STENTING ESOPHAGEAL DISEASE

NICOLINE C.M. VAN HEEL

Stenting Esophageal Disease

Nicoline C.M. van Heel

Cover: Elly Hemmes
Layout and printing: Optima Grafische Communicatie, Rotterdam, The Netherlands

The work presented in this thesis was conducted at the Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, The Netherlands.

Financial support for printing this thesis was kindly given by the Department of Gastroenterology and Hepatology, Erasmus University Medical Center Rotterdam, Nederlandse Vereniging voor Gastroenterologie, Abbott Immunology B.V., Zambon Nederland B.V., Roche Nederland B.V., Olympus Nederland B.V., UCB Pharma B.V., Ferring B.V., Cook Medical, MSD, Pentax Nederland B.V., Abbott Products B.V., Boston Scientific Nederland B.V., Dr. Falk Pharma Benelux B.V., J.E. Jurriaanse Stichting, Vifor Pharma Nederland B.V.

Stenting Esophageal Disease

Stenttherapie bij slokdarmaandoeningen

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. dr. H.G. Schmidt
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
donderdag 22 december 2011 om 11:30 uur

door

Nicoline Carolina Maria van Heel

geboren te Leusden

PROMOTIECOMMISSIE

Promotor:	Prof. dr. E.J. Kuipers
Overige leden:	Prof. dr. H.W. Tilanus
	Prof. dr. M.J. Bruno
	Prof. dr. J.F.W.M. Bartelsman

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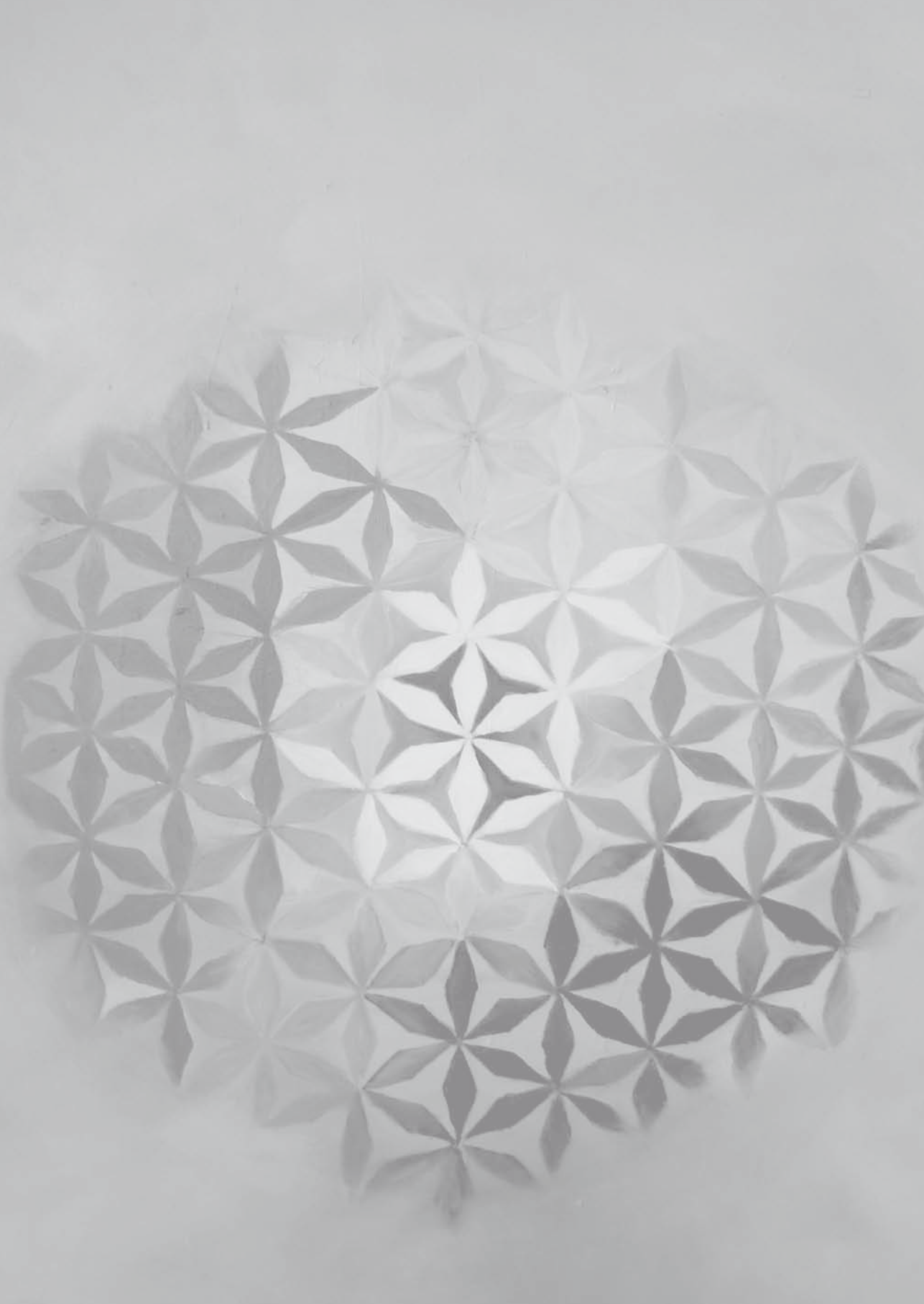

Chapter 1

Introduction and outline of the thesis

INTRODUCTION

In 1885, Charles Symonds placed the first rigid endoprosthesis across a malignant esophageal stricture.[1] With the introduction of the fiberoptic endoscope and the development of the rigid Celestin tube nearly one century later, the revolution was initiated.[2] Over the past 2 decades, esophageal stents have drastically improved. Prior to 1990, stents were made from rigid polyvinyl plastic or rubber. These prostheses were able to restore luminal patency, however placement was difficult and bleeding, pain, and perforations frequently occurred.[3] In the early nineties, rigid endoprostheses were replaced by uncovered self-expandable metal stents (SEMS). SEMS placement appeared to be less invasive, provided wider lumen, and was associated with fewer complications. However, new problems soon appeared.[4-5] Through the uncovered mesh tumor ingrowth frequently occurred, leading to recurrent dysphagia shortly after placement. To impede tissue ingrowth, SEMS were modified with a plastic or silicone layer in the middle of the endoprosthesis.[6-8] These partially-covered SEMS (PCSEMS) were not only able to re-open a blocked esophagus, but also sealed malignant esophagorespiratory fistulae. In 2001, removable fully covered metal stents (FCSEMS) and plastic stents (SEPS) were introduced. The ability to remove these stents after deployment has opened up new applications, such as the insertion of a stents as a temporary device in patients with benign esophageal fistulae or stenosis and to bridge chemo- and radiotherapy in patients with malignant esophageal disease.[9-10] Initial results were suboptimal as well. Fully-covered expandable stents were associated with a higher migration rate. SEMS are generally preloaded in a thin delivery catheter, yet FCSEPS require being loaded onto the significantly larger and stiffer delivery device.[11-12] Various stent designs are shown in Figure 1.

Figure 1. Current generation covered self-expandable stents.
Left to right: Ultraflex stent, Evolution stent, Hanarostent, Polyflex stent.

Esophageal stents in malignant disease

Esophageal cancer represents one of the most lethal malignancies worldwide. The incidence of esophageal carcinoma is rising rapidly in developed countries because of an increase in the frequency of adenocarcinoma, at a rate exceeding that of any other neoplasm.[13] The most common symptom of esophageal cancer at the time of presentation is dysphagia. Malignant dysphagia is defined as difficulty in swallowing due to stenosis of the esophageal lumen, and correlates with more than 50% occlusion of the esophageal lumen. Sialorrhea is a devastating symptom associated with esophageal obstruction. The rapid accumulation of saliva and regurgitation is a common complaint that causes daytime misery with frequent spitting, as well as insomnia and the increased risk of aspiration pneumonia. The majority of patients have incurable disease at the time of diagnosis because of distant metastases, locally advanced disease or their poor medical condition.[14-15] The palliative management of patients with a malignant esophageal obstruction is a clinical challenge. General supportive care, relief of pain, and restoration of adequate nutritional status, are all essential components of optimal therapy. The gastroenterologist has to balance the benefits of restoring luminal patency by SEMS on patients' quality of life in the context of a short life-expectancy, with the risk of procedural complications and the burden of reinterventions. Although chemotherapy and radiotherapy are sometimes beneficial, they may require several weeks to improve dysphagia.[16] Generally, a more rapid relief of dysphagia is desired. Currently, SEMS placement is the most widely used palliative treatment in patients with malignant dysphagia.[17] Adequate placement immediately restores luminal patency and thereby improves oral intake and quality of life.[18-20]

Esophageal stents in benign disease

Benign esophageal leaks comprise asset of life-threatening conditions that require early recognition and aggressive management. Lesions include iatrogenic perforations, anastomotic leaks after surgery, and transmural tears due to Boerhaave's syndrome.[21-23] The mortality rate of esophageal perforation is reported to be as high as a 100% when left untreated, as a result of mediastinitis, sepsis and multiple organ failure.[24] A small subset of patients can be treated conservatively with nil per mouth, antibiotics and drainage of pleural empyemas. Surgical treatment options include esophageal repair and esophagectomy; the mortality rate after surgery is in the range of 12 – 50%.[25-28]

A benign esophageal stricture is frequently encountered as a complexity in endoscopic practice.[29] They can result from peptic injury, radiation injury, caustic injury and anastomotic lesions. For centuries, the gold standard for esophageal strictures has been dilation therapy.

While initial dilation typically results in symptomatic relief, recurrence of the stricture is a common phenomenon.

Over the past few years, stents have been used as a temporary device to firmly seal the lesion or to restore luminal patency in patients with benign esophageal disease. Thus far, this application is limited because of serious concerns regarding the long-term complications and hitches relating to stent extraction.[30-31]

AIM OF THE THESIS

The aim of the thesis is to explore new applications and designs to improve benefits, and to overcome limitations of self-expandable stents in patients with malignant and benign esophageal disease.

OUTLINE OF THE THESIS

By measures of mortality and morbidity gastrointestinal (GI) cancers are leading the field of oncology. Between one fifth and one quarter of all human cancers arise in the digestive system. Many patients with gastrointestinal cancer present with incurable disease. As locally advanced cancer often goes with distant metastases, treatment options are mostly limited to systemic treatment or local palliation only. Despite the many enhancements in cytotoxic therapy and novel biologic agents, overall progress in the outcome of metastatic disease is poor. In **chapter 2** we focus on recent developments in cancer prevention, detection and the approach to early cancer.

Surgical resection is the only curative treatment option for invasive esophageal cancer. However, despite careful staging and advances in adjuvant therapy and surgical techniques, 5-year survival rates rarely exceed 40%.[32-33] Many patients present with locoregional recurrence and distant metastasis die within 2 years after curative esophagectomy.[34] Treatment of patients with local disease recurrence aims at relieving dysphagia. The clinical efficacy of SEMS in patients with dysphagia or fistula caused by recurrent cancer after esophagectomy is not well documented. We therefore assessed in **chapter 3** the safety and efficacy of SEMS insertion in a cohort of patients with this condition.

Malignant extrinsic compression can be caused by local recurrence of cancer after esophagectomy, pulmonary cancer, mediastinal cancer, or metastatic disease.[35-36] Most patients with dysphagia due to malignant extrinsic compression are incurable and have a life expectancy

of less than 6 months after initial symptoms. Treatment of patients with non-resectable metastatic disease is palliative; by relieving dysphagia, nutritional intake can be maintained and quality of life improved.[20] The vast majority of previous studies tend to combine intrinsic and extrinsic malignancies. However dysphagia due to extrinsic compression differs essentially from dysphagia due to primary esophageal cancer. It generally presents late in the disease, it causes displacement of the lumen rather than structuring and is associated with a broad set of symptoms and a brief life-expectancy. For this reason, in **chapter 4** we investigated the safety and efficacy of SEMS placement in patients with extrinsic compression.

A wide variety of expandable esophageal endoprostheses have been developed, aiming to improve the therapeutic outcome and to reduce the need for endoscopic reintervention during the course of the disease. Unfortunately, the number of reinterventions remain significant.[37-39] Currently, the Ultraflex® stent is worldwide most frequently used. The Evolution® stent has recently been introduced to the market. This stent differs considerably from the current available SEMS: in delivery system, size, shape, flares, and covering. In **chapter 5**, we aimed to assess whether such new design is superior to the conventional Ultraflex stent for the palliative management of patients with malignant dysphagia or esophageal fistulae.

Covered self-expandable metal stents (SEMS) were introduced as a permanent device for the palliative therapy of esophageal carcinoma. The newest generation SEMS with a covering membrane prevents tissue ingrowth and allows sealing of a fistula. In addition, the cover also facilitates SEMS removal by preventing stent embedment.[40] Currently, SEMS are increasingly used as a temporary device in patients with benign esophageal defects and stenosis, or to bridge chemo-radiotherapy in patients with malignant esophageal disease.[41-47] However, severe complications during SEMS removal have been reported but most series published to date are small.[30-31, 43, 46, 48-49] Hence, this prompted us to evaluate in **chapter 6** our experience with endoscopic SEMS removal in the largest cohort of patients to date with benign and malignant esophageal disease and to identify factors associated with SEMS removal outcome.

Over the last few years, good results for the management of benign esophageal perforations have been reported by temporary deployment of a covered self-expandable stent to firmly seal the lesion.[9, 41-42, 48] Although stent placement is a minimal invasive procedure,[50-52] stent therapy is associated with severe complications including hemorrhage, incomplete sealing, perforation, and stent migration.[37-38] Even though some of the newer stents are labeled as being removable, extraction can be complex due to embedding of the endoprostheses into the mucosal wall.[48] The optimal duration of stent therapy has not been established.[48, 53] The aim of **chapter 7** was to evaluate the outcome of temporary esophageal stenting in the management of benign perforations.

Major drawbacks of the current available stents are the re-occurrence of dysphagia and leakage caused by SEMS migration. Features in the design of the stent that help to prevent migration, including the type of covering, also hamper stent removal once they are in position. Because to date no randomized studies have been published comparing fully-covered SEMS and partially-covered SEMS, in **chapter 8** we compared their efficacy in patients with benign esophageal disease in a randomized controlled study design.

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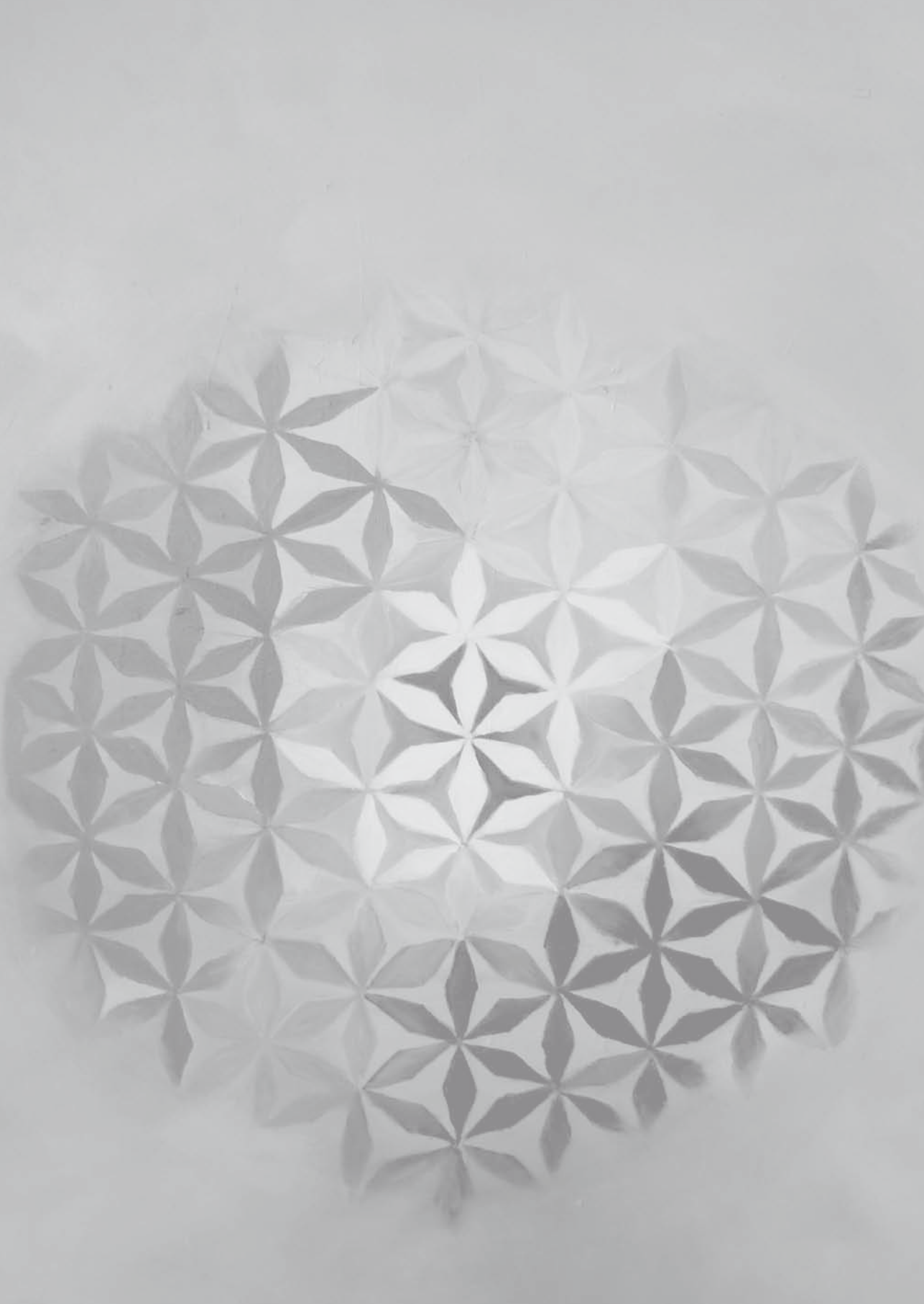

Chapter 2

Are we making progress in diagnosing and preventing gastrointestinal cancers?

Jelle Haringsma, Nicoline C.M. van Heel, Ernst J. Kuipers

Departments of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Therapeutic Advances in Gastroenterology 2010; 3(4): 213–220

INTRODUCTION

By measures of mortality and morbidity gastrointestinal (GI) cancers are leading the field of oncology. Between one fifth and one quarter of all human cancers arise in the digestive system. Many patients with cancer of the digestive system present with incurable disease. As locally advanced cancer often goes with distant metastases, treatment options are mostly limited to systemic treatment or local palliation only. Despite the many enhancements in cytotoxic therapy and novel biologic agents, overall progress in the outcome of metastatic disease is poor.[1-2]

The fact that most GI cancers are for long preceded by recognizable, treatable precursor lesions has posed great challenges. Primary prevention strategies seek to prevent the formation of cancer in an otherwise healthy population. Secondary prevention activities are aimed at early disease detection, thereby increasing the opportunities for interventions to prevent progression of the disease. Advanced diagnostic and therapeutic tools have been developed to detect and treat cancerous lesions at the earliest stage. With these tools and increased awareness of their impact, early treatment and prevention have become a major task for the modern gastroenterologist. In this review we focus on recent developments in cancer prevention, detection and the approach to early cancer.

RISK FACTORS AND PRECURSOR LESIONS

Pathogenesis of most GI cancers follows a sequential, multistep process with well-defined biological stages, developing from low-grade dysplasia to high-grade dysplasia, and finally to invasive carcinoma.[3-4] This is a complex process in which various acquired and inborn genetic factors are involved. Chronic injury and inflammation play a critical role in the majority of GI cancers. The inflammatory process induces oxidative stress, and initiates replacement of injured and damaged cells by a continual regenerative process with risk of DNA damage and uncontrolled cell proliferation.[5]

There are numerous well-recognized conditions in the GI tract that predispose to cancer. Such premalignant conditions include Barrett's metaplasia and achalasia of the esophagus, atrophy and metaplasia of the stomach, chronic inflammation of the biliary tract and pancreas, chronic inflammatory bowel disease, and colonic polyp syndromes.

The use of biomarkers for risk identification may have infinite potential. There have been several attempts to identify markers of tumor DNA shed from tumors into stool. Although there is evidence that this noninvasive approach is useful, there are still important barriers in

terms of sensitivity, specificity, and cost. At present, a panel of DNA markers can identify over 50% of patients with colorectal cancer (CRC) and many patients with advanced adenomas.[6]

Risk scores based on simple clinical, histological, and serological parameters can already serve as a practical tool to select patients for surveillance endoscopy. Intragastric extent of intestinal metaplasia is an example of an indicator for gastric cancer risk that can be assessed by a score based on individual risk factors.[7]

SCREENING AND SURVEILLANCE

The key purpose of screening and surveillance protocols is the detection of presymptomatic curable disease. It is of crucial importance for the efficacy of screening and surveillance programs that the natural history of the target disease consists of a sequential process with well-defined biological stages, and that in this sequence a so called critical point along its natural history is identified. This critical point is best described as the point during the multistep process before which treatment is either more effective than afterwards, or equally effective but easier to apply.[8] This critical point should be noticeable by a reliable and efficient screening technique. Furthermore, the critical point has to lie between the earliest possible time of diagnosis and the usual time of clinical diagnosis.

Some GI cancers in various risk areas do not satisfy the basic conditions, whereas others are unbiased candidates for effective large-scale screening and surveillance programs. For those candidates, such as Barrett's, gastric premalignant lesions and colon adenomas, the effect of surveillance on the incidence of advanced cancer and mortality has to be proven before launching large-scale stratified screening and surveillance programs.[9-12] The availability of mass screening programs in high-risk countries for gastric cancer has substantially decreased mortality.[13] In contrast, in North America and Europe where such programs are lacking and few gastric cancers are detected at an early stage, cancer survival is significantly worse.[14] For CRC in the Western world a trend towards such reduction is documented.[15] For esophageal cancer, even in the setting of Barrett's metaplasia, survival benefit has not convincingly been shown.

CHEMOPREVENTION

To reduce the incidence and outcome of GI cancer, chemoprevention strategies represent an alternative approach to screening and surveillance programs.[16] This can be achieved for various tumors with a variety of methods, some of which required maintenance treatment

whereas others only require a single short-term intervention. One of the most remarkable examples in the latter group is chemoprevention of gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma by antimicrobial therapy against Helicobacter pylori. H. pylori eradication leads to a rapid resolution of chronic active gastritis. This can to some extent be accompanied by a regression of atrophic gastritis, but, it seems, not of intestinal metaplasia. Several large randomized prospective studies have reported that H. pylori eradication thus reduces the incidence of gastric cancer. A recent meta-analysis of seven large studies reported that H. pylori eradication was in the first years thereafter associated with a 35% reduction in gastric cancer incidence.[17] All of these studies were performed in areas with a high gastric cancer incidence, in particular in Asia. It thus remains unclear whether these results can be translated to other populations. We do however know that the development of gastric cancer after H. pylori eradication is not only an early phenomenon, but can still occur more than a decade after eradication.[18] Further studies, in particular in Western populations, are badly needed.

With respect to long-term chemoprevention, the group of drugs that has generated the most attention is the nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit the cyclooxygenase enzymes. Well-conducted animal studies, as well as epidemiologic studies in humans, have shown that the regular use of NSAIDs is clearly associated with a reduction of GI cancer risk.[19-22] The protective effect is dose-dependent and is directly related to the duration of exposure.[23-24] However, traditional NSAIDs are known to cause renal toxicity as well as injury to the mucosa of the digestive system, resulting in renal failure, bleeding, ulceration and stricturing of the GI tract. The cyclooxigenase-2 (COX-2) selective inhibitors were considered in the search for an alternative chemopreventive agent with fewer side effects. Recent large-scale studies have shown an increased risk of cardiovascular events, raising serious concerns on the safety of COX-2 inhibitors in chemoprevention strategies.[25-26] Furthermore, a subset of GI cancers (20%) has low expression of COX-2, indicating that these tumors could be less responsive to COX-2 prevention.

A second category of drugs that are widely investigated for chemoprevention of upper GI cancers, both alone and in combination with NSAIDs, are proton-pump inhibitors. These studies focus in particular on the effect of proton-pump inhibitor maintenance therapy and the risk of development of esophageal adenocarcinoma in patients with Barrett's esophagus. Several cohort studies have shown that proton-pump inhibitor therapy cannot fully prevent the development of Barrett's esophagus,[27] although it is unknown whether they slow the rate of development of Barrett's metaplasia. Furthermore, there are several cohort studies which report that proton-pump inhibitor therapy decreases the progression of pre-existent Barrett's mucosa to dysplasia and cancer, yet this observation is not consistent throughout

the complete literature.[28] This implies that much further research is needed in the coming years on this very important topic.

A third category under investigation as chemopreventive agents for GI cancer are statins. In humans simvastatin and pravastatin are associated with a reduced CRC rate in patients with coronary artery disease, with a relative risk reduction of 47% after 5 years.[29] Although statins have been shown to be associated with an acceptable adverse effect profile in patients with hypercholesterolemia, their longterm toxicity in patients without hyperlipidemia has yet to be assessed.

Estrogen may prevent the CRC by decreasing the production of secondary bile acids, by decreasing production of insulin-like growth factor 1, or by exerting a direct effect on the epithelium. Estrogen in combination with progesterone can induce a 37% reduction in CRC incidence in women. However, such hormonal treatment is associated with increased incidences of cardiovascular events, breast cancer, thromboembolic events and stroke.[30]

Mesalamine has been studied mostly in the setting of prevention of CRC in patients with inflammatory bowel disease. While some studies show an impressive protective effect, others have failed to confirm these findings.[31-32]

Altogether, this indicates that the potential chemoprevention strategies have to be re-evaluated and effective chemoprevention remains at best at the horizon.

IMAGING EARLY CANCER

For all GI cancers, the most significant prognostic factor for survival is the stage at diagnosis.[33-34] In the majority of patients with symptoms, the cancer has invaded into the muscularis propria or beyond. Early cancer is defined as tumor limited to the mucosa or extending into the submucosa but not invading the outer muscular wall. If diagnosed in an early stage, GI cancer is curable and has an excellent prognosis (Table 1). Since asymptomatic patients are

TABLE 1. Five-year relative survival rate by stage.

TNM classification	Esophageal cancer	Gastric cancer	Colorectal cancer
0	>95%	>90%	>95%
I	50-80%	50-80%	90-95%
II	10-40%	30-50%	70-85%
III	10-15%	10-20%	35-66%
IV	<5%	<5%	<5%

TNM, Tumor-Node-Metastases

not routinely exposed to early cancer diagnosis, these early cancers are either picked up through dedicated screening and surveillance, or during medical work-up for other reasons.[35]

Despite the many enhancements in diagnostic radiology and promising developments in the field of immunochemical detection, endoscopy with histological biopsy continues to play a leading role in the diagnosis of early GI cancer.[36]

Endoscopic detection of cancer in its early stage can be difficult as most early neoplastic lesions have a normal macroscopic appearance. Precursor abnormalities and early lesions are frequently overlooked, even by the experienced endoscopist. Random biopsy protocols such as in Barrett's esophagus also frequently miss dysplastic or cancerous areas.[37] Novel enhancements in endoscopic imaging techniques facilitate visualization and increase detection of early neoplastic lesions to a great extent. The leading enhancement techniques are high-resolution imaging, magnification endoscopy, spectral filtering techniques, and autofluorescence endoscopy.[38-42] Although still in their infancy, these imaging techniques have already started to take the place of chromoendoscopy and meticulous random biopsy protocols.

MANAGEMENT OF PRECURSOR LESIONS AND EARLY CANCER TREATMENT

Surgery is still considered the standard treatment for patients with GI cancer. For many years however, endoscopic therapy has become available for certain precursor lesions and early cancer, with significant benefits and excellent outcome. Colonoscopic snare resection of stalked polyps has been employed successfully since the early 1970s.[43] Subsequently, various other techniques have been developed to routinely remove precursor lesions from the GI tract at endoscopy, including hot biopsy removal, cold snaring, piecemeal resection, and argon plasma coagulation. While protruded lesions up to 2 cm in the colorectum can be easily excised by these techniques, other nonprotruded lesion types and superficial cancers in the intestine, stomach and esophagus can be removed with more advanced endoscopic resection techniques. Although standard polypectomy can be considered a form of endoscopic resection, this terminology generally applies for 'deeper' types of resection, extending into the submucosa. The most widely applied techniques for endoscopic resection are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).[44-47]

The feasibility, safety, and results of endoscopic resection predominantly depend on operator experience.[48] Recent long-term studies have shown that prognosis of complete en-bloc EMR for differentiated, nonulcerated mucosal early gastric cancers under 20 mm is comparable to surgical treatment with 10-year survival rates as high as 99%.[49] Other studies have shown the cost efficacy of such approach.[50] Although some advocate endoscopic treatment of

smaller undifferentiated cancers and early cancers invading the submucosa,[51] generally only high-grade dysplasias and well differentiated nonulcerated GI cancers that are limited to the mucosa are candidates for endoscopic resection, as these lesions have a well-determined low risk for lymph node metastasis.[52-55] En-bloc resection is preferred over piecemeal resection, irrespective of the resection technique employed.[56]

The risk of complications using these endoscopic minimally invasive resection techniques (i.e. bleeding, perforation, stenosis), are significant, but low in comparison with the risks of a surgical procedure.[57] En-bloc resection techniques for larger lesions carry a considerably higher complication rate than EMR techniques, even in the hands of experts.[48]

ARE WE MAKING PROGRESS?

GI cancer is amongst the most common cancers and a major cause of caner-related death around the world. The incidence, diagnostic techniques, therapeutic options have undergone major changes over the last six decades, but the prognosis generally remains poor, especially in advanced stages and in spite of aggressive adjuvant therapy and advances in surgical resection techniques. At the same time the understanding of carcinogenesis has advanced considerably leading to a marked shift towards risk stratification, prevention, early detection, and early treatment.

The results of primary prevention strategies are lagging behind the initial expectations, yet the availability of mass screening programs in high-risk populations has already substantially decreased mortality in certain cancers.[58-60] It is important to note that benefit should exceed the burden of large-scale surveillance programs and such benefit remains controversial as long as documented reduction on cancer mortality is lacking.[61]

The reason for the increased detection of early cancer is not only the success of the mass screening programs but also the awareness of physicians towards recognizing individual risks, and the attitude towards detecting early cancer in asymptomatic subjects. It may be that the paradigm shift to recognition of precancerous lesions in the GI tract is the cornerstone of progress made in preventing GI cancer and early interventions. GI cancers, which were previously considered fatal, may now be managed at an early and curable stage.

In such approach, successful prevention of GI cancer relies upon the identification of risk factors and risk groups, availability of early detection and treatment protocols, expert centers for applying these measures to patients, and continuous evaluation of and development of procedures applied. The goal of screening and surveillance is to diagnose precursor lesions

and early stage cancer and to intervene at a critical point in order to prevent progression to advanced cancer or preclude mutilating therapy. Studies have shown a survival benefit if the cancers are detected by endoscopic screening rather than when presenting with symptoms.

Surgery has long been the standard treatment also for patients with early GI cancer; however there is a shift toward alternative less-invasive organ-sparing therapy. Endoscopic tools for the complete removal of early cancerous lesions have been developed with significant benefits and excellent outcome. These endoscopic techniques carry considerably lower morbidity, mortality, and long-term side effects as compared with surgical intervention. These benefits outweigh even the higher risk of local cancer recurrence. Some of these techniques such as polypectomy for the prevention of colon cancer have been employed for decades and have been proven safe in the hands of many. Given the risks and the lack of long-term outcome data for some of the newer and more aggressive endoscopic techniques, these should be restricted to experienced endoscopists in expert centers because it requires high levels of endoscopic skill and experience.

FUTURE DIRECTIONS

In recent years important advances have been achieved in the adjuvant treatment of advanced cancers, where small yet firm survival benefits were demonstrated for perioperative chemotherapy and postoperative chemoradiotherapy. Even though patient prognosis for advanced disease remains very poor with median survival times rarely approaching 1 year, efforts to improve outcome of multimodality treatment for advanced disease should continue. Yet, one of the greatest challenges now facing this field is the identification of patients at risk and assessing individuals for the presence of precursor lesions with the aim of targeting only those with a survival benefit with the psychological and physical burden of regular surveillance. The use of biomarkers and simple clinical scoring systems for risk identification both have a great potential and hence provide an opportunity for less-invasive, more-effective screening and surveillance. Attempts are being made to validate these approaches in routine clinical practice.

