatment, either because surgery would not be curative for their disease or because their overall physical status prohibits such an invasive procedure.

Duodenal stents were introduced as an endoscopic palliative therapy in the 1990s, and have been described as a safe, minimally invasive, and cost-effective option for palliative treatment [2]. Because patients with malignant GI obstruction are generally older, may have several contraindications to invasive procedures, and may have a relatively short anticipated life expectancy (typically estimated to be ≤ 6 months), stent placement may be preferable to open surgical intervention. Further, stent placement allows faster resumption of food intake and a shorter hospitalization compared to surgical gastrojejunostomy (open [3,4] or laparoscopic [4]). Therefore, stent placement is the first-line treatment for malignant gastric outlet obstruction in patients with a single, localized distal gastric and/or small bowel stricture. In recently published reports, technical success rates of endoscopic stent placement for malignant obstruction range from approximately 92% to 100%, whereas clinical success rates are lower and range from approximately 80% to 91% [2,5-8].

The objective of this study was to describe the outcomes of uncovered self-expanding metal stent placement in the palliative treatment of gastric outlet obstruction caused by malignant neoplasms.

Methods

Patient enrollment

This prospective, observational, multicenter registry enrolled 108 patients who required palliative treatment for malignant gastric outlet obstruction between December 2009 and June 2011. Six hospitals in 5 countries participated in this trial, and approval was obtained from each site's ethics committee or institutional review board. Patients were not enrolled if they had a benign cause of stricture or obstruction, enteral ischemia, suspected or impending small-bowel perforation, coagulopathy, intra-abdominal abscess or perforation, conditions that precluded endoscopic therapy, or strictures that did not allow passage of a wire guide or stent. Patients signed a data collection agree-

ment/informed consent form before enrollment and were assigned a baseline gastric outlet obstruction scoring system (GOOSS) [9] score (0 = no oral intake; 1 = liquid diet; 2 = soft solid diet; 3 = low residue or normal diet). Data were collected through Internet-based case report forms.

Device

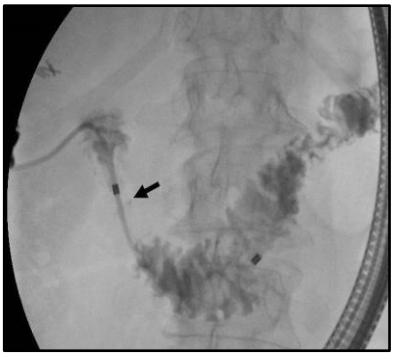
Patients underwent placement of the Evolution Duodenal Stent (Cook Ireland, Limerick, Ireland) in accordance with standard medical practice of the site, the investigator, and the device Instructions for Use. The Evolution Duodenal Stent is an uncovered, self-expandable metal stent constructed from a single woven nitinol wire. The stent is manufactured in lengths of 6, 9, and 12 cm. All stents have a body diameter of 22 mm and a flare diameter of 27 mm at the proximal and distal ends. The stent introducer system accepts a 0.035-inch guidewire and is inserted through at least a 3.7 mm working channel of a therapeutic endoscope. The delivery handle facilitates single-handed stent deployment and recapture, if stent repositioning is needed during deployment.

Procedure

Stent placement was achieved using either a forward-viewing operative gastroscope or a lateral-viewing duodenoscope. Patients were under conscious or deep sedation according to anesthesiologist availability. Pre-stent stricture dilation with a balloon or passage of the endoscope was performed at the discretion of the physician. The stricture was traversed with a catheter/guidewire, and stricture length was estimated and compared to the nominal stent length indicated by radiopaque markers on the inner stent delivery catheter. Stents were deployed under fluoroscopic and endoscopic guidance. Stent position (Fig. 1) and expansion (Fig. 2) could be assessed by passage of contrast through the stent after deployment.

Figure 1. Duodenal stricture caused by pancreatic cancer. A. Injection of contrast demonstrates the stricture (arrow). B. A 9 cm Evolution Duodenal Stent was placed and good passage of contrast is shown.

A



B

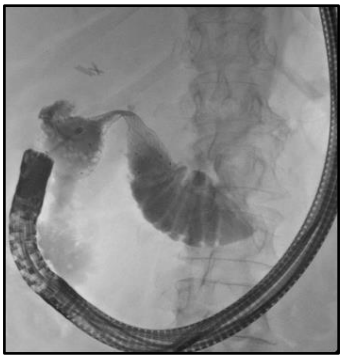
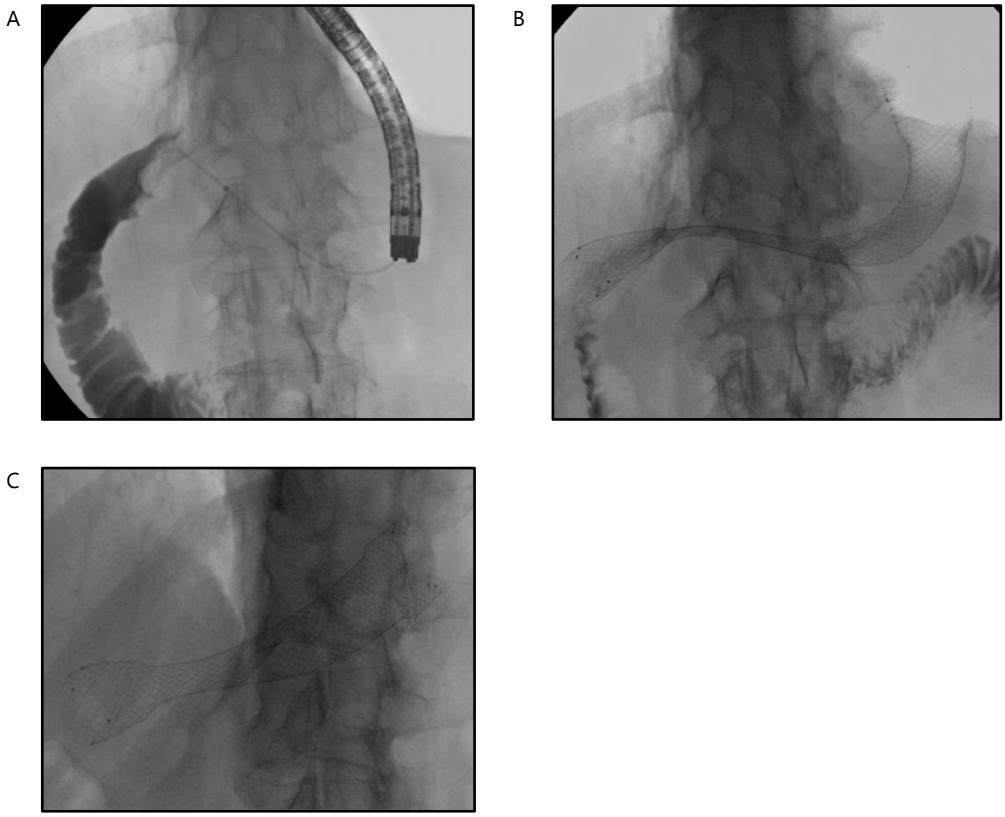


Figure 2. Gastric antral stricture caused by gastric cancer. A. A catheter is placed across the stricture. B. A 12-cm Evolution Duodenal Stent was placed. C. The stent is fully expanded after 48 hours.



Definitions and study endpoints

Technical success was defined as the ability to deploy the stent successfully. Clinical success was considered to be relief of obstructive symptoms and/or improvement of oral intake at 14 days.

The primary study endpoint was stent patency at 14 days after stent implantation. Loss of stent patency included reintervention for stent occlusion or migration (eg, surgical removal of the stent or placement of an additional stent) or stent occlusion determined by the investigator based on signs and symptoms during follow-up.

Secondary endpoints were stent patency at 1, 2, 3, and 6 months and GOOSS scores at 14 days and 1, 2, 3, and 6 months after stent deployment, technical success of stent deployment, adverse events, and patient survival (ie, confirmed implant duration).

Patient follow-up

Patient follow-up included an outpatient clinic visit at 14 days post-procedure and telephone contacts at 1, 2, 3, and 6 months post-procedure. Follow-up was discontinued at 6 months or when the patient died or underwent a reintervention for gastrointestinal obstruction.

Statistics

Sample size was calculated based on patency at 14 days post-procedure. The calculation assumed a patency rate of 90%, a confidence interval of 95%, a power of 80%, and a margin of error of 6%. From this, it was determined that 97 patients were required to meet study goals and that as many as 110 patients would be enrolled to account for possible loss of patients during follow-up.

Continuous variables were described by means, standard deviations, or median values, and categorical variables were given as counts and percentages. Analyses were completed on a per-patient, per-procedure, or per-stent basis, as appropriate. Kaplan-Meier analysis was used to describe stent patency over time. A Cox proportional hazards analysis was performed to identify factors that could lead to loss of stent patency. SAS software (version 9.3; SAS Institute, Inc, Cary, NC) was used to analyze the data.

Results

Patient population

The mean patient age was 65.8 ± 13.0 years (range 34-93 years) and 51.9% of patients were male. The most common primary malignancy was pancreatic cancer (Table 1). Before study enrollment, nearly 30% of patients had undergone chemotherapy for the treatment of biliary, pancreatic, or duodenal malignancy. Four patients underwent treatment for malignant gastroduodenal obstruction before enrollment. Two patients had a stricture or stenosis at the site of a previous GI anastomosis. Biliary obstruction occurred before gastric outlet obstruction in 41.1% of patients and was most commonly treated with endoscopic biliary stent placement. The most common locations of gastroduodenal stricture were the duodenal bulb and second duodenal segment. The mean stricture length was 3.8 ± 1.6 cm (range 1-10 cm). Pretreatment GOOSS scores indicate that most patients (92.5%) had altered their diet in some manner to compensate for the malignant obstruction (Table 2). Many patients reported moderate to severe vomiting or nausea at baseline.

