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Jeanin E. van Hooft

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Jeanin E. van Hooft
Jolleymanhof 51,
1019 GW Amsterdam
j.e.vanhooft@amc.nl
06-14676576

Danielle Langeloo
D.Langeloo@home.nl
06-25028539

Eveline Schurink
eveline.schurink@uff.co.za
+27-76 963 7505

Jeanin E. van Hooft
voor het bijwonen van de
openbare verdediging van
het proefschrift van

Endoscopic
treatment of
gastrointestinal
strictures
Endoscopic treatment of gastrointestinal strictures

Jeanin E. van Hooft
Endoscopic treatment of gastrointestinal strictures
Thesis, University of Amsterdam, The Netherlands

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Endoscopic treatment of gastrointestinal strictures

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aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het college voor promoties ingestelde
commissie, in het openbaar te verdedigen in de Aula der Universiteit
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door

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Faculteit der Geneeskunde
Respect things on faith, but doubt gets you an education.
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Chapter 1

Introduction and outline of the thesis
Introduction and outline of the thesis

The gastrointestinal tract consists of consecutive tubular structures extending from the mouth to the anus. An abnormal narrowing in the gastrointestinal tract is either called stenosis (from Ancient Greek στένωσις, ‘narrowing’) or stricture (from Latin strictus, ‘tighten, compress’); two different words for the same entity.

The origin of the stenosis or stricture varies widely from congenital, inflammatory to malignant. If a stricture prevents the normal transit of the food and digestive fluids, it causes an obstruction. Patients with an obstruction usually present with nausea, vomiting, abdominal distension and/or abdominal pain. The obstruction may be accompanied by several complications, for example dehydration or electrolyte abnormalities because of vomiting. Respiratory problems can also arise from pressure on the diaphragm by a distended abdomen, and aspiration can lead to a pneumonia. Other complications include bowel ischemia and perforation from prolonged distension of the colon. To prevent these complications resolution of the obstruction is needed.

For decades the only option to resolve a stricture was surgery, consisting of either resection of the stricture, creation of a bypass or construction of a stoma.

There has been progress since the early 1950s when a tiny camera attached to a flexible tip with a light bulb (“gastro camera”) was invented. The “gastro camera” made it possible to photograph parts of the intestine.

With the introduction of the fibre-optic endoscope a new era, combining diagnostic and therapeutic endoscopy, dawned. Although the initial imaging quality was poor, a reasonable attempt to visualize the cause of complaints could be made. In addition, small instruments like forceps could be advanced through the working channel in order to collect tissue for analysis. Further technical developments led to the introduction of video-endoscopes. The increased resolution was a tremendous boost for imaging and the development of innovative endoscopic therapies.

Subsequently, surgeons no longer had a monopoly on the treatment of strictures. Benign strictures in the esophagus could now be treated with tapered plastic tubes, also called bougies, which gradually stretched the stricture. In addition, malignant strictures could be palliated with an endoscopically inserted plastic tube that kept the stricture open.

After the initial enthusiasm had subsided, it became clear that there was still room for improvement. Patients that had short, concentric, straight and relatively wide strictures, such as those found in Schatzki’s rings, esophageal webs or peptic strictures, could be adequately treated with Savary bougie dilations. For patients with complex, angulated, irregular and severely narrowed strictures, like anastomotic strictures, this technique appeared less successful. To adequately treat these strictures, multiple dilation sessions with intervals of 1 to 2 weeks appeared to be necessary. An effective single-step technique is eagerly awaited. In this thesis we have investigated two innovative single-
step techniques for the treatment of complex strictures. In chapter 2 we report the first results of the treatment of esophagogastric anastomotic strictures with a biodegradable stent. In chapter 3 electrocautery incisions of the anastomotic stricture were compared to traditional Savary dilations.

The plastic tubes initially used to treat malignant strictures frequently led to complications such as perforation and migration. Adjustments to this technique were obviously required. Uncovered self-expandable metal stents followed in the late eighties. These stents were mounted in a constrained position on a delivery catheter. Because of the outer diameter of the delivery catheter, these stents could initially not be placed through the endoscope. A guide wire had to be positioned endoscopically after which the endoscope was removed and the stent placed over the guide wire under fluoroscopic control. Although the first self-expandable stents were a great step forward, they could only be used in the very proximal or distal parts of the gastrointestinal tract because they had to be placed over a guide wire.

Further improvement was made in the late nineties when the delivery system became smaller and allowed for stents to be placed through the working channel of the endoscope. Now for the first time duodenal stenting for malignant gastric outlet obstruction came into the picture. Specially designed stents for gastroduodenal use became available and chapter 4 reports on the initial multicenter results of such a new enteral stent. The short-term clinical results were encouraging and therefore a large prospective study with the same stent was initiated. The focus of this study was on quality of life in addition to technical and clinical success (chapter 5). Though the technical and clinical success rates were high, the global quality of life did not improve for the remainder of patients’ life. This is probably related to the devastating malignancies of the patients.

Realistic estimation of a patient’s life expectancy might enhance the selection of optimal treatment for individual patients. Chapter 6 reports on independent predictors of survival in patients who presented with incurable malignant gastric outlet obstruction. Although not included in this thesis, a randomized controlled trial has been conducted to compare the gold standard: surgical gastrojejunostomy with endoscopic stent placement for the palliation of malignant gastric outlet obstruction. A gastrojejunostomy appeared to be beneficial in a specific group of patients with an expected survival of 2 months or longer. Building on these results, an endoscopically created gastrojejunal anastomosis appeared a very interesting option (chapter 7).

The availability of through-the-scope enteral stents also boosted colonic stenting. An alternative for palliative surgery in patients with metastatic or local irresectable disease was now within reach. A randomized clinical trial aiming to assess whether a nonsurgical policy, with endoluminal stenting, was superior to surgical treatment in patients with stage IV left-sided colorectal cancer and imminent obstruction is described in chapter 8a and 8b.
Lastly, **chapter 9** reports on colonic stenting in case of acute left-sided colonic obstruction compared to emergency surgery. Here we present results of a randomized controlled trial, designed to show that stent placement at the moment of acute obstruction would prevent emergency surgery. This gives way to improvement of the patient’s clinical condition and to elective operations with considerable less mortality and morbidity.