Detection of the precancerous lesions in a high risk population is an essential clinical goal. New optical developments are rapidly in progress. Ongoing research, teaching and training are essential to optimize detection skills. Endoscopy will continue to play a leading role in the treatment of patients with an identified precursor lesion or mucosal cancer, but minimally invasive surgical techniques can also be developed to be used as an alternative in cases referred for maximally invasive surgical resection at present. Expectations for future technology are high; however, to establish the value of various advanced diagnostic and therapeutic tools in preventing GI cancer, long-term outcomes of randomized controlled trials are required.

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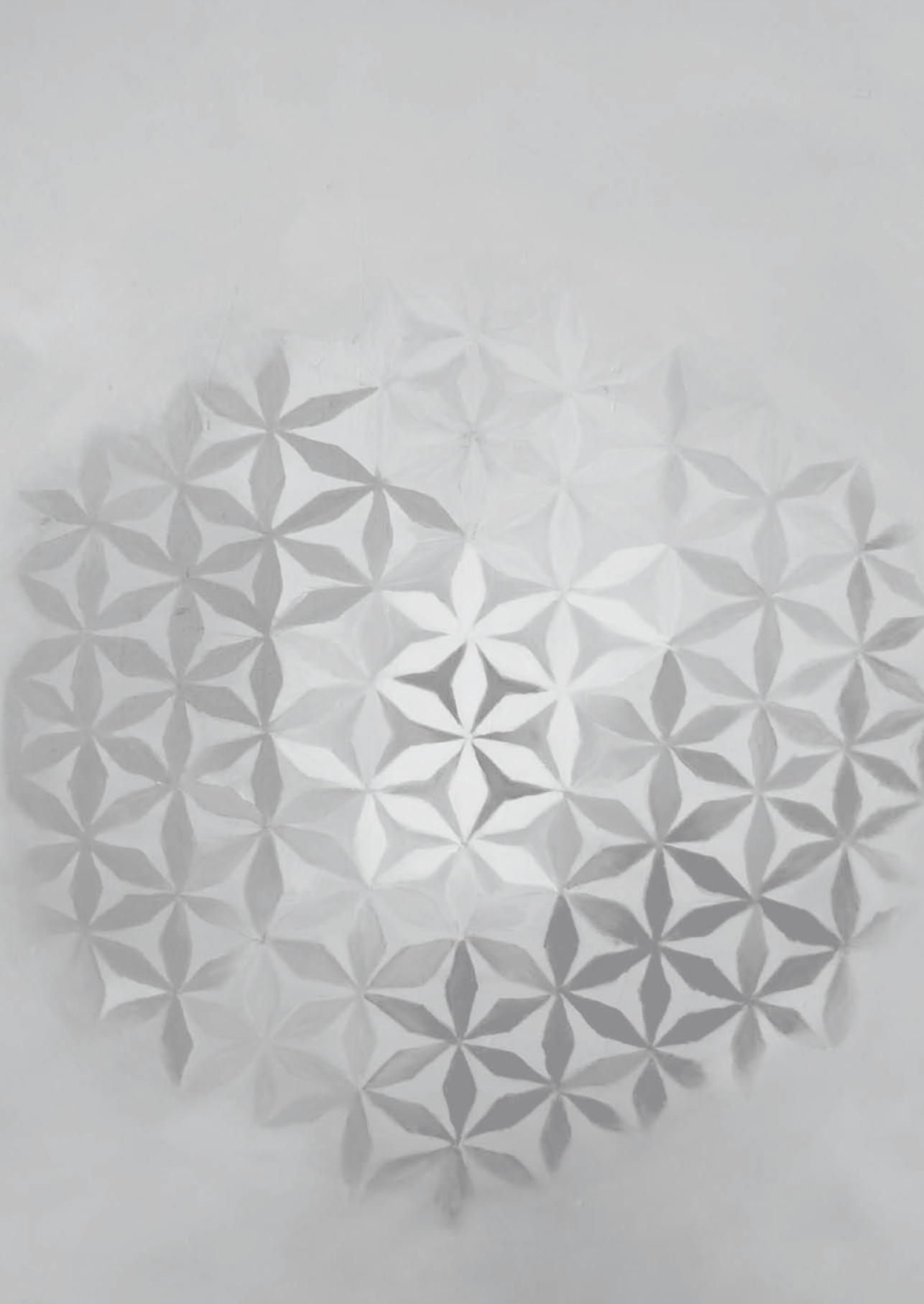

Chapter 3

Esophageal stents for the palliation of malignant dysphagia and fistula recurrence after esophagectomy

Nicoline C.M. van Heel, Jelle Haringsma, Manon C.W. Spaander, Paul Didden, Marco J. Bruno, Ernst J. Kuipers

Departments of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Gastrointestinal Endoscopy 2010;72(2):249-54

ABSTRACT

Background: Despite advances in staging methods, surgical techniques, and adjuvant treatment, recurrent cancer after esophagectomy is a major cause of morbidity and mortality.
Objective: Our purpose was to investigate the safety and efficacy of a self-expandable metal stent (SEMS) in patients with dysphagia or fistula caused by recurrent cancer after esophagectomy.
Design: Prospective, observational study with standardized treatment and follow-up.
Setting: Single university center.
Patients: In 81 patients with recurrent cancer after previous surgical esophagectomy, 100 esophageal SEMSs were inserted for dysphagia (n = 66) or fistula formation (n = 15).
Interventions: Stent placement.
Main Outcome Measurements: Technical and functional outcome, complications, and survival.
Results: The SEMSs restored luminal patency in 65 (98%) of 66 patients and sealed malignant fistulae in 14 (93%) of 15 patients. Stent dysfunction occurred in 24 (30%) of 81 patients. They all were successfully managed by subsequent endoscopic intervention. After stent placement, a total of 16 complications were observed. Major complications occurred in 9 (11%) of 81 patients, mild complications occurred in 7 (9%). The overall 30-day mortality rate after stent insertion was 25%. Progression of the disease resulted in death after a median interval of 70 days (range 1 day to 91 months).
Limitations: Nonrandomized design.
Conclusions: SEMS placement in recurrent esophageal cancer after surgical resection offers adequate palliation by relieving dysphagia and sealing off esophageal respiratory fistulae. Therefore, in these patients who have a relatively short life expectancy, SEMS placement should be considered the treatment of choice.

INTRODUCTION

Surgical resection is the only curative treatment option for invasive esophageal cancer. However, despite careful staging and advances in adjuvant therapy and surgical techniques, 5-year survival rates rarely exceed 40%.[1-2] Many patients present with locoregional recurrence and distant metastasis die within 2 years after curative esophagectomy.[3] Treatment of patients with local disease recurrence aims at relieving dysphagia.

Studies have shown that luminal patency is restored in the majority of patients with inoperable malignant stenosis by placing a self-expandable metal stent (SEMS).[4] SEMSs are also effective in sealing esophago-respiratory fistulae.[5] They are technically easy to insert, and placement is successful in close to 100% of patients. Although SEMS placement is a minimally invasive procedure,[6-8] it carries the risk of severe complications, including perforation, hemorrhage, stent occlusion, and migration.[9-10] In 40% of patients, dysphagia recurs because of stent migration and tissue in- and overgrowth.[11]

The clinical efficacy of SEMSs in patients with dysphagia or fistula caused by recurrent cancer after esophagectomy is not well documented. We therefore assessed the safety and efficacy of SEMS insertion in a cohort of patients with this condition.

METHODS

This prospective observational study was conducted in a large tertiary referral center and was approved by the institutional research committee. Between 1994 and 2009, all patients with dysphagia or respiratory fistula caused by recurrent malignancy after previous surgical esophagectomy were included when undergoing SEMS placement. Exclusion criteria were a tumor length of more than 13 cm or a lesion within 2 cm of the upper esophageal sphincter.

Demographic data and clinical data were prospectively collected in a database. At 4 weeks after stent placement, patients were contacted by telephone. In case of complications or stent dysfunction patients were seen for evaluation and subsequent intervention. The general practitioner was contacted in case of missing follow-up information.

A variety of partially and fully covered SEMSs were inserted. These stents consisted of woven, knitted, zig-zag, or laser-cut metal mesh cylinders. After release, they continued to expand until they reached the preset maximum expanded diameter. Stent bodies had an internal diameter ranging from 17 to 20 mm. Small-diameter stents were SEMSs with an internal body of 18 mm or less.

The type of stent was selected depending on the availability at that time and the physicians' preference. The length of the SEMS was selected according to the size and location of the obstruction with the proximal and distal funnel extending approximately 2 cm outside the stenosis. SEMSs were placed under endoscopic and fluoroscopic control, in accordance

with a standard protocol.[11] Immediately after the procedure, a small amount of clear liquid was given by mouth to evaluate passage, retrosternal pain, and aspiration. Dysphagia was scored before SEMS insertion according to the following classification: 0 = ability to eat a normal diet, 1 = ability to eat some solids, 2 = ability to eat semisolids only, 3 = ability to swallow liquids only, 4 = complete dysphagia.[12] Technical success was defined as dysphagia grade 0 or complete closure of the fistula with improvement of aspiration symptoms within 7 days after stent placement. Stent dysfunction was classified as incomplete sealing of the esophageal leak or dysphagia caused by stent migration, stent obstruction or tumor in- and overgrowth. Complications were defined as either mild or severe according to published criteria.[11] Severe complications included perforation, fistula, aspiration pneumonia, stridor, and haemorrhage. Mild complications included either retrosternal pain and symptomatic gastroesophageal reflux. All patients were followed until death.

Statistical analysis

Numerical data were expressed as mean and standard deviation or median and the interquartile range, as appropriate. Student t test, the chi-square test, and Pearson's correlation or their nonparametric equivalents were used when appropriate. A Cox regression model was used to explore the effect of the variables on time until complications occurred or recurrent dysphagia/leakage. The Kaplan-Meier method was used to calculate survival from the date of stent insertion until the date of death. Statistical analyses were conducted using SPSS software version 15.0 (SPSS Inc, Chicago, Ill). Two-sided P values <0.05 were considered significant.

RESULTS

Patient characteristics

In 81 esophagectomy patients, a total of 100 esophageal SEMSs were inserted for palliation of recurrent tumor growth. Baseline patient characteristics are summarized in Table 1. Tumor recurrence became apparent at a median interval of 17 months after esophageal resection (range 2 months – 10 years). Lesions were classified histologically as squamous cell carcinomas in 31% and adenocarcinomas in 69%. Ten (12%) patients previously received radiotherapy, 17 (21%) chemotherapy, and 15 (19%) received both radiotherapy and chemotherapy after the diagnosis of recurrent cancer. On inclusion, 66 (81%) patients presented with dysphagia, and 15 (19%) patients had a malignant esophagogastric respiratory fistula. In 50 (62%) patients, the tumor was located within 4 cm of the upper esophageal sphincter. Eighteen (22%) patients had recurrence extending into the proximal esophagus, 32 (40%)

TABLE 1. Baseline characteristics of patients

Age, y, mean ± SD	62 ± 11
Sex, no. (%)	
Male	61 (75)
Female	20 (25)
Stent indication, no. (%)	
Dysphagia	66 (81)
Fistula	15 (19)
Tumor length, cm, mean ± SD	6 ± 3
Tumor histology, no. (%)	
Adenocarcinoma	56 (69)
Squamous cell carcinoma	25 (31)
Dysphagia score before treatment	
Grade 2	2 (2)
Grade 3	43 (54)
Grade 4	36 (44)
Previous radiation and/or chemotherapy, no. (%)	
Total	42 (52)
Chemotherapy	17 (21)
Radiation	10 (12)
Radiation and chemotherapy	15 (19)
Tumor location	
≤ 4 cm of the upper esophageal sphincter	50 (62)
>4 cm of the upper esophageal sphincter	31 (38)

SD, Standard deviation.

patients at the anastomosis, and 31 (38%) patients distal to the anastomosis in the tubular stomach. Fifty (62%) patients had an intrinsic stenosis, and 16 (20%) had extrinsic esophageal compression caused by mediastinal metastasis. Forty-nine (60%) patients initially received a partially covered stent; all others (40%) received a fully covered stent (Table 2). In our study, 78% of patients received a small-diameter stent, all other stents were large diameter.

TABLE 2. Stent type

Stent	Type	No. (%)
Ultraflex	Partially covered	37 (46)
Niti-S	Fully covered	14 (17)
Flamingo Wallstent	Partially covered	12 (15)
Z-Stent	Fully covered	11 (14)
Hanarostent	Fully covered	6 (7)
Alimaxx-E	Fully covered	1 (1)

Stent therapy

Luminal patency

The median survival time after stenting for all patients with stenosis was 70 days (range 1 day - 34 months). Stent insertion was technically successful in all but one patient (98%)

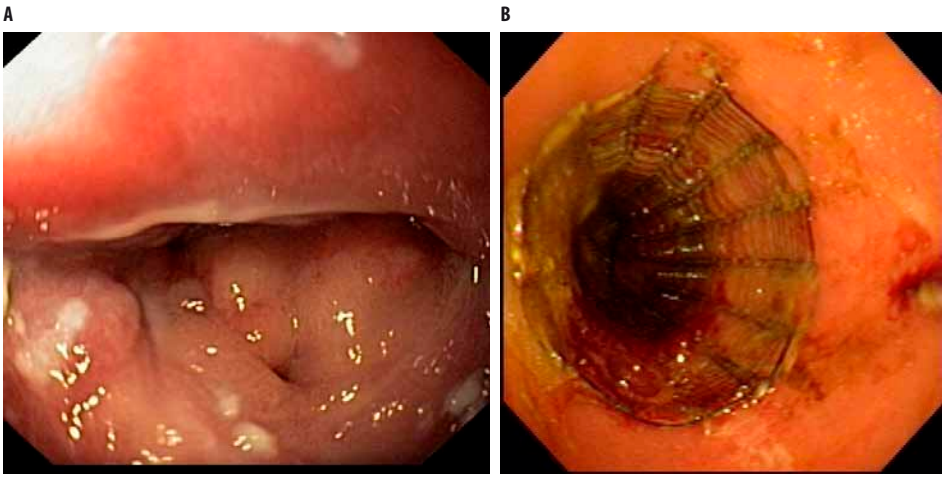

Figure 1

A. Endoscopic view of recurrent malignant stenosis at the anastomosis after gastric interposition.

B. Restoration of the luminal patency after SEMS insertion.

(Figure1). Median duration of primary stent patency was 56 days (range 1 day – 33 months) (Figure 2). A total of 20 episodes of stent dysfunction occurred in 18 (27%) of 66 patients at a median of 38 days post-SEMS insertion (range 2 – 406 days). Stent dysfunction was caused by tissue in- or overgrowth (n=8), stent migration (n=9), and food impaction (n=3). Tissue in- and overgrowth occurred at a median of 119 days post-SEMS insertion (range 33 – 297 days); 5 patients were successfully treated with a second SEMS. Six (24%) of 25 fully covered stents versus 3 (7%) of 41 partially covered SEMS migrated (p=0.07) at a median time interval

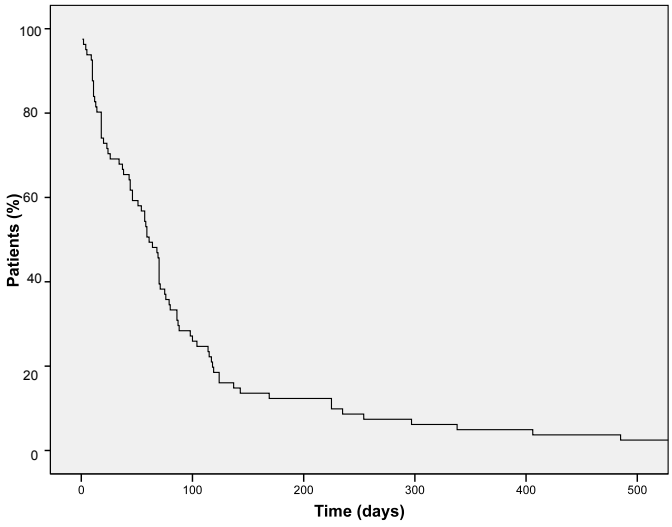

Figure 2. Duration of luminal patency and fistula sealing in 81 consecutive patients with an esophageal SEMS for recurrent esophageal cancer.

of 66 days after SEMS insertion (range 12 – 406 days). Of these patients, 6 patients required a second SEMS. Food bolus impaction occurred in 3 (20%) patients at a median interval of 11 days after SEMS insertion; all 3 were successfully cleared endoscopically. Insertion of a second SEMS was successful in all patients (100%). Median patency of these stents was 59 days (range 5 – 286 days).

Fistula sealing

The median survival time of patients with malignant fistula caused by tumor recurrence was 73 days (range 10 days – 91 months). The coated segment of the stent effectively sealed fistulae in all but 1 patient (93%). This patient was successfully treated with a second stent. Stent dysfunction occurred in 6 (40%) of 15 patients. In 5 (33%) patients, additional stents were successfully inserted to manage stent migration (n=4) and persistent leakage during stent treatment (n=1). Two out (22%) of 9 fully covered stents versus 2 (33%) of 6 partially covered SEMSs migrated at a median time interval of 5 months post-SEMS insertion (range 5 days – 11 months). Food bolus impaction occurred in one patient 17 days post-SEMS insertion, this patient was also successfully treated endoscopically by stent clearance.

Overall complications and mortality

Mild complications after stent placement occurred in 7 (9%) patients including retrosternal pain and symptomatic gastroesophageal reflux. Major complications occurred in 9 (11%) patients. Stridor developed immediately after insertion in 3 patients with a lesion within 4 cm of the upper esophageal sphincter. In all 3 patients, the stent was removed, and they were managed conservatively. Three patients had an upper GI hemorrhage from the tumor site at a median time interval of 26 days after SEMS insertion (range 11 days – 10 months). The bleeding subsided spontaneously in 1 of these patients; the other 2 patients died of the persistent bleeding. An esophageal fistula developed during stent treatment in 2 patients, both of which were located at the distal funnel of the partially covered stent at a median time interval of 48 days post-SEMS insertion. These wall defects were successfully sealed with an additional stent. One patient had a stent-induced ulceration after stent migration at 7 months after SEMS insertion and required endoscopic stent extraction. The overall 30-day mortality rate after stent insertion was 25%. Progression of the disease resulted in death after a median time interval of 70 days (range 1 day - 91 months). Variables including stenosis or fistula, histology, stent type, stent size, and previous therapy were not independently associated with the development of stent associated complications, recurrent dysphagia, or survival. Similar results were obtained when the variables were entered into a multivariate Cox regression model.

DISCUSSION

Even after curative surgery, the median esophageal cancer-specific survival is only 38 months. The esophageal cancer-free survival rate at 1, 2, and 5 years reportedly is approximately 84%, 65%, and 41%, respectively.[1] Stenosis caused by locoregional recurrence or obstructive mediastinal metastasis develops in a subset of patients with cancer recurrence.[3, 13-15] Although chemotherapy and radiotherapy can be effective for symptom relief for locoregional tumor recurrence, it can take as long as several weeks for such therapy to relieve dysphagia.[16-17] Given the short life expectancy in these patients, a more rapid relief is usually required. SEMSs have been successfully used since the early 1990s for palliation of primary esophageal cancer.[12, 18-22] However, the efficacy of SEMS therapy in patients with recurrent cancer after esophagectomy is not well established. The current cohort study, which is the largest published to date, shows a clear benefit of SEMS therapy in patients with recurrent tumor growth after esophagectomy. SEMS placement was effective in patients with intrinsic and extrinsic esophageal lesions and restored luminal patency in 98% of patients, which is comparable to previous smaller series.[7, 15, 23] Recurrent dysphagia occurred in 27% of patients; all patients were successfully managed by endoscopic reintervention.

Esophageal respiratory fistulae occur in 5% to 10% of patients with esophageal cancer.[19, 24] In our series, 19% of patients with recurrent cancer after gastric tube interposition presented with a fistula. This represents a devastating complication leading to recurrent pulmonary infections and the inability to eat or even swallow saliva. This condition is associated with a very high short-term mortality.[25] The technical success of fistula sealing by SEMSs was 93%, which is within the range of the 80% to 100% reported by other series.[19] In the majority of patients with cancer recurrence after esophagectomy, the fistula or stenosis is located close to the upper esophageal sphincter. At this location, SEMS placement may cause foreign body sensation, tracheal compression, or respiratory fistula.[26-27] It has been hypothesized that stents should have a body diameter of 18 mm or less to avoid these complications.[4] In our series, however, stridor developed in 3 (4%) patients and a fistula developed in 2 (2%) patients after stent placement, despite the use of small-diameter stents in 4 of them. None of the patients reported globus sensation.

Approximately half of the patients had undergone chemotherapy and/or radiotherapy before stent insertion. The use of SEMSs in combination with chemotherapy and radiotherapy is controversial.[11, 28-32] Kinsman et al. reported a complication rate of 36% and a mortality rate of 23% in patients with radiation and/or chemotherapy, compared with 3% and 0% respectively, in patients without previous therapy.[32] In our series, however, no differences were seen with respect to the incidence and character of complications and stent dysfunction between patients with or without previous chemo/radiotherapy.

Stent migration is one of the most frequently reported causes of stent dysfunction. This was also the main cause of stent dysfunction in our series. The reported migration rate

ranges from 7% to 58%.[33-36] Reportedly, fully covered stents are more prone to migration than partially covered stents. In our series, the overall difference in stent migration, 8 of 32 fully covered versus 5 of 49 partially covered stents, was not statistical significant. The need for additional stents to manage stent dysfunction was considerable; in our series, nearly 1 of every 4 patients needed an additional stent. Other recent studies reported comparable or even higher numbers of additional stents to manage stent dysfunction.[11, 20, 37-38] The reported median survival after cancer recurrence ranges from 7-16 months.[3, 14] The recurrent tumor has often spread significantly before compromising the esophageal lumen or the patency of the wall. This may contribute to the short median survival of 70 days in our series. Various factors, such as stenosis or fistula, histology, stent type (partially vs fully covered), and previous therapy did not seem to influence survival.

SEMS placement in recurrent esophageal cancer after surgical resection offers adequate palliation by relieving dysphagia and sealing off esophageal respiratory fistula. Therefore, in these patients who have a relatively short life expectancy, the implantation of SEMSs should be considered the treatment of choice.

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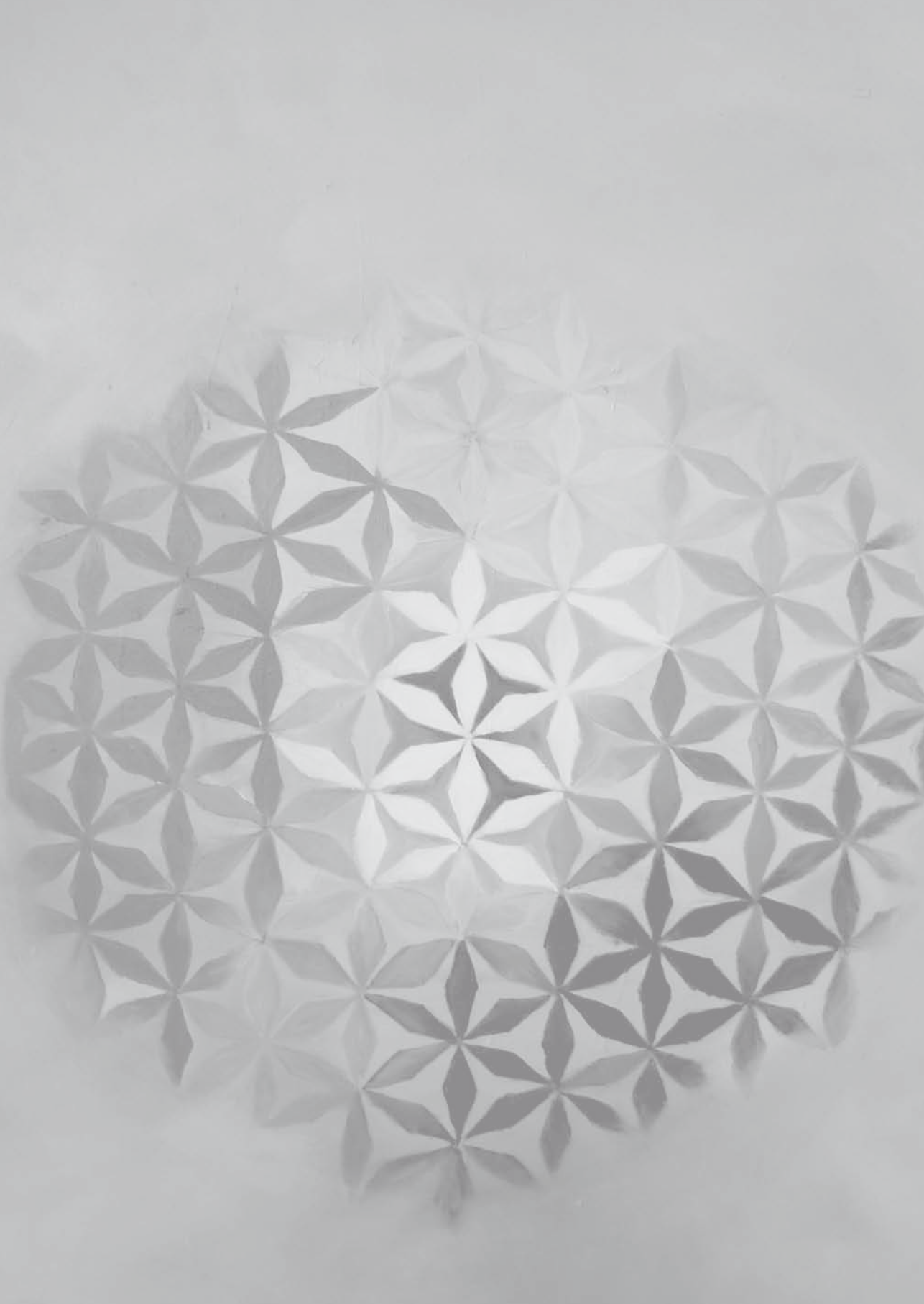

Chapter 4

Esophageal stents for the relief of malignant dysphagia due to extrinsic compression

Nicoline C.M. van Heel, Jelle Haringsma, Manon C.W. Spaander, Marco J. Bruno, Ernst J. Kuipers

Departments of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Endoscopy 2010;42(7):536-40

ABSTRACT

Background and study aims: In patients with primary esophageal cancer, luminal patency can be restored by placement of a self-expandable metal stent (SEMS). The use of SEMS in patients with dysphagia caused by malignant extrinsic compression has largely been unreported. In this study we evaluated the efficacy of SEMS in a large cohort of patients with malignant extrinsic compression.

Patients and methods: This is a prospective single-center study. Between 1995 and 2009, 50 consecutive patients with malignant extrinsic compression who had undergone SEMS placement were included (mean age 64 years; 37 males). In the majority of patients, extrinsic esophageal compression was caused by obstructive pulmonary cancer (n=23) and by mediastinal metastasis after esophagectomy for esophageal cancer (n=16).

Results: Stent placement was technically successful in all patients. Severe complications occurred in 5/50 patients (10 %) including perforation during dilation prior to stent insertion (n=2) and hemorrhage (n=3). Two patients (4 %) died from bleeding. Mild complications were seen in 9/50 patients (18 %). Recurrent dysphagia occurred in eight patients (16 %) and was successfully managed by subsequent endoscopic intervention. Median survival after stent placement was 44 days (range 5 days–2 years). The median stent patency of 46 days in this series exceeded median patient survival.

Conclusions: Insertion of a SEMS is an effective palliative treatment for patients with dysphagia due to malignant extrinsic compression. In spite of the short survival, some patients present with recurrent dysphagia, which can be managed effectively by endoscopic re-intervention.

INTRODUCTION

Most patients with dysphagia due to malignant extrinsic compression are incurable and have a life expectancy of less than 6 months after initial symptoms. Malignant extrinsic compression can be caused by pulmonary cancer, mediastinal cancer, metastatic disease, or local recurrence of cancer after esophagectomy.[1-2] Treatment of patients with nonresectable malignant stenosis is palliative; by relieving dysphagia, nutritional intake can be maintained and quality of life improved.[3] Studies have shown that luminal patency is restored in the majority of patients with esophageal cancer by placement of a self-expandable metal stent (SEMS). SEMS are technically easy to deploy and placement is successful in up to 100%. Although SEMS placement is a minimally invasive procedure,[4-6] it can lead to several complications, including perforation, haemorrhage or ulceration.[7-8] Dysphagia recurs in some patients, due to food bolus obstruction, stent migration and tissue ingrowth and overgrowth.[9]

Little is known about the results of SEMS placement in patients with dysphagia caused by malignant extrinsic compression. The aim of this study was to establish the safety and efficacy of SEMS placement in patients with this condition.

PATIENTS AND METHODS

This prospective trial was conducted in a large tertiary referral center and was approved by the institutional ethics committee. Between 1995 and 2009, all patients with dysphagia due to malignant extrinsic compression and who underwent SEMS placement were included. Exclusion criteria were a tumor length of more than 13 cm, and an obstruction within 2 cm of the upper esophageal sphincter. Diagnosis of extrinsic esophageal compression was based on radiologic and endoscopic imaging. Demographic data, clinical data, and procedural data were collected at inclusion. At 4 weeks after stent placement, patients were contacted by phone. In case of complications, or stent dysfunction patients were seen for evaluation and subsequent intervention. The general practitioner was contacted in cases of missing follow-up information (e. g. due to death).

Available stents were covered and had a body diameter ranging from 16 mm to 20 mm and a length ranging from 8 cm to 17 cm. The length of the SEMS was selected according to the size and location of the obstruction, with the proximal and distal funnel extending approximately 2 cm outside the stenosis. Selection of the type of stent was tailored to each particular case depending on the clinical situation, anatomic location of the lesion, and the physician's preference.

Stents were placed under endoscopic and fluoroscopic control, according to a standard protocol. Immediately after the procedure, a small amount of clear liquid was given by mouth to evaluate passage, retrosternal pain, and aspiration. Dysphagia was scored prior to stent

insertion, according to the following classification: 0=ability to eat a normal diet; 1=ability to eat some solids; 2=ability to eat semisolids only; 3=ability to swallow liquids only; 4=complete dysphagia.[10] Technical success was defined as successful stent deployment at the required position. Stent dysfunction was defined as dysphagia due to tissue ingrowth or overgrowth, stent migration or food bolus impaction. Complications were defined as either mild or severe according to published criteria.[9] Severe complications included perforation, fistula, aspiration pneumonia and haemorrhage. Mild complications included either retrosternal pain or symptomatic gastroesophageal reflux. All patients were followed until death.

Statistical analysis

Numerical data were described by using the mean with standard deviation or median with interquartile range, as appropriate. Functional and technical outcome, complications, stent patency, and survival were analyzed with chi-squared testing and Kaplan-Meier curves. Statistical analyses were conducted using SPSS software (SPSS 15.0, Chicago, Illinois, USA). Two-sided P-values of < 0.05 were considered to be significant.

RESULTS

Patient characteristics

A total of 50 patients underwent esophageal stent placement for malignant extrinsic compression. The mean age at stent insertion was 64 years (range 41-83 years). Baseline patient characteristics are summarized in Table 1. The following stents (n=54) were placed in a cohort of patients; 32 partially covered stents (59%) and 22 fully covered stents (41%). In the majority of patients, extrinsic esophageal compression was either caused by obstructive pulmonary cancer (n=23), or due to mediastinal metastasis after surgical resection for esophageal cancer (n=16). Other causes included mediastinal metastases of breast cancer (n=4) (Figure1), melanoma (n=2), thyroid carcinoma (n=1), sarcoma (n=1), synovia carcinoma (n=1) or metastasis of unknown origin (n=2). Of the 16 patients with mediastinal metastasis after esophagectomy for esophageal cancer, five patients (31 %) had recurrence extending into the proximal esophagus, three patients (19 %) at the anastomosis, and eight patients (50 %) distal to the anastomosis in the tubular stomach. Four patients (8 %) with obstructive pulmonary cancer received an airway stent immediately prior to esophageal stent placement. Almost half of the patients had received radiation and/or chemotherapy prior to stent placement.