Procedural details

A total of 108 patients underwent 108 duodenal stent procedures in which 110 stents were deployed. Technical success was achieved in 99.1% of procedures. One patient with technical failure of stent placement (ie, the stent was deployed too far distally) under-

went successful placement of a second stent during the same procedure. One patient with a long stricture underwent placement of 2 stents. Procedures were performed via a lateral-viewing duodenoscope in 66.7% of cases and via a forward-viewing gastroscope in the remaining 33.3%. Pre-stent stricture dilation was performed in 17 patients (15.7%); this was accomplished in most cases (16 patients) by passage of the endoscope. Twelve patients (11.1%) also underwent biliary stent placement during the duodenal stent placement procedure: 11 patients had 1 biliary stent placed and 1 patient had 2 biliary stents placed.

The most frequently deployed stent length was 9 cm (47.3%), followed by 12 cm (30.0%) and 6 cm (22.7%) lengths. After the procedure, patients remained hospitalized for a mean of 5.6 ± 7.0 days (range 0-37 days).

Table 1. Baseline patient and stricture characteristics.

Characteristic	% of patients
Primary malignancy	
Pancreatic cancer	53.7
Gastric cancer	13.0
Cholangiocarcinoma	6.5
Gallbladder cancer	6.5
Duodenal carcinoma	4.6
Ampullary carcinoma	2.8
Other[a]	13.0
Previous treatment of biliary, pancreatic, or duodenal malignancy[b]	
Chemotherapy	29.9
Radiation	6.5
Previous treatment of malignant gastroduodenal obstruction[b]	
Surgical bypass	2.8
Duodenal stent placement	0.9
Treatment of biliary obstruction before enrollment[2]	
Total	41.1
Percutaneous	7.3
Endoscopic stent placement	31.8
Open surgery	1.9
Location of stricture/stenosis	
Distal stomach	11.1
Distal stomach/duodenal bulb	6.5
Duodenal bulb	29.6
Duodenal bulb/second duodenal segment	8.3
Second duodenal segment	27.8
Second/third duodenal segment	3.7
Third duodenal segment	6.5
Fourth duodenal segment	6.5

[a] Other malignancies included non-Hodgkin lymphoma; intraabdominal small cell sarcoma; metastatic and/or primary tumors of the lung, breast, ovary, kidney, urinary tract, or colon; and tumor around the head of the pancreas.

[b] Information available on 107 patients.

Table 2. Baseline GOOSS score and obstructive symptoms.

Characteristic	% of patients
GOOSS score	
No oral intake (0)	40.7
Only liquid diet (1)	37.0
Soft solid diet (2)	14.8
Low residue or normal diet (3)	7.4
Obstructive symptom	
Abdominal pain	
None	34.3
Moderate	62.0
Severe	3.7
Vomiting	
None	16.7
Moderate	43.5
Severe	39.8
Nausea	
None	10.2
Moderate	57.4
Severe	32.4
Regurgitation	
None	30.6
Moderate	40.7
Severe	28.7

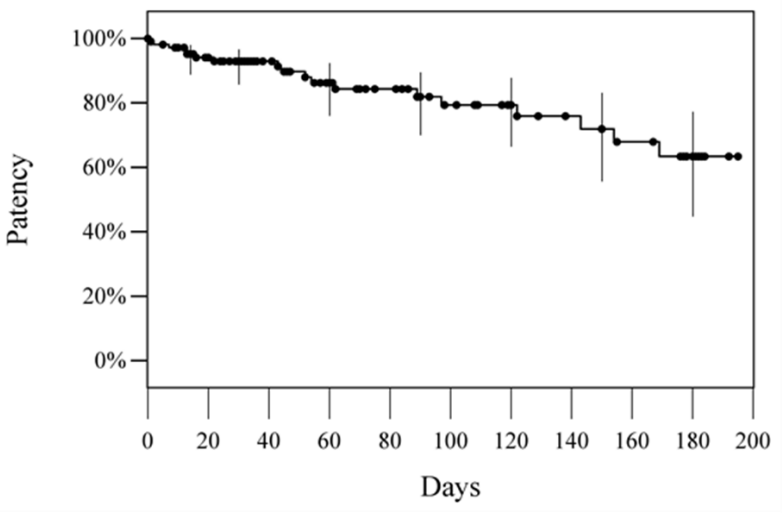
Stent patency

Stent patency at 14 days was 94.6% (88/93). Before 14-day follow-up, 5 patients lost stent patency and underwent additional stent placement or surgery. Stent patency beyond 14 days was assessed by Kaplan-Meier analysis (Fig. 3). At 60 days, the estimate of stent patency was 86.2%. The median implant duration (a conservative estimate of survival) was 47 days (range 0-195 days). Thus, stent patency was acceptable for the median patient survival. At 180 days, the estimate of stent patency was 63.4%; however, only 10.2% of patients (11/108) were alive at 180 days.

Post-treatment GOOSS scores

Eight patients began the study with GOOSS scores of 3, but each patient had at least 1 obstructive symptom of moderate severity necessitating stent placement. However, because these patients could not experience improved GOOSS scores after treatment, analyses of post-treatment GOOSS scores are based on the 100 patients with baseline GOOSS scores less than 3. The median GOOSS score increased by 1 point (interquartile range 1) from baseline to the first follow-up assessment.

Figure 3. Kaplan-Meier estimates of stent patency over time. The Kaplan-Meier curve and corresponding life table are shown. Vertical bars represent confidence intervals of 95%.



Days post-procedure	Estimate ± standard error (%)	Cumulative no. of patients failed	Cumulative no. of patients censored	Patients remaining at risk
30	92.9 ± 2.6	7	28	73
60	86.2 ± 4.0	11	51	46
90	81.9 ± 4.9	13	62	33
180	63.4 ± 8.4	18	81	9

Post-treatment obstructive symptoms

Throughout the study, more than 73% of patients experienced either stabilization or improvement of all combined obstructive symptoms when compared to baseline (Table 3). Five of the 8 patients who had baseline GOOSS scores of 3 experienced improvement in at least 1 obstructive symptom after stent placement.

Clinical success

At 14 days after stent placement, 84.5% (82/97) of patients experienced clinical success. When patients with a baseline GOOSS score of 3 were excluded from the analysis, the clinical success rate was 87.6% (78/89).

Table 3. Change in severity of obstructive symptoms (abdominal pain, vomiting, nausea, and regurgitation) after stent placement.

	14 days	1 month	2 months	3 months	6 months
No. of patients available for follow-up	97	74	46	37	11
Patients with all symptoms maintained or improved compared to baseline, %	87.6	81.1	73.9	78.4	90.9
Patients with any symptom worsened compared to baseline, %	12.4	18.9	26.1	21.6	9.1

Adverse events

There was no device- or procedure-related mortality in this study. The most common GI adverse event was stent occlusion (Table 4). Stent occlusion occurred from 1 to 172 days after stent placement. Occlusion was most often caused by tumor ingrowth and was most often treated by placement of an additional stent. Occlusion was not likely related to the duodenal stent in 2 patients: 1 patient had occlusion due to a migrated biliary stent and 1 patient experienced duodenal reocclusion and late stent migration (146 days after initial stent placement). In the latter case, occlusion was likely secondary to stent migration, which occurred after chemotherapy; this patient also underwent additional stent placement.

Early stent migration (2 days after stent placement) occurred in 1 patient; this patient then underwent surgical gastroenteroanastomosis. One intraprocedural duodenal perforation occurred in a patient while the stricture was crossed with the catheter and guidewire; this patient was successfully treated by placement of a covered stent into the uncovered stent during the same procedure. Therefore, this perforation was considered procedure related and not stent-related. The second case of duodenal perforation occurred 82 days after stent placement when a common bile duct stricture developed in the patient; the duodenoscope was able to pass through the mesh of the uncovered stent, and a biliary stent was successfully placed, but peritonitis developed 24 hours later in this patient. This patient underwent laparotomy, abdominal drainage, and subsequent placement of a covered duodenal stent. This event was considered to be related to the difficult biliary stent procedure and not the duodenal stent. Endoscopic intervention was not required for the 5 patients with GI bleeding or the 2 patients with severe abdominal pain. Two of the 5 incidents of GI bleeding were due to metastatic gastric ulceration and both incidents of abdominal pain were related to progression of the tumor mass; thus, these events were not related to the duodenal stent. Additional GI events were experienced by 17 patients. These events included nausea and/or vomiting, pancreatitis, cholangitis, jaundice, biliary obstruction, chemotherapy related gastritis, ileus, infected bilio-

ma, and infected tumor mass causing portal vein thrombosis and liver abscesses. None of these additional events were considered to be stent-related. Although the overall GI adverse event rate was 32.4%, the stent-related adverse event rate was 19.4%.

Table 4. GI adverse events

Adverse event	Total no. of events	% of patients (n/N)	Stent-related events	% of patients (n/N)
Stent occlusion	19	15.7 (17/108)[a]	17	14.8 (16/108)
GI bleeding	6	4.6 (5/108)[b]	4	3.7 (4/108)
Duodenal perforation	2	1.9 (2/108)	0	0
Severe abdominal pain	2	1.9 (2/108)[c]	0	0
Stent migration	2	1.9 (2/108)	2	1.9 (2/108)
Other GI events	21	15.7 (17/108)	0	0
Total	52	32.4 (35/108)	23	19.4 (21/108)

[a] One patient had 3 occlusive events; 1 event involved obstruction of the duodenal stent by a biliary stent (the biliary stent was removed).
[b] One patient had 2 separate bleeding events.
[c] This is pain reported as an adverse event, not as an obstructive symptom.

Survival

Patients who completed 6-month follow-up had a median survival of 182 days (range 178-195 days). Patients who died before 6-month follow-up had a median survival of 52 days (range 9-180 days).

Cox proportional hazards analysis

A Cox proportional hazards model was used to identify risk factors leading to loss of stent patency. The predictors selected for the model include age, sex, baseline GOOSS score, stricture dilation before stent placement, gastric or duodenal stent placement, tumor type, and length of stenosis. No significant predictors were identified in the model; however, the trend suggested that patients undergoing duodenal stent placement were 4.1 times more likely to have loss of stent patency than patients undergoing gastric stent placement (ie, distal stomach or distal stomach and first part of the duodenum).