This thesis is a journey through narrowings in different areas of the gastrointestinal tract; from the esophagus via stomach and duodenum down to the colon. This expedition involved innovative new endoscopic techniques for the treatment of these strictures showing several highlights, but also some unexpected letdowns.
Endoscopic treatment of benign anastomotic esophagogastric strictures with a biodegradable stent (ESBIO study)

Jeanin E. van Hooft, Mark I. van Berge Henegouwen, Erik A. Rauws, Jacques J. Bergman, Olivier R. Busch, Paul Fockens
Abstract

**Background:** Benign postsurgical esophagogastric anastomotic strictures are a cumbersome complication requiring repetitive endoscopic intervention before a remission is achieved. An effective one-step technique is eagerly awaited.

**Objective:** To investigate the efficacy and safety of a biodegradable uncovered expandable stent (SX-ELLA Biodegradable Esophageal Stent) for the treatment of postsurgical esophagogastric anastomotic strictures.

**Design:** Prospective, single-center, feasibility cohort study.

**Setting:** Tertiary referral center.

**Patients:** Ten patients with dysphagia grade 2 to 4 caused by a benign postsurgical esophagogastric anastomotic stricture were included.

**Intervention:** Endoscopic placement of a self-expandable biodegradable esophageal stent.

**Outcome measurements:** Primary endpoint was defined as number of re-dilations within 6 months after stent placement. Secondary endpoints: improvement of dysphagia score, 7-day visual analogue pain score, stent dissolution, and other complications.

**Results:** Stents were successfully inserted in all 10 patients. In 6 patients placement of the biodegradable stent proved an effective one-step treatment. Four patients developed signs of re-obstruction treated with re-dilations in 3 and removal of an impacted food bolus in one patient. Compared to baseline, dysphagia score at 1 week, 3 months, and 6 months follow-up improved significantly. The stent appeared to be well tolerated with low pain score in the first week after stent placement. No stent collapse with blockage of the esophageal lumen or serious adverse events were observed.

**Limitations:** Small patient group, short follow-up, single center.

**Conclusion:** Placement of a biodegradable esophageal stent may be an effective and safe one-step treatment in patients with dysphagia caused by postsurgical esophagogastric anastomotic strictures.
**Introduction**

Postoperative benign fibrotic strictures of a cervical esophagogastric anastomosis occur in 5 to 46% of patients, mostly within 6 months after the esophageal resection. Factors independently related to development of benign anastomotic strictures are cardiovascular disease, gastric tube compared to colonic interposition and postoperative anastomotic leakage. These strictures bring about morbidity because of dysphagia and weight loss, leading to a decreased quality of life. Esophagogastric anastomotic strictures belong to the group of complex esophageal strictures. Several methods have been described to treat these strictures, including balloon dilation, Savary bougy dilation and Eder Puestow olive dilation. None of these conventional methods proved to be superior over others with regard to efficacy and safety. Complex esophageal strictures require a median of 3 to 7.5 dilation sessions when using a conventional dilation technique to achieve remission. To reduce the number of treatment sessions dilation has been combined with intralesional steroid injections, revealing a reduction of dilation sessions in uncontrolled series.

Another treatment modality is electrocautery incision of the stricture: a recently published randomized controlled trial showed electrocautery incision to be equivalent to Savary bougy dilation in previously untreated anastomotic strictures.

Self-expandable metal stents (SEMS) have also been considered as dilation therapy for the treatment of anastomotic strictures. In several clinical series however significant problems were encountered after stent placement. These included difficulty to remove the stent, ingrowth of granulation tissue with subsequent obstruction of the uncovered part of the stent, as well as pain. As a consequence self-expandable plastic stents (SEPS) were developed to preclude these complications. The first results with SEPS for the treatment of benign anastomotic strictures revealed easy removal of all SEPS 6 weeks after stent placement and a long-term relief of dysphagia in 80% of the patients. In the mean time several studies on SEPS have revealed a long-term clinical success rate of well below 50%, a migration rate of about 50% and severe complications in 6% of the patients.

Embroidering on these techniques the ideal stent for a benign stricture should not migrate and should overcome ingrowth of granulation tissue which often occurs after having a stent in situ for a longer period. In this regard an interesting option could be an uncovered biodegradable stent which dissolves spontaneously after placement.

**Patients and Methods**

The current ESBIO study, was designed as a prospective, single-center, feasibility study to evaluate the efficacy and safety of a self-expandable biodegradable uncovered
stent. The protocol was approved by the Medical Ethical Committee of the Academic Medical Center in Amsterdam. The study has been conducted at the department of Gastroenterology and Hepatology of the Academic Medical Center at the University of Amsterdam. All participants provided written informed consent.

Patients
From January 2009 to February 2010, consecutive patients older than 18 years of age with an esophagogastric anastomotic stricture presenting within 6 months after surgery and a dysphagia score 2 to 4 were considered for this study. Exclusion criteria were previous endoscopic treatment of the anastomotic stricture, suspicion of malignancy, anastomotic stricture longer than 3 cm, and upper esophageal sphincter within 1.5 cm of the stricture.

Materials and intervention
In this study a biodegradable uncovered expandable stent (Figure 1), 60 mm long with a body diameter of 25 mm and a flare diameter of 31 mm, was used (SX-ELLA Biodegradable Esophageal Stent BD, ELLA-CS, Hradec Kralove, Czech Republic). This stent has been Conformité Européenne (CE) approved and holds an indication for the use in benign strictures (peptic, anastomotic, caustic and post-irradiation). The stent is made of polydioxanone monofilaments and dissolution occurs 11 to 12 weeks following implantation. The stent has to be manually mounted on a delivery system shortly before implantation, the outer diameter of the delivery system is 9.4 mm. Stent placement was done with the patient under conscious sedation (midazolam or fentanyl). If a pediatric endoscope (Olympus XP-160 or similar) could not pass the stricture, a guidewire was placed under fluoroscopic guidance and dilation with Savary bougies till 10 mm was performed. After reintroduction of the endoscope, the length of the stricture
was measured. The proximal part of the stricture was marked with intramucosal injection of a radiopaque contrast agent to facilitate accurate stent placement. A guidewire was placed in the antrum of the stomach. The biodegradable uncovered expandable stent was placed with the proximal end 1.5 cm above the anastomotic stricture. The correct position of the stent was confirmed using fluoroscopy and endoscopy.