TABLE 1. Baseline characteristics of patients

Age, y, mean ± SD	64 ± 10
Sex, no. (%)	
Male	37 (74)
Female	13 (26)
Stenosis length, cm, mean ± SD	5 ± 3
Dysphagia score before treatment	
Grade 2	2 (4)
Grade 3	31 (62)
Grade 4	17 (34)
Origin of malignancy, n (%)	
Pulmonary carcinoma	23 (46)
Esophageal cancer	16 (32)
Mamma carcinoma	4 (8)
Others	7 (14)
Prior radiation and/or chemotherapy, n (%)	
Total	21 (42)
Chemotherapy	12 (24)
Radiation	5 (10)
Radiation and chemotherapy	4 (8)

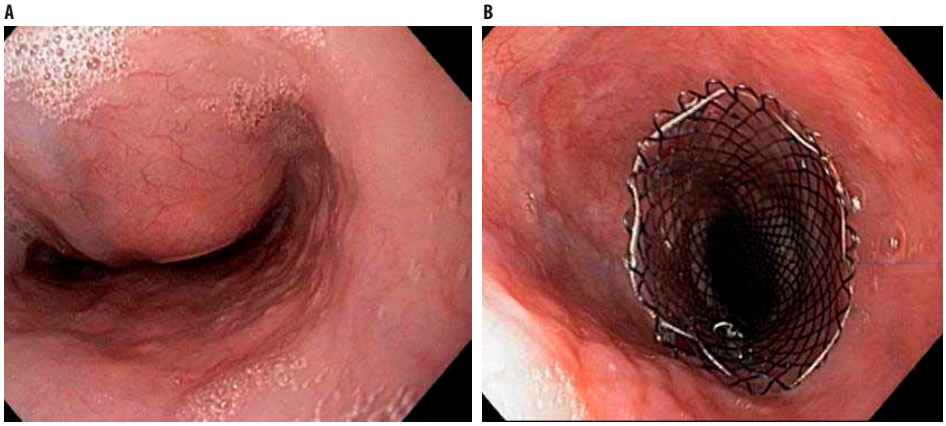

Figure 1. A 74-year-old patient presented with grade 3 dysphagia, due to mediastinal breast cancer metastases.
A. Endoscopic view.
B. A partially covered stent was placed into the esophagus.

Stent insertion and patency

In all patients, stent insertion was technically successful and adequately restored luminal patency. Stent dysfunction occurred in eight patients (16 %) – four of the 32 patients with partially covered stents (13 %) and four of the 22 with fully covered stents (18 %) (Table 2). Stent dysfunction occurred at a median time interval of 46 days post-SEMS insertion (range 2–406 days). Three patients experienced food bolus impaction within 1 week of stent placement; they were successfully treated endoscopically. Two additional stents were inserted for tumor overgrowth at 28 and 119 days, respectively, post-SEMS insertion. One partially covered and

TABLE 2. Recurrent dysphagia in 50 patients with extrinsic compression

Stent brand	n (%)*	Covering	Recurrent dysphagia, n (%)
Ultraflex stent	28 (52)	Partially covered	Total: 4 (14) Tumor overgrowth, 1 Tissue ingrowth, 1 Stent migration, 1 Food bolus obstruction, 1
Z-Stent	9 (17)	Fully covered	Total: 1 (11) Food obstruction, 1
Niti-S stent	8 (15)	Fully covered	Total: 2 (25) Stent migration, 1 Food bolus obstruction, 1
FlamingoWallstent	4 (7)	Partially covered	Total: 0 (0)
Alimaxx-E stent	2 (4)	Fully covered	Total: 0 (0)
Hanarostent	1 (2)	Fully covered	Total: 1 (1) Tumor overgrowth, 1
Polyflex	1 (2)	Fully covered	Total: 0 (0)
SX-Ella stent	1 (2)	Fully covered	Total: 0 (0)

*In total, 54 stents were placed.
Ultraflex stent, Boston Scientific, Natick, Massachusetts, USA
Z-Stent, Cook Medical, Bloomington, Indiana, USA
Niti-S stent, Taewong Medical, Seoul, Korea
FlamingoWallstent, Boston Scientific
Alimaxx-E stent, Alveolus Inc., Charlotte, North Carolina, USA
Hanarostent, MI Tech, Seoul, Korea
Polyflex, Rüsch AG, Kernen, Germany
SX-Ella stent, Ella-CS, Hradec Králové, Czech Republic

one fully covered stent migrated and were both removed and replaced by partially covered Ultraflex stents at 195 and 406 days respectively, post initial SEMS placement. One patient was successfully treated for hyperplastic tissue ingrowth with argon plasma coagulation at 58 days post-SEMS insertion. The duration of stent patency was not significantly associated with age, prior therapy or stent type (partially covered vs. fully covered). In the two patients with an esophageal perforation caused by prior dilation of the stenosis, the fistula was successfully sealed with the covered SEMS.

Complications

A total of 12 complications occurred during stent treatment. In nine patients (18 %) mild complications including retrosternal pain and symptomatic gastroesophageal reflux occurred within 5 days of SEMS insertion. Hemorrhage was the only severe stent-related complication encountered, and was fatal in two patients. One patient with extrinsic compression due to metastatic synovial sarcoma with tumor growth through the esophageal wall had a self-limiting tumor bleed 12 days post-SEMS insertion. Two patient died of a massive gastrointestinal bleed within 7 days post-SEMS insertion.

Survival

The 30-day mortality rate after stent insertion was 36%. Progression of disease resulted in death in all patients after a median interval of 44 days (range 5–774 days) (Figure 2).

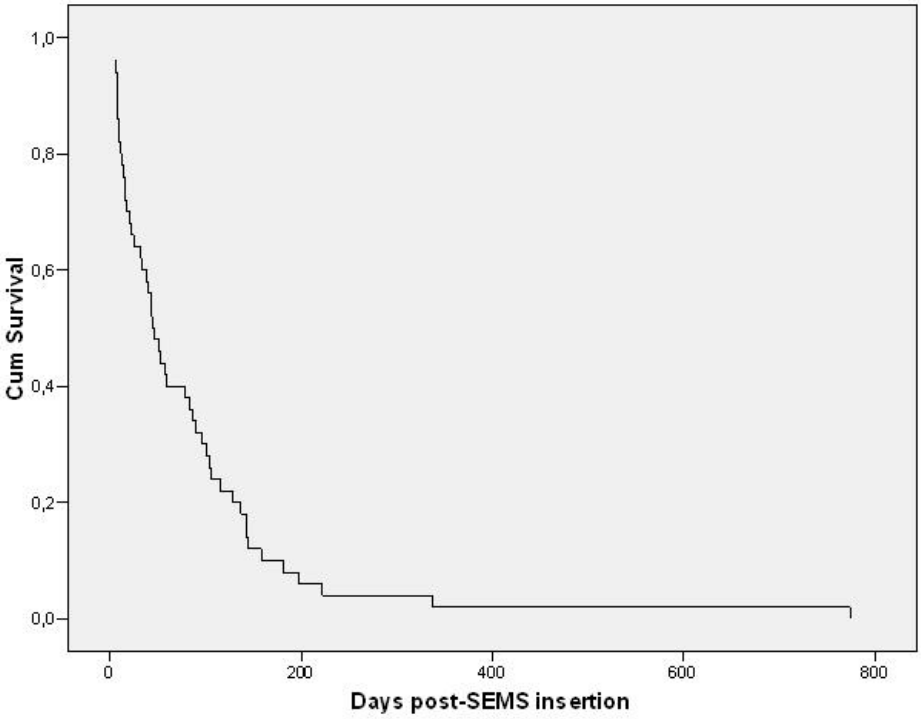

Figure 2. Kaplan-Meier curve: overall survival of 50 patients after stent placement. SEMS, self- expandable metal stent.

DISCUSSION

The palliative management of patients with a malignant esophageal obstruction is a clinical challenge. The gastroenterologist has to balance the benefits of restoring luminal patency by SEMS on patients' quality of life in the context of a short life-expectancy, with the risk of procedural complications. Although chemotherapy and radiotherapy are sometimes beneficial, they may require several weeks to improve dysphagia [11]. Generally, a more rapid relief of dysphagia is required. Currently, SEMS placement is the most widely used palliative treatment in patients with malignant dysphagia.[12] This immediately restores luminal patency and thereby improves oral intake and quality of life.[3, 13-14] The efficacy of SEMS in patients with extrinsic compression however, has not been well established.

More than a decade ago, two limited series were published describing stent therapy in patients with malignant extrinsic compression using non-covered SEMS. Bethge et al. compared stent placement therapy in 24 patients with dysphagia caused by esophageal cancer versus stent therapy in 22 patients with extrinsic compression. Dysphagia improved in both groups. However, a significantly greater improvement was observed in patients with intrinsic stenosis. The mean survival time in patients with extrinsic compression was 89 days.[15] In the second series, by Gupta et al., stents were placed in 17 patients with extrinsic compression, leading to an improvement of dysphagia in all but one patient (94%). Recurrent dysphagia occurred in four patients (24%), major complications in one (6%), and minor complications in four patients (24%). Mean survival time was 63 days.[5] Most of the stents used in these series were uncovered, a feature that has more recently been associated with shorter stent patency in patients with intrinsic malignant strictures.[16] To date, there are no published series evaluating covered SEMS for extrinsic malignant stenosis.

In the majority of patients, dysphagia due to malignant extrinsic compression is caused by pulmonary carcinoma or by the recurrence of esophageal cancer after surgery.[5, 15] SEMS insertion is a relatively easy procedure in most patients with primary esophageal cancer, with a success rate as high as 100%.[1, 17-18] In this cohort too, procedural success was 100%. Procedure-related complications occurred in two patients at endoscopic dilatation of a tight stenosis prior to stent insertion. These perforations were successfully sealed with the covered SEMS.

One of the most frequently reported causes of stent dysfunction is stent migration, which reportedly ranges between 7% and 58%.[16, 19-21] Migration is influenced by several factors. Partially covered stents reportedly tend to migrate less often than fully covered stents, and uncovered segments rapidly become embedded into the mucosal wall.[22] Chemo- or radiotherapy after SEMS insertion also increases the risk of migration by reducing the tumor mass.[23] Therefore, the use of SEMS in combination with chemotherapy or radiotherapy is controversial.[19, 24-27] In this series stent migration occurred in only 4% of patients (one fully and one partially covered stent). Based on this observation, we cannot exclusively recommend the use of partially covered stents in these patients. The low migration rate can be partly explained by the short median survival, but furthermore likely resulted from the fact that most patients suffered from a considerable tumor mass adjacent to the esophagus which thus offered firm fixation of the inserted stent.

Another common cause of stent dysfunction in primary gastroesophageal cancer is stent occlusion by tumor ingrowth or overgrowth, which in published series ranged from 25% to 40%.[4, 19, 27-29] The incidence of tissue ingrowth is higher with the use of partially covered stents than with fully covered stents. As all malignancies were located extrinsically in our series, we saw no dysphagia due to malignant tissue ingrowth. In one patient stent occlusion was caused by the growth of benign hyperplasic tissue through the uncovered distal segment. This was successfully managed with argon plasma coagulation. The literature shows that the

use of SEMS in patients with intrinsic esophageal cancer has led to severe complications, including hemorrhage, abscess formation, and an aorta-esophageal fistula.[3, 30-32] In our series, three severe complications occurred, all severe hemorrhages, two of which were fatal. This is remarkable as the esophageal narrowing was caused by a tumor located extra-esophageal and most bleeds during stent therapy are thought to result from a tumor bleed.[1, 7] In a recent series in which self-expandable plastic stents were placed for benign esophageal stenosis, therapy was also complicated by bleeding in one patient and resulted in death.[33] Therefore it is not only the tumor that can lead to severe bleeding but also erosion and necrosis of the esophageal wall into major vessels.[33-34]

Bethge et al. reported a shorter survival time in patients with extrinsic compression (89 days) compared to patients with intrinsic tumors (163 days).[15] Survival after placement is obviously a function of the timing of stent insertion in relation to the disease stage. In our series, 96% of patients had grade 3-4 dysphagia on inclusion. Median survival time in our series was only 44 days. In patients with extra-esophageal tumors, the tumor has to have spread and grown substantially in order to compromise the esophageal lumen. This may explain the relatively short survival period of these patients over that of patients with intrinsic esophageal tumors.[19, 29] In our series, the type of stent (partially vs fully covered) and radiation and/or chemotherapy prior to stent placement, did not influence the clinical outcome.

In conclusion, our results demonstrate that despite a particular poor life expectancy, insertion of self-expandable metal stents offers good palliation in patients with dysphagia caused by malignant extrinsic esophageal compression. In spite of the short survival, some patients present with recurrent dysphagia an this can be managed effectively by endoscopic re-intervention.

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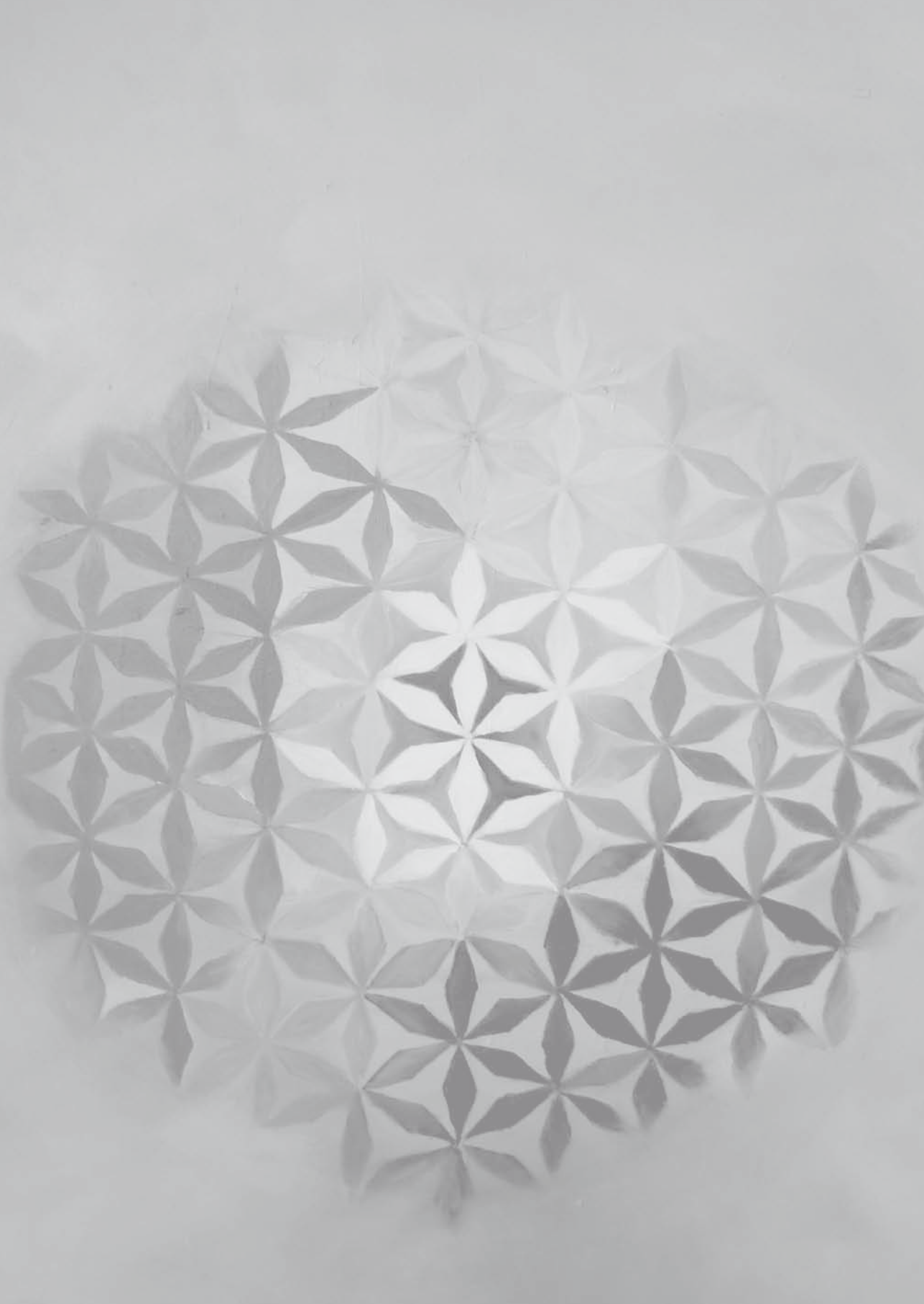

Chapter 5

Comparison of two expandable stents for malignant esophageal disease: a randomized controlled trial

Nicoline C.M. van Heel[1], Jelle Haringsma[1], Henk Boot[2], Annemieke Cats[2], Steven A.L.W. Vanhoutvin[2], Ernst J. Kuipers[1]

[1]Departments of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[2]Departments of Gastroenterology and Hepatology, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Submitted

ABSTRACT

Objectives: Self-expanding metal stents (SEMS) provide effective palliation in patients with malignant dysphagia. However, although life expectancy is generally limited, reintervention rates due to stent dysfunction are significant. New SEMS are being designed to overcome this drawback. In the present study, we aimed to assess whether the new design Evolution stent is superior to the conventional Ultraflex stent for the palliative management of patients with malignant dysphagia or esophageal fistulae.

Methods: In a multi-center randomized clinical trial, consecutive patients with stenosis or fistula due to malignant esophageal disease were randomized to placement of a conventional Ultraflex® stent or the new Evolution® stent. Patients were followed by scheduled telephone calls at one and three months after SEMS insertion.

Results: A total of 80 patients (73% male; median age 67 years (range: 40-92 years)) were included. One patient refused follow-up. Technical success was 100% in both groups. Reintervention rate was 15/40 (38%) for the Ultraflex and 4/39 (10%) for the Evolution stent (p=0.004). Major complications including aspiration pneumonia and bleeding occurred more frequently with the Ultraflex stent (10/40 (25%)) compared to the Evolution stent (3/39 (8%)) (p=0.04). There was no difference in overall survival between the two groups.

Conclusions: The Ultraflex stent and Evolution stent are equally effective in the relief of malignant dysphagia and sealing fistulae. Ultraflex stent is associated with more stent dysfunction and a significantly higher major complication rate. Patients treated with an Evolution stent also needed significantly fewer reinterventions than those treated with an Ultraflex stent. This sets the preference for the Evolution stent over the Ultraflex stent for patients with malignant esophageal disease.

INTRODUCTION

Esophageal cancers are among the leading causes of cancer-related death worldwide. The incidence of esophageal carcinoma is rising rapidly in developed countries because of an increase in the frequency of adenocarcinoma.[1] The 5-year survival of patients with esophageal cancer remains below 20% despite multimodality treatment and concentration of care. The majority of patients with esophageal cancer have inoperable disease at presentation. In these patients palliative therapy is the only treatment option. Placement of a self-expandable metal stent (SEMS) is a rapid means to restore luminal patency and/or to seal esophageal fistulae. Nutritional intake can be effectively restored, thereby significantly improving the quality of life.[2-3] Ideally this is accomplished in a single procedure, without the need for additional procedures (reinterventions) within the limited further life-span of these patients.

A wide variety of expandable esophageal endoprostheses have been developed to improve therapeutic outcome and to reduce the need for endoscopic reintervention during the course of the disease. Unfortunately, reinterventions remain common.[4-6] Currently, the Ultraflex® stent is worldwide most frequently used. The Evolution® stent has recently been introduced as an alternative with modified characteristics, including adaptations in the delivery system, flares, diameter and covering. In this prospective randomized study, we aimed to assess whether the new design Evolution stent is superior to the conventional Ultraflex stent for the palliative management of patients with malignant dysphagia or esophageal fistulae.

METHODS

Study design and patients

STEnts for esophageal MAlignant disease (STEMA) trial was a randomized open multicenter trial. Patients were eligible for inclusion if they had inoperable esophageal cancer, complicated by esophageal stenosis and/or fistula formation, with an indication for permanent stent insertion. Patients were ineligible for inclusion if they presented with lesions within 2 cm from the upper esophageal sphincter, lesions longer than 11 cm, or with active bleeding at endoscopy.

Stent placement was performed in two hospitals, the Erasmus MC University Medical Center Rotterdam and the Antoni van Leeuwenhoek Hospital - Netherlands Cancer Institute, Amsterdam the Netherlands. The ethical committees of both participating centers approved the study. All patients provided written informed consent before enrolment.

Randomization

Patients were randomly assigned (1:1) to Ultraflex stent or Evolution stent insertion. Randomization was done by computer-generated blocks of 10, stratified by centre. Patients and investigators were not masked to treatment allocation. All authors had full access to all the data in the study and had shared responsibility for the decision to submit the report for publication.

SEMS and stent insertion procedures

Patients were treated with an Ultraflex stent or an Evolution stent (Figure 1). The Ultraflex stent (Boston Scientific, Natick, MA) consists of a partially covered knitted nitinol wire tube. The cover consists of a polyurethane layer that covers the midsection of the stent extending up to 1,5 cm on each end. The stent is available in 3 lengths: 100 mm, 120 mm and 150 mm. The stent has a body diameter of 18 mm and a proximal flare with a diameter of 23 mm.

The Evolution stent (Cook Medical, Limerick, Ireland) has a pistol-grip delivery system that allows controlled release while the stent can be recaptured during release. The "lasso" loop on the proximal end enables stent repositioning and removal after placement. The cover consists of a silicone layer that covers the midsection of the stent extending up to 1,5 cm

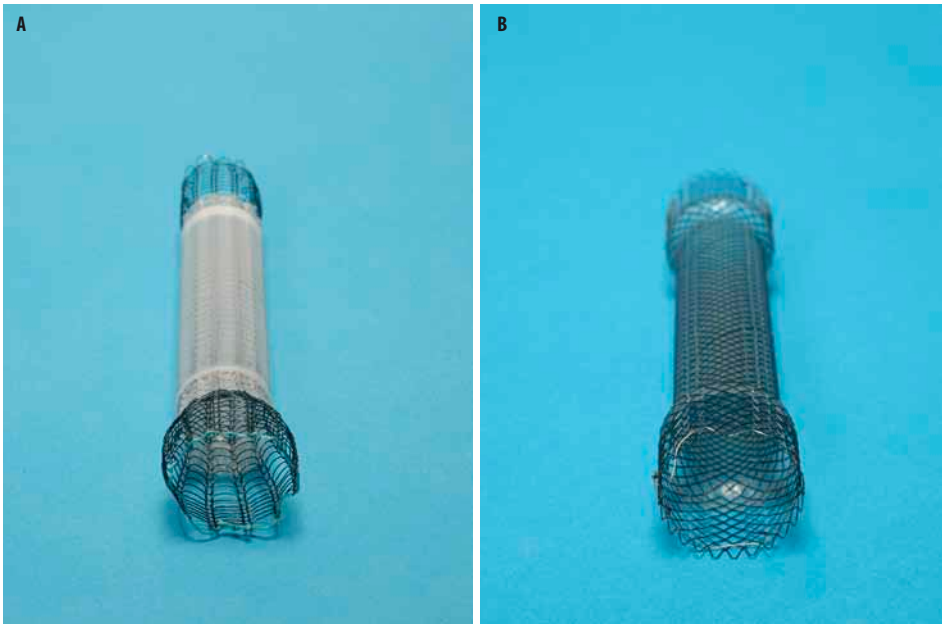

Figure 1. Stents used in this trial: Ultraflex stent (A) Evolution controlled release stent (B)

on each end. The stent has a body diameter of 20 mm and two distal flanges of 25 mm in diameter. The stent is available in 4 lengths: 80, 100, 125 and 150 mm.

All procedures were performed under conscious sedation. The lesion was inspected using a flexible video endoscope. The distance between the dental incisors and the proximal border of the tumor and the length of the lesion were measured. Stent length was based on the length of the lesion; the stent length was chosen at least 3 cm longer than the stricture length, to allow for deployment of the flanges above and below the proximal and distal tumor shoulder. The stent was positioned over a guidewire and deployed under fluoroscopy. One hour after the procedure patients were given a small amount of clear liquid by mouth to evaluate passage, retrosternal pain and aspiration. Resumption of oral intake was permitted on the day of implantation.

Study outcomes

The primary outcome was the 90-day endoscopic reintervention rate. Secondary outcomes were technical success, stent dysfunction, complications and survival. Dysphagia was scored prior to SEMS insertion and 30 days thereafter, according to the following Atkinson Dysphagia was scored prior to SEMS insertion and 30 days thereafter, according to the following Atkinson Dysphagia Score; 0=ability to eat a normal diet, 1=ability to eat some solids, 2=ability to eat semisolids only, 3=ability to swallow liquids only, 4=complete dysphagia.[7] Technical success was defined as dysphagia improvement or complete closure of the fistula with improvement of aspiration symptoms after stent placement. Stent dysfunction was classified as incomplete sealing of the esophageal leak, recurrent dysphagia, e.g. due to stent migration, stent obstruction or tumor overgrowth. Complications were defined according to the published nomenclature for classification of complications.[8] Severe complications included perforation, fistula, (aspiration) pneumonia, stridor and overt haemorrhage. Mild complications included retrosternal pain, symptomatic gastro-esophageal reflux or foreign body sensation.

Follow-up

Patients were evaluated prior to stent placement, at 30 and 90 days after SEMS insertion by scheduled telephone interviews, until new stent placement or death. In case of complications or stent dysfunction, patients were seen for re-evaluation. All evaluation items were recorded in the case record form.

Randomization

We calculated that a sample size of 80 would provide 80% power to detect a relative reduction in reintervention rate by at least 50% in favor of the new stent design.[9] All analyses were based on the intention-to-treat principle. For comparison of baseline characteristics, differences in continuous variables were analyzed by t tests, and differences in categorical variables by χ^2 tests. Complications and recurrent dysphagia in the two groups were compared with Kaplan-Meier and log-rank tests to adjust for time of occurrence of the event and survival differences. Survival of the two groups was calculated and compared using Kaplan-Meier curves and log-rank test. A significance level of 0.05 with two-sided testing was used, and all analyses were performed in SPSS® version 17 (IBM, USA).

RESULTS

Patient characteristics

Between June, 2009, and January, 2011 a total of 80 consecutive patients with malignant esophageal stenosis or fistulae due to malignant disease were randomized to either the Ultraflex stent or the Evolution stent group. Table 1 shows the baseline characteristics of the

Table 1: Baseline characteristics

	Ultraflex stent (n=40)	Evolution stent (n=40)
Age (years, mean (SD))	67 (12)	67 (10)
Men/women	32/8	26/14
Dysphagia score before treatment (mean (SD))	2.9 (0.8)	3.1 (0.6)
Tumor location from incisor teeth (cm, mean (SD))	33 (7.0)	28 (6)
Length stent (cm, mean (SD))	11.3 (1.8)	11.0 (2.8)
Indications for palliative treatment		
Metastasis	2 (5)	5 (13)
Esophageal cancer	38 (95)	35 (87)
Tumor histology		
Squamous cell carcinoma	8 (20)	15 (38)
Adenocarcinoma	30 (75)	20 (50)
Other	2 (5)	5 (13)
Esophagorespiratory fistula		
Yes	4 (10)	3 (8)
No	36 (90)	37 (92)
Previous chemo and/or radiotherapy		
Yes	30 (75)	25 (63)
No	10 (25)	15 (37)

Data are numbers (%) unless otherwise specified

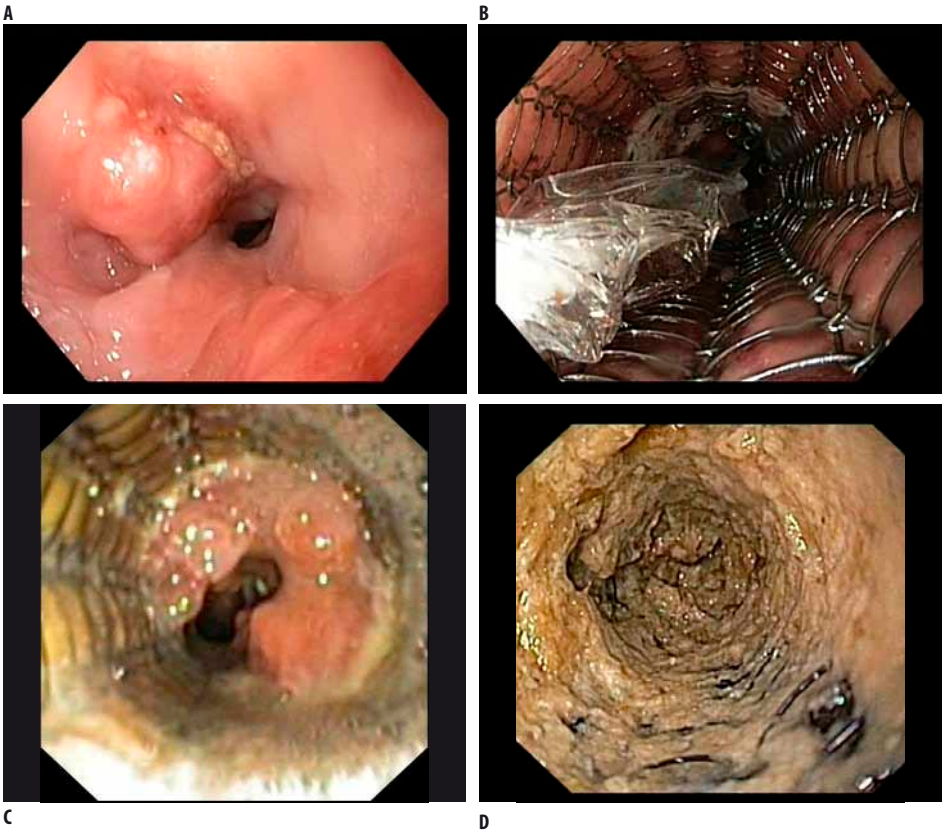

Figure 2. A. Endoscopic view showing malignant esophageal stenosis in the distal esophagus. B. The Ultraflex stent was positioned over a guidewire and deployed under endoscopic view, showing full expansion after placement. C. Granulomatous tissue growth in the distal uncovered segment, 6 weeks after placement of an Ultraflex stent. D. Food bolus obstruction.

two groups. Study groups were similar in terms of all baseline clinical- and procedural characteristics. Indications for stent therapy included primary esophageal cancer (n=73, 91%), and mediastinal metastasis of pulmonary cancer and breast cancer (n=7, 9%). Prior to inclusion 8 patients had received radiotherapy (10%), 15 chemotherapy (19%), and 32 both (40%). On inclusion 73 (91%) presented with dysphagia (Figure 2a), and 7 patients (9%) had a malignant esophago-respiratory fistula. In 11 patients (14%), the tumor was located within 2-4 cm of the upper esophageal sphincter.

Stent therapy

In this cohort, 40 (50%) Ultraflex stents and 40 (50%) Evolution stents were placed (Figure 2b). The initial stent insertion procedure was performed without any procedure related and was

technically successful in all patients (100%). One (1%) patient with an Evolution stent refused follow-up.

A statistically significant difference was observed between two stent groups for the primary outcome. Fifteen (38%) patients required endoscopic reintervention within 90 days after Ultraflex stent placement, versus 4 (10%) patients after Evolution stent placement (p=0.004). Table 2 shows the reinterventions performed. In these 19 (24%) patients, a total of 22 reinterventions were performed to manage persistent dysphagia (n=1), recurrent leakage (n=1), stent migration (n=4), tissue in- or overgrowth (n=9) (Figure 2c), or food obstruction (n=7) (Figure 2d). Recurrent symptoms of leakage or dysphagia occurred more frequently in the Ultraflex stent group than in the Evolution stent group (n=16 vs n=3, p<0.001).

TABLE 2. Complications and persistent or recurrent dysphagia after stent placement

	Ultraflex stent (n=40)	Evolution stent (n=39)	P
Endoscopic reinterventions	**15 (38%)**	**4 (10%)**	**0.004**
Desobstruction	7	0	-
Radiotherapy	1	0	-
Stent removal	3	2	-
Extra stent placement	7	2	-
Balloon dilation	1	0	-
Stent dysfunction	**16 (40%)**	**3 (8%)**	**<0.001**
Persistent dysphagia	0	1	-
Migration	3	1	-
Tissue in- or overgrowth	8	1	-
Food bolus obstruction	7	0	-
Leakage	1	0	-
Total complications	**15 (38%)**	**10 (26%)**	**0.257**
Major complications	**10 (25%)**	**3 (8%)**	**0.038**
(aspiration)pneumonia	3	2	-
Severe pain	0	1	-
Hemorrhage	7	0	-
Minor complications	**5 (13%)**	**7 (18%)**	**0.500**
Mild retrosternal pain	5	5	-
Gastroesophageal reflux	0	1	-
Foreign body sensation	0	1	-

*More than one complication arose in some patients.