Discussion

Studies comparing duodenal stent placement with open gastrojejunostomy (GJJ) have shown that stent placement is at least an equivalent treatment, and in some respects is a preferred treatment over surgery. Patients who undergo stent placement have experienced both a shorter time to achieve oral intake and a shorter hospital stay compared with patients who undergo open GJJ [3]. Duodenal stent placement has also been described as a more cost effective therapy. The shorter hospital stay associated with duodenal stent placement contributes to the significantly lower initial cost compared with open GJJ [10,11] and laparoscopic GJJ [4].

Data from the SUSTENT study suggest that GJJ should be primarily considered for patients with an expected survival of 2 months or longer and that stent placement should be primarily considered for patients with a shorter anticipated survival [12]. However, of the 77 patients eligible for the study, 38 patients declined to participate because they preferred to undergo stent placement and did not want to be randomized to surgery. Therefore, patient perception of procedure invasiveness is also a factor in the choice of treatment strategy.

In the present study, we prospectively evaluated outcomes of treatment with the new uncovered Evolution Duodenal Stent. The controlled stent release allowed safe and effective stent deployment. The results, in terms of technical and clinical success, compare favorably with the results of several studies of duodenal stent placement reported to date (Table 5) [5-8,13-23]. Stent-related dysfunction was observed in 14.8% of patients in the present series, mostly related to tumor ingrowth. It is well known that recurrent obstruction caused by stent dysfunction is the major shortcoming of self-expandable metal stents, usually necessitating repeat endoscopic intervention. Stent occlusion has occurred in as many as 21.6% of patients in available case series data (Table 5). It has been assumed that covered stents should be more resistant to occlusion caused by tumor ingrowth or overgrowth; however, this should be balanced against the risk of stent migration. One study comparing uncovered and covered stents found that the rate of stent occlusion was similar between groups and that patients in the uncovered stent group were less likely to require reintervention for either stent occlusion or migration than patients in the covered stent group [24]. Further, patients treated in that study experienced similar clinical outcomes and adverse event rates. Given these data, uncovered stents are a better choice for gastric outlet obstruction, especially when the stent will cover the papilla of Vater, because uncovered stents will permit the flow of bile into the duodenum.

Table 5 – Comparison of published duodenal stent systematic reviews and studies.

Ref.	Stent(s)*	Technical success, %	Clinical success, %	Stent migration, %	Perforation and/or hemorrhage, %	Stent occlusion /obstruction, %
Dormann et al, 2004[13]	Multiple[a]	97.0	89.0	5.1	1.2	17.2
Graber et al, 2007[14]	Wallstent	98.0	NR	2.0	3.9	21.6
Jeurnink et al, 2007[15]	Multiple[b]	96.0	89.0	NR	NR	NR
Lowe et al, 2007[16]	Multiple[c]	96.6	NR	1.1	1.1	8.0
Mutignani et al, 2007[17]	Diamond, Wallstent, or WallFlex	96.9	89.1	1.6[d]	1.6	12.5
van Hooft et al, 2007[18]	WallFlex	91.9	85.5	0[e]	4.8	3.2[f]
Phillips et al, 2008[19]	Wallstent, Alimaxx, or Bard	100.0	91.3	4.3	0	8.7
van Hooft et al, 2009[20]	WallFlex	98.0	84.3	2.0	4.0	17.6
Shaw et al, 2010[21]	WallFlex	92.9	NR	1.4	2.9	4.3
Dolz et al, 2011[22]	WallFlex, Wallstent, or UltraFlex	92.2	NR	0	9.1	2.6
Lee et al, 2011[7]	Wallstent	100.0	91.2	4.3[g]	0	17.5
Mendelsohn et al, 2011[6]	WallFlex or Wallstent	95.5	82.3	1.0	2.0	16.9
van Hooft et al, 2011[8]	Niti-S duodenal	96.2	85.1	3.8	0	21.2
Cha et al, 2012[23]	Niti-S pyloric[h], UltraFlex, or WallFlex	96.5	80.0	2.4	3.5	16.5
Costamagna et al, 2012[5]	WallFlex	98.0	90.8[i]	1.5[j]	3.5	12.9
Tringali et al, 2013 (present study)	Evolution Duodenal Stent	99.1	84.5[k]	1.9	3.7	14.8
All clinical trials	Average (range)	96.6 (91.9–100.0)	86.8 (80.0–91.3)	2.2 (0–5.1)	2.8 (0–9.1)	13.0 (2.6–21.6)

NR: not reported.

* Uncovered stents deployed for gastric outlet obstruction, where possible.

[a] Stents included Enteral Wallstents, other Wallstents, InStents, UltraFlex stents, Choo/Song Stents, and other undefined stents.

[b] Stents included Enteral Wallstents, Niti-S stents, esophageal Memotherm stents, UltraFlex stents, Choo stents, Gianturco-Z stents, Song stents, Flamingo Wallstents, and Endocoil stents.

[c] Stents included Enteral Wallstents, Hanorostents, Flamingo stents, Cook II esophageal stents, and Choo stents.

[d] Two intraprocedural migrations were considered migrations in the report; however, they are considered to be technical failures for the purpose of this tabular summary.

[e] One intraprocedural migration was considered a migration in the report; however, it is considered to be a technical failure for the purpose of this tabular summary.

[f] Two intraprocedural occlusions were considered occlusions in the report; however, they are considered to be technical failures for the purpose of this tabular summary.

[g] The publication does not state whether these events occurred with duodenal or colonic stents.

[h] This publication did not separate results based on covered or uncovered stent placement.

[i] Seven patients who began the study with gastric outlet obstruction scoring system scores of 3 (ie, low residue or normal diet) were excluded from the analysis of clinical success.

[j] Four intraprocedural migrations were considered migrations in the report; however, they are considered to be technical failures for the purpose of this tabular summary.

[k] Clinical success at 14 days after stent placement.

In general, stent occlusion can be effectively managed by placement of an additional stent [2]. One group investigated the effect of the type of stent placed as a stent-in-stent reintervention for primary stent occlusion [25]. The technical success rate of secondary stent placement was 100% and the clinical success rate was 88.3%; further, there was no significant difference in adverse event rates between covered and uncovered stents. Therefore, although primary stent occlusion may be a common occurrence after stent placement, it can be easily and effectively treated by secondary stent placement.

Although it has been suggested that certain patients may benefit more from endoscopic stent placement than others, there is no clear definition of what characteristics should direct care towards stent placement versus surgery. One study failed to identify any factors (such as age, sex, serum albumin, or chemoradiation) that predicted survival of patients who underwent stent placement for malignant gastroduodenal obstruction [19]. However, a recent publication analyzed pooled data from the DUOFLEX and DUONITI studies and demonstrated that a World Health Organization performance score of 3 or 4, use of pain medication stronger than tramadol, and a high pain score on the European Organisation for Research and Treatment of Cancer questionnaire (EORTC QLQ-C30 version 3) were all predictive of shorter survival [26]. Further, a patient having all 3 of these predictive characteristics had a 30-day survival rate less than 10%. Another study investigated factors leading to reintervention after stent placement (although this study included both gastroduodenal and colonic stent placement) and found that only stent angulation was a significant predictor of reintervention among the 11 factors included in the model [7]. One study evaluated variables associated with stent patency with a model including age, sex, site of lesion (peripyloric vs duodenal), type of malignancy (gastric, pancreatic, or other), chemotherapy after stent placement, and World Health Organization score [27]. Results of their Cox regression analysis showed that duodenal lesions were the only significant prognostic factor associated with a loss of stent patency. The Cox proportional hazards model applied to the present study also demonstrated a trend toward worse stent patency rates for patients who underwent stent placement for duodenal stricture or obstruction. Our model contained only 19 gastric stent patients (17.6% of the study population) compared to 89 duodenal stent patients (82.4% of the study population). However, this is an interesting avenue for future investigations.

The presence of peritoneal carcinomatosis was not evaluated in the present study, but according to a recent experience [6], carcinomatosis is not a contraindication for duodenal stent placement in the absence of multiple intestinal strictures and clinical signs of intestinal obstruction.

Manufacturers typically recommend avoidance of chemotherapy and/or radiation after enteral stent placement for malignant gastric outlet obstruction because of the risk of stent migration and/or mucosal bleeding or erosion. However, some data suggest that chemotherapy after stent placement (controlled for patient age and survival < 30 days) is

associated with an increased duration of subsequent oral intake [28]. One study reported that patients with enteral stents who responded to chemotherapy had higher rates of stent migration than non-responders in a univariate analysis, but this association was not shown on multivariate analysis [29]. In these patients, first-line administration of chemotherapy and a long time to disease progression were closely correlated, and both were independent predictors of stent patency. Conversely, other studies have shown no effect of chemotherapy on enteral stent patency in patients with pyloric or duodenal obstruction [23]. Therefore, this is also an important area for further investigation.

This study is limited by its observational design and lack of a control group for comparison. Stent placement was performed at tertiary centers by endoscopists experienced in the procedure; therefore, the data may not generalize to other patient populations.

In summary, these data are in accordance with other published studies that demonstrate that endoscopic stent placement for malignant gastric outlet obstruction is generally safe and effective as a palliative therapy for patients with unresectable disease. Stent placement results in prompt relief of obstructive symptoms and improves GOOSS scores.

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Chapter 8

Efficacy and safety of a partially covered stent in malignant gastric outlet obstruction: a prospective Western series

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Introduction

Malignant gastric outlet obstruction is a late complication of advanced gastric and periampullary malignancies with significant morbidity, including nausea, vomiting, poor nutrition, and dehydration [1]. In the Western world malignant gastric outlet obstruction is mainly caused by obstruction of the duodenum caused by periampullary malignancies, whereas in Asian countries, obstruction at the level of the stomach caused by gastric cancer (primary or postoperative recurrence) is seen more commonly. The classic procedure to alleviate obstructive symptoms is a surgical gastrojejunostomy. However, a gastrojejunostomy is associated with a high morbidity and mortality rate [2, 3]. Use of endoscopic self-expandable metal stents (SEMSs), usually uncovered, is a good alternative providing a rapid relief of symptoms [4-7]. The main disadvantage of uncovered stents is recurrent obstruction (18%), primarily due to tumor ingrowth, necessitating repeated endoscopic interventions [5]. Covered stents may overcome this problem. A few studies have assessed the clinical outcome of covered stents in malignant gastric outlet obstruction in an Asian population. Although effective in preventing tumor ingrowth, covered stents had a tendency to migrate more frequently [8-17]. A more migration-resistant design for covered stents would be desirable to reduce this migration risk.
In this prospective, multicenter study we therefore evaluated the clinical and technical efficacy of a newly designed partially covered, double flare-shaped, duodenal SEMS for malignant gastric outlet obstruction in a Western population.