Data collection
After obtaining informed consent and before stent placement (baseline) patients’ demographics, clinical characteristics, medication use, severity of dysphagia and pain score were gathered by a research nurse. Procedure-related data were noted down by the treating physician.

After stent placement patients were contacted by a research nurse to investigate on the pain score at day 1, 2 and 7, and on dysphagia score and complications weekly for the first month and thereafter monthly. At 3 months a follow-up gastro-duodenoscopy was planned to check for stent dissolution. Patients were followed for 6 months.

Definitions and endpoints
The primary endpoint of the study was defined as number of re-dilations per patient because of recurrent esophageal stricture within 6 months after stent placement. Secondary endpoints were improvement of dysphagia score at 1 week, 3 and 6 months; pain score at day 1, 2 and 7; stent dissolution and other complications.

Esophageal stricture was defined as a stricture in the esophagus which could not be traversed by a therapeutic endoscope (diameter 11 mm). A re-dilation was performed in case of clinical recurrence of dysphagia (score 2 to 4) with an apparent stricture at endoscopy.

Dysphagia was scored as follows: score 0 - ability to eat a normal diet; score 1 - ability to eat some solid food; score 2 - ability to eat semisolids only; score 3 - ability to swallow liquids only; score 4 - complete obstruction.15;16 A visual analogue scale (VAS) pain score ranging from 0 (no pain) till 10 (worst possible pain) was used to investigate thoracic pain. Stent dissolution was graded as follows: completely dissolved stent, partially dissolved stent without blocking the esophageal lumen, partially dissolved stent with blocking the esophageal lumen (collapsed stent), stent configuration unchanged since placement. The following complications were defined: perforation, bleeding requiring blood transfusion, stent migration, esophageal re-obstruction, gastrointestinal obstruction because of stent migration, stent-related pain requiring treatment with morphinomimetics for over 24 hours, removal of the stent because of intolerable foreign object feeling or untreatable pain.
Safety was defined as absence of serious adverse events related to the procedure or device, serious being defined as those events leading to death, requiring admission to the intensive care or leading to surgical (re-)intervention.

Statistics
The aim of this feasibility study was to investigate the efficacy of a biodegradable uncovered expandable stent as reflected by the need of re-dilations. This pilot study is descriptive by nature, therefore no formal power calculation has been performed. In this study 10 patients with an untreated anastomotic esophageal stricture were planned to be included.

Descriptive statistics were used for data of all included patients (intention-to-treat). Depending on distributional proportion, Wilcoxon matched-pairs signed-rank test (dysphagia score) was used to assess improvements from baseline. Dysphagia and pain score data are graphically depicted as means ± 1 standard error for visualisation purposes. Statistics were performed using the SPSS (version 16.0) software package (SPSS, Chicago, Ill). Statistical significance was set at $P < 0.05$.

Results
Between January 2009 and February 2010 16 patients were screened for inclusion, 10 patients (8 men, 2 women; mean age ± standard deviation (SD) 62 ± 6.8 years) fulfilled all criteria and were included. Nine patients had undergone esophagectomy because of esophageal carcinoma, 1 patient because of a Boerhaave’s syndrome. Two patients had anastomotic leaks postoperatively. Patient demographics, stricture and stent placement characteristics are further summarized in table 1.

Primary endpoint
In 6 patients, placement of the biodegradable stent proved an effective one-step treatment for their stenosis without the need for re-intervention during 6 months follow-up. Signs of re-obstruction occurred in 4 patients. One patient had food impaction 74 days after stent placement for which an endoscopic desobstruction was performed, the remaining 15 weeks of follow-up were uneventful. Two patients had obstruction caused by hyperplasia in the area of the stent and 1 patient had a recurrence of the anastomotic stricture: 103, 109 and 132 days after stent placement. Symptoms resolved after 3, 5 and 9 additional dilation sessions respectively.
Secondary endpoints

Figure 2 reflects the mean dysphagia score over time: dysphagia score at 1 week, 3 months, and 6 months improved significantly compared to baseline (p = 0.004, p = 0.006, p = 0.004). Figure 3 shows the mean VAS pain score at baseline and during the first week after stent placement. No stent-related pain requiring treatment with morphinomimetics occurred. The per-protocol follow-up endoscopy 3 months after stent placement revealed that 3 stents were completely dissolved. None of the partially dissolved stents, however, were obstructing the esophageal lumen. Signs of tissue hyperplasia in the area of the stent was noticed in 6 out of 10 patients, yet in only 2 patients this was associated with symptoms of dysphagia. These two cases have been described in the paragraph on the primary endpoint.

Apart from signs of re-obstruction in 4 patients (as presented above) no complications were observed.

### Table 1. Patient demographics, stricture and stent placement characteristics.

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<tr>
<td>Number of patients, n</td>
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<tr>
<td>Sex, male; female, n</td>
<td>8;2</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>62 (6.8)</td>
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<tr>
<td>Dysphagia score, mean (SD)</td>
<td>2.5 (0.71)</td>
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<td>Number of patients on proton pump inhibition, n</td>
<td>4</td>
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<td>Number of patients using analgetics*, n</td>
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<td>Upper margin stricture** (cm), mean (SD)</td>
<td>21.4 (1.6)</td>
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<td>Length stricture (cm), median (range)</td>
<td>1 (0.5-3)</td>
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<td>Upper margin stent** (cm), mean (SD)</td>
<td>19 (1.1)</td>
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<tr>
<td>Number of dilatations prior to stent placement, n</td>
<td>2</td>
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<tr>
<td>Number of technical problems, n</td>
<td>0</td>
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<tr>
<td>Number of complications during placement, n</td>
<td>0</td>
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*One patient used paracetamol combined with diclofenac and one only paracetamol.
**Measured from the incisors.
Discussion