Tumor overgrowth and stent migration were mostly managed by placement of a second stent and food obstruction by endoscopic desobstruction.

After 30 days, the Atkinson Dysphagia Score had improved from a mean of 3.0 to 0.5 in both study groups. In a multivariate analysis variables including the indication for stent therapy, prior therapy, and stent location were not independently associated with the therapeutic outcome in both groups.

Complications

With respect to the overall complications at 3 months, a total of 15 complications (38%) occurred in patients randomly assigned to the Ultraflex group, versus 10 (26%) in the Evolution group (p=0.26) (Table 2). Thirteen complications were major and 12 were minor. Significantly more Major complications occurred after Ultraflex stent placement than after Evolution stent placement (p=0.04). Complications consisted predominantly of hemorrhage, which occurred in 7 patients after Ultraflex stent insertion compared to none of the patients treated with an Evolution stent. Bleeding resolved spontaneously in all patients. Two patients required blood transfusion. Five patients developed a (aspiration) pneumonia after stent placement; two of them died as a consequence, despite antibiotic treatment.

No significant differences were noted between the two groups with respect to the incidence of mild complications. Mild complications included pain, gastroesophageal reflux and foreign body sensation. One patient in the Evolution treated group demanded SEMS removal because of severe chest discomfort, in all others (n=10) retrosternal pain was treated effectively with analgesics.

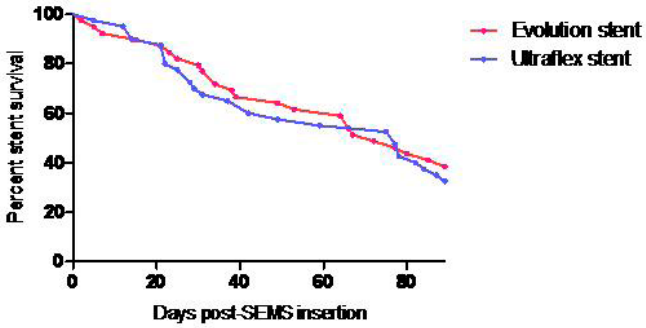

Figure 3: Overall stent survival after treatment.

Survival

Median follow-up was 77 days (range: 1-90 days) after Ultraflex stent and 75 (range: 1–90 days) after Evolution stent placement (p=0.23; Figure 3). Thirty-nine patients were followed until death, 10 until stent replacement and 30 until 90 days of follow-up. By the end of follow-up, 36 patients had died from tumor progression, 2 from aspiration pneumonia, and 1 from complications of recurrent esophageal leakage. The 30-day mortality did not differ between groups (Ultraflex n=10 versus Evolution n=7, p=0.45)

DISCUSSION

This randomized controlled trial in patients with malignant esophageal stenosis and esophago-respiratory fistula compared the most frequently used Ultraflex stent with the newly designed Evolution controlled release stent. Stent placement was successful in all patients in both study arms, and both stents were equally effective in improving food intake. However, placement of an Evolution stent was in comparison with the Ultraflex stent associated with lower reintervention rates and fewer major complications.

In the Ultraflex group, 38% of patients required one or more interventions to manage stent dysfunction within 90 days after initial stenting, which is in line with previous published series.[10-12] Yet, only 10% of patients in the Evolution group required endoscopic re-interventions. The latter is low compared with the literature on malignant esophageal stenting. To date no comparative studies have been published with the Evolution stent, but one recent uncontrolled study with this new device reported a 25% dysphagia recurrence at a median survival of 88 days.[13]

Endoscopic reinterventions are generally associated with patients burden, as well as significant costs and risks. They have a negative impact on the quality of life, even when they are frequently successful.[10] The majority of our patients needed additional treatment for tumor overgrowth or food bolus obstruction. Food impaction only occurred after Ultraflex stent placement, which may be due to the smaller stent diameter. Previous series have reported similar association between stent size and the risk of food bolus obstruction.[14] While others noted stent migration as predominant cause of stent dysfunction, migration was only observed with 8% of the Ultraflex stents and 3% of the Evolution stents. [9, 11, 15] This is at the lower end of the reported 4-18% migration rate of the Ultraflex stent and the 5% migration rate of the Evolution stent.[13, 16-17]

The observed overall complication rate of 32% in our series is substantial, yet in the middle of the range in recent reports.[18-20] In our series major complications arose more often after Ultraflex stent placement. The most common complication was hemorrhage, remarkably this only occurred in the Ultraflex stent group.

The reported rate of stent procedure-related mortality is up to 54%, which is higher than in our study (3%).[15, 18, 21] Within 1 month after SEMS insertion, two patients died from aspiration pneumonia and sepsis despite administration of antibiotics. Minor complications including retrosternal pain following stent placement requiring administration of analgesic medication are frequently observed and resolve spontaneously in the majority of patients within a few days.[4, 22-23] Persistent severe pain is uncommon and was observed in one patient after proximal stent placement, this stent was successfully removed after 23 days. Complications were not related to stent location or prior therapy, which accords with results elsewhere.[4, 12, 24] However, this latter finding is in disagreement with some other reports.[23, 25-26]

The success rate of placement was 100% in both study groups. Apparently the type of introduction system did not influence the placement outcome. Stent placement resulted in sealing off esophagorespiratory fistulae and restoring luminal patency in all but one patients. There were no significant differences between the two stents in the improvement of dysphagia or fistulae sealing at 1 and 3 months interval.

The observed benefits in the performance of the Evolution stent may likely be ascribed to the new stent design and resulting physical characteristics. The Evolution stent has a higher hoopstrength (radial force) than the Ultraflex, it has silicone internal and external coatings to prevent ingrowth, large dual flanges to prevent migration, and a larger stent diameter to avert food-bolus obstruction.

To our knowledge, previous randomized controlled trials with the Ultraflex endoprosthesis, did not show any significant differences in therapeutic outcome between two types of SEMS. In the first randomized controlled trial, Siersema et al. compared the Ultraflex stent, Flamingo Wallstent and Gianturco-Z stent, and observed no clear differences in complication and recurrent dysphagia rate.[17] Sabharwal et al. compared the Ultraflex stent with the Flamingo Wallstent. The two SEMS types showed similar efficacy in relieving malignant dysphagia and were associated with similar complication rates.[5] In a more recent series, Conio et al. compared the self-expandable metal Ultraflex stent with the self-expandable plastic Polyflex stent in 100 patients with a malignant esophageal disease, with a significant higher complication rate in the plastic stent group, leaving covered SEMS as the treatment modality of choice for patients with malignant esophageal disease.[16]

The strengths of this study include its prospective randomized design and high rate of follow-up evaluation (99%). The study is relatively large thereby providing the power to reach statistical significance in primary and secondary parameters. Performance of the study at a two institutions over a short period of time with expert endoscopists in SEMS placement assured relative uniformity of care to minimize confounders. Follow-up evaluation of patients by telephone interview at scheduled time intervals enabled us to capture all complications that occurred after discharge. A potential weakness is the inclusion of patients with either stenosis or fistula into the study, as these symptoms pose different demands to the performance of the stent, and thereby to the design. Yet only seven patients presented with fistula, equally divided over both groups. This subgroup was too small to allow for subgroup comparison. Another weakness is that our follow-up was limited to 90 days post stent insertion. In this study 30 patients were still alive with their initial stent in situ at this end-point (38%). Evaluation of stent performance after reaching this endpoint is often more difficult, as the clinical condition often prohibits reintervention, and the ability to swallow becomes increasingly difficult to analyze in view of tumor progression and the declining clinical performance.

In conclusion, the present study indicates that the Ultraflex stent and Evolution stent are equally effective in the relief of malignant dysphagia and sealing fistulae. However, Ultraflex stent placement is associated with more stent dysfunction and a significantly higher major

complication rate. Patients treated with an Evolution stent also needed significantly fewer reinterventions than those treated with an Ultraflex stent. This sets the preference for the Evolution stent over the Ultraflex stent for patients with malignant esophageal disease.

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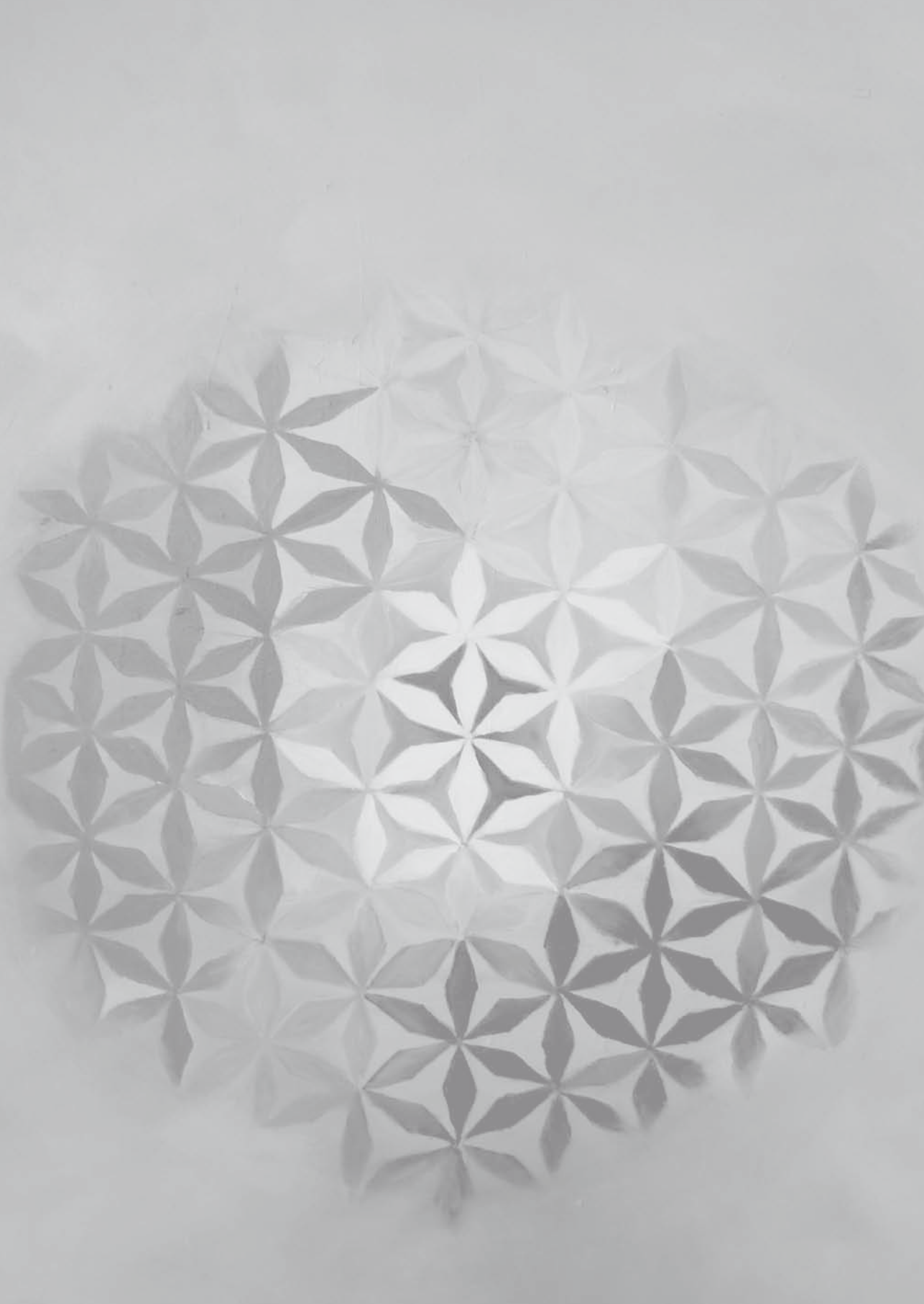

Chapter 6

Endoscopic removal of self-expandable metal stents from the esophagus

Nicoline C.M. van Heel[1], Jelle Haringsma[1], Bas P.L. Wijnhoven[2], Ernst J. Kuipers[1]

[1]Departments of Gastroenterology and Hepatology, and [2]Surgery, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Gastrointestinal Endoscopy 2011;74(1):44-50

ABSTRACT

Background: Self-expandable metals stents (SEMSs) have increasingly been used as a temporary device to bridge chemoradiotherapy in patients with malignant esophageal disease or in patients with benign esophageal defects or stenosis.
Objective: To evaluate the outcome of removal of SEMSs in a large cohort of patients with benign and malignant esophageal disease.
Design: Observational study with standardized treatment and follow-up.
Setting: Single university center.
Patients: Between 2001 and 2010, 95 consecutive patients referred for endoscopic SEMS extraction were included.
Interventions: Endoscopic stent removal.
Main Outcome Measurements: Technical and functional outcome and complications.
Results: A total of 124 stent extractions were undertaken in 95 patients; both partially covered (68%) and fully covered (32%) SEMSs were removed. Three patients had 2 overlapping SEMSs in place. Successful primary removal was achieved in 89%; the secondary removal rate was 96%. Uncomplicated primary removal rate was significantly higher for fully covered versus partially covered stents (P= 0.035) and for single versus overlapping stents (P = 0.033). Patients with a complicated stent removal had the stent in place significantly longer compared with patients with an uncomplicated primary stent removal (126 days vs 28 days; P = 0.01). Surgical removal was required in 3 patients (2.4%). Six moderate and severe complications (5%) related to the endoscopic extraction occurred.
Limitations: Retrospective, nonrandomized study design.
Conclusions: Primary endoscopic removal of an SEMS is feasible in the majority of patients with benign and malignant esophageal disease. A longer duration of SEMS therapy and the use of partially covered SEMSs both impeded SEMS removal. Moreover, overlapping SEMSs should be avoided for temporary use because stent disintegration and subsequent complications may occur.

INTRODUCTION

In the early 1990s, self-expandable metal stents (SEMSs) were introduced for the palliative therapy of esophageal carcinoma. The design of the conventional SEMS aims at restoring luminal patency while minimizing the risk of stent migration in patients with a short life expectancy.[1-3] However, features in the design of the stent that help to prevent migration also hamper stent removal once they are in position, particularly after longer periods of time. Currently, both fully covered and partially covered SEMSs are used. The covering membrane prevents tissue ingrowth and allows sealing of a fistula. In addition, the cover also facilitates SEMS removal by preventing embedding of the stent.[4]

The ability to remove these stents has opened up new applications, such as the insertion of an SEMS as a temporary device in patients with benign esophageal defects or stenosis and to bridge chemoradiotherapy in patients with malignant esophageal disease. [5-11] However, severe complications during SEMS removal have been reported, but most series reported to date are small. [7, 10, 12-15] Hence, this prompted us to evaluate our experience with endoscopic SEMS removal in a large cohort of patients with benign and malignant esophageal disease and to identify factors associated with SEMS removal outcome.

METHODS

We performed a retrospective analysis from our prospective stent database. Institutional review board approval was obtained to publish these results. All patients referred for endoscopic SEMS removal for benign and malignant esophageal disease from 2001 to 2010 were identified and included in the analysis. Patients with migrated stents were excluded from the study. Demographic and clinical data including stent type, stent location, underlying disease and stent indication, the technical outcome of stent removal, and procedure-related complications were extracted from our database. All patients were followed for at least 6 months after complete stent removal or until death.

Complications were classified according to the published nomenclature for classification of complications.[16] Uncomplicated removal was defined as successful removal on the first attempt without complications. Complicated primary removal was defined as removal failure and/or stent removal with complications on the first attempt.

Stent removal

Stent removal techniques varied according to the type of stent. All procedures were performed with the patient under conscious sedation by using a standard video gastroscope (GIF-240, GIF-160, GIF-180, GIF-H180; Olympus Optical Co, Tokyo, Japan). Partially covered

SEMSs were removed by grasping the distal edge of the stent with retrieval forceps. The distal end of the stent was subsequently inverted, and the stent was removed by gradual traction on the distal end leading to complete inversion (Video 1, available online at www.giejournal.org). Fully covered SEMSs were removed by pulling the proximal retrieval lasso or by grasping the proximal metal end of the stent with a polypectomy snare. No overtube or retrieval cap was used. Removal of a stent-in-stent was considered a single extraction procedure. After stent removal, retrieved SEMSs were carefully examined for completeness, and the esophagus was inspected endoscopically. Patients were admitted overnight for clinical observation if no new stent was inserted. A same-day esophagogram with gastrografin was performed only in case of clinical or endoscopic suspicion of perforation or persistent fistula. A clear liquid diet was first started in the absence of such suspicion to be expanded in the next hours in the absence of symptoms suggesting complications.

Statistical analysis

Numerical data are presented as the mean with the standard deviation or median with the interquartile range (IQR), as appropriate. The Student t test, chi-square test, and Pearson's correlation or their nonparametric equivalents, were used when appropriate. A Cox regression model was used to explore the effect of the variables on time until complications occurred. Statistical analyses were performed with SPSS software, version 17.0 (SPSS Inc, Chicago, Ill). Two-sided P values <0.05 were considered significant.

RESULTS

Patient characteristics

A total of 95 patients underwent a total of 124 endoscopic SEMS removals. Fifty-five of 95 patients (58%) were male; the mean age was 61 years at inclusion (standard deviation 15 years, range 14–90 years). Baseline patient characteristics are summarized in Table 1. After initial SEMS removal, 29 patients (31%) required placement of another stent and subsequent repeat extraction. Twenty-four of these 29 patients (83%) with benign and 5 of 29 patients (17%) with malignant esophageal disease required stent replacement. The indications for stent removal in patients with malignant incurable disease included stent-related complications, therapy failure, and stent removal before surgery. Three patients (3%) had 2 SEMSs in place (stent-in-stent). Eighty-six of 124 temporary SEMSs (69%) were inserted for benign esophageal disease (Figure 1A) and 38 (31%) for a malignancy. Fifty SEMSs (40%) were placed for stenosis and 74 (60%) were placed for fistulae. SEMSs were partially covered (n=84, 68%) (Figure 1B) or fully covered (n=40, 32%). Twenty-seven of 124 SEMSs (22%) were placed across

TABLE 1. Baseline characteristics of patients

Age, y, mean ± SD (RANGE)	61 (14-90)
Sex, no. (%)	
Male	55 (58)
Female	40 (42)
Indication stent removal, no. (%)	
Benign disease	71 (57)
Stent related complications	20 (16)
Therapy failure	22 (18)
Abscess drainage	2 (2)
Bridge to surgery	9 (7)
Benign esophageal disease, no. (%)	86 (69)
Malignant esophageal disease, no. (%)	38 (31)
Esophageal stenosis, no. (%)	50 (40)
Esophageal fistula, no. (%)	74 (60)
Duration stent therapy, median (range)	30 (1-587)

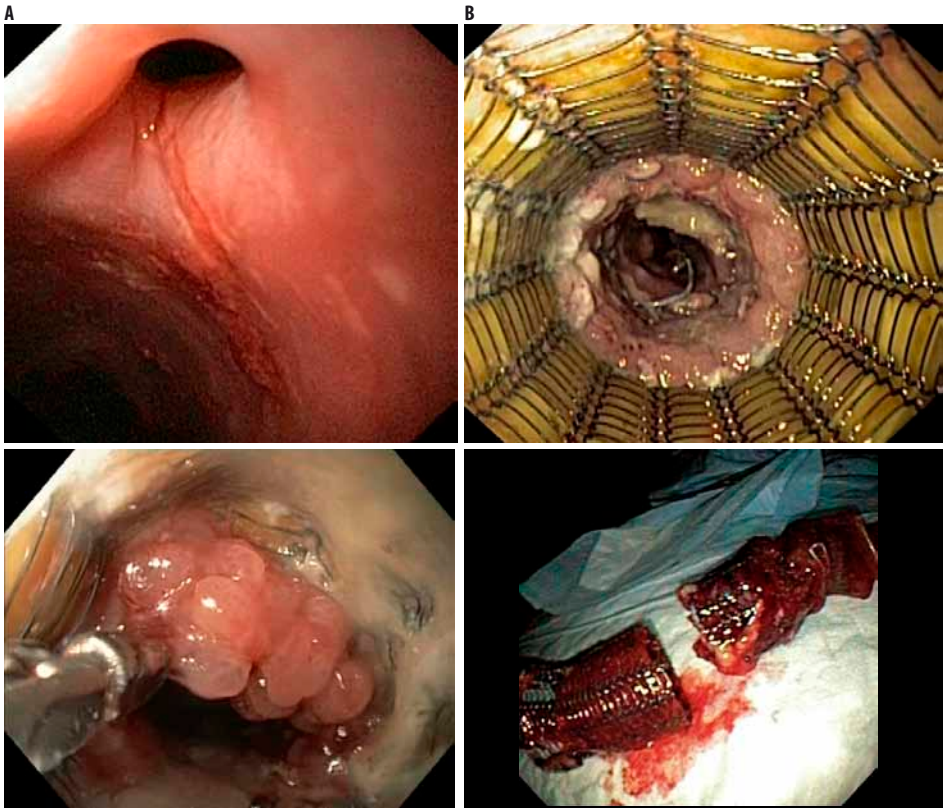

Figure 1.

A. Endoscopic view showing a benign esophageal fistula in the distal esophagus. B. Full expansion of the Ultraflex stent and complete sealing of the esophageal wall 3 months after stent insertion. Granulomatous tissue growth is visible. C. The distal edge of the uncovered segment is graspedwith retrieval forceps. D. Stent breakage occurred as a result of endoscopic traction.

the gastroesophageal junction. The shaft diameter ranged between 16 and 20 mm. Median stent length was 12 cm (IQR 2 cm, range 7-15 cm). Median duration of stent therapy was 30 days (IQR 26 days, range 0-587 days). Indications for stent removal are summarized in Table 1.

Uncomplicated stent removal

SEMS removal was successful and uncomplicated in 89% (110/124). Median time interval (indwelling time) to uncomplicated removal was 28 days (IQR 22 days, range 1 to 393 days). Of these, 76 of 110 SEMSs (69%) were inserted for benign esophageal disease and 34 of 110 SEMSs (31%) for malignant esophageal disease; 71 SEMSs (65%) were partially covered, and 39 SEMSs (35%) were fully covered. One patient had a stent-in-stent (1%).

Complicated stent removal

SEMS removal was complicated in 11% (14/124). Median time interval to complicated removal was 126 days (IQR 248, range 14-587). Ten of 14 SEMSs (71%) had been inserted for benign disease and 4 SEMSs (19%) for a malignancy; 13 SEMSs (93%) were partially covered and 1 (7%) was fully covered. Two patients (18%) had a stent-in-stent. Of the 12 patients in whom the primary attempt at stent removal failed, 9 (75%) underwent a second attempt. The secondary success rate in these patients was 33%; 4 SEMSs (44%) were removed in 2 to 7 endoscopic sessions. This brought the overall success rate of endoscopic removal to 96%. Surgical removal was deemed necessary in 3 of 124 (2.4%); 2 SEMSs were removed by minigastrotomy to allow endoscopic access for distal antegrade removal because endoscopic retrograde removal had failed, and 1 SEMS was removed during radical esophagectomy. In the latter patient, the stent had been placed as a bridge to surgery. In 2 patients (1.6%) with a malignancy and poor prognosis, the embedded stent was left in place without further attempts at endoscopic removal.

During 6 removal procedures (4.8%), moderate or severe complications occurred. Five stents (4.0%) broke during stent extraction, necessitating multiple endoscopic sessions to remove the fragments (Figure 1C,D). In 2 of 5, parts of the broken stent remained embedded in the esophageal wall. One of these 2 patients had failed to comply with the original appointment for timely stent removal and had been lost to follow-up without a permanent residence and contact address. He came back 84 weeks after stent placement with dysphagia. Stent disruption occurred during stent extraction. A filament migrated over the next 3 years and perforated the thoracic vertebrae, which resulted in osteodiscitis and a thoracic empyema. This patient, in whom the SEMS had been placed for Boerhaave's syndrome, required an esophageal resection. In the other patient with an irretrievable stent fragment, an esophagorespiratory fistula developed after an interval of 11 months. In 1 patient, retrieval of the SEMS was complicated by a sleeve mucosectomy of the proximal esophagus (Figure 3), resulting in

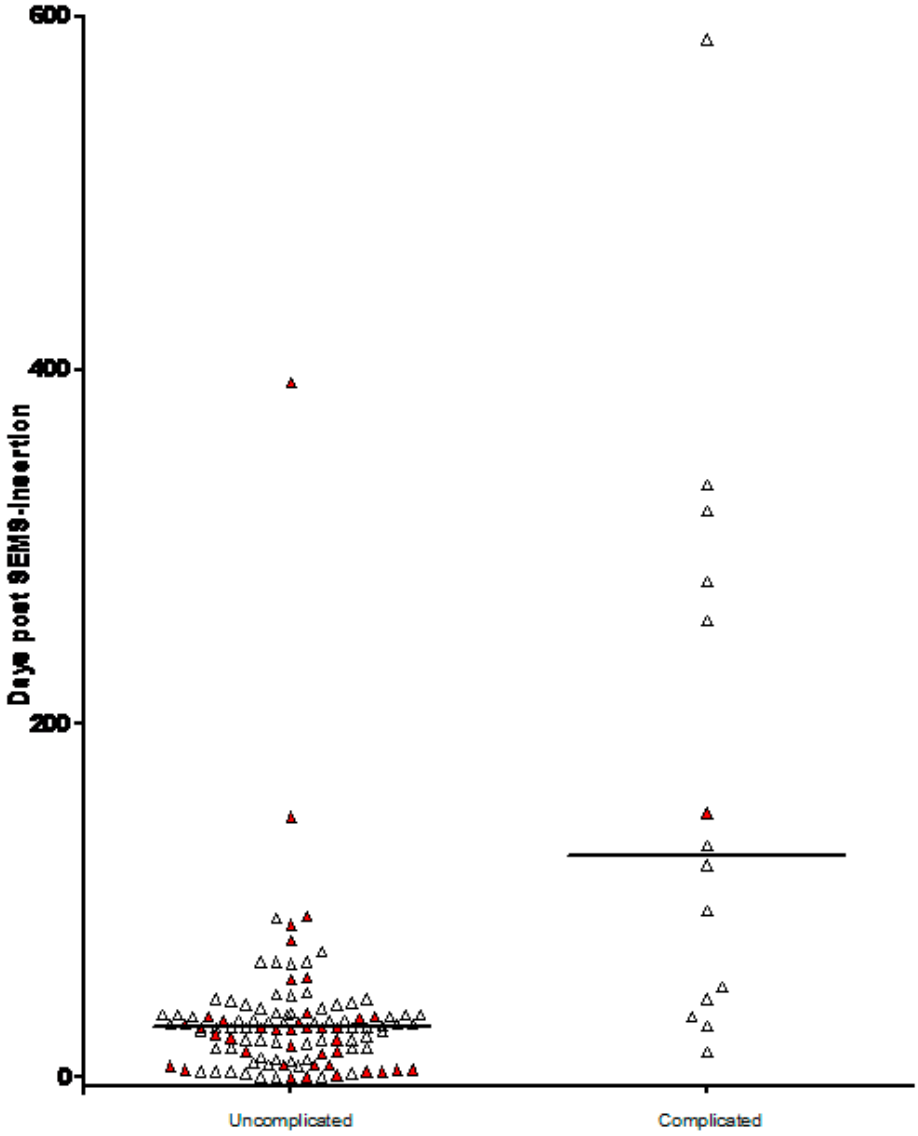

Figure 2. This figure demonstrates the influence of the duration of stent therapy on the outcome of stent removal. The gray triangles represent fully covered SEMSs and the white triangles partially covered SEMSs. Patients with a failed or complicated stent extraction had the stent in place significantly longer compared with patients with an uncomplicated primary stent extraction (126 days vs 28 days; $P = .01$).

a proximal stenosis. In this patient, removal took place 4 months after SEMS insertion, after 4 failed attempts elsewhere that had included application of argon plasma coagulation. Minor self-limiting postprocedure bleeding occurred during removal of 2 SEMSs (1.6%).

Stent removal outcome was time dependent; patients with an uncomplicated SEMS extraction had the stent in place for a significantly shorter time compared with patients with

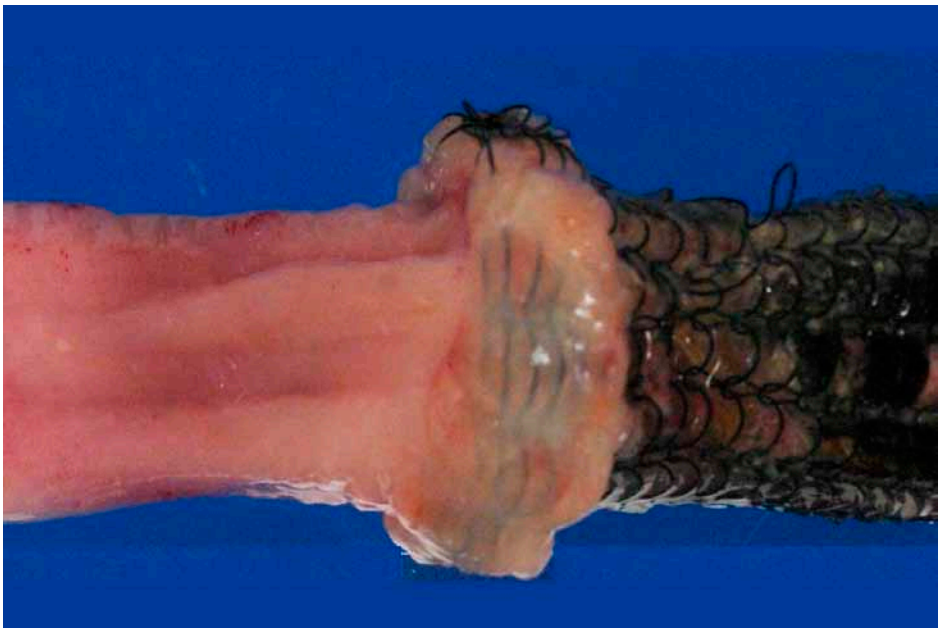

Figure 3. Sleeve mucosectomy complicating partially covered SEMS removal 4 months after insertion.

a complicated SEMS extraction (P=0.006) (Figure 2). We also found significant difference in the success rate of stent removal between partially and fully covered SEMSs (85% vs 99%, P=0.035) and between 1 versus 2 stents (99% vs 86%, P=0.033). Removals of 4 of 27 SEMSs (15%) placed across the gastroesophageal sphincter and 10 of the remaining 97 SEMSs (10%) were complicated, which did not reach statistical significance (P=0.50). No clinically significant differences were found in the stent removal outcome between benign and malignant disease and between fistulae and stenoses. Other variables including stent type, luminal diameter, and stent size were also not independently associated with the stent removal outcome (Table 2).