Patients and methods

Patients
In this prospective, multicentre study, which started in August 2010, consecutive patients with malignant gastric outlet obstruction were enrolled and treated with a partially covered duodenal stent. Patients were included if they had obstructive symptoms with a Gastric Outlet Obstruction Scoring System (GOOSS) score of ≤ 1 (ie, no oral intake or only liquid diet) because of malignant gastro-duodenal obstruction caused by incurable malignancy. Exclusion criteria were before-procedure evidence of additional strictures in the GI tract, previous treatment with SEMS for the same condition, unsuccessful placement of a preventive biliary stent if required, and being unfit for endoscopy. The institutional review boards at all 3 hospitals approved the study. All patients gave signed informed consent for stent placement. The expected number of eligible patients to be included at the participating hospitals was 25 in 1 year.

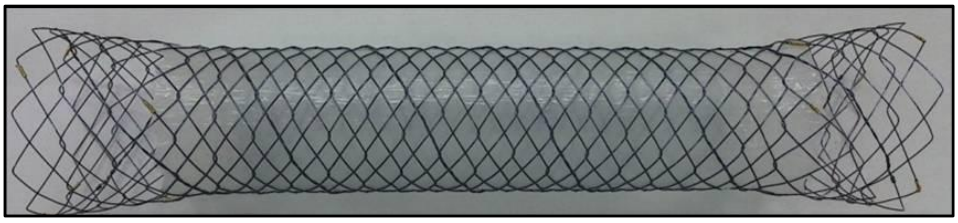
Methods
All patients were evaluated before stent placement, at 3 days, 2 and 4 weeks, and afterwards at a 4-week intervals until 24 weeks after the procedure or until death. Follow-up

assessments were performed by using telephone interviews and included evaluation of obstructive symptoms with the GOOSS. The GOOSS consists of 4 grades: 0, no oral intake; 1, liquids only; 2, soft solids; 3, low residue or full diet. Clinical success was defined as an improvement of the GOOSS to ≥ 2 after the procedure. Adverse events were recorded and graded as recommended by Cotton et al [18].

Stent placement

The newly developed, partially covered stent (Hanarostent duodenum/pylorus M.I. Tech, Seoul, Korea) is constructed of a single nitinol wire. The middle part of the stent is completely covered with a silicon membrane, which is in contrast with the uncovered proximal and distal end for anti-migration. Both ends of the stent are flare shaped and radiopaque markers are located on both ends and at the center of the stent (Fig. 1). The diameter of the stent is 20 mm and lengths of 60 and 90 mm are available. The standard procedure for duodenal stent placement by using a therapeutic endoscope (working channel > 3.7 mm) was carried out in this study. All procedures were performed by experienced interventional endoscopists with ample experience in placement of duodenal stents. In all cases, the stent overlapped the proximal and distal border of the stricture by least 1 cm and was positioned under endoscopic and fluoroscopic guidance. All procedures were performed with the patients under conscious sedation, by using midazolam and/or fentanyl. In all patients in whom the covering of the stent would bridge the ampulla of Vater, first a biliary metal stent was inserted to prevent biliary outflow occlusion, either by ERCP or percutaneous intervention. In case a biliary metal stent had already been placed prior to duodenal obstruction, this stent was left in place.

Figure 1. The partially covered Hanarostent.



Results

From August 2010 until January 2011, 9 patients (4 men, 44%; mean age 71 years, range 56-93 years) with malignant gastric outlet obstruction were enrolled. In January 2011 the study was terminated prematurely because of a substantial number of stent fractures. Gastric outlet obstruction was caused by distal gastric cancer (n=3), pancreatic cancer (n=3), cholangiocarcinoma (n=1) and metastases in the pancreatic head originating from

colon (n=1) and breast cancer (n=1). The GOOSS score before stent placement was 1 in 5 patients and 0 in 4 patients. Four patients were treated with palliative chemotherapy, 2 patients before and 2 patients after stent placement. Final analysis was performed on the 9 included patients. All patients completed the study protocol.

Biliary drainage

Prior to duodenal stent placement, the biliary system was successfully drained with a metal stent in 7 patients (5 by ERCP and 2 by percutaneous intervention). In 2 patients with a malignant stricture at the distal stomach biliary drainage was not necessary, because the covering of the duodenal stent did not occlude the ampulla of Vater.

Outcomes

Stent placement was technically successful in 8 of 9 patients (89%). Six 9-cm and three 6-cm stents were used. In 1 patient the stent was inserted too distally and could not be repositioned. Subsequently, a second uncovered stent was adequately positioned, and the first stent was removed through the uncovered stent using an Alligator Jaw grasping forceps (Olympus Ltd., Tokyo, Japan).

Clinical success was achieved in 7 of 8 patients (88%) with an improvement of GOOSS scores to 3 in 5 patients, and to 2 in 2 patients. GOOSS scores did not improve in 1 patient, who had severe gastroparesis because of diffuse type gastric cancer. Luminal re-occlusion was excluded by upper endoscopy, and the patient was treated conservatively. The median procedure related hospital stay was 4 days (range 1-6). The median follow-up after stent placement was 121 days (range 8-168). Three patients were still alive at the end of follow up (24 weeks).

Adverse events

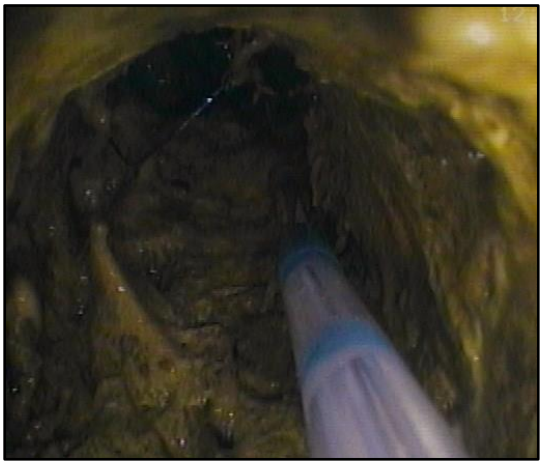
A total of 12 adverse events occurred in 7 patients, including 1 fatal, 8 moderate and 3 mild adverse events. The moderate adverse events encountered were recurrent obstruction due to fracture of stent wires (n=3) or stent migration (n=2), bacteremia (n=2) and pneumonia (n=1). All stent occlusions were caused by debris and food adhering to loose struts pointing towards the lumen. After cleaning of the stent, the presence of loose struts compromising the lumen was clearly visible on endoscopic examination (Fig. 2). These fractures were demonstrated at 46, 79 and 109 days after stent insertion and were effectively managed with an additional uncovered SEMS.

Stent migration occurred twice in 1 patient, 2 and 109 days, respectively, after stent placement. This patient received a second partially covered SEMS (Hanarostent) after 2 days because of proximal migration of the stent. The second event with distal migration at 109 days also was complicated by stent fracture (see earlier). Subsequently, both stent fracture and migration of the stent(s) were successfully treated with an additional third uncovered SEMS.

Two patients developed a pulmonary infection with possible relation to the stent or procedure (15 and 26 days after stent insertion), graded as moderate and fatal. One patient died because of respiratory insufficiency, whereas the other patient was treated with antibiotics with good outcome. Two moderate events of bacteremia were encountered in 1 patient at a late stage (27 and 83 days after stent insertion). Despite extensive additional investigations, the origin could not be identified and it remains uncertain whether these events were stent related. Mild adverse events included postprocedural abdominal pain (n=2) and jaundice (n=1). Abdominal pain occurred 4 and 7 days after stent insertion. Jaundice developed after 148 days and is unlikely to be related to the stent. Additional analysis was rejected because of rapid clinical detoriation and patients' preference. Patient characteristics and outcome are summarized in Table 1.

Figure 2A and 2B. Endoscopic view of loose struts, obstructing the lumen of the self-expandable metal stent. Images were taken after removing of a large amount of debris and food.

A



B

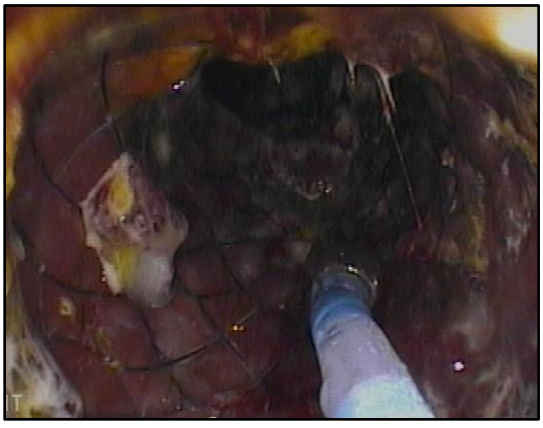


Table 1. Characteristics and clinical outcome of patients after stent placement.

Patient	Age, y	Sex	Tumor origin	Technical succes	Clinical succes	Adverse events (days after stent)	Survival
1	57	M	Gastric cancer	Yes	Yes	Obstructive jaundice (148)	Alive at 24 weeks
2	87	F	Gastric cancer	Yes	Yes		Alive at 24 weeks
3	93	F	Pancreatic cancer	Yes	Yes	Abdominal pain (7)	8 (days)
4	67	F	Gastric cancer	Yes	No	Pneumonia (15)	16 (days)
5	71	F	Metastasic colon cancer in the pancreatic head	Yes	Yes	Abdominal pain (4)	23 (days)
6	56	M	Pancreatic cancer	No[Δ]	-		42 (days)
7	69	M	Pancreatic cancer	Yes	Yes	Bacteremia (27, 83), stent fracture (79)	121 (days)
8	84	M	Cholangiocarcinoma	Yes	Yes	Stent fracture (46)	156 (days)
9	56	F	Metastasic breast cancer in the pancreatic head	Yes	Yes	Stent migration (2, 109), pneumonia (26), stent fracture (109)	Alive at 24 weeks

[Δ] Stent inserted too distally, followed by adequate positioning of a second uncovered self-expandable metal stent and removal of the first stent.