Benign cervical postsurgical esophagogastric anastomotic strictures cause major morbidity and occur in many patients after esophagectomy.\textsuperscript{3} Endoscopic per oral dilation with bougies or balloons is considered the treatment of choice for these strictures.\textsuperscript{3} Because of extensive fibrosis and a severely narrowed esophageal lumen anastomotic strictures are considered complex, and often require repeated dilation with intervals of 1 to 2 weeks. Dilation of complex strictures have to be performed with a median of 3 to 7.5 sessions but incidentally up to 28 sessions are needed to achieve remission.\textsuperscript{2;3;8;9} Several new techniques have been studied recently: intralesional steroid injections,
electrocautery incisions of the stricture, SEMS and SEPS placement.\textsuperscript{10-13} The major drawback of SEMS appeared to be ingrowth or overgrowth of hyperplastic tissue while SEPS revealed a high migration rate. Only intraluminal steroid injection led, in uncontrolled studies, to a reduction of the number of interventions and a longer time-interval between dilation sessions. We conducted this pilot study to see if a biodegradable stent would be able to further reduce the number of re-dilation sessions and could overcome the drawback of SEMS and SEPS.

In 6 patients, placement of the biodegradable stent proved an effective one-step treatment for their stenosis without significant side-effects.

Whereas conventional techniques are typically executed on an interval basis applying “the rule of 3” (corresponding with a total of 3 times 1 mm increase in diameter) and thus require multiple endoscopic procedures, the biodegradable stent causes a gradual dilation during several weeks with a continuous increase in diameter till 25 mm.

Signs of re-obstruction occurred in 4 patients: three underwent re-dilation and 1 had a partially occluded stent caused by food impaction which was cleaned endoscopically. In 2 of these patients the re-obstruction was caused by tissue hyperplasia at the level of the stent. In fact, the per-protocol endoscopy 3 months after stent placement showed signs of tissue hyperplasia in 6 out of 10 patients but it had only clinical consequences in 2 patients as mentioned above. In a recent overview hyperplastic tissue ingrowth or overgrowth was the cause of recurrent dysphagia in 17% of patients treated with a partially/uncovered SEMS for benign esophageal strictures.\textsuperscript{13} It is speculated that this hyperplasia is related to the radial force, the size of the stent and the duration of stenting. Since we used a biodegradable stent, we can not exclude the possibility that the chemical dissolution of the stent may also have influenced tissue hyperplasia.

It is unknown if reflux of gastroduodenal contents may contribute to hyperplasia formation. Because of a lack of data suggesting a protective effect we did not routinely prescribe acid suppressant medication following stent placement.

The dysphagia score improved in 1 week in all but 1 patient, all patients were free of dysphagia 1 and 2 months after stent placement; thereafter re-obstruction caused by stricture formation requiring re-dilation occurred in 3 patients. The reoccurrence of the stricture appeared to be related to changes in stent integrity and decrease of radial forces that occurred 6 to 8 weeks after placement caused by dissolution of the polydioxanone monofilaments. Dissolution was expected to be complete 11 to 12 weeks after implantation. In our series the follow-up gastro-duodenoscopy at 3 months showed complete stent dissolution in 3 patients, while in the other 7 patients the stent had partially dissolved without actually blocking the esophageal lumen, which had been a severe problem in several patients according to the reports of two study groups in the mid-1990s.\textsuperscript{17,18}

Because of the relatively large diameter of our esophageal stent, flare 31 mm and body 25 mm, thoracic pain and foreign object feeling were anticipated, especially during
the first days after stent placement because of the gradual expansion of the stent. We therefore registered pain medication and pain score at baseline and did an intensive follow-up during the first 7 days. Our pilot study revealed however that neither during the first week, not even for a short period, nor during the remainder of the follow-up morphinomimetics had to be prescribed.

Besides re-obstruction no other complications such as perforation, bleeding, stent migration or gastrointestinal obstruction due to stent migration occurred.

We realize that the limited number of patients in our pilot study is a drawback although all published series on biodegradable stents for esophageal strictures were small, describing between 2 and 13 patients. In addition stents in these studies were placed for a variation of indications: anastomotic as well as caustic and post endoscopic mucosal resection\textsuperscript{19,20}. We carefully selected consecutive patients with benign cervical postsurgical esophagogastric anastomotic strictures without prior treatment of their strictures and all occurring within 6 months after surgery which makes our cohort much more homogeneous than other published series. To further determine the position of this new, in our view promising technique in the treatment algorithm for benign cervical anastomosis, larger and preferably randomized studies are needed.

\section*{Conclusion}

Placement of the SX-ELLA biodegradable esophageal stent in patients with dysphagia caused by benign anastomotic esophageal strictures appears to be an effective and safe one-step treatment.
Reference List


Chapter 3

A randomized comparison of electrocautery incision with Savary bougienage for relief of anastomotic gastroesophageal strictures

Marjan L. Hordijk, Jeanin E. van Hooft, Bettina E. Hansen, Paul Fockens, Ernst J. Kuipers

Gastrointestinal Endoscopy 2009; 70: 849-855
Abstract

Background: Benign gastroesophageal anastomotic strictures are common and often refractory to treatment. Various endoscopic dilation techniques have been reported, but none of these methods has been proven to be superior.

Objective: Comparison of efficacy and safety of dilation of previously untreated anastomotic strictures by using electrocautery incision (EI) and Savary bougienage (SB).

Design: Randomized, prospective study.

Setting: Multicenter study.

Patients: Sixty-two patients with an anastomotic stricture after esophagogastronomy and dysphagia Atkinson grade II to IV were included.

Interventions: Patients were treated with EI or SB.

Main Outcome Measurements: Objective and subjective results were compared with baseline and 1, 3, and 6 months after the first treatment. Complications of both treatments were noted. Primary endpoints after 6 months were the mean number of dilation sessions and success rate (percentage of patients with ≤5 dilations in 6 months). Study participation ended after 6 months or if dysphagia grade II to IV recurred despite 5 treatment sessions.

Results: No complications occurred with both treatments. There was no significant difference between the EI and SB group in the mean number of dilations (2.9; 95% CI, 2.7-4.1 vs 3.3; 95% CI, 2.3-3.6; P=0.46) or the success rate (80.6% vs 67.7%, P = .26, and 96.2% vs 80.8%, P = .19).