TABLE 2. Stent removal

	Uncomplicated	Complicated	P
No. (%) of stents	110 (89)	14 (11)	
2 overlapping stents, no. (%)	1 (1)	2 (14)	.033
1 stent, no. (%)	109 (99)	12 (86)	
Partially covered stent, no. (%)	71 (65)	13 (13)	.035
Fully covered stent, no. (%)	39 (35)	1 (3)	
Esophageal fistula, no. (%)	64 (58)	10 (71)	.399
Esophageal stenosis, no. (%)	46 (42)	4 (29)	
Benign esophageal disease, no. (%)	76 (69)	10 (71)	.563
Malignant esophageal disease, no. (%)	34 (31)	4 (29)	
Duration therapy, days, (range)	28 (0 - 393)	131 (14 - 587)	0.006

DISCUSSION

Covered SEMSs have become the treatment of choice for malignant stenosis and esophagorespiratory fistulae. SEMSs are generally used as palliative treatment for patients with a limited life expectancy, with no intention of subsequent stent removal.[17] Side effects such as ulceration, stricture formation, perforation, and bleeding are well-known complications of long-term stent placement.[10, 18-21] To avoid these complications, timely removal of SEMSs in patients with benign esophageal disease is crucial. Currently, covered SEMSs have been increasingly used as a temporary device in patients with benign esophageal perforations or stenosis. [8, 10, 22-27] Stents are also successfully used as a bridge to therapy and to maintain oral intake before surgery or chemotherapy and radiotherapy.[28-29]

Some studies reported unacceptable rates of complications caused by temporary stent placement. [14, 30-32] In 1 series using SEMSs for benign indications, half of the patients experienced a complication. [22] A pooled analysis of 10 studies of self-expandable plastic stent placement for benign strictures revealed a major complication rate of 9%, a migration rate of 24%, and a reintervention rate of 21% in 130 cases.[33] A similar analysis of 12 studies evaluating SEMSs in 168 cases revealed similar results (complication rate of 10%, migration rate of 14%, and an efficacy of <50%).[34] Based on these prohibitive rates, some authors have suggested that expandable stents should not be inserted temporarily.[14, 30-31, 35-36] In the United States, the self-expandable plastic Polyflex stent is the only stent currently approved for removal after long-term placement. The currently available SEMSs have not received U.S. Food and Drug Administration approval for removability. [37]

Severe complications from SEMS removal have also been reported.[7, 10, 12-15, 22-23] In a large series describing nonsurgical removal of 119 fully covered nitinol stents, Yoon et al reported a success rate of 99% and only 1 major complication. The latter, a major bleeding, resulted in death. [7] In this study, however, almost one fourth of the stents (23%) had migrated and were retrieved from the stomach or proximal esophagus. In a more recent study, Eloubeidi and Lopes[24] described a series of 22 successful fully covered nitinol stent removals with 1 stent fracture and no major complications related to the retrieval procedure. Leers et al.[38] described removal of 26 partially covered stents in a series of 31 patients with esophageal leaks and perforations without complications. Similar findings with regard to the safety of stent removal after short-term placement have been reported in smaller series.[5-6, 39] In our study, the largest series of esophageal stent removals to date and the first series describing a variety of partially and fully covered SEMSs, 124 esophageal SEMS removals were attempted in 95 patients at a single institution. Stents that had migrated were excluded from analysis because they are mobile and pose a distinct challenge to the endoscopist. All patients were followed until complete stent removal; thus, we were able to assess the feasibility and complications of this intervention.

The uncomplicated primary removal rate was 89%, which is lower than the 97% to 100% in previously published series.[7, 24, 40] However, this series included both fully and partially covered SEMSs, a variety of indications, and indwelling time after insertion. After 1 to 7 endoscopic sessions, 96% of all stents were removed endoscopically; 3 stents (2.4%) were surgically removed and 2 stents (1.6%) were left in place. Successful endoscopic removal was time dependent; patients with an uncomplicated primary SEMS extraction had the stent in place for a significantly shorter time compared with patients with a complicated or failed SEMS extraction. Previously published series reported controversial data on the optimal stenting period.[8, 10, 22, 30, 41-42] Most series recommend stent removal between 3 and 10 weeks.[8, 22, 43] However, Choi et al. reported successful stent removal even after 8 years.[41] Based on our results, we advocate removing the SEMSs within 6 weeks after placement in patients in whom stent removal is deemed necessary regardless of stent type. In cases of persisting symptoms after stent removal, placement of another stent is the preferred approach.[10, 37]

An important finding of this study is the significant difference in the success rate of stent removal between partially and fully covered SEMSs. This is related to stents becoming embedded. Partially covered SEMSs are prone to tissue ingrowth through the uncovered mesh.[4, 44] In our series, removal of 13 partially covered SEMSs failed because of embedded stents. Two previous studies have reported its mechanism: initially, pressure necrosis is caused by the radial force of the stent, leading to migration of the struts of the stent into the mucosa and submucosa, followed by a chronic lymphocytic inflammatory reaction, mucosal hyperplasia, and subsequent fibrosis.[45-46] Although tissue ingrowth is beneficial for preventing stent migration, it makes removal complex and challenging. Jaganmohan and Raju[15] reported that fully covered SEMSs can also become embedded in the esophageal wall; this was also encountered in 1 case in our series. It has been suggested that pressure necrosis of the ingrown hyperplasic tissue into the uncovered segments can be created by the insertion of a self-expandable plastic stent through the SEMS to facilitate SEMS removal.[8, 47-50]

Complications occurred in 6% of the SEMS removals. The most commonly encountered complication was stent breakage, which occurred as a result of endoscopic traction with retrieval forceps in 5 of 124 removals (4%); similar rates have been reported by other groups (0%-5%).[7, 24, 38, 40, 51-52] Caution should be taken when using overlapping SEMSs as a temporary device; 2 patients with SEMS breakage had overlapping stents in place ($P<0.05$). In case of stent breakage and possibly incomplete endoscopic stent removal, careful endoscopic evaluation or surgery should be considered to ensure that all broken segments have been removed. Broken filaments may migrate and may lead to life-threatening complications such as perforation and empyema, which occurred in 2 patients a number of years after SEMS removal.

There are some limitations to the study. First, various endoscopic removal techniques were used for a wide range of stents that differed in flexibility, radial force exerted, luminal diameter, and stent material. Multiple endoscopic removal techniques have been described in the

literature, including pulling the proximal lasso, distal-to proximal invagination of the stent, and the use of an overtube, retrieval hoods, and retrieval hooks. [7-8, 53-54] We used 2 removal techniques: the stent inversion technique for a partially covered SEMS and stent retrieval by pulling the proximal edge or lasso of the stent with retrieval forceps in a fully covered SEMS. No firm conclusions can be drawn regarding the most advantageous removal technique or the optimal stent design. The principal limitation of this study is the retrospective and nonrandomized design, a shortcoming that was also observed in similar previous studies[5, 11, 24] and that will be unlikely to overcome because it will be difficult to randomize sufficient numbers of patients to different extraction techniques.

In conclusion, this study shows that endoscopic removal of partially and fully covered SEMSs is feasible in the majority of patients with benign and malignant esophageal disease and provides a basis for using SEMSs as a short-term treatment, but with a considerable amount of caution. Both a longer period of stent placement and the use of partially covered SEMSs are associated with a negative effect on stent removal outcome. Moreover, overlapping SEMSs should be avoided for temporary use because stent disintegration and subsequent devastating complications may occur. These findings do not provide firm guidance on the optimum choice of temporary SEMSs in relation to indwelling time. We know that partially covered SEMSs are less likely to migrate but are more difficult to remove and that fully covered SEMSs have a higher migration rate but are easier to remove. Current prospective comparative trials will certainly shed more light on this issue and may provide a more differentiated view on optimal timing of SEMS extraction in relation to stent type.

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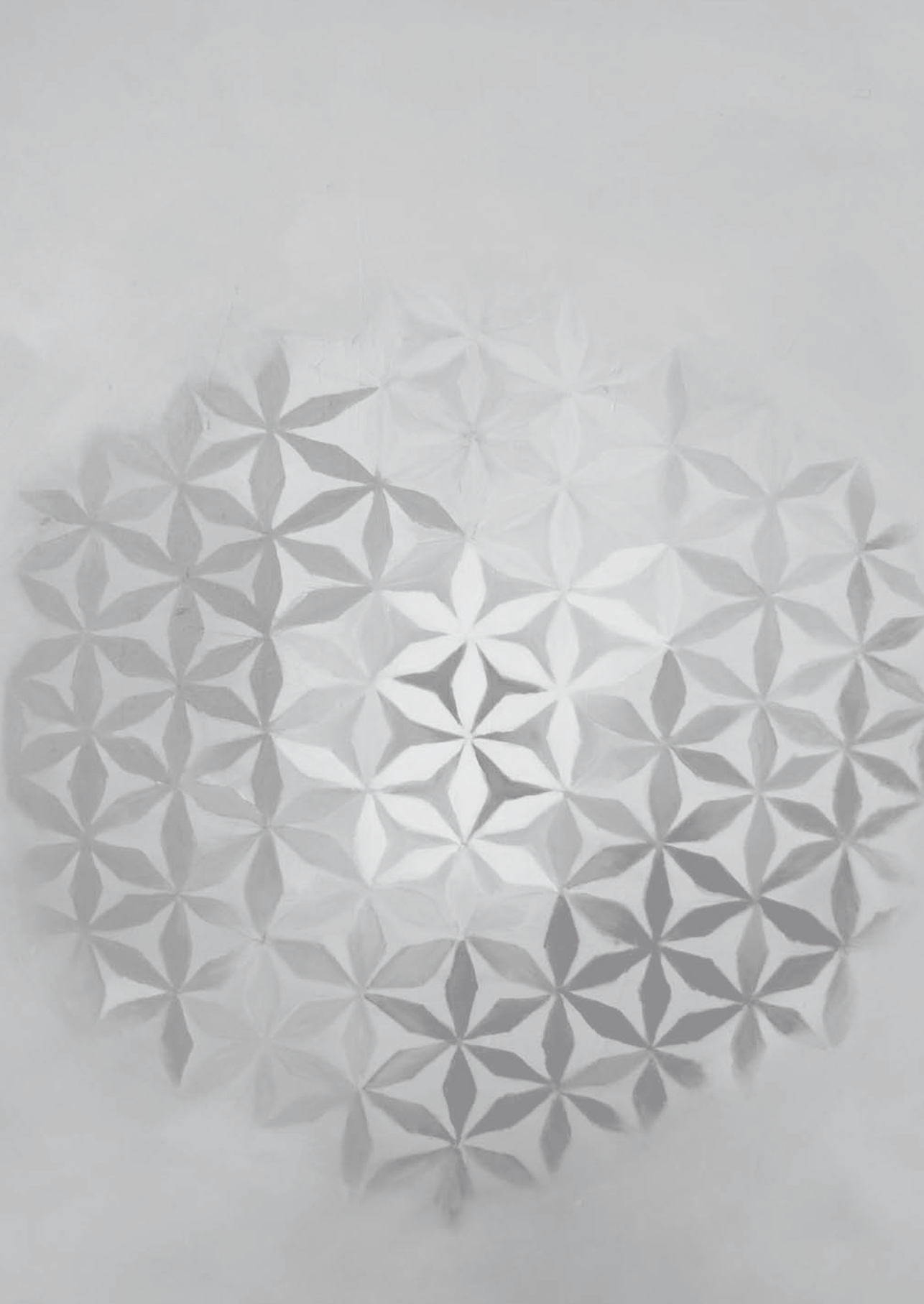

Chapter 7

Short-term esophageal stenting in the management of benign perforations

Nicoline C.M. van Heel, Jelle Haringsma, Manon C.W. Spaander,
Marco J. Bruno, Ernst J. Kuipers

Departments of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

The American Journal of Gastroenterology 2010;105(7):1515-20.

ABSTRACT

Objectives: The standard approach to benign esophageal perforations consists of conservative treatment or surgery. In this study, we investigated the efficacy of short-term stent placement for nonmalignant esophageal perforations.

Methods: This is a prospective single-center study of patients with benign esophageal perforations in whom a removable self-expandable stent was placed. Data were collected from a prospective database, endoscopy records, and operation reports. To obtain follow-up data, we contacted the patients, their relatives, or their general practitioner.

Results: A total of 33 patients underwent stent insertion owing to an iatrogenic perforation (n = 19), Boerhaave's syndrome (n = 10), or other causes (n = 4); this resulted in an immediate and complete sealing of the lesion in 32 patients (97%). Stents migrated in 11 patients (33%). Four patients required an esophageal resection for failed stent therapy (n = 3) and failed stent removal (n = 1). The 90-day mortality rate was 15% . A total of 33 endoscopic stent extractions were attempted. Overall, 23 stents were extracted within 6 weeks (group I) and 10 stents between 6 and 84 weeks (group II). Extractions were uncomplicated in all patients in group I (100%) vs. in 5 patients in group II (50%) (P = 0.001). Six extraction-related complications occurred in group II, including two self-limiting bleedings, three stent fractures, and one impacted stent.

Conclusions: In patients with a benign esophageal perforation, temporary stent therapy is effective and provides a good alternative to surgery. Complications due to stent removal can be prevented by removal of the prosthesis within 6 weeks after insertion, without compromising the efficacy of treatment.

INTRODUCTION

Benign esophageal perforation is a life-threatening condition that requires early recognition and aggressive management. The mortality rate of esophageal perforation is reported to be as high as a 100% when left untreated.[1] A small subset of patients can be treated conservatively with nil per mouth and pleural drainage. Surgical treatment options include esophageal repair and esophagectomy; the mortality rate after surgery is in the range of 12-50%.[2-5] Over the past few years, good results for the management of benign esophageal perforations have been reported by temporary deployment of a covered self-expandable stent to firmly seal the lesion.[6-9] Indications included iatrogenic perforations after dilation of caustic lesions, anastomotic leaks after surgery, and lesions due to Boerhaave's syndrome.[10-12] Although stent placement is a minimally invasive procedure,[13-15] stent therapy is associated with severe complications, including haemorrhage, incomplete sealing, perforation, and stent migration.[16-17] Furthermore, even though some of the newer stents are labeled as being removable, extraction can be complex due to embedding of the endoprostheses into the mucosal wall.[6] The optimal duration of stent therapy has not been established.[6,18] The aim of this study was to evaluate the outcome of temporary esophageal stenting in the management of benign perforations.

METHODS

This prospective cohort study was conducted in a large tertiary referral center. From 2001 to 2008, all patients with benign esophageal perforations referred to the Departments of Gastroenterology and Hepatology at the Erasmus MC were included. Demographic data such as age, gender, and cause of esophageal perforation were retrieved from a prospective database. Clinical data such as location and size of the lesion, stent type and the technical outcome of stent insertion were retrieved from endoscopy records. Follow-up data on complications, re-interventions and survival were retrieved from electronic hospital records, including endoscopy and operation reports. In case of missing follow-up information, we contacted the patients, their relatives, or their general practitioner.

Stent placement was performed under endoscopic and fluoroscopic control, according to manufacturer's directions and standard protocol.[19] Immediately after the procedure a small amount of clear liquid was administered by mouth to evaluate passage, retrosternal pain, and aspiration. Pleural cavities were drained with thoracostomy drains. Broadspectrum antibiotics were administered intravenously. Technical success was defined as successful stent deployment at the required position with no evidence for persistent leakage under contrast fluoroscopy. Stent dysfunction was classified as either incomplete sealing of the esophageal leak, stent migration, or dysphagia due to stent obstruction. Therapy failure was defined as

persistent leakage during stent therapy or after stent extraction. Complications were defined as either mild or severe according to published criteria.[19] Severe complications included perforation, fistula, aspiration pneumonia and hemorrhage. Mild complications included retrosternal pain or symptomatic gastro-esophageal reflux. Patients were classified into two groups, namely short-term stenting (group I) and long-term stenting (group II). Short-term stenting was defined as stent therapy for < 6 weeks, and long-term stenting was defined as stent therapy for ≥ 6.[20]

Stent extraction

Stent removal techniques varied somewhat according to the type of stent. The Ulatraflex stent®(Boston Scientific, Natick, MA) and Hanarostent® (M.I. Tech, Seoul, Korea) were extracted most frequently. Ultraflex stents were generally removed by grasping their distal edge with a forceps and pulling the stent inside out. Hanarostents were removed by using the retrieval lasso located on the proximal end of the stent.

Statistical analysis

Numerical data were described using mean with s.d. or median with interquartile range, as appropriate. Cox regression analysis was used to evaluate the effect age, cause of the perforation, and the time interval to stent therapy on treatment outcome. The Kaplan-Meier method was used to calculate survival from the date of stent insertion to the date of death, and if patients were still alive to January 1, 2009. Statistical analyses were conducted using SPSS software (SPSS 15.0, Chicago, IL). Two-sided P values < 0.05 were considered significant.

RESULTS

Patient characteristics

Between 2001 and 2009, 33 patients underwent esophageal stent insertion for a benign perforation. In this cohort, 50 esophageal stents were inserted: 45 self-expandable metal stents (SEMSs) (90%) and 5 self-expandable plastic stents (10%). In all, 38 of these stents were partially covered (76%) and 12 were fully covered (24%) (Table 1). Baseline patient characteristics are summarized in Table 2 . The mean age at stent insertion was 57 years (range 13 – 87 years). The majority of perforations were iatrogenic (n = 19) (Figure 1). Other causes included Boerhaave's syndrome (n = 10), foreign body ingestion (n = 1), trauma (n = 1), and

TABLE 1. Stent types

	n (%)
FerX-Ella stent (Ella-CS, Hradek Kralove, Czeck Republic)	1 (2)
Flamingo Wallstent (Boston Scientifi c, Natick, MA)	3 (6)
Polyflex stent (Rüsch AG, Kernen, Germany)	5 (10)
Hanarostent (M.I. Tech, Seoul, Korea)	6 (12)
Ultraflex stent (Boston Scientifi c, Natick, MA)	35 (70)

anastomotic leakage after surgery (n = 2). Overall, 14 patients (42%) required a stent in the proximal or mid-thoracic esophagus, 19 patients (58%) in the distal esophagus. A computed tomography scan was performed in 12 of 33 patients (36%) before stent insertion. In all 12 patients, mediastinal air and pleural effusions were observed on the scan. One of 12 patients (3%) had a thoracic abscess.

Stent therapy

Stent insertion was technically feasible in all patients (100%); all stents showed adequate deployment after release (Figure 2). The median time interval between the perforation and stent insertion was 1 day (range 0 – 14 days). Initial stent insertion resulted in an immediate and complete sealing of the esophageal wall in all but one patient (97%). The latter patient with Boerhaave's syndrome had a very large leak, which was insufficiently covered by the stent and underwent an esophageal resection 1 day after stent placement. Before stent placement, this patient had been considered by the surgeon as ineligible for repair. Two patients developed secondary leakage within 1 week despite an in situ stent. Both patients also underwent subsequent esophageal resection. Together, these three patients (9%) with

TABLE 2. Baseline characteristics of patients

Age, y, mean ± SD (RANGE)	57 ± 18 (13-87)
Sex, no. (%)	
Male	22 (67)
Female	11 (33)
Etiology, no. (%)	
Iatrogenic lesion	19 (58)
Boerhaave's syndrome	10 (30)
Anastomotic leakage	2 (6)
Trauma	1 (3)
Foreign body ingestion	1 (3)
Location lesion, no. (%)	
Proximal / mid-esophagus	14 (42)
Distal esophagus	19 (58)
Initial stent type, no. (%)	
Partially covered	30 (91)
Fully covered	3 (9)
Stent size, cm, mean ± SD (range)	12 ± 1 (9-14)

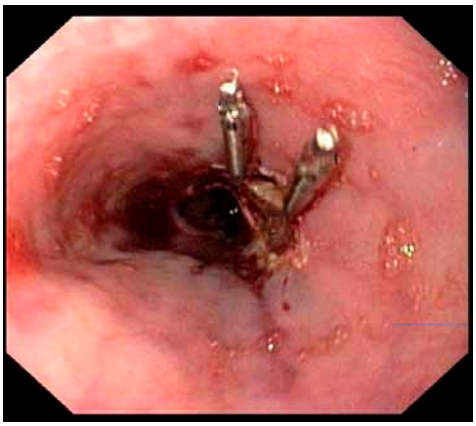

Figure 1. Endoscopic view showing an iatrogenic perforation marked with two clips in the distal esophagus.

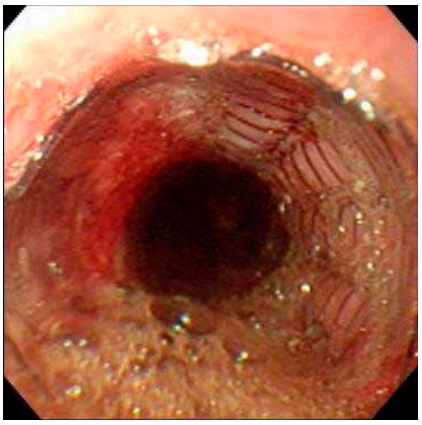

Figure 2. Endoscopic view after stent insertion, showing full expansion of the stent and complete sealing of the esophageal wall.

therapy failure were the only patients treated with esophageal resection; no patients were treated with surgical esophageal repair. During further follow-up, 12 of the 33 patients (36%) required a total of 17 additional stents because of recurrent leakage, while the stent was in situ (n = 4) or following stent migration (n = 4), development of a second esophageal wall perforation (n = 1), or recurrent leakage after stent extraction (n = 8). Stent migration was managed by stent repositioning (n = 4), stent removal (n = 1), additional stent insertion (n = 4), or no intervention as the stent evacuated spontaneously and the perforation site had closed (n = 2).

Additional therapy

All patients received broad-spectrum antibiotics intravenously. In all, 5 of 33 patients (15%) underwent surgical debridement of a pleural empyema, and all patients underwent percutaneous drainage of the pleural cavity.

Outcome

In all, 7 of our 33 patients (21%) died, 5 of them within 90 days after stent insertion. Overall, 4 of 33 patients died from progressive multiple organ failure due to uncontrollable sepsis, 1 died after developing multiple spontaneous gastrointestinal perforations as part of a crest syndrome, 1 died due to complications after esophageal resection, and 1 died after gastric surgery. In this limited series, the overall mortality rate was not associated with age, gender, cause of the perforation, or the time interval to stent therapy. A total of 26 patients (79%) survived. Three of them had undergone esophagectomy with stent removal during surgery.

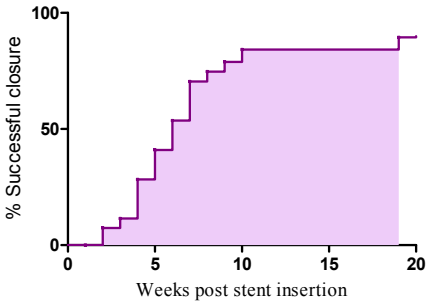

Figure 3. Successful closure of the esophageal defect vs. time after stent insertion in 23 patients.

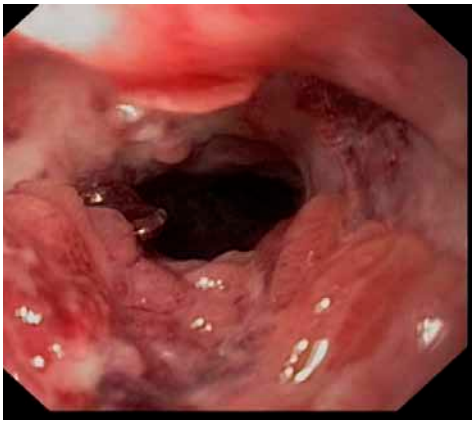

Figure 4. Endoscopic view after stent extraction. The former perforation is entirely closed. Granulomatous tissue growth is visible.

In the remaining 23 patients, successful closure of the esophageal defect had been achieved with stent therapy. Closure was confirmed after a median duration of 6 weeks after initial stent insertion (range 1 – 102 weeks) (Figure 3). All these 23 patients underwent endoscopic stent extraction with a total of 33 stents being removed after a median of 5 weeks after stent insertion (range 1 – 84 weeks). A total of 23 stent extractions were performed within 6 weeks after stent insertion (group I). In all, 10 stent extraction procedures were performed after 6 – 84 weeks (group II) (Table 3). One patient in group I (4%), vs. three patients in group II (30%) had multiple stents in place (NS). All 23 stent extractions were successful and without complications in group I (100%) (Figure 4), vs. 5 of 10 stent extractions in group II (50%) (P = 0.001). During stent extraction in group II; six complications occurred in five patients including two self-limiting bleedings, three stent fractures, and one stent impacted on endoscopic retrieval. In the latter patient, a surgical mini-gastrotomy was performed to remove the stent. Two of three patients with a broken stent had a complete endoscopic stent removal each after three attempts. The third patient refused further treatment after initial stent insertion. This patient presented with dysphagia 84 weeks later at which time stent disruption occurred

TABLE 3. Stent extraction

	Complicated	Uncomplicated
Number of extractions	5	28
Stents		
Partially covered	3	23
Fully covered	0	3
Stent – in – Stent	2	2
Time interval		
< 6 weeks	0	23
≥ 6 weeks	5	5

during stent extraction. The stent was still incompletely removed after nine attempts. This patient subsequently developed a stenosis with a thoracic empyema and finally required an esophagectomy. At surgery, it was found that a strand from the stent had perforated a thoracic vertebrae. After a median follow-up of 2 years, none of the surviving patients reported stent-related dysphagia or other long-term side effects.

DISCUSSION

Stent placement is the standard treatment in patients with a malignant esophageal perforation. [6,21] The primary goal of this therapy is to immediately seal the esophageal perforation to prevent further leakage.[9] Until recently, stent insertion was not considered in the treatment of benign esophageal perforations, mainly because available stents could not be removed. Some newly designed stents are more easily extractable and have been used for the treatment of nonmalignant esophageal disease.[8-9,22-23] Thus far, this application is limited because of serious concerns regarding the long-term complications and hitches relating to stent extraction.[24-25]

Despite these concerns, stent placement was in recent years the treatment of first choice for all patients with a benign esophageal perforation referred to our unit. This occurred irrespective of the underlying condition. The exceptions were patients with perforations of the cervical esophagus and anastomotic leaks after esophageal resection. They were mostly treated conservatively or by surgical deviation and subsequent repair; only two patients with anastomotic leaks were considered for stenting and were included in this study. For any other condition, such as Boerhaave's syndrome and iatrogenic perforation, all patients underwent stenting with the exception of 5 of 15 patients with Boerhaave's syndrome. These patients were primarily referred to the surgery unit. The evaluation for surgery was performed by the collaborative team of surgeons and gastroenterologists.

The proportion of perforations directly sealed after use of a covered stent in malignant fistula is in the range of 90 – 100%.[6,9,26] Our series corresponds with these success rates; in 32 of 33 patients (97%), the lesion was directly sealed after stent insertion. One patient with Boerhaave's syndrome had a very large esophageal tear, which was insufficiently covered by the stent and which before stent placement had been considered by the surgeon as ineligible for repair. Two patients developed secondary leakage within 1 week, and therefore these patients required surgery. Direct referral to surgery would have spared these patients the burden of endoscopy with stent placement. These patients did not differ with respect to relevant baseline details such as location, size, and duration of the perforation with other patients in whom stent therapy proved to be successful, and who were thus spared the burden of surgery. In this balance, with a good success rate of stenting as therapy with fewer morbidity and mortality rates than in published surgical series, we consider it relevant to

offer patients with benign esophageal perforation stent therapy as first treatment option, irrespective of the underlying condition.[2-5] Further series have to increase our knowledge on patient selection, optimal stent designs, and treatment protocols for this indication.

In accordance with smaller series, the most common cause of therapy failure was stent migration (33%).[27] This migration rate is high compared with the migration rate in malignant stenosis, but this is conceivable because of the absence of a stenosis securing the stent position.[28-29] In all cases, stent migration was successfully managed by either stent replacement or stent repositioning.

There are no accepted criteria with regard to the optimal duration of stent therapy. Ideally, a single stent would have to seal the esophageal wall defect, permit normal food intake, allow the esophageal wall to heal, and be easy to extract, thereby minimizing the number of complications while preserving the esophagus. With regard to the duration of stent therapy, this poses conflicting demands. In a normal esophagus, healing of the esophageal wall may take several weeks to months. Fischer et al. experienced successful esophageal healing and stent removal within average of 4 weeks after insertion, and in another case report, a stent was retrieved uneventfully after 8 months.[8,18] Nevertheless, severe complications after long-stay stent insertion have been documented in a number of reports, including the development of an epidural abscess and an aorta- esophageal fistula.[30-31] Cwikiel et al. placed nitinol stents in healthy pigs and observed significant inflammatory change with degeneration of the muscular layer, 1 – 8 weeks after insertion. After a prolonged stenting period, the deeper wall layers also became affected. In the same article, the authors observed the same phenomenon in patients with benign stenoses treated by a nitinol stent when removed after 4 – 7.5 months after insertion. After 7.5 months, the stent was deeply embedded into the wall and this patient required an esophageal resection.[32] Two studies reported severe secondary obstruction requiring esophagectomy after long-term stenting.[25,33] In our series, we observed one stent-induced stricture in a patient with a stent in place for 84 weeks. Stents were retrieved endoscopically after a median of 5 weeks after stent insertion (range 1 – 84 weeks). Complete closure of the defect was observed in 23 of 33 patients (70%) at a median of 6 weeks after initial treatment (range 1 – 102 weeks). All stent extractions within 6 weeks after insertion were uneventful. Importantly, this study shows a considerable rate of serious complications in those cases in which stents were extracted after ≥ 6 weeks after stent insertion. In all, 10 stents were in place for ≥ 6 weeks (range 6 – 84 weeks) and all were firmly embedded into the esophageal mucosa. Extraction resulted in six major complications. These observations should caution clinicians to leave stents in for a prolonged period of time, although it should be noted that the two groups were not similar with regard to the disease characteristics and the number of stents inserted. In the prolonged stenting group, three patients had two stents in place. Given the small number of cases, it remains speculative whether this is indeed associated with specific introduction or stent removal problems.

On the basis of these results, no firm guidelines with regard to optimum choice of stent type can be given for this indication, given the limited number of patients and the wide variety of SEMSs used. Overall therapeutic outcome depends both on successful sealing of the wall defect and the success of subsequent SEMS removal. As both fully and partially covered SEMSs differ in both respects, a comparative study is currently being performed in our institution. Self-expandable plastic stents have been described to provide an alternative for SEMSs in the treatment benign esophageal disease, mainly for the ease of stent extraction.[7,34-36] Reportedly, however, plastic stents are associated with a higher migration rate and furthermore, they require being loaded onto the significantly larger and stiffer delivery device. In stenotic disease, plastic stent insertion requires more commonly previous dilation compared with the use of SEMSs.[37-38] In a recent study, 40 patients underwent plastic stent placement for benign esophageal stenosis, 22 serious complications occurred including one death, and the success rate of stenting was only 40%.[36] In our series, five plastic stents were used. In none of these any complications occurred. Despite the use of stent therapy, antibiotics and thoracic drainage, a total of seven of our patients died as a result of esophageal perforation or underlying disease. All these patients were deemed unfit for surgery leaving stent insertion and supportive care as the only option. The degree of mediastinal sepsis as seen on computed tomography scan before stent insertion was not predictive for progressive sepsis. The time interval between the perforation and treatment may be of critical importance for the outcome of the therapy. Three reports in the literature have suggested that an increased delay worsens the patients' prognosis.[5,9,39] From our data, we cannot extract such correlation. In fact, this study confirms that even in long-standing perforations, those who would otherwise undergo esophageal resection can still be good candidates for stent treatment.

In conclusion, temporary endoscopic placement of a stent is safe and effective in patients with a benign esophageal perforation. Although preservation of the esophagus is secondary to survival, this study shows that the esophagus can be preserved in the majority of patients. The migration rate is high; however, this can be effectively managed by stent repositioning or placement of a second stent. Complications due to stent removal can be prevented by removal of the stent within 6 weeks after insertion.