Discussion

In this multicentre, prospective study we intended to assess the efficacy and safety of a newly designed, partially covered, duodenal SEMS in a Western population. This double-flared, partially covered design seems effective in reducing obstructive symptoms with promising migration rates. However, recurrent obstruction due to stent disintegration caused by breakage of the wires led to early termination of the study

Recurrent obstruction after uncovered duodenal stent placement occurs in approximately 20% of the patients and is mainly caused by tumor ingrowth through the meshes [5]. It is known from Asian studies that covered stents can reduce the re-obstruction rate by preventing tumor ingrowth [8-16]. In our series, none of the patients had re-obstruction

caused by tumor ingrowth. Although some tissue infiltration, presumably intima hyperplasia, was seen through the uncovered flares of the stent, this finding did not explain recurrent obstructive symptoms. This significant advantage of covering the stent with an impermeable membrane is unfortunately counteracted by a high migration rate, with a reported incidence of 26% [11]. Besides the smooth surface of the coverage, which enables the stent to migrate more easily, one can hypothesise that the shape of the stent also is of relevance. Therefore, in this series we tested a stent with a double flare-shape and uncovered ends at both sides, two properties that may counteract the tendency of a covered stent to migrate more easily. In this limited prematurely discontinued series stent migration occurred in one patient only. In this patient two events of migration were reported, the second occurring while two stents were in place.

The present study was discontinued prematurely because of a high incidence of broken struts of the stent in 3 out of 9 patients. The broken struts with adherent food occluded the lumen of the stent, resulting in recurrent obstructive symptoms in all 3 patients. Although all patients were successfully managed with additional metal stent placement, this observation reveals an important safety issue. Occurrence of this uncommon complication has been described with covered as well as with uncovered stents [5, 14, 15, 17]. One could propose that stent failure is primarily caused by insufficient physical durability of the wires. In our study, all events occurred at a late stage (46, 79 and 109 days) after stent placement without any signs of a defect mesh framework at the time of deployment. Mechanical failure may have been provoked by, continuous peristaltic movements exerting considerable strain on the wire mesh. These forces obviously must be endured for long periods of time, and such a requirement puts a high demand on the technical design and physical properties of the stent and its materials. One could hypothesize that in Asian populations with gastric cancer hypochlorhydria or achlorhydria might have a protective effect on stent corrosion. Conversely, in Western patients with mainly periampullary cancer, acid related corrosive effects may promote mechanical failure. The observations of the present study have prompted the manufacturer, M.I.Tech, to work on improvements of the Hanarostent's material and design. An upgraded version of the partially covered duodenal stent has recently become available in Korea. This stent is constructed of a newly designed wire system to provide more strength and endurance. In addition to a smaller cell cavity between the wires, the thickness of the nitinol wire has been increased. Furthermore, enlarging the diameter of the proximal flare could be another interesting feature, potentially limiting the risk of distal migration. These new developments are currently being evaluated.

Not in all patients obstructive jaundice occurs before or coinciding with the development of gastric outlet obstruction [19]. Because the papilla may become occluded or inaccessible after placement of a covered stent, we recommend that in all patients adequate bile outflow is guaranteed with a biliary stent. However, this does not seem to be required when occlusion of the papilla is not expected, as in our two patients with distal gastric

cancer. It should be noted that one of these two patients developed jaundice after approximately 5 months, which was not further analyzed. Because of this long time interval, it seems unlikely that jaundice in this patient was caused by bile outflow occlusion due to the covering of the duodenal stent.

We acknowledge the following limitations of our study, which are mainly due to the small number of included patients. Any other confounding factors that may influence mechanical failure of the stent cannot be explored. Furthermore, clinical benefits of a partially covered, double flare shaped stent should be confirmed in larger studies before considering this type of stent as first line treatment in malignant outlet obstruction.

In conclusion, although limited by a small number of patients, this study demonstrates a high clinical efficacy rate of the partially covered duodenal Hanarostent in malignant outlet obstruction. However, fracture of wires occurring in one-third of patients leading to recurrent obstruction is a major concern. Routine use of this type of stent should therefore not be recommended until applicability and safety of the upgraded version of the stent have been demonstrated.

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Chapter 9

Summary and General discussion

Introduction

The incidence of cancers of the upper gastrointestinal tract is rising [1]. Unfortunately, these cancers are frequently diagnosed at an advanced, incurable stage. In case of incurable disease one should aim for optimal palliative care. Dysphagia and vomiting are the most common symptoms to palliate in malignant diseases of the upper gastrointestinal (GI) tract. Obstruction of the esophagus results in dysphagia, while vomiting is the most pronounced symptom in case of strictures in the distal stomach or duodenum. Both result in anorexia, weight loss and weakness, and are associated with a reduced quality of life. Ideally, palliative therapy for GI strictures should be well tolerable and result in a rapid and long-term relief of obstructive symptoms, without the risk of adverse events. Endoscopically inserted self-expandable metal stents (SEMS) play an important role in the palliative management of malignant upper GI obstruction [2]. SEMS are easy to insert and are highly effective in improving obstructive symptoms [3, 4]. Unfortunately, SEMS therapy is also associated with disadvantages, such as SEMS related adverse events including recurrent obstruction [3, 4]. This thesis aims to increase our insights of the efficacy and adverse events of SEMS therapy.

SEMS for malignant esophageal obstruction

In **Chapter 2** we describe a general overview of the current knowledge on SEMS in esophageal disease. Various types of esophageal SEMS are currently available worldwide [5]. Although the basic principle of all SEMS is more or less the same, differences exist in construction, material, shape, diameter and other features [6]. Although a substantial number of studies on SEMS have been published in the last decennia, most knowledge is derived from uncontrolled trials evaluating technical feasibility and efficacy of one particular SEMS. For malignant dysphagia, the number of randomized trials on clinical outcome is limited. In general, all SEMS are effective in providing rapid relief of malignant dysphagia. The radial expansion of all SEMS is sufficient to restore luminal patency on the short term. However, on the long-term recurrent obstruction due to SEMS dysfunction may occur [7]. In **Chapter 3** we report the results of a retrospective analysis of 1011 patients who underwent esophageal SEMS placement for malignant esophageal disease over a time span of more than two decades. Despite the introduction of new types of SEMS, the incidence of re-obstruction has not improved over the years. Overall recurrent obstruction remained unchanged over time at approximately 30%. Significant tumor in- and overgrowth was the most common cause for recurrent obstruction, occurring in 13.7%, followed by migration in 11.4%, food occlusion in 7.1% and other causes in 1.2% of patients. Migration rate increased over time and was associated with a fully covered (FC) SEMS design (HR 1.65, 95% CI 1.10-2.49, p=0.02) and smaller (up to 20 mm) diameter SEMSs (HR 4.30, 95% CI 1.05-17.72, p=0.04). That FC SEMS are associated with an

increased migration risk was also demonstrated in a retrospective study [8]. In our study, we have shown that occurrence of tumor growth was almost decreased by half for FC SEMS (HR 0.60, 95% CI 0.40-0.90, p=0.01). Importantly, this beneficial effect seems to outweigh the drawback of migration, as the risk of all-cause recurrent obstruction was diminished for a FC SEMS (HR 0.77, 95% CI 0.61-0.98, p=0.03). This is relevant information and favors the use FC SEMS in malignant esophageal disease. However, our results should be interpreted with some caution due to the retrospective nature of our study. In addition, information on the specific location of tumor growth, either in- or overgrowth, was unavailable. A previous randomized trial demonstrated that partially covered SEMS are superior to uncovered SEMS with less obstructive ingrowth [9]. In order to clarify whether extending the covering to the whole SEMS length is truly beneficial, we conducted a randomized controlled trial comparing a PC with a FC SEMS of which results are reported in **Chapter 4**. Ninety-eight patients with malignant dysphagia were included in this study. Recurrent obstruction was the primary outcome measure and patients were followed until death, second SEMS insertion or SEMS removal. The strength of this study was that both SEMS were identical in design with the exception of the length of covering. The PC SEMS was designed with a silicone covering attached on the inner side of the body of the stent, leaving both flares uncovered. In contrast, the covering of the FC SEMS extends over the entire length of the stent, including both flares. The Wallflex PC and FC SEMS (Boston Scientific) were used for the purpose of this study, which is a relatively new type of esophageal SEMS. We found that the overall rate of recurrent obstruction was similar between both SEMS (FC SEMS 18%, PC SEMS 22%, p=0.65). Thus, the length of covering doesn't seem to matter for this specific brand of SEMS. Both the PC and FC SEMS (Wallflex, Boston Scientific) can be considered for palliative treatment of malignant esophageal obstruction. It is evident that extension of the covering is beneficial to reduce ingrowth through the meshes. However, potential disadvantages, such as tissue overgrowth and migration ought to be minimized for FC SEMS to be more favorable than PC SEMS. Tissue overgrowth over the edge of the flare can be caused by malignant tumor growth or benign reactive tissue hyperproliferation. Although malignant tumor overgrowth may happen when a SEMS too short in length is placed, it is usually related to rapid progression of the disease, independent of the type of SEMS. In contrast, benign reactive tissue growth only develops in the presence of a SEMS [10]. Although the exact pathogenesis still remains to be elucidated, it is a known fact that a hyperproliferative tissue reaction may occur when a foreign body is present. The severity is probably dependent on the type of material, as well as contact-surface, -force and –duration. At present, the optimal construction and design to prevent reactive tissue formation is unknown. Recently, more insight has gained in the radial and axial force patterns of the available esophageal SEMS [11]. A high axial force pattern could be one of the factors that plays a role in the occurrence of tissue overgrowth. In such case one side of the flare presses firmly in the esophageal wall which may result in more tissue reac-

tion. Therefore, we believe that SEMS with a low axial force profile with flares more in line with the contour of the esophageal wall, are more favorable. For the same reasons, larger diameter flares may only increase tissue reaction and may not be preferred. The Wallflex SEMS used in our randomized trial has a relatively high axial force and is designed in a dog-bone shape. Both features may cause this SEMS to be more prone to tissue overgrowth. Indeed, we noticed several cases of overgrowth in the FC Wallflex SEMS group in which the flare was pressed in the esophageal wall. It should be mentioned that the data to support these considerations is limited and more studies are needed for better understanding.