Limitations: In a small study with negative primary endpoints, secondary endpoints and subgroup analyses are hypothesis generating only.

Conclusions: This prospective trial demonstrated that EI of gastroesophageal anastomotic strictures is a safe therapy and equivalent to SB as a primary therapy. EI can be used as an alternative or additional therapy for SB.
Introduction

Benign gastroesophageal anastomotic strictures occur in 5% to 46% of patients after resection of the esophagus for esophageal cancer.1-4 Dysphagia caused by stricture formation is a major source of morbidity and can drastically impair quality of life.5 Postoperative complications, such as anastomotic leakage, fistula formation, and ischemia of the proximal gastric tube, contribute to anastomotic stricture formation.2 Various endoscopic dilation techniques have been reported for the treatment of these strictures, but no method has been proven to be superior.1-4;6-8 The success rate of dilation therapy with Savary bougies (SB), balloons, or Eder-Puestow olives ranges from 70% to 90%.1-4;6-9 Dilation therapy often has to be repeated to achieve a sustained ability to pass solid foods. The median number of dilation sessions can vary from 2 to 9 per patient, and as many as 39% of patients with postoperative anastomotic stricture require more than 3 dilation sessions to achieve adequate results.1-6 In refractory strictures, self-bougienage with Maloney dilators may be a safe and effective alternative.10 Other therapies that have been described for postoperative anastomotic stricture dilation are intralesional steroid injection combined with dilation therapy and self-expandable stents. Success rates with these therapies have been variable.5;7;11-16 Electrocautery incision (EI) therapy of GI strictures has been reported in a small series of patients with a Schatzki ring and has also been used for the management of circular anastomotic strictures after GI surgery.17-31 In our series of 20 patients with gastroesophageal anastomotic strictures refractory to SB, EI with a needle-knife proved to be safe and effective.21 Based on these results, we designed a prospective, randomized, controlled study. The aim of this study was to compare the efficacy and safety of EI therapy with standard dilation therapy with SB and to assess quality of life after both treatments.

Patients and methods

This multicenter, randomized, controlled clinical trial was designed and executed following the principles outlined in the CONSORT (Consolidated Standards of Reporting Trials) statement.32;33 The study was conducted at the Departments of Gastroenterology and Hepatology of the Erasmus MC (University Medical Center), Rotterdam, and the Academic Medical Center of the University of Amsterdam in The Netherlands. The protocol was approved by the Medical Ethics Committees of both participating centers, and the study was then registered with Current Controlled Trials Ltd (registration number ISRCTN81239664), London.34 After written informed consent was obtained, patients were randomized to either dilation with EI or SB.
Patients

Between June 2004 and February 2007, all patients with an esophageal anastomotic stricture after an esophagogastrostomy who had dysphagia Atkinson grades II to IV were considered for inclusion in this trial. Exclusion criteria were previous dilation, suspicion of recurrent malignancy, bleeding diathesis, respiratory failure, severe or unstable cardiac disease, thoracic aortic aneurysm, and anastomotic leakage or infection.

Clinical care and assessment

On inclusion, patient characteristics, medical history, use of medication, indication for surgical resection, and body weight were carefully documented. All perioperative complications and details of the administration of any neoadjuvant therapy were obtained from the hospital charts. Dysphagia was graded as Atkinson grades I to IV (I, normal passage of solids and liquids; II, for solids; III, for semisolids; and IV, for liquids). Symptoms were scored by using questionnaires designed for benign esophageal stenosis (EORTC Health-Related Quality of Life Questionnaires SF-36 C-30 version 3 and OES 18).35,36 Follow-up data were obtained at 1, 3, and 6 months after the first procedure. Body weight was recorded, dysphagia was graded, and the symptoms were scored by using a questionnaire on each of these occasions. In addition, two 5-point Likert scales were used, the first immediately after the first procedure to assess how patients had tolerated it, and the second at 1, 3, and 6 months follow-up to assess their satisfaction with the results of the therapy.

The treating physician performed the endoscopic evaluation of the stricture at baseline and, if repeat endoscopy was necessary, describing the location of the stricture in centimetres from the incisors, the length of the stricture, and the ability to pass the videogastroscope through the stricture before and after the procedure. Endoscopy was repeated during follow-up if a patient had more than 3 kg of weight loss or recurrent dysphagia grades II to IV. If there was a recurrent stricture, repeat dilation was performed in exactly the same manner as at baseline. Recurrent stricture was defined as either no passage of the standard videogastroscope or only with pressure. Retreatment and time interval between dilation sessions were noted. The incidence, character, and severity of complications of treatment with EI or SB were recorded.

The primary endpoints of this study were the number of dilation sessions at 6 months and the proportion of patients requiring 5 or fewer dilation procedures in 6 months (the success rate). Secondary endpoints were the time interval between the treatment sessions, weight change, quality of life scores from questionnaires, the patients’ ability to tolerate the first dilation procedure, and satisfaction after therapy at 1, 3 and 6 months follow-up. Recurrence of dysphagia grades II to IV despite 5 treatment sessions, was considered a treatment failure.
Endoscopic interventions

Upper GI endoscopy was performed by an experienced endoscopist with the patient under conscious sedation by using midazolam (Dormicum; Roche Nederland BV, Mijdrecht, The Netherlands) in a dose of 2.5 to 7.5 mg, administered intravenously. The diameter of the stricture was estimated by passing the tip of the endoscope (GIF Q160, diameter 9.5 mm; Olympus Optical Co, Hamburg, Germany) or the outer sheath of the needle-knife catheter (1.7-mm needle diameter, 4-mm needle length) (Wilson-Cook Medical Inc, Winston-Salem, NC) through the stricture. The diameter of the stricture was graded as 9.5 mm or more when the endoscope passed effortlessly, between 2 and 9.5 mm when the endoscope passed with pressure or not at all, and as 2 mm or less (pinpoint) when the outer sheath of the needle knife could just pass the stricture or not pass through at all. If indicated biopsy specimens of the stricture were obtained to rule out tumor recurrence. If histology showed tumor recurrence, an alternative therapy was offered.