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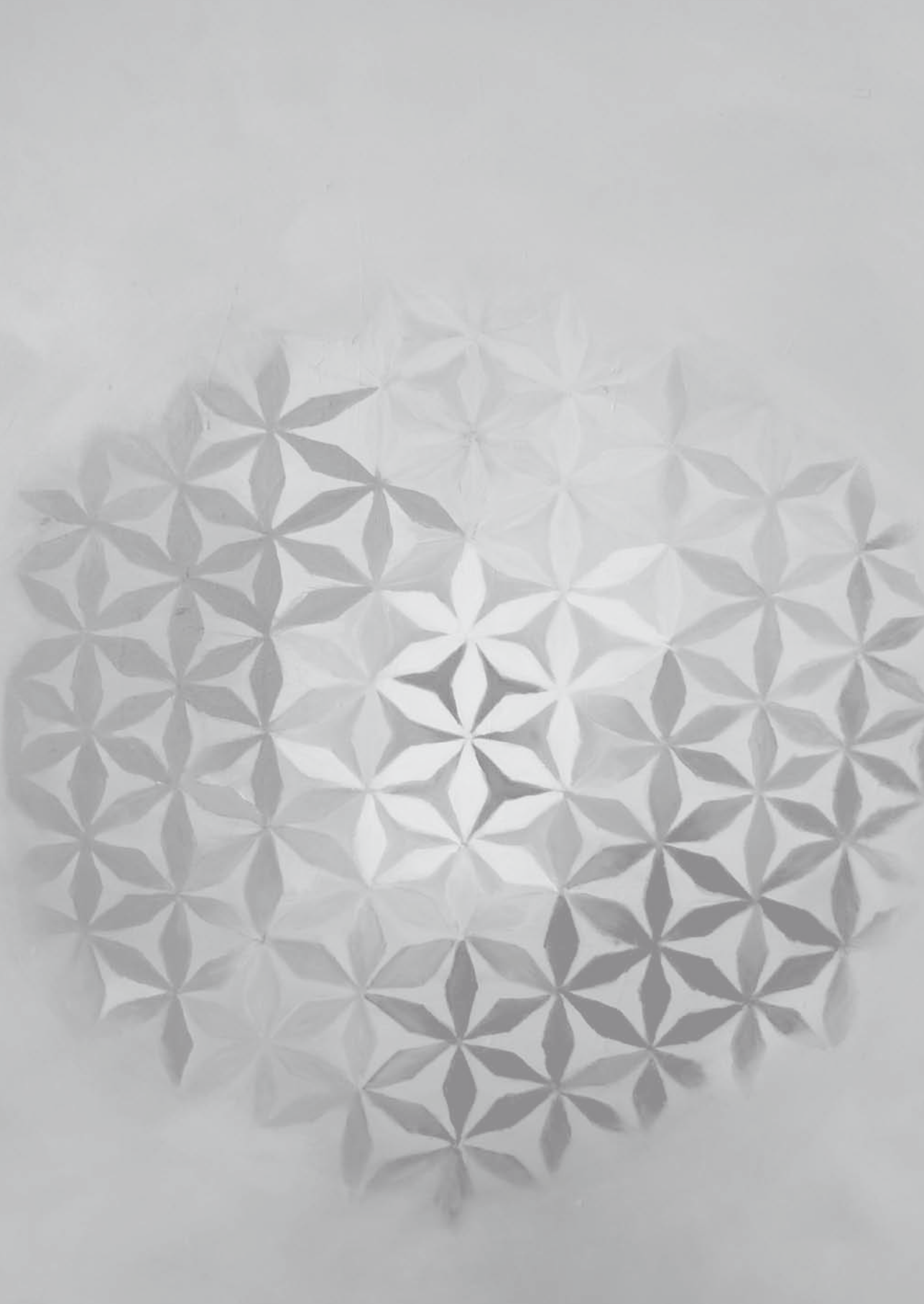

Chapter 8

Partially- versus fully-covered expandable metal endoprosthesis for benign esophageal disease: a randomized controlled trial

Nicoline C.M. van Heel, Jelle Haringsma, Ernst J. Kuipers

Departments of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Submitted

ABSTRACT

Background and study aims: Self-expandable metal stent (SEMS) therapy has become a good alternative to surgery for patients with non-malignant fistula and stenosis of the esophagus. A major drawback of the current available stents is their migration tendency. Stent design features that help to prevent migration such as the type of covering, also hamper stent removal. We performed this trial to compare partially-covered SEMS (pcSEMS) with fully-covered SEMS (fcSEMS) in patients with non-malignant esophageal disease.

Patients and methods: Patients with non-malignant esophageal disease with an indication for temporary SEMS placement were randomly assigned to fcSEMS or pcSEMS placement. SEMS removal was scheduled 4 weeks post-SEMS insertion.

Results: Forty-four patients (M/F 34/10, mean age 66; range 21 - 83 years) were randomized, 32 had a esophageal perforation or fistula, and 12 had a non-malignant esophageal stenosis. They were treated with a total of 22 pcSEMS and 22 fcSEMS. Functional success was achieved in 43 (98%) patients; pcSEMS therapy failed in one patient due to ineffective sealing of the perforation. Stent migration occurred in 4 (18%) patients with a pcSEMS, and in 8 (36%) patients with a fcSEMS (p=0.21). Two (5%) patients died due to infectious complications of the perforation. One (2%) patient had progression of underlying disease impeding further intervention or stent removal. A total of 41 SEMS were successfully removed; 21 pcSEMS were removed after a median duration of 29 days, and 20 fcSEMS after 27 days. Two (9%) severe complications occurred during pcSEMS removal, and no complications occurred during fcSEMS removal (p=0.24).

Conclusions: Both fcSEMS and pcSEMS are equally effective for the treatment of non-malignant esophageal disease, in particular sealing of non-malignant esophageal wall defects and restoring luminal patency. Migration is fairly common with both types of stents. Since removal of pcSEMS is considerably more complex than removal of fcSEMS, we advocate the use of fully covered stents for non-malignant esophageal disease.

INTRODUCTION

Self-expandable metal stents (SEMS) are increasingly used in non-malignant esophageal disease as minimally invasive alternative to surgery. SEMS can effectively restore luminal patency in patients with esophageal strictures, and are also an effective treatment for esophageal fistulae or perforations.[1-2] In a recent study, we reported the outcome of temporary SEMS placement in 33 patients with a non-malignant esophageal fistulae and perforations.[3] In this study we were able to seal various leaks and fistulae in 97% of cases. The 90-day mortality rate was 15%, which is less than previous surgical series.

SEMS were originally designed for use in patients in whom no other treatment options were available, in particular patients with locally advanced or metastatic cancer. To prevent migration most SEMS are partly uncovered. The uncovered part of the stent rapidly embeds in the mucosa, thus firmly anchoring the stent to the wall. It was thought that this would make stent removal difficult and hazardous. However, further experience showed that stent placement was feasible, in particular when performed within 6 weeks after stent placement.[3-4] SEMS therapy has now become a good alternative to surgery for patients with non-malignant fistula and stenosis of the esophagus, however it is also associated with risks and procedure-related mortality has been reported.[1, 5-8] These are in particular related to stent migration and mucosal ingrowth.

For this reason, different stent designs are being considered. The risk of mucosal ingrowth and subsequent stent removal failure can theoretically be reduced by the use of fully-covered stents. A major drawback of these stents is their risk of migration, especially in the absence of a stricture, as is often the case in non-malignant esophageal perforation or fistula. Stent design features that help to prevent migration generally hamper stent removal. This holds especially for partial covering of the endoprosthesis. To date no randomized comparative studies have been published on stent therapy for non-malignant esophageal disease. In this prospective randomized study, we aimed to compare fully-covered SEMS (fcSEMS) and partially-covered SEMS (pcSEMS) for this indication.

METHODS

Study design and patients

This randomised controlled open trial was conducted at the Erasmus University Medical Center, Rotterdam the Netherlands. Patients were eligible for inclusion when they had non-malignant esophageal perforation or fistula, or stenosis, with an indication for temporary stent therapy. Patients were ineligible for the trial if they presented with lesions within 4 cm from the upper esophageal sphincter, or with lesions larger than 9 cm, or with active bleeding at endoscopy. The study was approved by the Institutional Review Board of the Erasmus MC. All patients provided written informed consent before enrolment.

Randomisation

Patients were randomly assigned (1:1) to placement of a partially-covered stent (Ultraflex stent®, Boston Scientific, Natick, MA USA) or a fully-covered stent (Hanarostent®, MI tech, Seoul South-Korea) (Figure 1). Randomisation was done by computer-generated blocks of 10. The randomisation procedure was stratified for two disease groups; perforation/fistulae and stenosis. The investigator performing the stent placement and stent removal procedures (JH) was by definition unblinded. Patients and the independent investigator evaluating outcome measures were blinded to the type of procedure. All authors had full access to all the data in the study and had shared responsibility for the decision to submit the report for publication.

Figure 1. Two stent types used in the present study, on the left side the partially covered Ultraflex stent, on the right site the fully covered Hanarostent.

Stent characteristics

Patients randomized to pcSEMS were treated with an Ultraflex stent, which consists of a partially covered knitted nitinol wire tube. The cover consists of a polyurethane layer that covers the midsection of the stent extending to 1.5 cm of each end. The stent is available in 3 lengths: 100 mm, 120 mm and 150 mm. The stent has a proximal flare with a size of 28 mm, and a diameter of 23 mm. Patients randomized to fcSEMS were treated with an Hanarostent, which consists of a series of segments of graduated polyurethane-covered 0,4-mm stainless steel wire in a cylindrical zigzag fashion segments interspersed with 3-mm sections consist-

ing of polyurethane only. This stent is available in 4 lengths: 80 mm, 110 mm, 140 mm and 170 mm. The stent has a proximal and distal flare of 26 mm and a diameter of 20 mm.

Insertion procedure

All procedures were performed under conscious sedation using midazolam. The lesion was located, inspected and measured with a flexible video endoscope (Olympus Q and 1T series). The distances from the dental incisors and to proximal and distal borders of the lesion were measured. Stent length was based on the length of the lesion; the stent length was chosen at least 3 cm longer than the lesion length, to allow for complete coverage with the stent coating and deployment of the flanges above and below the proximal and distal lesion margins. All stents were positioned over a guidewire and deployed under fluoroscopy or direct endoscopic view. One hour after the procedure patients were given a small amount of clear liquid by mouth to evaluate passage, retrosternal pain and esophago-respiratory leakage. Resumption of oral intake was permitted on the day of SEMS placement.

Removal procedure

Patients were scheduled to undergo stent removal 28 days post-SEMS insertion. The distance from incisor teeth to the upper edge of the stent was carefully measured prior to stent removal. Partially covered Ultraflex stents were removed by grasping the distal edge of the stent from inside the endoprosthesis with a retrieval forceps. The distal end of the stent was subsequently inverted and removed, as has been described previously.[4] Hanarostents were removed by pulling the proximal retrieval lasso. No overtube or retrieval cap was used. After stent removal, the SEMS was carefully examined for completeness and the esophagus was inspected endoscopically. Patients were admitted overnight for clinical observation. A contrast swallow study with watery contrast was performed on the same-day only in case of clinical or endoscopic suspicion of perforation or persistent fistula. A clear liquid diet was started in the absence of such suspicion.

Follow-up

Patients were interviewed at the day of stent removal and by telephone four weeks after stent removal by one of the authors (NVH) using a protocol-approved questionnaire. In case of complications or stent dysfunction, patients were seen for re-evaluation. Patients were followed to the end-point, being either stent dysfunction requiring re-intervention, 4 weeks post stent removal, or patient death.

Outcome parameters

The primary outcome for this study was the symptomatic stent migration rate. Secondary outcomes included the technical success, functional success, stent position change, procedural complications, 30-day mortality rate and removal success rate. Symptomatic stent migration was defined as a >2 cm change in the distance between the upper incisors and the proximal end of the device. Technical success was defined as stent deployment at the required position. Functional success was defined as relief of dysphagia, respectively fistula sealing. Stent position change was defined as a change of more than 2 cm in the position of the proximal flange at removal not causing recurrent symptoms. The dysphagia grade was assessed according to the Atkinson's dysphagia score as follows: 0 = no dysphagia; 1 = ability to swallow some solid foods; 2 = ability to swallow semisolid foods; 3 = ability to swallow liquids only; and 4 = complete dysphagia.[9] Complications were classified as major or minor according to published criteria.[10] Stent removal rate was defined as the rate of complete endoscopic stent removal in a single session.

Statistical analysis

A previous study showed a 5% migration rate for pcSEMS, which is nearly 40% less than the reported migration rate of fcSEMS.[11-14] With a 5% type I error with 80% statistical power, the required number of patients in each group was determined to be 20 to be able to demonstrate a 40% difference in migration rate between treatments. Data were analyzed on an intention to treat basis. For comparison of baseline characteristics, differences in continuous variables were analyzed by t tests, and differences in categorical variables by χ^2 tests. Complications and recurrent dysphagia or leakage in the two groups were compared with Kaplan-Meier and log-rank tests to adjust for time of occurrence of the event and survival differences. Survival of the two groups was calculated and compared using Kaplan-Meier curves and log-rank test. A two-sided P value < 0.05 was considered statistically significant. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS® version 17; IBM, USA).

RESULTS

Patient characteristics

Of the 46 patients screened for eligibility, 44 patients were included and treated between June, 2008 and June, 2010. All patients were followed to the study endpoints, and none was lost to follow-up (Figure 2). Twenty-two (50%) patients were assigned to the partially-covered Ultraflex stent and 22 (50%) to the fully-covered Hanarostent. Table 1 shows the baseline

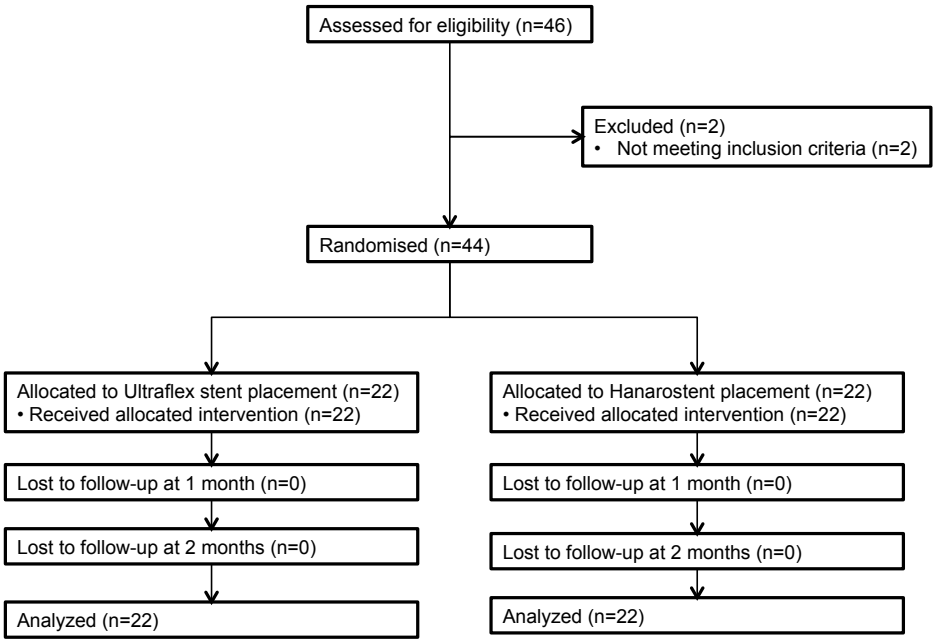

Figure 2: Enrolment, randomisation, and follow-up of study patients

characteristics for the two groups. Study groups were similar in terms of all baseline clinical and procedural characteristics. On inclusion, 32 (73%) patients presented with esophageal leaks, and 12 (27%) patients with dysphagia due to a non-malignant stenosis. Esophageal leaks included iatrogenic perforations (n=14, 32%), surgical anastomotic leaks (n=11, 25%), Boerhaave's syndrome (n=6, 14%), and fistula of unknown origin (n=1, 2%). In this group, 17 (53%) pcSEMS and 15 (47%) fcSEMS were inserted. Esophageal stenosis included anastomotic strictures after surgery (n=3, 7%), treatment-refractory achalasia (n=3, 7%), radiation strictures (n=3, 7%), post-EMR strictures (n=1, 2%) and strictures of unknown origin (n=2, 5%). In this group, 5 (42%) pcSEMS and 7 (58%) fcSEMS were inserted. Median Atkinson dysphagia score in both groups was 3 on inclusion.

Table 1: Baseline characteristics

	Ultraflex stent (n=22)	Hanarostent (n=22)
Age (years, mean (SD))	65 (10)	66 (16)
Men/women	16 / 6	18 / 4
Lesion location from incisor teeth (cm, mean (SD)	30 (8)	28 (8)
Length stent (cm, mean (SD)	11 (2)	11 (4)
Indications for SEMS treatment	17 (77)	15 (68)
Perforation Stenosis	5 (23)	7 (32)
Dysphagia score before treatment (mean (SD)	3 (0.4)	3 (0.4)

Data are numbers (%) unless otherwise specified

Stent therapy

Initial stent insertion was technically successful in all patients (100%) and no procedure-related complications occurred. Symptomatic SEMS migration occurred in 4 (18%) patients with a pcSEMS, and in 8 (36%) patients with a fcSEMS (p=0.21). SEMS migration caused recurrent symptoms of leakage in 8 (18%) patients, and recurrent dysphagia in 4 (9%) patients, after a median of 4 days post-SEMS insertion. These patients were all managed endoscopically by stent repositioning (n=4, 9%), stent replacement (n=5, 11%), or stent removal (n=3, 7%).

Functional success was achieved in 43 (98%) patients; pcSEMS therapy failed in one patient due to ineffective sealing. In this patient SEMS removal was performed within 24 hours after implantation. Stent position change occurred significantly less often in pcSEMS (n=6) than fcSEMS (n=14) (p=0.015).

SEMS removal and follow up

Two (5%) patients with an esophageal leak died during SEMS therapy because of infectious complications despite administration of broad spectrum antibiotics, 12 and 30 days after

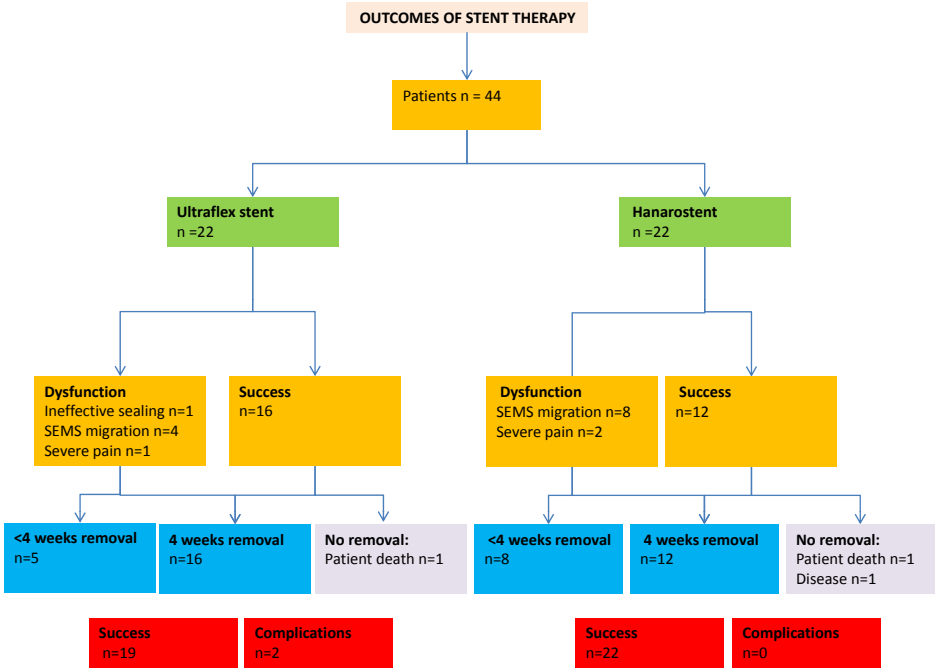

Figure 3. Outcomes of SEMS therapy

stent placement. One (2%) patient with a benign esophageal perforation had progression of underlying disease impeding further intervention or stent removal.

A total of 41 SEMS were successfully removed; 21 pcSEMS were removed after a median duration of 29 days, and 20 fcSEMS after 27 days (Figure 3). On follow-up, the median dysphagia score was 3. Dysphagia improved at 28 days post SEMS removal in 3 out of 12 (25%) patients, only 1 (8%) patient remained symptom free. The degree of improvement was not different among the 2 groups. Within 1 month after SEMS removal, 23 (52%) patients received additional therapy to manage persistent leakage (n=17, 39%), or recurrent dysphagia (n=6, 14%).

Complications

A total of 5 complications occurred related to SEMS therapy, all consisting of pain following placement. There was no significant difference in complication rate between patients treated with pcSEMS (n=2, 9%), versus fcSEMS (n=3, 14%) (p=0.33). In 2 (5%) patients pain was managed by the administration of oral analgesics. In 3 (7%) patients, endoscopic stent removal was required. Stent-related pain was observed in none of 32 patients with esophageal fistula, versus 5 of 12 patients with strictures ($p < 0.001$).

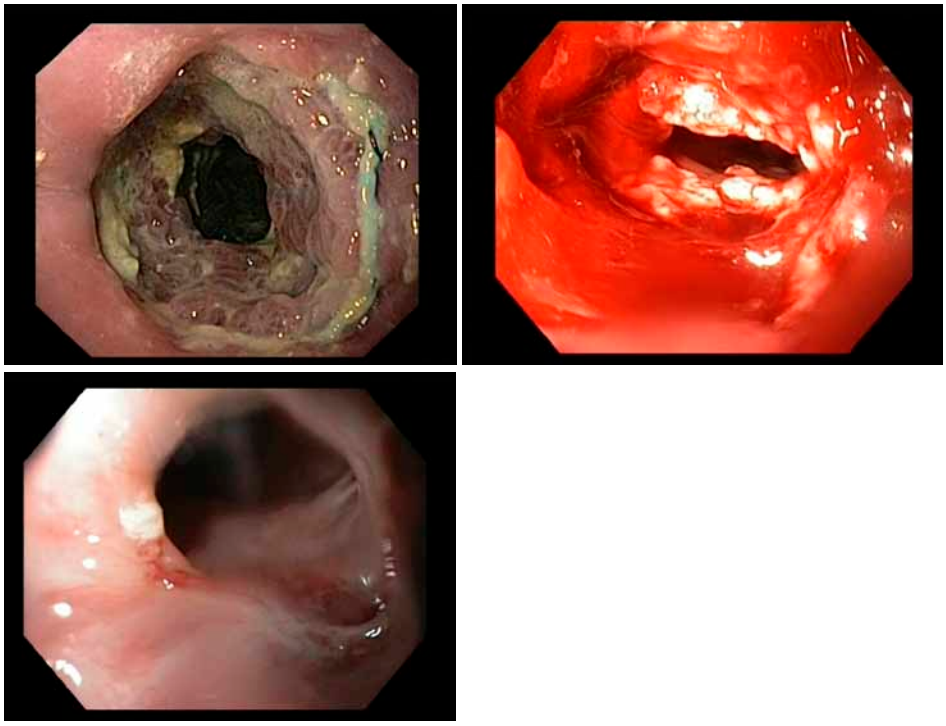

Figure 4. Partially covered SEMS removal resulted in mucosal damage and severe stenosis after healing, requiring repeated dilation

Two (9%) severe complications occurred during pcSEMS removal, and no complications occurred during fcSEMS removal (p=0.24). In one patient, stent breakage occurred on removal. This stent was completely removed in 2 endoscopic sessions. After one pcSEMS removal, a narrow stenosis developed requiring repeated dilation (Figure 4). Variables including stent type, stenosis or fistula, stent location and size were not independently associated with the development of major complications, recurrent dysphagia/leakage, or survival. Similar results were obtained when the variables were entered into a multivariate Cox regression model.

DISCUSSION

This randomized controlled trial in patients with benign esophageal stenosis and esophageal fistulae compared the partially-covered Ultraflex® stent with the newly designed fully-covered Hanarostent®. SEMS migration and subsequent relapse of fistulae or dysphagia occurred more often in fcSEMS than in pcSEMS, however this difference was not statistically significant. A change in the position of the stent, not giving rise to recurrence of symptoms and therefore not considered clinically relevant, occurred significantly more often in fcSEMS. Stent placement was successful in all patients in both study arms, and stents were equally effective in restoring luminal patency and sealing esophagorespiratory fistulae. Generally SEMS were poorly tolerated in patients with benign refractory strictures and long-term clinical results were unsatisfactory. In contrast, results of SEMS placement in esophageal leaks were positive. In spite of removal within one month after insertion, pcSEMS removal resulted in severe complications in 9%.

In recent years, a multitude of studies have shown that temporary stent placement is effective in patients with benign esophageal disease.[1, 15] With the deployment of a self-expandable stent, successful sealing and restoration of luminal patency is achieved in the range of 90-100%.[16-22] For non-malignant esophageal leaks, these results are confirmed in our current series. The minimally invasive nature of expandable stents is appealing, but concerns are raised about the complications during SEMS treatment and SEMS removal.[23-25] During SEMS therapy reintervention rates reportedly range from 35% to 40%, mainly due to migration of the device.[19, 26-27] FcSEMS are more prone to migration than pcSEMS as the full covering prevents the metal wires from imbedding into the tissue. However, the downside of this is that tissue ingrowth increases the risk of stent removal.[2, 28]

To date no randomized controlled trials have been published comparing partially versus fully covered SEMS for temporary use. In this series, a total of 22 fcSEMS and 22 pcSEMS were inserted in patients with benign esophageal perforations (n=32) and stenosis (n=12). A higher migration rate occurred in fcSEMS than in pcSEMS (36% versus 18%), however this was not statistically significant. In an attempt to decrease the rate of stent migration, various modifications have been proposed, including the use of clips, silk threads connecting the stent to the patient's earlobe,

and even pre-treatment with circumferential EMR of the middle of the esophagus for stricture formation, with ambiguous results.[17, 29-31] These techniques were not applied in our series.

Ideally, complete closure of the defect and restoration of luminal patency is achieved in a single procedure. However SEMS removal is required within a limited time-interval, as prolonged stenting beyond a period of six weeks leads to an increased risk of complications.[1, 4] In the present series, after 4 weeks of stenting closure of the leak was achieved in 52%, half of the study population required additional therapy to allow complete closure. In 7 out of 12 patients (58%) with refractory strictures, SEMS were removed within four weeks because of intolerance to SEMS therapy or SEMS migration. Only one (8%) patient was free of dysphagia one month after SEMS removal. In a recent published series from our institution, SEMS were placed in 33 patients with benign esophageal leaks. This led to healing in 70% of patients after a median duration of 6 weeks.[1] Eloubeidi et al. reported recently their experience with fcSEMS in 16 patients with esophageal leaks and 19 patients with benign esophageal strictures. SEMS were in position for a median interval of 58 days (range 6-300 days). The authors also reported higher rates of clinical success in patients with leaks than those with stenosis (44% vs 21% respectively).[27] Another study reported outcomes in 30 patients treated with 84 SEMS for benign esophageal strictures. The results in this study were disappointing as persistent improvement after stent removal was only achieved in 5 of 30 patients (17%).[32] Based on these results, the use of SEMS for refractory stenosis cannot be routinely recommended and should be limited to strict indications.

Despite the superiority of uncovered SEMS over their covered counterparts in preventing stent migration, they have their own limitations. Partially-covered devices have been associated with epithelial hyperplasia. Embedding the stent in the esophagus, making their removal particularly difficult. Tissue ingrowth is created by a local fibrotic reaction and proliferation of granulation tissue.[33] This tissue reaction can be clinically manifest as early as 2 weeks after stent placement, but occurs more often after a longer time-interval.[4, 34] In a recent published retrospective series of 110 SEMS removals in patients with benign and malignant esophageal disease, successful removal of both partially- and fully-covered SEMS was feasible at first attempt in the majority of cases. Prolonged stent therapy was associated with increased numbers of complications.[4] Therefore in our series, SEMS were removed within 1 month post-SEMS insertion. Despite of this short time-interval, severe complications occurred during two (9%) pcSEMS removals. No complications occurred with fcSEMS (ns).

The strengths of this study are the prospective randomized design and the robust short-term follow-up after removal. This enabled us to assess both clinical outcomes as well as all the complications. However, this study has several limitations. First, the 2 types of SEMS used in this series were not only different in the extent of their covering, but also in an array of characteristics including their expansible force, length of their flanges, and diameter. Therefore, not only covering, but also other factors may have attributed to the observed differences. Secondly, the clinical success rates reported are based on observations at the

time of stent removal and one-month after SEMS removal; long-term success rates cannot be determined. However, re-occurrence of benign esophageal leaks after closure, as opposed to re-stricturing of benign stenosis, is a rare event. Thirdly, this is a single center study performed in a unit with an exceptionally high volume of SEMS placements and all stents in this study were placed and removed by an expert endoscopist (JH) in this field.

In conclusion, this randomized controlled trial showed that both the partially-covered Ultraflex stent and the fully-covered Hanarostent are equally effective in sealing non-malignant esophageal fistulae and restoring luminal patency. A major drawback of these stents is the re-occurrence of dysphagia and leakage caused by SEMS migration, with no significant difference between the two stent types. SEMS in patients with refractory strictures were poorly tolerated and furthermore the short-term effects on the dysphagia score were dissatisfying. All SEMS were successfully removed at one month post SEMS insertion. However during 2 pcSEMS removals severe complications occurred. Since removal of partially covered stents is considerably more complex than removal of fully covered stents, we advocate the use of fully covered expandable metal stents for this indication. Additional studies and modified stent designs are needed to further characterize which patients can benefit from these interventions, and which type of stent is most suitable for temporary use.

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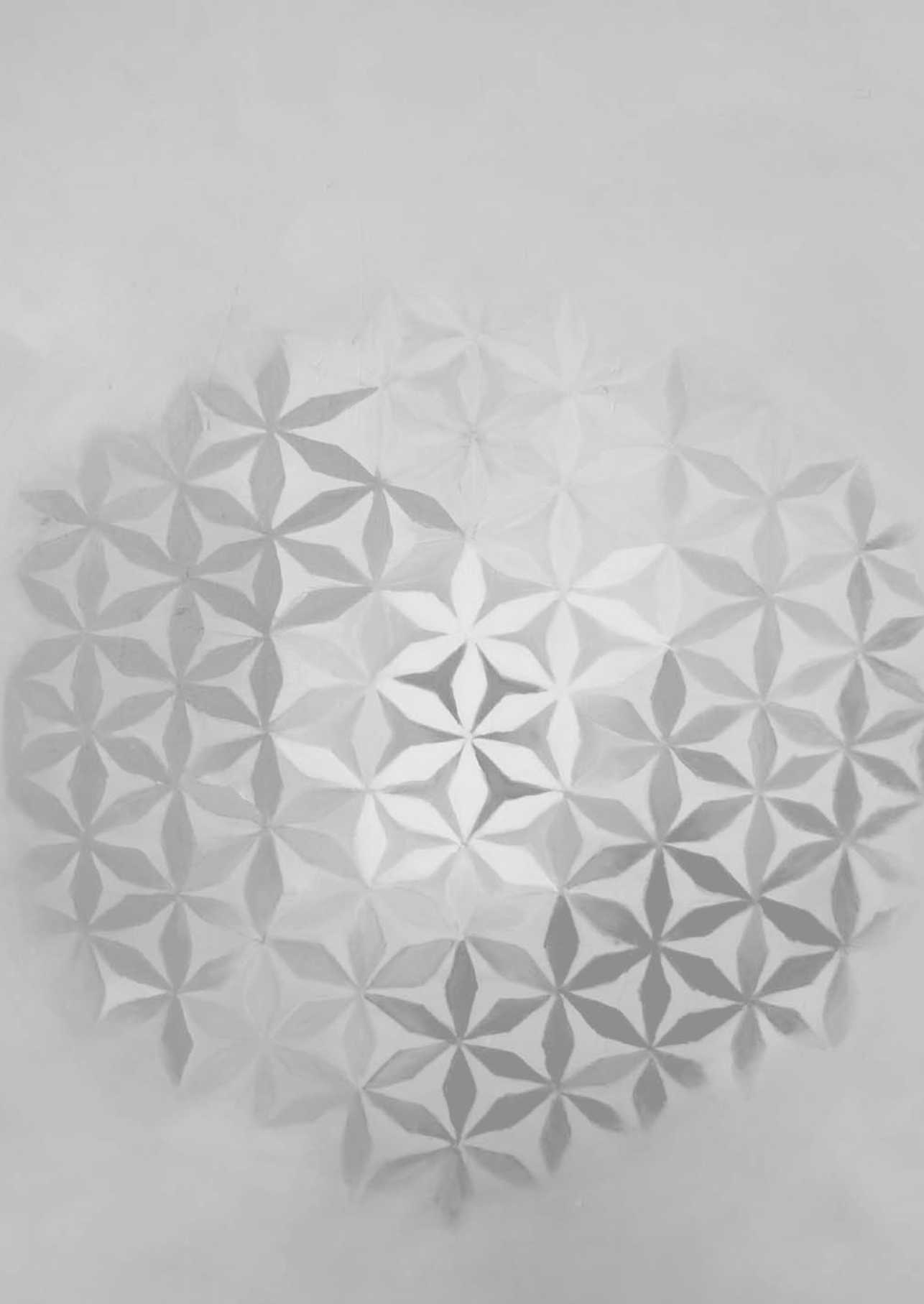

Chapter 9

General discussion and future perspectives

INTRODUCTION

Self-expanding metal stents (SEMS) have become a leading palliative therapy for dysphagia resulting from esophageal cancers. This device immediately restores luminal patency and thereby improves oral intake and quality of life. In recent years, the indications for covered metal stents have gradually expanded to a variety of benign esophageal conditions of the upper gastrointestinal tract. SEMS consist of woven, knitted, zig-zag or laser-cut metal mesh cylinders, which exert self-expandable radial force until they reach their maximum fixed diameter. They are generally made from a grid of stainless steel or nitinol and are covered with a polyethylene, polyurethane, or silicone layer. Placement of a SEMS in the esophagus is performed by appropriately trained endoscopists after comprehensive interdisciplinary collaboration with relevant specialty teams, including gastroenterologists, oncologists, and surgeons.