Migration is another drawback of FC SEMS and has been described in up to 35% in observational studies, usually occurring downwards [12-18]. We found a relatively low FC SEMS migration in our randomized study, corresponding to previous reports on the Wallflex SEMS with rates of approximately 10% [16, 17]. This might be related to the effective anti-migration features of this particular SEMS, including a dog-bone shape and a covering overlying the inner side of the metal framework. Several other endoscopic techniques have been investigated to resist dislocation. Larger-diameter SEMS have been associated with less migration, but might be more prone to major complications, such as fistula [7, 19, 20]. Other integrated features include larger diameter flares, outer struts, rings or flaps [12-14, 18]. It is hard to say whether these techniques are truly beneficial in preventing dislocation, since controlled trials are lacking. An alternative approach is the application of anchoring devices, such as over-the-scope clips and sutures, to fixate the SEMS to the esophageal wall [21-23].

SEMS-related adverse events, other than SEMS dysfunction, are frequently encountered. Adverse events after SEMS placement are often hazardous for patients and can sometimes be fatal. In **Chapter 3** the frequency of adverse events after 1011 palliative SEMS insertions is described over a 23 year period. This study demonstrates that the overall incidence of adverse events is considerable, almost 50%, including 20.6% major adverse events. Major complications include perforation, hemorrhage, pneumonia, fistula, fever and pressure necrosis. We noticed that the incidence of major complications has declined up to 2009, mainly due to a lower occurrence of perforation and hemorrhage. Omitting pre-SEMS dilation has probably contributed to a reduced perforation incidence. In addition, hemorrhage was associated with distal tumors and over time a shift was noted towards more proximal tumors being stented. After 2009, however, the rate of major complications increased. Not new SEMS related features, but enhanced patient vulnerability seems to be responsible. The use of prior chemoradiotherapy has intensified after 2009 and this was recognized as the only significant risk factor for major complications (HR 1.83 [95% CI 1.19-2.81]. The effect of chemo- and radiotherapy prior to SEMS placement has been a matter of debate. Although some studies have denied an association with the occurrence of adverse events [19, 24-26], our results are in line with more recent data showing a higher risk in pretreated patients [27-30]. In our analysis a signifi-

cant association was seen in patients who have undergone both chemo- and radiotherapy, indicating that these patients are more prone to SEMS related complications. This also suggests a cumulative toxic effect of both treatment modalities as the association did not hold for either treatment alone. Especially pulmonary infections were more commonly seen after chemoradiotherapy. Possible mechanism include pulmonary toxicity leading to diminished respiratory tract cleaning and immunosuppressive status [31]. The negative influence of previous chemoradiotherapy is also illustrated in **Chapter 5**. Here we describe the outcome of 13 patients who underwent palliative SEMS placement for malignant dysphagia after definitive chemoradiotherapy. In recent years, definitive chemoradiotherapy has become a curative alternative in patients both with an irresectable locally advanced (T4) carcinoma as well as in patients who are unfit for surgery due to co-morbidity [32-34]. In this series, major adverse events were frequently encountered, occurring in 7 out of 13 patients (54%). The majority of these events were related to pulmonary infections or tracheal- or aortic-fistula. It seems that especially tumors invading surrounding structures (T4) are at risk for esophago-respiratory or –aortic fistula. This is probably caused by continuous stent pressure on a vulnerable esophageal wall due to radiation-induced ischaemic changes. It is known that the toxicity of radiotherapy is dose-dependent and we presume that the relatively high external radiotherapy dose of 50.4 Gy induces an even more deleterious effect. The relation between previous radiotherapy and stent-related esophago-respiratory fistula has also been demonstrated in a recent case-control study [27]. In this study, also a trend towards a dose-dependent relation was reported. However, statistical significance was not reached, probably due to a relatively small number of subjects with fistula.

Pain is one of the most devastating symptoms in incurable patients. In our 23-year retrospective analysis (**Chapter 3**) we noticed that postprocedural pain seems to be more frequently encountered over the years. The rate increased from approximately 25% to almost 50% in the 2 most recent time periods (2010-2017). Whether this observed increase is related to under-reporting in the past is uncertain, but pain has never been the primary focus of interest in past studies evaluating outcome after SEMS insertion. In **Chapter 6** we describe a two-week prospective evaluation of pain experience in 65 patients with malignant esophageal disease. We noticed that two-thirds of patients develop significant pain after SEMS placement with a concomitant increase of analgesic use, including opiates. Although the severity of pain seems to decline after the first day, more than 30% of patients were still in need of opiates after the two weeks. Our results outline the importance of proper pro-active pain management, especially shortly after SEMS placement. Information and instructions should be provided to every patient undergoing palliative SEMS treatment. In addition, health care providers should be easily accessible to prescribe analgesics if needed. Pain probably has a multifactorial etiology, including patient- and SEMS-characteristics. In this study we were unable to identify risk factors for the development of significant pain, most probably due to a small cohort size. Remarka-

bly, we observed a relatively high rate of severe pain after SEMS placement in our randomized trial comparing PC versus FC SEMSs (**Chapter 4**). Almost 20% of patients experienced retrosternal pain and in the majority hospital admission and opiates were required. The Wallflex SEMS was used in this study and similar findings on this particular SEMS have been reported in previous studies [16, 35]. This SEMS has a dog-bone shape and exerts a high axial force. These particular features could be of potential influence on for pain development after SEMS deployment and deserve further investigation.

SEMS for malignant gastric outlet obstruction

Multiple types of duodenal SEMS are available worldwide. Although the basic principle is similar, differences exist in construction, material and deployment system. In **Chapter 7** we describe the clinical outcome of a new duodenal uncovered SEMS (Evolution SEMS, Cook Medical) in a large prospective cohort of 108 patients with malignant gastric or duodenal strictures. This SEMS is made from nitinol providing flexibility, has flared ends as anti-migration feature, and a small cell size to withstand ingrowth. In addition, the deployment system includes a recapture mechanism to facilitate correct positioning. Successful technical deployment of the SEMS was achieved in 99.1%. Clinical success after 14 days with a relief of obstructive symptoms and/or improvement of oral intake was experienced in 85% of patients. A gradual decline in SEMS patency was seen over time with SEMS dysfunction occurring in 17% of patients. In most patients occlusion was caused by tumor ingrowth through the meshes of the SEMS and most cases were successfully managed with an additional SEMS. The only other SEMS-related adverse event was gastrointestinal hemorrhage occurring in 3.7%. The clinical results from this study are in accordance with earlier studies, indicating that this SEMS is generally safe and effective for malignant outlet obstruction [4, 36-38]. However, this study does not prove its superiority over other SEMS available. Considering the published results of duodenal stenting of the last two decades, it becomes clear that an improvement in SEMS performance is hard to achieve. One can assume that not only SEMS-related factors but also certain patient and tumor characteristics are involved in the pathogenesis of SEMS dysfunction.
The knowledge on the influence of patient-related factors on SEMS dysfunction is limited. Only a few studies are available, of which the results are difficult to interpret and to compare [39-43]. Most reports lack uniformity with heterogeneity in the study population and the use of different sets of variables. In our prospective cohort study (**Chapter 7**) we could not identify any patient- or disease related factors associated with stent dysfunction. However, only a few variables were considered for analysis. Some studies have suggested that rapid progression and an advanced stage of disease may put patients at a higher risk of SEMS dysfunction. SEMS overgrowth was found to be associated with presence of bile duct stenosis and liver metastasis [43], while on the other hand

palliative chemotherapy and a longer time to disease progression improve stent patency [39, 41, 42].

Little is known about the influence of specific SEMS features and the development of SEMS dysfunction for malignant gastric outlet obstruction. Several characteristics could be relevant, including length, diameter and shape of the SEMS, material and structure of the wires, size of the cells between the wires, axial and radial forces, and the presence of a covering. The difficulty is that it is almost impossible to evaluate the impact of each of these features separately. Clinical outcome of new SEMS designs are generally evaluated in single-arm prospective studies and the number of randomized trials is limited. To our knowledge, the covering of the SEMS is the only characteristic of which the effect has been assessed in comparative studies [44-46]. Overall SEMS patency seems similar, but patterns of dysfunction were different. While covered SEMS are able to prevent ingrowth, they are associated with migration more frequently. Various anti-migration features have been developed in order to prevent dislocation. In **Chapter 8** we describe the clinical outcome of a newly developed covered duodenal SEMS with two distinct anti-migration features: a double flare shaped design and uncovered ends. It was hypothesized that these two features result in better adhesion of the SEMS to the enteral wall. Indeed, SEMS migration was seen in only 1 of 9 patients. However, the study was prematurely ended due to mechanical failure of the SEMS with broken struts occluding the lumen in three of the nine included patients. Due to the small patient group, the value of the applied anti-migration features still remains to be determined. The reason for SEMS failure and breakage of the struts is still unclear, but could be related to insufficient physical durability, strong peristaltic enteral movements, and/or acid corrosion. In contrast to the esophagus, the lumen in the distal stomach and especially the proximal duodenum run an angulated course and stents are subjected to forceful peristaltic contractions. It seems worthwhile to perform a new clinical trial using a covered SEMS with the same anti-migration features, but with a durable and flexible framework. Mechanical fixation of the SEMS to the enteral wall has been proposed as an alternative solution to prevent dislocation. In malignant gastric outlet obstruction only the experience of standard through-the-scope (TTS) clips has been described, showing promising results in a prospective series of 25 patients [47]. The disadvantage is that TTS clips only grasp small and superficial tissue, which will probably not provide long-lasting fixation. Using over-the-scope-clips or suturing devices could potentially be more beneficial. These techniques seem to provide better fixation of SEMS in esophageal disease, but have never been tried for duodenal SEMS [21-23].