SB dilation was performed with Savary Gilliard bougies (Wilson-Cook Medical Inc). Stepwise dilation to 16 mm was generally achieved in 1 session, although multiple sessions within a week were sometimes required when there was a pinpoint stricture or when a lot of pressure was needed to pass even a small bougie.1-3 EI therapy was performed as described in our earlier study, with the tip of the endoscope positioned just proximal to the stricture, and the needle-knife catheter advanced through the working channel.21 A bimodal blended electrocautery current was used (ERBE ICC 200; ERBE Electromedizin GmbH, Tübingen, Germany) with software-controlled fractionated cuts (Endocut). The effective cutting power was maximized at 120 W for 50 ms. The maximum coagulation power during the forced coagulation mode was 45 W for 750 ms. With the needle-knife catheter under direct vision, multiple longitudinal incisions were made around the circumference of the stenotic ring. The number and radial position of the incisions were chosen to completely open the rim of the stricture. The required length of the cut was chosen according to the length of the fibrotic stricture determined at endoscopy. The depth of the incision, estimated by comparison with the length of the needle-knife, was not more than 4 mm. The procedure was terminated when the endoscope could easily pass the stricture (Figure 2-5). After EI or SB therapy, patients remained in day care observation for 2 hours in accordance with our standard procedures. Patients were allowed to drink water when awake and were discharged only when the endoscopist was satisfied that there were no symptoms suggestive of a complication. After the procedure, the patients remained on a liquid diet for the first day and resumed solid foods thereafter.

Statistical analysis

For sample size calculation, the distribution of the number of dilation sessions was assumed to be normal. However, this assumption may not be valid and therefore, to take
this into account, an extra 10% (approximate extra numbers needed for a nonparametric test) of the calculated sample size was added. The mean number of dilations over the 6-months timeframe was set for EI at 1.5 and for SB at 3. The estimated common standard deviation was 2.00. We thus calculated that a sample of 31 patients per treatment group would be required to provide a statistical power of 0.80 with a 2-tailed significance level of .05. An interim analysis was planned when 14 patients from each treatment arm had completed the study. The trial coordinator and participating physicians were unaware of the results of the interim analysis. For randomization, an independent research nurse used a permuted-block scheme. The opaque envelopes containing the assigned treatment were stratified per center. The patients were not blinded to the treatment received. SPSS software, version 15.0.0 (SPSS Inc, Chicago, Ill), was used for all statistical analyses. Analysis of the different endpoints was performed by applying the t test for analysis of paired continuous data with a normal distribution, the Mann-Whitney U test for nonparametric data, and the \( \chi^2 \) test or Fisher’s exact test to analyze categorical variables. The Poisson regression was used to estimate the mean number of dilations needed in 26 weeks, expressed as dilation incidence rate per 26 weeks, for both treatment arms. With the Poisson regression, censoring is taken into account and the Poisson regression allows for adjustment of baseline variables such as stricture length. The difference between the 2 study arms was expressed, by using the Poisson regression, as the relative rate (RR). The analysis of the difference in the number of weeks between dilations in the 2 treatment groups was analyzed by using the Kaplan-Meier survival analysis and Cox
regression, adjusting for the fact that 1 patient may have multiple dilations and can be censored before week 26. The symptom scores in the EI and SB groups were compared with those at baseline and at 1, 3, and 6 months after the first treatment. The overall subjective criteria scores for both treatments were also compared.

Results

Between June 2004 and February 2007, 62 patients (50 men, 12 women; age 41-76 years; mean 61.7) were included (Figure 1). All patients had undergone a trans-hiatal esophagectomy and intrathoracic gastric tube reconstruction with cervical anastomosis because of esophageal cancer. The end-to-side anastomoses were located at 17 to 20 cm from the incisors, were hand sewn, and no flap was brought up to the anastomosis. At baseline, the EI and SB treatment groups showed no significant differences with respect to sex, age, weight, estimated diameter of the stricture, time between surgery

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Electrocautery incision (n = 31)</th>
<th>Savary bougienage (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>24 (77.4)</td>
<td>26 (83.9)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>61.7 (7.5)</td>
<td>61.8 (9.1)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>70.0 (12.4)</td>
<td>73.6 (10.9)</td>
</tr>
<tr>
<td>Stricture length,* (cm)</td>
<td>1.35 (1.2)</td>
<td>0.55 (0.4)</td>
</tr>
<tr>
<td>Range</td>
<td>0.2 - 5.0</td>
<td>0.2 - 2.0</td>
</tr>
<tr>
<td>Dysphagia score,† n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade II</td>
<td>11 (35.5)</td>
<td>12 (38.7)</td>
</tr>
<tr>
<td>Grade III</td>
<td>18 (58.1)</td>
<td>17 (54.8)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>2 (6.4)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Estimated diameter stricture, mm, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥9.5</td>
<td>15 (48.4)</td>
<td>18 (58.1)</td>
</tr>
<tr>
<td>2.0-9.5</td>
<td>6 (19.3)</td>
<td>7 (22.6)</td>
</tr>
<tr>
<td>≤2</td>
<td>10 (32.3)</td>
<td>6 (19.3)</td>
</tr>
<tr>
<td>Peri-operative complications, n (%)</td>
<td>9 (29.0)</td>
<td>8 (25.8)</td>
</tr>
</tbody>
</table>

* P = .002 (n-Whitney <.001). † Grade I, normal passage of solids and liquids; grade II, for solids; grade III, for semisolids; grade IV, for liquids.
Figure 2. Esophageal anastomosis with a complex long stricture before EI therapy.

Figure 3. Esophageal anastomosis with a complex long stricture during EI therapy. Incisions are made in the upper part of the stricture.

Figure 4. Esophageal anastomosis with a complex long stricture after EI therapy. Working downward, incisions are made in the lower part of the stricture.