MAIN OUTCOMES

Stenting malignant esophageal disease

By measures of mortality and morbidity, gastrointestinal (GI) cancers are dominating the field of oncology. Between one fifth and one quarter of all human cancers arise in the digestive system. Many patients with digestive cancer present with incurable disease. Advanced diagnostic and therapeutic tools have been developed to detect and treat cancerous lesions at the earliest stage. A review (**chapter 2**) focused on recent developments in prevention, detection and the approach to early gastrointestinal cancer. The incidence, diagnostic techniques, and therapeutic options have undergone major changes over the last six decades, but the prognosis generally remains poor. This in particular pertains to advanced stage disease, in spite of aggressive adjuvant therapy and advances in surgical resection techniques. As locally advanced cancer often goes with distant metastases, treatment options are mostly limited to systemic treatment or local palliation. Rapid and persistent palliation of dysphagia is the main challenge in patients with incurable esophageal cancer.

Brachytherapy and stent placement are the two evidence-based treatment options in these patients. Two randomized controlled trials comparing brachytherapy with stent-therapy showed that SEMS placement provides more rapid palliation of dysphagia as compared to brachytherapy.[1-2] The difference in efficacy decreases gradually over time, and after 3 months brachytherapy seems to provide better palliation. However in the study of Homs et al. nearly half of the patients in the brachytherapy group received additional stent therapy, and only 2% of the patients in the stent therapy group received additional brachytherapy.[1] Therefore,

the positive long-term effects of brachytherapy can partly be explained by additional SEMS placement during follow-up, because of insufficient brachytherapy effect.

Even after curative surgery, the median esophageal cancer-specific survival is only 38 months. The esophageal cancer-free survival rate at 1, 2, and 5 years is approximately 84%, 65%, and 41%, respectively.[3] Many of these patients present with recurrent dysphagia as a signal of recurrent disease.[4-7] Although chemotherapy and radiotherapy can be effective for symptom relief for locoregional tumor recurrence, it can take as long as several weeks for such therapy to relieve dysphagia.[1, 8] Given the short life expectancy in these patients, more rapid relief is usually required. We performed a prospective observational study evaluating SEMS therapy in patients with recurrent cancer after esophagectomy (**chapter 3**). In this series, we placed 100 SEMS in 81 consecutive patients with cancer recurrence. Respiratory fistulae and esophageal stenosis were present in 19% and 81% respectively. Fistulae represent a devastating complication leading to recurrent pulmonary infections and the inability to eat or even swallow saliva. This condition is associated with very high short-term mortality.[9] The technical success of fistulae sealing and restoring luminal patency by SEMS placement was 93% versus 98% respectively.[10] In the majority of patients with cancer recurrence after esophagectomy, the fistula or stenosis is located close to the upper esophageal sphincter. At this location, SEMS placement may cause foreign body sensation, trachea compression, or respiratory fistula.[11-12] It has been hypothesized that stents should have a body diameter of 18 mm or less to avoid these complications.[13] In our series, however, three patients (4%) developed a stridor and two patients (2%) developed a fistula after stent placement, despite the use of small diameter stents in four of them. None of the patients reported globus sensation. This study showed that SEMS placement in recurrent esophageal cancer after surgical resection offers adequate palliation. Stent dysfunction occurred in 30% of patients. They all were successfully managed by subsequent endoscopic intervention without complications.

Tumors causing extrinsic compression of the esophagus also may also be responsible for malignant dysphagia. In the majority of patients, dysphagia due to malignant extrinsic compression is caused by pulmonary carcinoma or by the recurrence of esophageal cancer after surgery.[14-15] There is some evidence that better dysphagia relief can be obtained when uncovered stents are utilized for intrinsic obstruction than for extrinsic obstruction.[14] To date, there are no published series evaluating covered SEMS for extrinsic malignant stenosis. We therefore performed a prospective observational study and included 50 consecutive patients with malignant extrinsic compression with an indication for stent therapy (**chapter 4**). Placement was successful in all patients. Procedure related complications occurred in two patients (4%) during endoscopic dilation of a tight stenosis prior to stent insertion. These perforations were successfully sealed with the covered SEMS. Recurrent dysphagia occurred in 16% and was successfully managed by subsequent endoscopic intervention. In this series, the type of stent (partially- vs fully-covered) and radiation and/or chemotherapy prior to

stent placement, did not influence the clinical outcome. Survival after stent placement is obviously a function of the timing of stent insertion in relation to the disease stage. In our series, 96% of patients had grade 3-4 dysphagia on inclusion, and the median survival time in our series was only 44 days. In patients with extra-esophageal tumours, the tumour has to have spread and grown substantially in order to compromise the esophageal lumen. This may explain the relatively short survival period of these patients over that of patients with intrinsic esophageal tumours.[16-17]

Endoscopic reinterventions are generally associated with patient burden, as well as significant costs and risks, even when they are successful.[18] A wide variety of expandable esophageal endoprostheses have been developed to improve therapeutic outcome and to reduce the need for endoscopic reintervention during the course of the disease. To our knowledge, previous randomized controlled trials did not show any SEMS significantly superior in all aspects to other SEMS types.[19-21] Currently, the Ultraflex® stent is worldwide most frequently used. The Evolution® stent has recently been introduced as an alternative with modified stent characteristics. To date no comparative studies have been published with the Evolution stent. One recent open-label study with this new device reported major complications in 8% and dysphagia recurrence in 25% at a median survival of 88 days.[22] We performed a prospective randomized controlled trial in 80 patients with malignant esophageal disease, and compared the conventional Ultraflex stent with the new design Evolution stent (**chapter 5**). This study showed that the Ultraflex stents and Evolution stents were equally effective in the relief of malignant dysphagia and sealing fistulae. The observed overall complication rate of 30% in our series was substantial, yet in the middle of the range in recent reports.[7, 10, 23] In our series major complications arose more often after Ultraflex stent placement. The most common complication was hemorrhage, which -remarkably- only occurred in the Ultraflex stent group. Patients treated with an Ultraflex stent also needed significantly more reinterventions than those treated with an Evolution stent. In the Ultraflex group, 38% of patients within 90 days required one or more interventions to manage stent dysfunction, which is in line with previous published series.[18, 24-25] Yet, only 10% of patients in the Evolution group required re-intervention. This is low compared with the literature on malignant esophageal stenting. These results set the preference for the Evolution stent over the Ultraflex stent for patients with malignant esophageal disease. The observed benefits in the performance of the Evolution stent may likely be ascribed to the new stent design and resulting physical characteristics. These characteristics include the higher hoopstrength (radial force), silicone internal and external coatings to prevent ingrowth, large dual flanges to prevent migration, and a large stent diameter to avert food-bolus obstruction as compared to the Ultraflex stent.

Stenting benign esophageal disease

SEMS are generally used as palliative treatment for patients with a limited life expectancy, with no intention of subsequent stent removal.[25] Side effects such as ulceration, stricture formation, perforation, and bleeding are well-known complications of long-term stent placement.[26-30] To avoid these complications, timely removal of SEMS in patients with benign esophageal disease is crucial. Currently, partially- and fully-covered SEMS have been increasingly used as a temporary device in patients with benign esophageal perforations or stenosis.[7, 30-36] Stents are also successfully used as a bridge to therapy and to maintain oral intake before surgery or chemotherapy and radiotherapy.[37-38] Some studies reported unacceptable rates of complications caused by temporary stent placement.[39-42] The main problem associated with partially-covered SEMS placement in benign esophageal disorders is endoscopic stent removal. Partially-covered devices have been associated with epithelial hyperplasia, embedding the stent in the esophagus, making their removal particularly difficult. Tissue ingrowth is created by a local fibrotic reaction and proliferation of granulation tissue.[43] This tissue reaction can be clinically manifest as early as 2 weeks after stent placement, but occurs more often after a longer time-interval.[44-45] We performed a prospective observational study and assessed the feasibility of SEMS removal in a large cohort of patients with malignant and benign esophageal disease (**chapter 6**). A total of 124 esophageal SEMS removals were attempted in 95 patients at a single institution. The uncomplicated primary removal rate was 89%, which is lower than the 97 to 100% in previously published series.[34, 46-47] However, this series comprised both fully- and partially covered SEMS, a variety of indications and dwell-time after insertion. After 1 to 7 endoscopic sessions, 96% of all stents were removed endoscopically; 3 stents (2.4%) were surgically removed and 2 stents (1.6%) were left in place. Successful endoscopic removal was time dependent; patients with an uncomplicated primary SEMS extraction had the stent significantly shorter in place as compared to patients with a complicated or failed SEMS extraction. These observations should caution clinicians to leave stents in for a prolonged period of time.

Complications occurred in 6% of the SEMS removals. The most commonly encountered complication was stent breakage, which occurred as a result of endoscopic traction with the retrieval forceps in 5 of 124 removals (4%). Similar rates have been reported by other groups (0-5%).[34, 46-50] Caution should be taken when using overlapping SEMS as a temporary device; 2 patients with SEMS breakage had overlapping stents in place ($p<0.05$). In case of stent breakage and possibly incomplete endoscopic stent removal, careful endoscopic evaluation or surgery should be considered to ensure that all broken segments have been removed. Broken filaments may migrate and subsequently may lead to life-threatening complications such as perforation or empyema, which occurred in two patients years after SEMS removal.

Despite serious concerns regarding the long-term complications and hitches related to the stent-extraction, stent placement was in recent years the treatment of first choice for all patients with a benign esophageal perforation referred to our unit.[39, 51] We performed a prospective series and studied the efficacy of short-term stent placement in 33 patients with non-malignant esophageal perforations (**chapter 7**). The proportion of perforations directly sealed after employment of a covered stent in malignant fistula is in the range of 90% to 100%.[52-54] In our series, 97% of the lesions was directly sealed after stent insertion. There are no accepted criteria with regard to the optimal duration of stent therapy. Ideally, a single stent seals the esophageal wall defect, permit normal food intake, allow the esophageal wall to heal, and be easy to extract, thereby minimizing the number of complications while preserving the esophagus. With regard to duration of stent therapy this poses conflicting demands. Previously published series reported controversial data on the optimal stenting period.[30-31, 33, 40, 55-56] Most series recommend stent removal between 3 and 10 weeks.[31, 33, 57] However, Choi et al. reported successful stent removal even after 8 years.[55]

In our series, stents were retrieved endoscopically after a median of 5 weeks post-stent insertion. Complete closure of the defect was observed in 23 out of 33 patients (70%) at a median of 6 weeks after initial treatment. All stent extractions within 6 weeks after insertion were uneventful. Importantly, this study shows a considerable rate of serious complications in those cases in which stents were extracted after more than 6 weeks after stent insertion. Ten stents were in place for more than 6 weeks and all were firmly embedded into the esophageal mucosa. Extraction resulted in 6 major complications. Based on our results, we advocate removing the SEMS within 6 weeks after placement in patients where stent removal is deemed necessary regardless of stent type. In case of persisting symptoms after stent removal, stent reinsertion is the preferred approach.[30, 58]

Overall therapeutic outcome depends both on successful sealing of the wall defect and the success of subsequent SEMS removal. As fully covered and partially covered SEMS differ in both respects, a comparative study was performed in our institution (**Chapter 8**). This randomized controlled trial included 44 patients with benign esophageal disease. A total of 22 fully-covered Hanarostents® and 22 partially-covered Ultraflex® stents were inserted in patients with benign esophageal perforations (n=32) and stenosis (n=12). Both partially-covered Ultraflex stents and fully-covered Hanarostents were highly effective in sealing fistulae and restoring luminal patency. A major drawback was the re-occurrence of dysphagia and leakage caused by SEMS migration, with no significant difference between the two stent types. All SEMS were successfully removed at one month post SEMS-insertion, however during 2 partially-covered SEMS removals severe complications occurred. After SEMS-removal closure of the leak was achieved in 52%, half of the study population required additional therapy to allow further mucosal healing. In 7 out of 12 patients (58%) with refractory strictures, SEMS were removed within four weeks because of SEMS intolerability and SEMS migration. Only

one (8%) patient was dysphagia free one month after SEMS removal. Eloubeidi et al. reported recently their experience with fully-covered SEMS in 16 patients with leaks/perforations and 19 patients with benign esophageal strictures. SEMS were in position for a median interval of 58 days (range: 6-300 days). They also reported higher rates of clinical success in patients with leaks than for stenosis (44% versus 21% respectively).[59] Holm et al. reported outcomes of 84 stents in 30 patients with benign esophageal strictures. In only 5 of 83 interventions (6%), long-term improvement was achieved after stent removal.[60] Based on these results, the use of stents for refractory strictures cannot be routinely recommended and should be limited to strict patient selection, until there is significant improvement in stent design.

CONCLUSIONS AND FUTURE DIRECTIONS

Technology in the field of gastroenterology is developing at an exponential pace. Detection of precancerous lesions in moderate to high risk populations is an essential clinical goal. New optical and therapeutic developments are rapidly in progress. Despite the many enhancements, overall progress in the outcome of esophageal cancer remains poor. The majority of patients with esophageal cancer have inoperable disease at presentation. In these patients palliative therapy is the only treatment option. This thesis showed that covered-expandable stents are highly useful in restoring luminal patency and sealing esophagorespiratory fistulae in patients with intrinsic and extrinsic lesions, and also in recurrent cancer after esophagectomy. Unfortunately, there are a number of shortcomings with the current stent designs. Shortcomings include chest pain, hemorrhage, stent migration, and the possibility of recurrent or unresolved dysphagia or leakage. With the modification of the conventional self-expandable metal stent, significant improvement in the therapeutic outcome has been achieved. With their potential for removability, stents can be effectively used for benign esophageal disease. Stenting have encouraged a shift away from conventional surgery, as they successfully seal perforations and allow mucosal wall healing. SEMS cannot be routinely recommended in the treatment of refractory benign esophageal strictures until there is significant improvement in the stent design as they are generally poorly tolerated and furthermore long-term outcomes are dissatisfied. The minimally invasive nature of expandable stents for benign esophageal disease is appealing, but serious complications during removal do occur. SEMS removal should be performed within a limited time-interval of less than 6 weeks, and furthermore overlapping stents should be avoided.

Stent designs will continue to evolve. Fully absorbable stent designs, radioactive stents, and drug eluting stents, that cause no tissue reaction are of particular interest to prevent complications of stent removal and may play a future role in the management of recurrent benign conditions, including refractory strictures or achalasia. Expectations for future technology are high; however to establish the value of various advanced diagnostic and thera-

peutic tools, long-term outcomes of randomized controlled trials are required. Furthermore, patients should be carefully selected and closely monitored.

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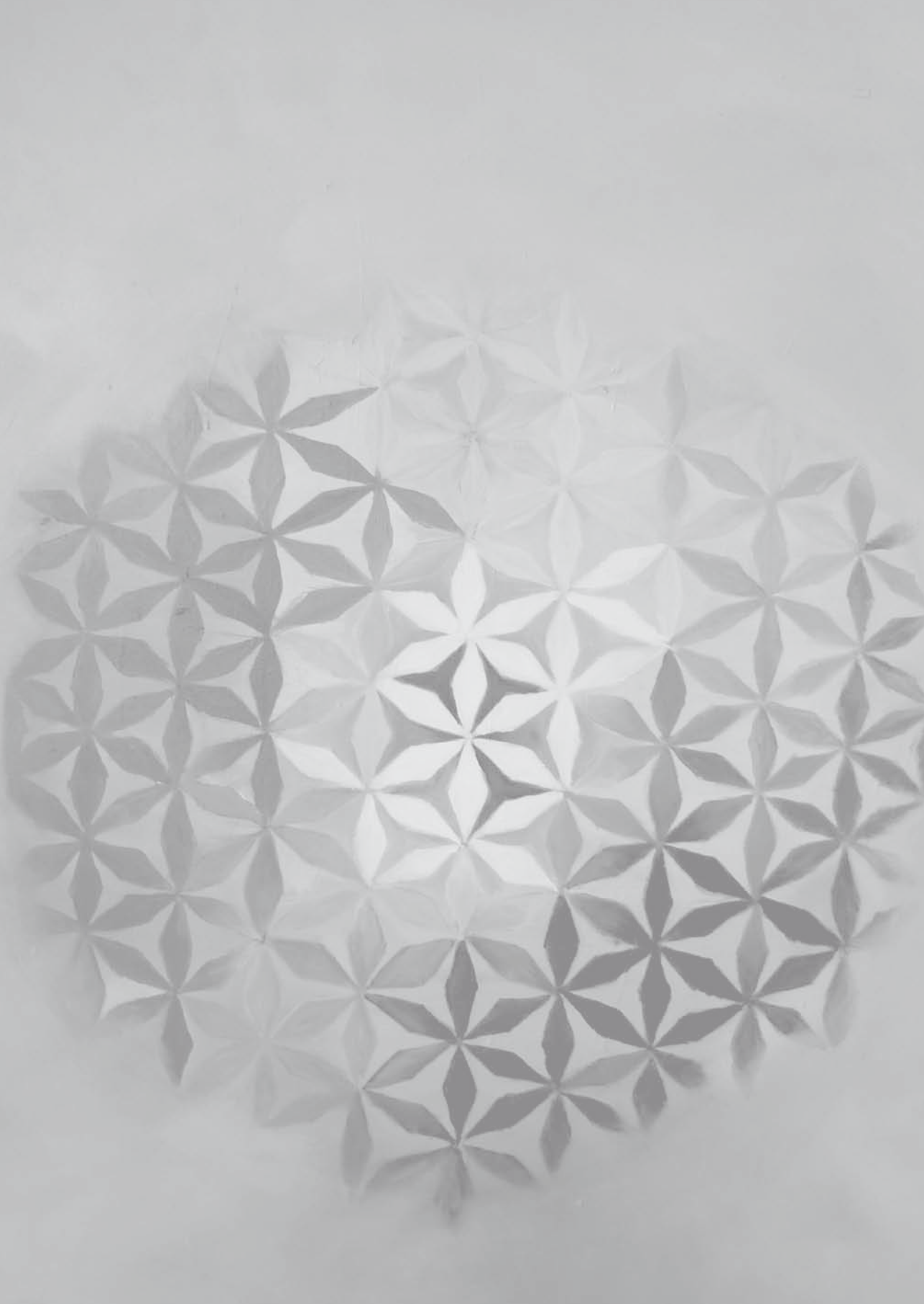


Summary

SUMMARY

The studies described in this thesis address the role of stent therapy in malignant and benign esophageal disease. Our set of studies summarized here, sheds new light on knowledge of the indications for esophageal stenting and the common drawbacks associated with different stent designs. These studies allow physicians to select stents for a particular condition as well as to anticipate complications such as stent dysfunction and difficulties concerning stent removal.

Chapter 1 describes the aims and the outline of this thesis.

Chapter 2 provides an overview of recent developments in prevention, detection and the approach to early gastrointestinal cancer. In addition, future directions to improve survival are discussed.

Chapter 3 and beyond then focus on the treatment of esophageal disease by means of self-expandable metal stents (SEMS). Chapter 3 describes the value of SEMS therapy in patients with recurrent cancer after previous surgical esophagectomy. In this prospective observational study of 81 patients with recurrent cancer after previous surgical esophagectomy, 100 esophageal SEMSs were inserted for dysphagia (n=66 patients) or fistula formation (n=15 patients). SEMS therapy restored luminal patency in 65 (98%) of 66 patients and sealed malignant fistulae in 14 (93%) of 15 patients. Stent dysfunction occurred in 24 (30%) of 81 patients. They all were successfully managed by subsequent endoscopic intervention. After stent placement, a total of 16 complications were observed. Major complications occurred in 9 (11%) of 81 patients, mild complications occurred in 7 (9%) of 81 patients. The overall 30-day mortality rate after stent insertion was 25%. Progression of the disease resulted in death after a median interval of 70 days (range 1 day - 91 months). These results demonstrate that insertion of SEMS offers good palliation in patients with recurrent esophageal cancer, by relieving dysphagia and sealing off esophageal respiratory fistulae. Therefore, in these patients who have a limited life expectancy, SEMS placement should be considered the treatment of choice.

Chapter 4 outlines the role of SEMS therapy in a large cohort of patients with malignant extrinsic compression of the esophagus. Between 1995 and 2009, 50 consecutive patients with malignant extrinsic compression who had undergone SEMS placement were included (94% male; mean age 64 years). In the majority of patients, extrinsic esophageal compression was caused by obstructive pulmonary cancer (n=23) and by mediastinal metastasis after esophagectomy for esophageal cancer (n=16). Stent placement was technically successful in all patients. Severe complications occurred in 5/50 patients (10%) including perforation

during dilation prior to stent insertion (n=2) and hemorrhage (n=3). Two patients (4%) died from bleeding. Mild complications were seen in 9/50 patients (18%). Recurrent dysphagia occurred in eight patients (16%) and was successfully managed by subsequent endoscopic intervention. Median survival after stent placement was 44 days (range 5 days - 2 years). The median stent patency of 46 days in this series exceeded median patient survival. These results demonstrate that insertion of a SEMS is an effective palliative treatment for patients with dysphagia due to malignant extrinsic compression. In spite of the short survival, some patients present with recurrent dysphagia, which can be managed effectively by endoscopic re-intervention.

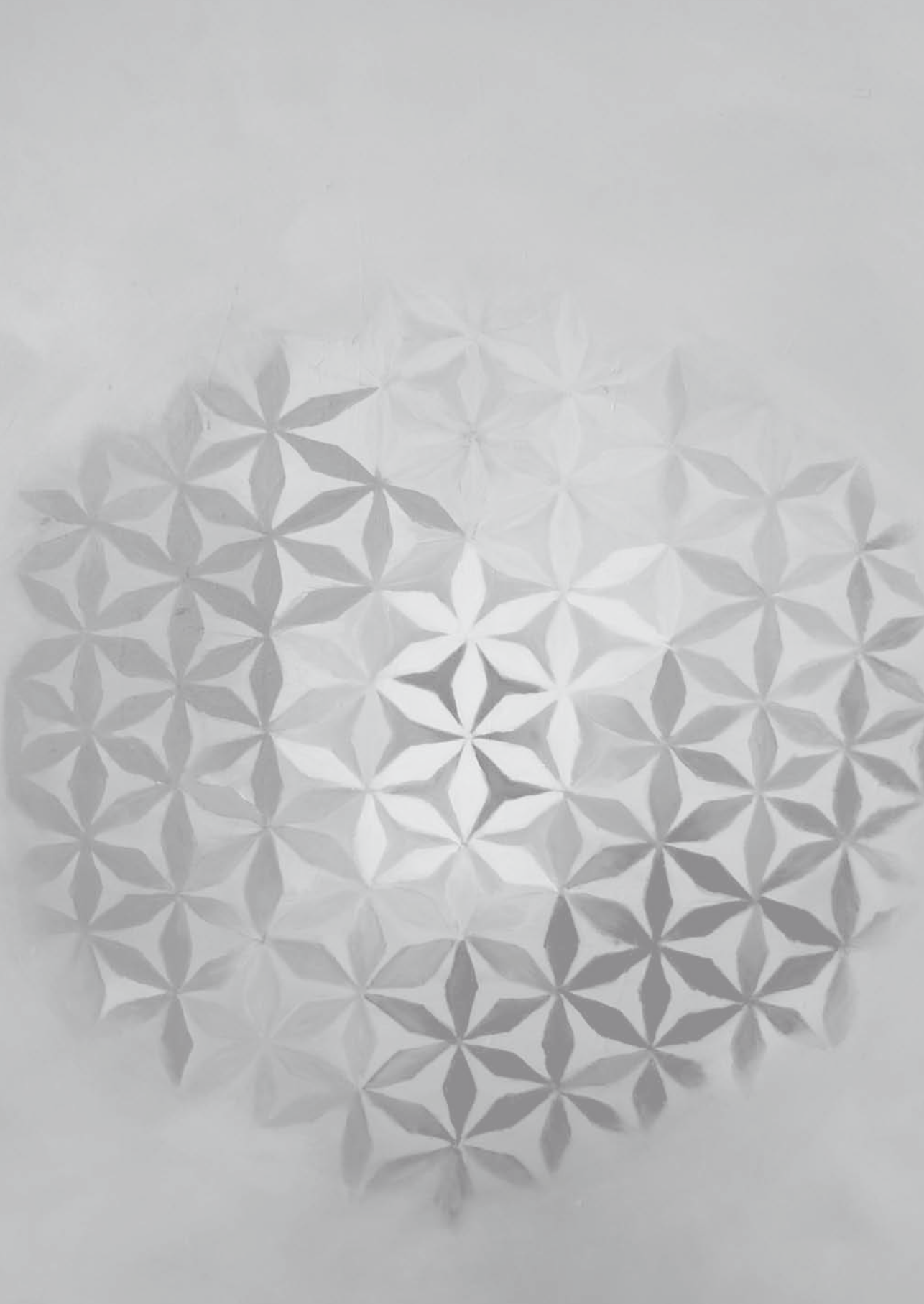
Chapter 5 describes a randomized controlled multi-center study, comparing the conventional Ultraflex® stent with the new Evolution® in 80 patients with malignant esophageal disease. Patients were followed by scheduled telephone calls at one and three months after SEMS insertion. A total of 80 patients (73% male; median age 67 years) were included. One patient refused follow-up. Technical success was 100% in both groups. Reintervention rate was 15/40 (38%) for the Ultraflex and 4/39 (10%) for the Evolution stent (p=0.004). Major complications including aspiration pneumonia and bleeding occurred more frequently in the Ultraflex group (10/40 (25%)) compared to the Evolution group (3/39 (8%)) (p=0.04). There was no difference in overall survival between the two groups. These results set the preference for the Evolution stent over the Ultraflex stent for patients with malignant esophageal disease.

Chapter 6 assessed the feasibility of SEMS removal. A total of 124 stent extractions were undertaken in 95 patients; both partially covered (68%) and fully covered (32%) SEMSs were removed. Three patients had 2 overlapping SEMSs in place. Successful primary removal was achieved in 89%; the secondary removal rate was 96%. Uncomplicated primary removal rate was significantly higher for fully covered versus partially covered stents (P=0.035) and for single versus overlapping stents (P=0.033). Patients with a complicated stent removal had the stent in place significantly longer compared with patients with an uncomplicated primary stent removal (126 days vs 28 days; P=0.01). Surgical removal was required in 3 patients (2.4%). Six moderate and severe complications (5%) related to the endoscopic extraction occurred. This study showed that primary endoscopic removal of a SEMS is feasible in the majority of patients with benign and malignant esophageal disease. A longer stent dwell time and the use of partially covered SEMSs both impede removal. Moreover, overlapping SEMSs should be avoided for temporary use because stent disintegration and subsequent complications may occur.

Chapter 7 evaluates the value of self-expandable metal stents in patients with benign esophageal perforations. Thirty-three patients underwent SEMS placement. Complete clo-

sure of the defect was observed in 70% at a median of 6 weeks after initial treatment. All stent extractions within 6 weeks after insertion were uneventful. Importantly, this study shows a considerable rate of serious complications in those cases in which stents were extracted after ≥ 6 weeks after stent insertion. In all, 10 stents were in place for ≥ 6 weeks (range: 6 – 84 weeks) and all were firmly embedded into the esophageal mucosa. Extraction resulted in six major complications. These observations should caution clinicians to leave stents in for a prolonged period of time. Although preservation of the esophagus is secondary to survival, this study shows that the esophagus can be preserved in the majority of patients.

Chapter 8 describes a randomized controlled trial, comparing the partially-covered Ultraflex stent® with the fully-covered Hanarostent®. This study included 44 consecutive patients with benign esophageal disease. Both the partially-covered Ultraflex stent and fully-covered Hanarostent were equally effective in sealing non-malignant esophageal fistulae and restoring luminal patency. A major drawback of these stents was the re-occurrence of dysphagia and leakage caused by SEMS migration, with no significant difference between the two stent types. SEMS in patients with refractory strictures were poorly tolerated and furthermore the short-term effects on the dysphagia score was dissatisfying. All SEMS were successfully removed at one month post SEMS-insertion. However during 2 partially-covered SEMS removals severe complications occurred. Since removal of partially covered stents is considerably more complex than removal of fully covered stents, we advocate the use of fully covered expandable metal stents for this indication.



Summary in dutch

SAMENVATTING

De hoofdstukken in dit proefschrift beschrijven de rol van stenttherapie bij patiënten met maligne en benigne slokdarmaandoeningen. De studies die hier in het kort worden samengevat, werpen een nieuw licht op de indicaties en op de voor- en nadelen van het gebruik van verschillende typen stents. Deze resultaten bieden artsen de mogelijkheid om stents voor een specifieke aandoening te selecteren en eveneens om te anticiperen op stent gerelateerde complicaties.

Hoofdstuk 1 beschrijft de doelstellingen en de hoofdlijnen van dit proefschrift.

Hoofdstuk 2 geeft een overzicht weer van recente ontwikkelingen op het gebied van de preventie en de behandeling van patiënten met een vroeg stadium van gastrointestinale tumoren.

Hoofdstuk 3 beschrijft de rol van zelf-ontplooibare metale stents (self-expandable metal stent (SEMS)) bij patiënten met een recidief slokdarmcarcinoom na een oesofagusresectie. In deze prospectieve observationele studie zijn 81 opeenvolgende patiënten geïncludeerd, waarbij in totaal 100 slokdarmstents zijn geplaatst. Bij 66 patiënten was een slokdarmstent geïndiceerd voor dysfagie op basis van een maligne slokdarmstenose, bij 15 patiënten was een stent geïndiceerd voor een maligne slokdarmfistel. Het plaatsen van een SEMS resulteerde in een goede doorgankelijkheid van de oesofagus bij 65 (98%) van de 66 patiënten en dichtte maligne slokdarmfistels af bij 14 (93%) van de 15 patiënten. Stent dysfunctie trad op bij 24 (30%) van de 81 patiënten. Deze patiënten waren allen succesvol behandeld middels een endoscopische reïnterventie. In totaal ontstonden er 16 complicaties na het plaatsen van een stent. Ernstige complicaties traden op bij 9 (11%) van de 81 patiënten, milde complicaties traden op bij 7 (9%) van de 81 patiënten. De 30-dagen mortaliteit na stentplaatsing was 25%. Progressie van de ziekte resulteerde in het overlijden van patiënten na een mediane duur van 70 dagen (variërend van 1 dag tot 91 maanden). Bovengenoemde resultaten tonen aan dat het plaatsen van een SEMS een effectieve behandeling biedt voor patiënten met een recidief maligniteit na een oesofagectomie. SEMS zijn effectief voor zowel het afdichten van slokdarmfistels alsmede voor het opheffen van stenosen. Bij deze patiënten met een zeer beperkte levensverwachting is het plaatsen van een SEMS de therapie van keuze.

Hoofdstuk 4 beschrijft de rol van SEMS therapie bij een groot cohort patiënten met dysfagie op basis van maligne extrinsieke compressie. Tussen 1995 en 2009 zijn er in totaal 50 patienten geïncludeerd. Bij de meerderheid werd extrinsieke compressie veroorzaakt door een obstructief longcarcinoom (n=23) en door mediastinale metastasen na een oesofagectomie (n=16). Plaatsing van een stent was bij alle patiënten technisch succesvol. Ernstige complica-

ties, waaronder bloedingen (n=3) en perforaties tijdens dilatatie voorafgaand aan het plaatsen van de stent (n=2), traden op bij 5/50 (10%) patiënten. Twee (4%) patiënten overleden ten gevolge van de bloeding. Milde complicaties traden op bij 9/50 (18%) patiënten. Recidief dysfagie ontstond bij 8 (16%) patiënten. Zij werden allen succesvol endoscopisch behandeld. De mediane overleving na de stentplaatsing was 44 dagen (variërend van 5 dagen - 2 jaar). In deze serie was de mediane doorgankelijkheid van de stent van 46 dagen langer dan de mediane patiënten overleving. Deze resultaten tonen aan dat het plaatsen van een SEMS een effectieve palliatieve behandeling is voor patiënten met dysfagie ten gevolge van maligne extrinsieke compressie. Bij een aantal patiënten ontstaat er opnieuw dysfagie ondanks hun korte levensduur. De meeste patiënten kunnen effectief behandeld worden middels een endoscopische interventie.