Conclusions and future perspectives

SEMS placement is currently an established palliative treatment for malignant upper gastrointestinal strictures with an excellent ability to restore luminal patency. This thesis shows that, despite technical developments and increasing experience, recurrent obstruction and other SEMS-related adverse events after esophageal SEMS insertion are still a major concern. Although modifications of SEMS design over the past decades were intended to be beneficial, increasing treatment efficacy and reducing adverse events have shown to be challenging. We demonstrated that covered SEMS are superior over uncovered SEMS, mainly due to less ingrowth. However, we could not show a beneficial effect of fully covered esophageal SEMS compared to partially covered SEMS in malignant dysphagia. Recurrent obstruction was related to complications other than ingrowth, such as overgrowth and migration, for which further stent design refinements need to be developed. However, little is known about the clinical consequences of other distinctive SEMS modifications and further research is indicated. It must also be taken into account that the type of patients that receive a SEMS is changing. In particular, the observation that more patients have been exposed to chemo- and/or radiotherapy is relevant. Major complications are seen more often, especially when both chemo- and radiotherapy have been applied. This mainly concerns pulmonary infections and fistula formation, probably due to the chemoradiotherapy-related esophageal and pulmonary injury, and continuous pressure of the SEMS. SEMS with a low pressure profile and less flared shape seem better suited in these circumstances and we believe this hypothesis deserves further investigation. In this thesis we also highlight the importance of retrosternal pain after SEMS placement which occurs more often than previously assumed. Adequate instruction and pro-active pain management are recommended, especially in the first days.

Technical adjustments have also been applied with regards to SEMS for malignant gastric outlet obstruction. However, this has not led to a significant reduction of SEMS-related adverse events. Nevertheless, this thesis demonstrates good clinical efficacy and an acceptable safety profile of a new uncovered duodenal SEMS within a large study population. Prospective registration and publication of the application of new devices is recommended. This may reveal potential technical shortcomings at an early stage as was seen in a clinical evaluation of a new partially covered duodenal SEMS. In multiple patients broken struts were encountered, which prompted for discontinuation of the trial. Although duodenal SEMS covering seems to prevent ingrowth, the benefit of anti-migration features remains to be established.

Technology in the field of SEMS therapy is continuously evolving. Future innovations to suppress tumor or tissue growth include drug-eluting stents and stents with the ability to release photothermal energy [48, 49]. These more advanced developments are to be encouraged. However, our knowledge of the mechanistic behaviour of metal stents in relation to anatomy and clinical outcome is still not fully evolved and deserves continued

investigation. Ideally, the effect of a single modification to a particular stent design should be established in preclinical testing before introduction in humans. The lack of access to representative animal or in vivo models is however challenging. Controlled trials on distinct SEMSs, preferably in a randomized fashion, should therefore be promoted. It is evident that combining efforts through multicenter collaborations is crucial in order to include a sufficient number of patients to provide strong scientifically sound recommendations. In addition, a more accurate assessment of the risk profile based on patient-related characteristics is needed. This should ultimately lead to individually based SEMS therapy to ensure an optimal clinical outcome.

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Appendix

Nederlandse samenvatting

Introductie

Kwaadaardige vernauwing, ook wel maligne obstructie genoemd, van het bovenste maag-darmkanaal is meestal een teken van kanker in een gevorderd stadium. Hierin kunnen twee groepen worden onderscheiden. De eerste groep bestaat uit maligne obstructie van de slokdarm en cardia, resulterend in klachten van dysfagie. De tweede groep bestaat uit maligne obstructie van distale maag en duodenum, ook wel maaguitgangsstenose genoemd, leidend tot klachten van braken. Wanneer genezing niet meer kan worden bereikt is adequate palliatie van deze klachten van essentieel belang. Hierin hebben endoscopisch ingebrachte zelf-ontplooiende metalen stents een belangrijke rol. Het is bekend dat deze minimaal invasieve behandeling tot snelle klachtenvermindering leidt door een verbeterde doorgang. Echter, na stentplaatsing kan terugkeer van obstructieve klachten optreden. Dit wordt met name veroorzaakt door weefselgroei door of over de mazen van de stent, stentmigratie en voedselimpactie in de stent. Ondanks dat het merendeel van deze complicaties effectief kan worden behandeld met een hernieuwde endoscopische interventie heeft het optreden nadelige consequenties op de kwaliteit van leven. Daarnaast zijn ook andere complicaties van gastro-intestinale stents bekend, zoals perforatie, fistelvorming, pijn, bloeding en luchtweginfecties. Op het gebied van stentontwerp zijn continue ontwikkelingen gaande om de uitkomst te verbeteren, met name gericht op het verminderen van terugkeer van obstructieve klachten na stentplaatsing.
In dit proefschrift wordt het klinische effect van nieuwe ontwikkelingen op gebied van stentontwerp beoordeeld bij patiënten met een maligne obstructie van het bovenste maag-darmkanaal. Ook wordt beoogd meer inzicht te krijgen in het optreden van complicaties na stentplaatsing. Hoofdstuk 2 t/m 6 zijn gewijd aan stents voor maligne obstructie van slokdarm en cardia, terwijl hoofdstuk 7 en 8 ingaan op stents voor maligne maaguitgangsstenose.

Belangrijkste resultaten

In **hoofdstuk 1** wordt een algemeen overzicht gegeven van maligne obstructie van het bovenste maag-darmkanaal. Hierin wordt ingegaan op incidentie, klinische presentatie en verschillende behandelmogelijkheden van zowel maligne obstructie van de slokdarm en cardia, als ook maligne maaguitgangsstenose. De huidige kennis omtrent het klinische effect en de complicaties van de verschillende stents wordt besproken. Na het vaststellen van de hiaten worden de doelen van dit proefschrift geformuleerd. Samengevat wordt beoogd het effect te evalueren van nieuwe ontwikkelingen om terugkeer van obstructie

na stentplaatsing te verminderen. Daarnaast wordt getracht meer inzicht te verkrijgen in stent-gerelateerde complicaties en risicofactoren hierop.

Hoofdstuk 2 is een uitgebreide beoordeling van de huidige literatuur over slokdarmstents bij zowel maligne als benigne aandoeningen. Metalen stents hebben een vooraanstaande rol in de palliatieve behandeling bij maligne ziekte, zowel bij een obstructieve als fistelende presentatie. Er zijn meerdere stents beschikbaar, welke o.a. verschillen in materiaal, vorm, omvang en bekleding. Alle stents zijn in staat om snel de klachten te doen verbeteren. Ook is aangetoond dat ingroei door de mazen kan worden voorkomen door de stent te bekleden met een plastic laag. Desondanks treedt bij ongeveer een derde van de patiënten terugkeer van obstructie op met noodzaak tot herhaalde endoscopische interventie. Er lijkt geen verschil in klinische uitkomst te bestaan tussen de beklede stents, alhoewel het aantal vergelijkende studies beperkt is. Er zijn specifieke eigenschappen ontwikkeld die migratie van beklede stents tegengaan, zoals een brede diameter, wijde uiteinden, onbeklede gedeelten en aan buitenzijde van de stent aangebrachte ringen. Ondanks dat deze maatregelen migratie mogelijk kunnen verminderen lijkt traumatische schade aan de slokdarm een risico te zijn. Overige ernstige complicaties na stentplaatsing zijn pneumonie, perforatie, fistelvorming, bloeding en retrosternale pijn en treden op in 30-35% van de patiënten. Bij benigne aandoeningen van de slokdarm hebben stents een minder prominente rol. Stents worden toegepast bij benigne refractaire stricturen, maar de lange termijn resultaten zijn matig en ernstige complicaties komen voor.

In **hoofdstuk 3** wordt de klinische uitkomst beschreven van slokdarmstents voor maligne aandoeningen over een tijdsperiode van 23 jaar. Met alle nieuwe technische innovaties is het belangrijk om na te gaan of dit heeft geresulteerd in een verbetering op gebied van effectiviteit en veiligheid. In totaal zijn 1011 patiënten retrospectief geanalyseerd bij wie een slokdarmstent is geplaatst tussen 1994 en 2017. Dit is het grootste geanalyseerde cohort tot nu toe. In de loop der jaren is het percentage patiënten dat behandeld is met chemo- en/of radiotherapie vooraf aan de stent plaatsing toegenomen. Ook neemt het aandeel proximale slokdarmtumoren toe en worden verschillende type stents gebruikt over de tijd. Terugkeer van obstructie werd gezien in 31.1% en dit percentage blijft onveranderd over de jaren. Het risico op migratie neemt toe in de loop van de jaren (HR 1.04 per 1-jaar toename). Risicofactoren voor migratie zijn volledige bekleding en reguliere diameter (t/m 20 mm) van een stent. Daarentegen vermindert een volledig beklede stent het optreden van tumor groei. Als we kijken naar terugkeer van dysfagie klachten, dan zien we dat een volledig beklede stent het beter doet. Dus het verlagen van het risico op tumor groei is groter dan het verhoogde risico op migratie. Overige stentgerelateerde bijwerkingen traden op in 46% (n=465), waarvan 20.6% (n=208) ernstige complicaties. Tot aan 2009 wordt een daling gezien in het aantal ernstige complicaties.

Dit lijkt te worden veroorzaakt door een vermindering in aantal perforaties en bloedingen. Na 2009 neemt het aantal ernstige complicaties weer toe. Eerdere chemoradiotherapie lijkt hiervoor verantwoordelijk. Deze voorbehandeling werd vanaf 2009 steeds meer toegepast en is ook geassocieerd met het optreden van ernstige complicaties. Deze resultaten laten belangrijke trends zien over de loop der tijd en tonen aan dat verbetering van stent behandeling nog steeds zeer gewenst is.