Figure 5. Esophageal anastomosis with a complex long stricture several weeks after EI therapy.
and first dilation, dysphagia score, perioperative complications, neoadjuvant therapy, and grading of quality of life by using the clinical questionnaires. The overall stricture length was significantly longer in the EI group ($P = .002$) (Table 1). Seventy-six percent of all dilation procedures (both EI and SB) were performed within 4 months after surgery. Perioperative complications had been present in 9 patients in the EI therapy group and in 8 patients in the SB group. Six patients were considered treatment failures because of persistent dysphagia grades II to IV despite 5 treatment sessions; 1 in the EI group and 5 in the SB group (Figure 1). In both study groups, 5 patients were censored before 6 months (Figure 1). After 6 months of follow-up, no complications from EI therapy or SB were seen. The primary endpoints showed no significant difference between the 2 groups of patients. The mean number of dilation sessions, expressed as dilation incidence rate per 26 weeks, showed no significant difference ($P = .46$; RR 1.1; 95% CI, 0.8-1.5; $P = .46$ of SB versus EI corrected for stricture length, RR 1.3; 95% CI, 0.9-1.8, $P = .14$), and the success rate did not reach significance ($P = .26$ and $P = .19$ respectively) (Table 2). Regarding the secondary endpoints after 6 months, the overall weight change was more favorable in the EI group ($P = .05$), and there was no significant difference between EI and SB with respect to the time interval between dilations ($P = .84$) (Table 2). During follow-up, significant improvements were noted in both treatment groups for the majority of the criteria scored with the clinical questionnaires when comparing the scores at 1, 3, and 6 months after treatment with baseline data ($P$ values varying between .01 and .001). There was no significant difference between IE and SB with regard to the criteria scored with the clinical questionnaires. Patients’ tolerability of the procedure, scored with the Likert scale, was significantly better with EI than with SB ($P < .001$). Patient satisfaction after therapy at 6-months follow-up was also significantly better with EI than with SB ($P = .002$).

<table>
<thead>
<tr>
<th>Table 2. Primary and secondary endpoints after 6-month follow-up.</th>
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<tbody>
<tr>
<td><strong>Electrocautery incision</strong> (n = 31)</td>
</tr>
<tr>
<td><strong>Primary endpoints</strong></td>
</tr>
<tr>
<td>Total no. of dilations/total follow-up, wk</td>
</tr>
<tr>
<td>Dilation incidence rate per 26 wk (95% CI)</td>
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<tr>
<td>Success rate, intention to treat, n (%)</td>
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<tr>
<td>Success rate, completed 26 wk (%)</td>
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<tr>
<td><strong>Secondary endpoints</strong></td>
</tr>
<tr>
<td>Weight change at end follow-up, kg, mean (SE)</td>
</tr>
<tr>
<td>Weeks between dilations, median (95% CI)</td>
</tr>
</tbody>
</table>
Discussion

Dysphagia caused by stricture formation after an esophagogastrostomy is a common complication and can be refractory to treatment.\textsuperscript{1-4;6-9;11-16} These strictures often lead to dysphagia and food regurgitation, which severely impair quality of life and adequate food intake. Most patients in whom stricture develops after a cervical esophagogastrostomy present within the first few months after surgery, as is shown in our current study.\textsuperscript{37} The anastomotic strictures are generally short and straight, but they can be longer and tortuous and extremely narrow.\textsuperscript{1-4;6} The endpoint in the bougie arm in this study was 16 mm because the fibrotic tissue of the stricture can resist SB with high bougie diameters, especially in pinpoint strictures. In these cases, the risk of perforation might be higher.\textsuperscript{1;2;21;37} Irrespective of the character of the stricture, esophageal dilation with EI or bougienage is rarely contraindicated.\textsuperscript{38} The complication rate of EI therapy, reported in small series of patients, seems to be low. Perforation has never been reported.\textsuperscript{17-31} After esophageal dilation with bougies or balloons, perforation and/or hemorrhage is reported to occur in 0.1% to 0.4% of patients.\textsuperscript{1;2;7-9;39} This may be a true difference; however, SB is judged by many to be a more straightforward procedure than EI and may therefore be performed by less experienced endoscopists. The authors also admit that there were far fewer EI cases than SB cases. For this reason, the confidence interval around the 0% complication rate with EI remains large. If EI was performed as much as SB, the complication rate could equal or even be higher than the rate observed with SB. This is, to our knowledge, the first randomized, controlled study comparing the efficacy and safety of primary EI therapy with SB in patients with an anastomotic esophageal stricture.\textsuperscript{35,36} In the present series of 62 patients, no complications occurred with either technique. This study shows that EI is equivalent to, but not superior to, SB as a primary therapy for esophageal anastomotic strictures. After a follow-up of 6 months, there was no significant difference between EI and SB with respect to mean number of treatment procedures or success rate. Despite randomization, there were significantly more long strictures in the EI group. One could hypothesize that this may have made it more difficult to demonstrate any superiority of EI over SB. As we know from our previous study, EI seems to be a good single treatment modality for refractory short-segment anastomotic strictures, whereas longer segment strictures appear to require repeated treatment sessions before similar results are obtained.\textsuperscript{21} This was a small study whose primary endpoints are negative. This means that the secondary endpoints and subgroup analyses after 6 months are hypothesis generating only and not positive or significant. Time interval between dilations seemed, from this study, to be the same in both EI and SB groups. Overall weight change seemed to favor EI. Weight change can be related to factors other than the endoscopic intervention, for example, the amount of elemental feeding consumed by the patients. There seemed to be an improvement in the majority of symptoms over time in both treatment groups. Patient satisfaction after treatment and
tolerance of the procedure seemed to be better with EI. However, subjective assessment by patients must be interpreted with great caution in this study; in the absence of blinding, there may be bias in favor of EI.

In conclusion, our prospective study demonstrated that EI of gastroesophageal anastomotic strictures is a safe therapy and equivalent to SB as a primary therapy. An expert endoscopist can easily use this quick and elegant method as an alternative or additional dilation therapy. In less experienced hands, EI should be used only as an alternative or additional therapy in cases in which dilation fails. EI should be available for therapeutic intervention for gastroesophageal anastomotic strictures. Subgroup analysis of patients with perioperative complications and more complex strictures and study of the impact of stricture length on treatment results with EI are areas for further attention.
Reference list


First data on the palliative treatment of patients with malignant gastric outlet obstruction using the WallFlex enteral stent: a retrospective multicenter study

J. van Hooft, M. Mutignani, A. Repici, H. Messmann, H. Neuhaus, P. Fockens

Endoscopy 2007; 39: 434-439
Abstract

**Background and study aims:** Gastric outlet obstruction can occur as a late complication of a variety of cancers. Palliation of the obstructive symptoms is the primary aim of treatment in these patients. Self-expandable metal stents have emerged as a promising treatment option. The purpose of this study was to investigate the short-term (30-day) clinical success and complication rate of a new enteral stent made of nitinol (Boston Scientific WallFlex stent).