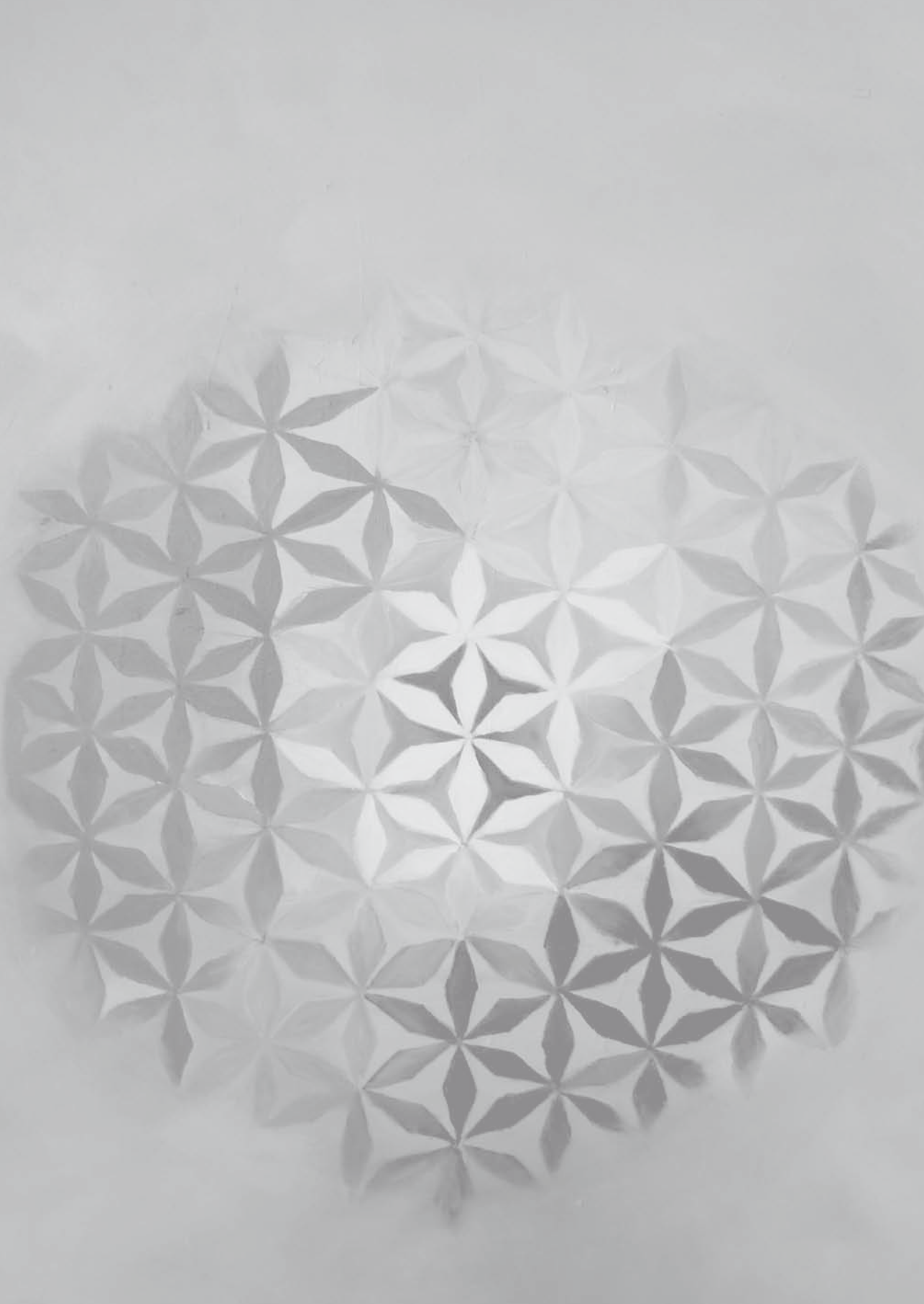
Hoofdstuk 5 omvat een multicenter gerandomiseerde studie, waar de conventionele Ultraflex® stent met de nieuwe Evolution® stent wordt vergeleken bij 80 patiënten met een maligniteit van de oesofagus. Eén en drie maanden na het inbrengen van een SEMS werden patiënten telefonisch geïnterviewd. In totaal werden er 80 patiënten geïncludeerd (73% man; mediane leeftijd 67 jaar), 1 patiënt weigerde follow-up. Stentplaatsing was technisch succesvol bij 100%. Het aantal reïnterventies bedroeg 15/40 (38%) voor de Ultraflex stent en 4/39 (10%) voor de Evolution stent (p=0,004). Ernstige complicaties waaronder een aspiratie pneumonie en bloedingen traden vaker op bij patiënten met de Ultraflex (10/40 (25%)) dan bij patiënten met de Evolution stent (3/39 (8%)) (p=0,04). Er was geen significant verschil in de mediane overleving tussen beide groepen. Op basis van deze resultaten verdient het plaatsen van een Evolution stent de voorkeur boven het plaatsen van een Ultraflex stent bij patiënten met een oesofagus maligniteit.

Hoofdstuk 6 beschrijft de haalbaarheid van SEMS verwijdering bij patiënten met benigne en maligne oesofagus aandoeningen. In totaal werden 124 stents verwijderd bij 95 patiënten; 68% was gedeeltelijk gecovered, 32% was volledig gecovered. Drie patiënten hadden twee overlappende stents in de oesofagus. Stentverwijdering was endoscopisch succesvol bij de eerste poging bij 89%. Bij herhaalde poging was stentverwijdering succesvol bij 96% van de patiënten. Ongecompliceerde primaire verwijdering was significant hoger bij patiënten met een volledig gecoverde stent dan bij patiënten met een gedeeltelijk gecoverde stent (P=0,035). Bovendien traden er significant meer complicaties op bij patiënten met een enkele stent dan bij patiënten met twee overlappende stents in de oesofagus (P=0,033). Patiënten met een gecompliceerde stentverwijdering hadden de stent significant langer in de oesofagus in vergelijking tot patiënten met een ongecompliceerde stentverwijdering (126 dagen versus 28 dagen; P=0,01). Bij drie (2,4%) patiënten werd de stent chirurgisch verwijderd. Zes (5%) matig ernstige tot ernstige complicaties ontstonden er gedurende of na het verwijderen van de stent. Deze studie toont aan dat een primaire endoscopische verwijdering van een

SEMS bij de meeste patiënten met een benigne of maligne oesofagus fistel of stenose succesvol is. Echter, als een stent voor een lange periode in de slokdarm zit, of als er 2 overlappende stents zich in de slokdarm bevinden, dan is het risico op het ontstaan van complicaties gedurende het verwijderen van deze stents aanzienlijk.

Hoofdstuk 7 evalueert de rol van SEMS therapie bij patiënten met benigne oesofagus perforaties. Bij 33 patiënten met een benigne laesie werd een SEMS tijdelijk in de oesofagus geplaatst. Na het endoscopisch verwijderen van de stent was bij 70% van de patiënten de perforatie succesvol geheeld. Alle stentverwijdering binnen zes weken na plaatsing verliepen ongecompliceerd. Dit onderzoek toont aan dat ernstige complicaties optraden bij het verwijderen van stents na een stent duur van ≥ 6 weken. In totaal werden 10 stents verwijderd na een periode van ≥ 6 weken (variërend van 6 - 84 weken). Deze stents waren allen ernstig ingebed in de mucosa van de oesofagus. Stentverwijdering bij deze groep resulteerde bij 6 patiënten tot ernstige complicaties. Deze observaties moeten clinici ervan behoeden om stents voor benigne indicaties voor een langere termijn dan 6 weken in de slokdarm te laten. Deze studie toont aan dat met behulp van stenttherapie de oesofagus behouden kan worden bij de meeste patiënten met een benigne oesofagus perforatie.

Hoofdstuk 8 beschrijft een gerandomiseerde trial waarin de gedeeltelijk gecoverde Ultraflex stent® met de volledig gecoverde Hanarostent® wordt vergeleken. In deze studie werden 44 opeenvolgende patiënten met een benigne slokdarmfistel of een benigne slokdarmstenose geïncludeerd. De partieel gecoverde Ultraflex stent en volledig gecoverde Hanarostent bleken vergelijkbaar effectief te zijn bij het afdichten van benigne fistels en bij het herstellen van de luminale doorgankelijkheid. Een belangrijk nadeel van deze behandeling was het opnieuw optreden van dysfagie of lekkage veroorzaakt door SEMS migratie; echter zonder significant verschil tussen beide typen stents. SEMS bij patiënten met refractaire stricturen werden over het algemeen slecht verdragen en bovendien was de verbetering van dysfagie vaak teleurstellend. Beide typen SEMS werden 1 maand na plaatsing succesvol verwijderd. Echter tijdens het verwijderen van 2 partieel gecoverde SEMS traden ernstige complicaties op. Aangezien het verwijderen van gedeeltelijk gecoverde stents aanzienlijk complexer is dan het verwijderen van volledig gecoverde stents, pleiten wij voor het gebruik van volledig gecoverde expandabele stents voor bovengenoemde indicaties.



List of publications

LIST OF PUBLICATIONS

1. **NCM van Heel**, J Haringsma, MCW Spaander, MJ Bruno, EJ Kuipers
Short-term esophageal stenting in the management of benign perforations.
The American Journal of Gastroenterology 2010;105(7):1515-20

2. **NCM van Heel**, J Haringsma, MCW Spaander, MJ Bruno, EJ Kuipers
Esophageal stents for the relief of malignant dysphagia due to extrinsic compression.
Endoscopy 2010;42(7):536-40

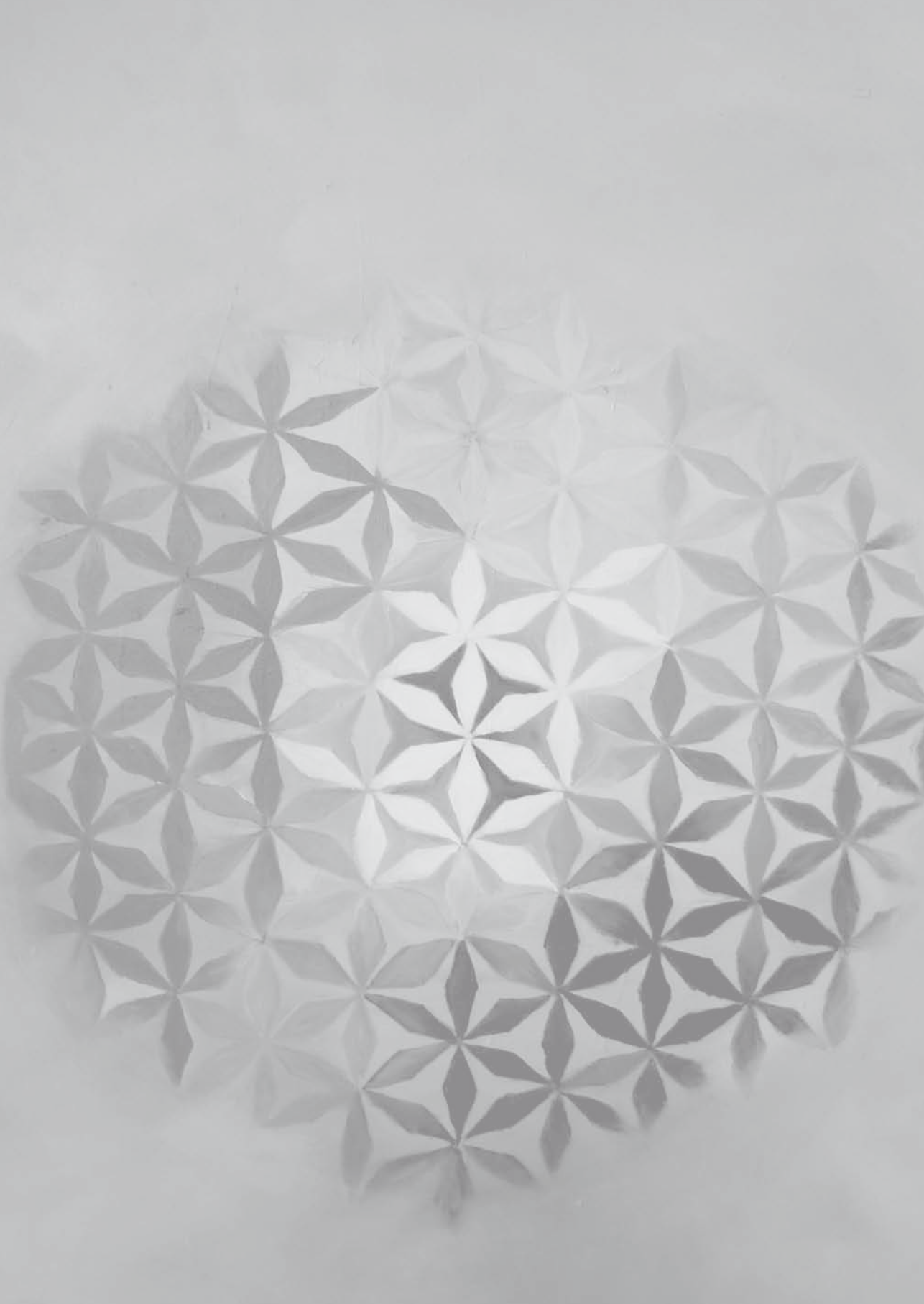
3. J Haringsma, **NCM van Heel**, EJ Kuipers
Are we making progress in diagnosing and preventing gastrointestinal cancers?
Therapeutic Advances in Gastroenterology 2010; 3(4): 213–220

4. **NCM van Heel**, J Haringsma, MCW Spaander, P Didden, MJ Bruno, EJ Kuipers
Esophageal stents for the palliation of malignant dysphagia and fistula recurrence after esophagectomy.
Gastrointestinal Endoscopy 2010;72(2):249-54

5. **NCM van Heel**, J Haringsma, BPL Wijnhoven, EJ Kuipers
Endoscopic removal of self-expandable metal stents from the esophagus.
Gastrointestinal Endoscopy 2011;74(1):44-50

6. **NCM van Heel**, J Haringsma, H Boot, A Cats, SALW Vanhoutvin, EJ Kuipers
Comparison of two expandable stents for malignant esophageal disease: a randomized controlled trial.
Submitted

7. **NCM van Heel**, J Haringsma, EJ Kuipers
Partially- versus fully-covered expandable metal endoprosthesis for benign esophageal disease: a randomized controlled trial.
Submitted



PhD portfolio

PHD PORTFOLIO

Oral Presentations

2011

Expandable metal stents for malignant esophageal stenosis: a randomized controlled comparison of the new Evolution stent versus the Ultraflex stent.
Digestive Disease Week, Chicago, USA.

Partially versus fully covered self-expandable stents for esophageal perforations and fistulae: a randomized controlled study.
Dutch Society of Gastroenterology, Veldhoven, the Netherlands.

Expandable metal stents for malignant esophageal stenosis: a randomized controlled comparison of the new Evolution stent versus the Ultraflex stent.
Dutch Society of Gastroenterology, Veldhoven, the Netherlands.

2010

Endoscopic extraction of self-expandable metal stents from the esophagus: outcomes and complications in 107 procedures.
Digestive Disease Week, New Orleans, USA.

Endoscopic extraction of self-expandable metal stents from the esophagus: outcomes and complications in 107 procedures.
Dutch Society of Gastroenterology, Veldhoven, the Netherlands.

2009

Complications of long-term esophageal stenting in the management of benign perforations.
Digestive Disease Week, Chicago, USA.

Long-term results of endoscopic ablation therapy for early Barrett's cancer.
Dutch Society of Gastroenterology, Veldhoven, the Netherlands.

2008

Temporary esophageal stenting in the management of benign esophageal disease.
Dutch Society of Gastroenterology, Veldhoven, the Netherlands.

Placement of self-expandable stents for non-malignant esophageal perforations.
United European Gastroenterology Week, Wien, Austria.

Poster Presentations

2011

Partially versus fully covered self-expandable stents for esophageal perforations and fistulae: a randomized controlled study.
Digestive Disease Week, Chicago, USA.

2010

Efficacy of esophageal metal stents for the relief of malignant dysphagia due to extrinsic compression in a large prospective series.
Digestive Disease Week, New Orleans, USA.

2009

Esophageal stents for the relief of malignant dysphagia due to extrinsic compression.
United European Gastroenterology Week, London, Great-Britain.

Primary endoscopic stenting versus surgery in the acute management of patients with Boerhaave's syndrome.
Digestive Disease Week, Chicago, USA.

2008

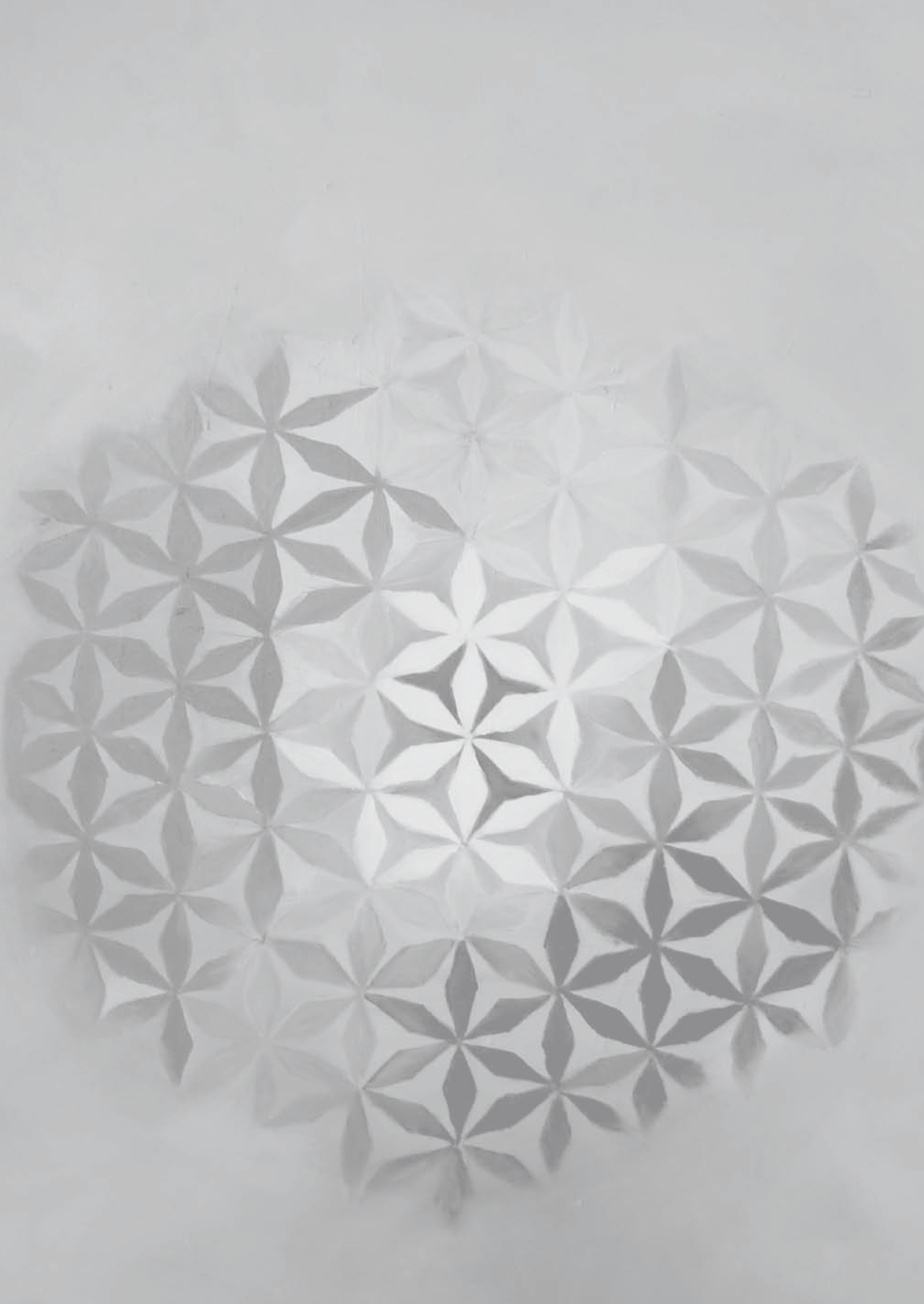
High complication rate in long-term esophageal stenting for non-malignant disease.
United European Gastroenterology Week, Wien, Austria.

Membership

Dutch Society of Gastroenterology

Courses

Introduction to clinical research - NIHES, Erasmus MC, Rotterdam, the Netherlands
Biostatics for clinicians - NIHES, Erasmus MC, Rotterdam, the Netherlands
Biomedical English writing - NIHES, Erasmus MC, Rotterdam, the Netherlands



Acknowledgements

Vanaf oktober 2007 heb ik aan dit project gewerkt, nu is het boek eindelijk klaar: Hoera!
Dit proefschrift was nooit tot stand gekomen zonder de hulp van velen.

Mijn grote dank gaat uit naar:

Allereerst alle patiënten. Deze uiteenzetting heeft niet tot stand kunnen komen zonder hun deelname en medewerking.

Mijn promotor, **Prof. dr. E.J. Kuipers**. Beste Ernst, hartelijk dank dat je mij de mogelijkheid hebt gegeven om mij te verdiepen in de wetenschap, in dat deel wat mij het meest heeft aangesproken binnen de muren van het Erasmus MC. Jouw perfecte dosering enthousiasme en zakelijke begeleiding, afgewisseld met je persoonlijke interesse, heb ik enorm gewaardeerd. Bovendien wil ik je bedanken voor je scherpzinnige feedback waarmee je mijn artikelen hebt beoordeeld. Ik vond het een eer om met je samen te mogen werken.

Drs. J. Haringsma. Beste Jelle, als geen ander ben jij zo betrokken geweest bij dit project. Ik heb veel van je geleerd door het delen van je kennis en de bijdrage aan de studies, zoals gepresenteerd in het proefschrift. Je hebt mij alle ruimte gegeven om mijzelf te ontplooien. Daarnaast heb ik de mogelijkheid om tussen de onderzoeksmomenten door endoscopische ervaring op te doen, waaronder 'het loodgieterswerk', enorm gewaardeerd. Ik wil je bedanken voor al je tijd en inzet in de afgelopen jaren.

Vervolgens wil ik **dr. R.A. de Man** bedanken voor het in mij gestelde vertrouwen om te mogen beginnen met de opleiding tot maag- darm- leverarts.

De leden van de **leescommissie** wil ik bedanken voor hun tijd en bereidheid mijn proefschrift te beoordelen. Mijn dank gaat tevens uit naar alle andere leden die zitting hebben willen nemen in de **promotiecommissie**.

Veel dank aan **het hele team van de maag- darm- leverziekten**, waaronder alle MDL-artsen, met in het bijzonder **Prof. dr. M.J. Bruno**, **drs. J.W. Poley** en **dr. M.C.W. Spaander**. Heel veel dank voor jullie hulp bij de inclusie en de behandeling van de patiënten, jullie kritische blik ten aanzien van het protocol, het manuscript en de presentaties. Veel dank gaat daarnaast uit naar de arts-assistenten, de secretaresses en de verpleging**.** De mogelijkheid die jullie mij hebben gegeven om patiënten te includeren en te scopiëren ondanks de overvolle agenda's, heb ik enorm gewaardeerd. Hartelijk dank voor jullie geduld en inzet.

Voor een optimale patiëntenzorg voor patiënten met slokdarmaandoeningen is een goede samenwerking tussen de maag- darm- leverziekten en de heelkunde zeer belangrijk. Een

speciaal woord van dank gaat daarom uit naar **Prof. dr. H.W. Tilanus** en **dr. B.P.L. Wijnhoven** van de vakgroep chirurgie. Hartelijk dank voor de aangename samenwerking.

Graag wil ik de vakgroep Maag- Darm- en Leverziekten van het Antoni van Leeuwenhoek Ziekenhuis in Amsterdam bedanken, waarbij in het bijzonder **dr. A. Cats** en **dr. H. Boot**. Hartelijk dank voor deelname aan mijn studie en de zeer prettige samenwerking.

De internisten en collega's uit Deventer Ziekenhuis wil ik niet alleen bedanken voor de goede werksfeer waarin ik nu mag werken, maar ook voor de mogelijkheid die mij werd geboden om op rustige momenten de puntjes op de i te zetten.

Daarnaast mijn statistische steun, beste **Caspar Looman**, hartelijk dank voor al je hulp bij de statistiek vragen.

Collega arts-onderzoekers, **Aafke, Ad, Aria, Caroline, Celine, Daphne, Edith, Erik, Femme, Geert, Jerome, Jildou, Jilling, Judith, Jurrien, Lauran, Leonie, Lieke, Lisette, Marjolein, Milan, Paul, Pieter-jan, Jerome, Judith, Renate, Robert, Roeland, Susanne, kleine en grote Vincent, Vera** en **Vivian,** heel erg bedankt voor al jullie gezelligheid. Nooit gedacht dat een goede sfeer en motiverende samenwerking zo belangrijk is voor je promotie traject. De uitjes, congressen, skireizen en bovenal de vele fietstochten door weer en wind zijn onvergetelijk.

Beste **Edmée** en **Margot**, lieve roomies, ik heb met jullie een onvergetelijke tijd 'op het dak' gehad. Naast het harde vlammen was er genoeg ruimte voor gezelligheid, goede gesprekken, hilariteit en het bespreken van frustraties. Enorm bedankt voor deze waardevolle periode. Lieve Eddy, heel fijn je vandaag deze speciale plek in wilt nemen.

Een proefschrift schrijven was mij niet gelukt zonder steun van velen, lieve **vrienden en familie**, enorm bedankt voor jullie belangstelling en support.

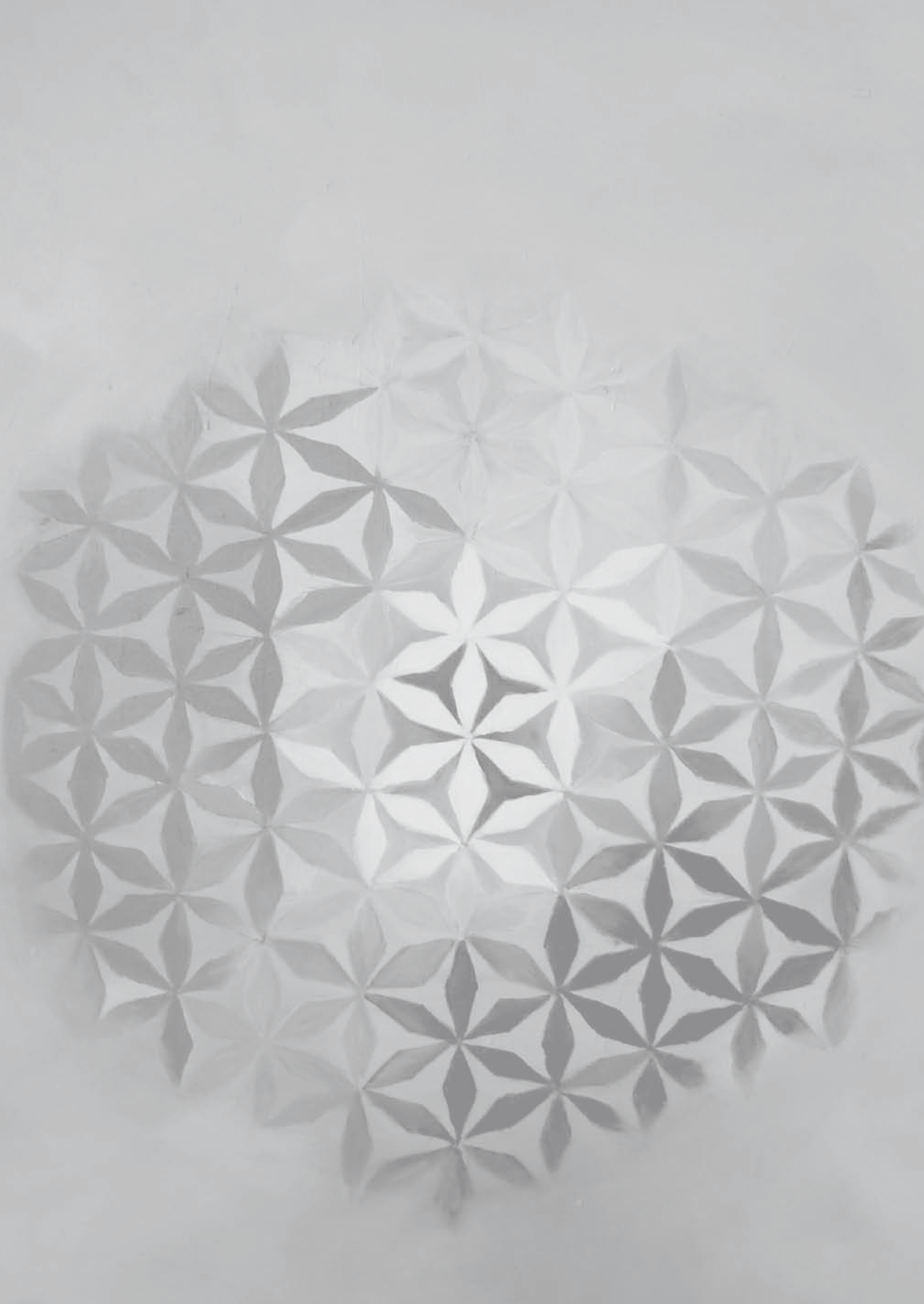
Beste **Nicole**, lieve Niccie. Bij de aanvang van de studententijd in Groningen leerden wij elkaar kennen. Als club- en huisgenootje in Groningen hebben wij veel lief en leed gedeeld. Daarnaast was je mijn steun en toeverlaat in hectische tijden. Enorm bedankt voor al je hulp. Met een jurist aan mijn zijde kan mij vandaag niets gebeuren!

Beste **Désirée**, lieve Dees, vanaf het moment dat we begonnen met ons promotie onderzoek waren we een soort van eenheid. Niet erg verwonderlijk dat niet iedereen onze namen uit elkaar kon houden. Dank voor al je gezelligheid, het medeleven en je talloze tips, fijn dat we

zoveel met elkaar hebben kunnen delen. Heel veel succes met de allerlaatste loodjes, ik ben erg benieuwd naar jullie kleine wonder. Heel fijn dat jij ook mijn paranimf wilt zijn.

Lieve **mam, pap** en **Léonie**, jullie steun heeft mij uiteindelijk hier gebracht. Jullie zijn de enigen die mijn project van begin tot eind hebben gemaakt en zo intens hebben meegeleefd. Zonder jullie steun had ik hier nu niet gestaan. Altijd hebben jullie voor mij klaargestaan op velerlei vlakken, heel veel dank voor werkelijk alles.

Bijzonder veel dank gaat uit naar **Joost**. Lieve Joost, het leven met jou maakt mij enorm gelukkig. Jouw liefde, begrip en onvoorwaardelijk steun betekenen ontzettend veel voor me. Dank voor je inzet en je kritische blik ten aanzien van dit schrijven. Jij hebt mij echt door de allerlaatste loodjes heen geholpen. Vanaf nu meer tijd voor leuke dingen. Met heel veel plezier kijk ik uit naar een mooie toekomst samen met jou!



Curriculum Vitae

CURRICULUM VITAE

De auteur van dit proefschrift werd op 8 januari 1981 geboren te Leusden. Na het behalen van haar VWO diploma, startte zij in 2000 met de studie geneeskunde aan de Rijksuniversiteit Groningen. Haar wetenschappelijke stage naar ijzerstapeling in de lever bij patiënten met leukemie heeft zij verricht voor een duur van 6 maanden in the Women's and Children's Hospital in Adelaide, Australië. In 2005 behaalde zij haar doctoraal examen. Gedurende de coschappen in het Deventer Ziekenhuis werd haar interesse al snel gewekt voor de maag-darm- leverziekten. Haar keuze coschap doorliep zij vervolgens op de afdeling Maag- Darm- en Leverziekten in het Haga Ziekenhuis in Den Haag, waarna zij haar artsexamen behaalde. In september 2007 startte zij met haar promotieonderzoek naar de rol van stenttherapie bij benigne en maligne slokdarmaandoeningen, onder begeleiding van drs. J. Haringsma en Prof. dr. E.J. Kuipers op de afdeling Maag- Darm- en Leverziekten van het Erasmus MC te Rotterdam. Sinds 2010 is zij in opleiding tot maag- darm- leverarts via het Erasmus MC (opleider: dr. R.A. de Man), waarbij de vooropleiding interne geneeskunde thans wordt verricht in het Deventer Ziekenhuis (opleider: dr. C.G. Vermeij).