Ondanks dat is aangetoond dat bekleding van de stent resulteert in minder terugkeer van obstructie, was het tot op heden onduidelijk welke mate van bekleding het meest efficiënt is. In **hoofdstuk 4** wordt de eerste gerandomiseerde multicentrische studie beschreven waarin een partieel beklede (PB) metalen stent wordt vergeleken met een volledig beklede (VB) versie in de palliatieve behandeling van dysfagie. Deze studie laat zien dat er geen verschil is tussen beide stents in stent-gerelateerde terugkeer van obstructie. Hiervoor zijn in totaal 97 patiënten behandeld met een PB (n=49) of VB (n=48) Wallflex stent® (Boston Scientific) en vervolgd voor maximaal 6 maanden. De VB stent is over de gehele lengte aan de binnenzijde bekleed met een siliconen laag, terwijl beide uiteinden van de PB stent onbedekt zijn. Terugkeer van obstructie trad op in 22% na PB stent en in 18% na VB stent (p=0.65). Er werden geen significante verschillen gezien in tumorgroei en migratie. Ook de tijdsduur zonder re-obstructie was gelijk tussen beide stents. Verder werd geen verschil gezien in het aantal patiënten met ernstige complicaties, 46% in de PB stent en 37% in VB stent groep (p=0.34). Ook kwaliteit van leven parameters waren gelijk tussen beide stents over de geanalyseerde periode. Deze resultaten tonen aan dat de afmeting van stentbekleding geen invloed heeft op de klinische uitkomst. Beide stents kunnen gebruikt voor maligne stricturen van slokdarm en cardia.

Definitieve chemoradiotherapie (CRT) is een curatieve behandeling voor slokdarmcarcinoom, die met name toegepast wordt bij irresectabel lokaal doorgegroeide kanker (T4) of bij patiënten die geen operatieve behandeling kunnen of willen ondergaan. Indien er na CRT sprake is van obstruerend recidief in de slokdarm is stentplaatsing over het algemeen de enige overgebleven palliatieve behandeling. In **hoofdstuk 5** worden de klinische uitkomsten hiervan gerapporteerd bij 13 patiënten die retrospectief zijn onderzocht. Er lijkt een relatief hoog risico op ernstige complicaties te bestaan bij deze patiëntengroep. Eerdere behandeling bestond uit externe radiatie met een cumulatieve dosis van 50.4 Gy gecombineerd met carboplatin en paclitaxel. Stents werden ingebracht na een mediane tijd van 375 dagen na eerdere CRT. Ondanks dat dysfagie in alle patiënten adequaat kon worden verholpen, werden 8 ernstige complicaties gezien in 7 patiënten (54%). Deze complicaties bestonden uit pneumonie (n=4), tracheosophageale fistel (n=2), fatale bloeding (n=1) en ernstige retrosternale pijn (n=1). Het is mogelijk dat CRT-gerelateerde pulmonale toxiciteit van invloed is in het ontstaan van pneumonie. Bovendien kan de relatief hoge radiatie dosis de slokdarmwand kwetsbaarder maken voor de

nadelige effecten van expansie van de stentuiteinden. Mogelijk dat dit resulteert in een hoger risico op fistelvorming. Ondanks dat de studiepopulatie klein is, suggereren deze resultaten dat een hoger complicatie-risico te verwachten is na eerdere behandeling met CRT. Patiënten dienen daar geïnformeerd over te worden.

Retrosternale pijn is een gekende complicatie van stentplaatsing in de slokdarm. Tot op heden is echter de kennis omtrent het vóórkomen en de behandeling hiervan beperkt. In **hoofdstuk 6** wordt hier aandacht aan gegeven. In een prospectieve studie is pijnbeleving op gestandaardiseerde manier beoordeeld gedurende 2 weken na stentplaatsing voor een palliatieve indicatie. Hieruit blijkt dat pijn een veelvoorkomend probleem is en dat dit meer optreedt dan eerder werd aangenomen. Pijnintensiteit werd dagelijks gerapporteerd volgens de numerieke rating schaal bij 65 patiënten. Significante pijn, gedefinieerd als een pijn score ≥ 4, was het meest frequent (60%) op de eerste dag. Hierna daalde het aantal patiënten tot 25% na 2 weken. Een gelijke trend werd waargenomen in het gebruik van analgetica, zowel in paracetamol als opiaten gebruik. Op dag 1 behoefte 78% van de patiënten pijnstillende medicatie en na 2 weken was dit percentage 62%. Deze resultaten tonen aan dat patiënten nauwlettend moeten worden vervolgd, met name kort na stentplaatsing. Zodoende kan adequate behandeling snel worden ingesteld. Risicofactoren voor het optreden van pijn konden niet worden gevonden. Om hier in de toekomst een uitspraak over te doen zal een grotere studiepopulatie nodig zijn.

Voor de behandeling van maligne uitgangsstenose zijn meerdere metalen stents beschikbaar. Ondanks dat de basale constructie en werking van deze stents gelijk is, zijn er wel verschillen aanwezig, onder andere in ontwerp, materiaal en inbrengsysteem. In **hoofdstuk 7** worden de klinische uitkomsten beschreven van een nieuwe metalen stent. De Evolution stent ® (Cook Medical) is een onbeklede stent die wordt gekenmerkt een kleine celmaat, wijde uiteinden en een uniek inbrengsysteem met terughaalfunctie. In een internationale multicentrische studie werden 108 patiënten behandeld met deze stent en prospectief vervolgd. In het overgrote merendeel van de patiënten verbeterden obstructieve klachten snel. Op basis van klinische presentatie en/of endoscopische beoordeling kon worden gesteld dat na 2 weken de stent doorgankelijk was bij 95% van de patiënten. Technisch succespercentage met correcte plaatsing was 99.1%. Het aantal stent-gerelateerde complicaties was acceptabel en gelijk met de resultaten uit eerdere studies. Obstructieve tumorgroei trad op in 15% van de patiënten en was de meest voorkomende oorzaak van terugkeer van obstructie. Stentmigratie werd gezien in 2% van de patiënten. Voor beide complicaties werd in het merendeel hernieuwde endoscopische interventie uitgevoerd. Deze bevindingen laten zien dat deze metalen stent effectief en veilig kan worden beschouwd voor de palliatieve behandeling van maligne maaguitgangsstenose.

Zoals ook in hoofdstuk 7 wordt beschreven is groei van tumorweefsel door de mazen van de stent heen de meest frequente reden voor terugkeer van obstructie bij maligne uitgangsstenose. Bekleding van deze stents, zoals dit ook bij slokdarmstents gedaan wordt, kan hiervoor een oplossing bieden. Een hoger migratie risico is echter een nadeel hiervan. **Hoofdstuk 8** is gewijd aan de klinische ervaring met een nieuwe beklede duodenumstent. De HANAROSTENT ® Duodenum/Pylorus (M.I.Tech) is een partieel beklede metalen stent waarvan alleen het centrale deel bekleed is. Daarentegen zijn beide uiteinden van de stent onbekleed en tevens wijd uitlopend om migratie tegen te gaan. Een prospectieve studie was opgezet om 25 patiënten met maligne uitgangsstenose te includeren. Na inclusie van 9 patiënten is echter om veiligheidsredenen besloten de studie voortijdig te staken. In 3 patiënten werd in-stent obstructie gezien welke veroorzaakt werd door gebroken metalen draden die in het lumen staken. Deze ongebruikelijke bevinding geeft aan dat de duurzaamheid van de metalen constructie zeer waarschijnlijk onvoldoende is. Wanneer verbeteringen in constructie zijn aangebracht, verdient de partiele bekleding in combinatie met bovengenoemde anti-migratie maatregelen hernieuwde analyse in een toekomstige prospectieve studie.

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Endoscopic SEMS placement in recurrent esophageal cancer after high-dose concomitant chemoradiotherapy. *Poster presentation Digestive Disease Week, Chicago, USA, 2011*

Palliation of anastomotic obstruction using self-expandable metal stents in recurrent gastric or pancreatic cancer. *Poster presentation Digestive Disease Week, New Orleans, USA, 2010*

Improving the quality of the pre-operative work-up of patients with esophageal carcinoma: implementation of a fast-track staging protocol. *Poster presentation Digestive Disease Week, Chicago, USA, 2009*

Presentations at national conferences

Recognition of T1 colorectal cancer – malignant polyp. *Netherlands Society of Gastroenterology (NVGE), Veldhoven, 2016*

T1 tumors of the digestive tract – malignant polyp. *Rotterdam, 2015*

Review of the GI year in motility disorders. *Amsterdam, 2015*

Ablation of Barrett's esophagus. Rotterdam, 2014

Radiofrequency ablation of Barrett's esophagus. *Advanced Therapeutic Endoscopy Live porcine model Hands-on EMR and ESD workshop, Rotterdam 2014*

Radiofrequency ablation of Barrett's esophagus. *Advanced Therapeutic Endoscopy Live porcine model Hands-on EMR and ESD workshop, Rotterdam 2013*

Review of the GI year in motility disorders. *Amsterdam, 2013*

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List of publications

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Curriculum Vitae

Paul Didden werd geboren op 19 maart 1981 te Dordrecht en is opgegroeid in Delft. In 1999 deed hij eindexamen Gymnasium op het Stanislas collega in Delft. Hierna begon hij aan de studie geneeskunde aan de Universiteit Leiden. In 2004 behaalde hij zijn doctoraal diploma, nadat hij zijn afstudeeronderzoek had afgerond op de afdeling Maag-, darm-leverziekten. Na het behalen van het arts-examen in 2006 was hij werkzaam als AGNIO interne geneeskunde in het Medisch Centrum Haaglanden. In 2007 begon hij de opleiding Maag-, darm-, leverziekten in het Erasmus Medisch Centrum (opleider Prof.dr. R.A. de Man). Gelijktijdig startte hij met promotieonderzoek onder begeleiding van prof. dr. M.J. Bruno en dr. M.C.W. Spaander. Na de opleiding te hebben afgerond in april 2013, begon hij als MDL-arts in het Erasmus Medisch Centrum met als aandachtsgebied interventionele endoscopie. In 2016 maakte hij de overstap naar het IJsselland ziekenhuis, waar hij een half jaar werkzaam is geweest. Op dit moment is hij MDL-arts in het Universitair Medisch Centrum Utrecht.