**Patients and methods:** Between December 2004 and 1 May 2005, 62 patients (35 men, 27 women; mean age 69.9 years) presenting with documented malignancy and symptoms of gastric outlet obstruction underwent endoscopic stenting with the new WallFlex enteral stent at one of the 15 European centers who were the first to have access to this new stent. Data were collected from charts, endoscopy procedure reports, and follow-up clinical visits. The gastric outlet obstruction scoring system (GOOSS) was used to grade the patients’ ability to eat.

**Results:** All 62 patients suffered from nausea, vomiting or inability to eat. A total of 66 enteral stents were placed. The median length of the stenosis was 4 cm. The clinical success rate was 85% on intention-to-treat basis. An improvement in the GOOSS score of 1 point was considered to be significant ($P<0.001$). Oral intake was possible, on average, 1 day after stent placement. The median hospital stay was 6 days. Thirty days’ follow-up data were available for 60 patients, 10 of whom developed complications during this period (17%).

**Conclusion:** In this first European series in which duodenal stenting was performed with the WallFlex enteral stent, the new stent appears to be effective and relatively safe for the palliative treatment of patients with malignant gastric outlet obstruction.
Introduction

Malignant upper intestinal obstruction can be a late complication of advanced gastric, duodenal or periampullary malignancies (including carcinoma of the head of the pancreas, distal bile duct, or ampulla of Vater). It causes significant morbidity, including nausea, vomiting, inability to eat, and loss of weight, leading to progressive deterioration in a patient’s quality of life.$^1,2$

Palliation of symptoms, including relief of intestinal obstruction, is the primary aim of treatment in these patients. Traditionally, the therapy of choice has been surgical gastrojejunostomy, combined with a biliary-gastrointestinal bypass in patients with concomitant biliary obstruction.$^3,4$

Unfortunately, performing a surgical gastrojejunostomy in patients with upper intestinal obstruction due to advanced cancer carries a considerable risk in terms of morbidity and mortality.$^5-12$

Delayed gastric emptying occurs postoperatively in up to 57% of patients, which can lead to a prolonged hospital stay.$^5,7,13$ In larger series, the median procedure-related hospital stay for patients undergoing a surgical gastrojejunostomy was 14 days (range 8.5-24 days).$^8,10-15$

In recent years, endoscopic placement of self-expandable metal stents has emerged as an attractive nonsurgical alternative for these patients. To date, studies (mainly uncontrolled) have revealed a high technical success rate, low intervention-related mortality, a short procedure-related hospital stay, and toleration of oral intake 24 hours after stent placement in most patients.$^{16,17}$ There have been complications, however. These can be major, such as perforation or bleeding, or minor, like re-obstruction, migration, pain, or biliary obstruction. Major complications occurred in around 1% of patients (range 0%-10%), while minor complications occurred in around 26% of patients (range 0%-30%).$^{12,16-18}$

Most of the published experience has been with the enteral Wallstent (Boston Scientific Corporation, Natick, Massachusetts, USA), a stainless-steel woven stent. This stent comes preloaded on a delivery system and can be deployed through the working channel of a therapeutic endoscope. The sharp ends of this stent are considered a disadvantage because they can cause injury to the normal gastrointestinal wall proximal and distal to the stricture. A new enteral stent made of nitinol, the Boston Scientific WallFlex stent has been introduced recently (Figure 1). The purpose of this study was to investigate the short-term (30-day) clinical success rate and complications of placing this new enteral stent. The study was performed in a multicenter cohort of patients who were the first in Europe to have this stent implantation.
Patients and methods

This retrospective study aimed to include all patients who had undergone placement of a WallFlex enteral stent for malignant gastric outlet obstruction between December 2004 and 1 May 2005 at 15 European centers. These 15 centers were the first to have access to the WallFlex stent in a limited launch program by the manufacturer.

Patients

The following inclusion criteria were used for this study: documented malignancy; symptoms of gastric outlet obstruction (including inability to eat a low-residue diet, and/or early satiety, and/or nausea, and/or vomiting); and WallFlex enteral stent placement after successful positioning of a guide wire across the stenosis between December 2004 and 1 May 2005.

Data collection

Data were obtained by the treating physician from hospital records, clinical notes, endoscopy procedure reports, and follow-up clinical visits after stent placement. Data collected included demographic information, and information on the type of malignancy, clinical complaints, the gastric outlet obstruction scoring system (GOOSS) score (Table 1) before and 1 week after stent placement, the type and number of enteral stents placed, the time to resumption of oral feeding, the length of hospital stay, and procedure- or stent-related complications occurring within 30 days.
Definitions

Clinical success was defined as increase of GOOSS score of at least 1 point and/or relief of symptoms (e.g. early satiety, nausea, vomiting) 1 week after placement of the enteral stent. GOOSS score of 2 or 3 were considered to be indicative of a satisfactory quality of diet.

The WallFlex enteral stent

All the patients were treated with the Boston Scientific WallFlex enteral stent. This is a through-the-scope, self-expanding metal stent made of nitinol. The use of nitinol and modification of the mesh structure have made this stent more flexible than the same company’s Wallstent enteral stent. In addition it demonstrates excellent radiopacity of the complete mesh structure and is reconstrainable up to 70% stent deployment (the point of no return), allowing easy repositioning and improving control. In contrast to the Wallstent enteral stent, it has a flare at the proximal end which minimizes the risk of migration and looped ends which reduce the chance of tissue injury. After complete deployment the WallFlex enteral stent can shorten by up to 45%, which is 5% less than the shortening of the Wallstent enteral stent.

The diameter of the new stent is 27 mm at the flared end and 22 mm at the body. It is available in three different lengths: 6 cm, 9 cm, and 12 cm. The stent comes preloaded on a 10-French delivery system and is CE-approved.

The stent was placed using the technique described by Adler et al. (Figure 2).

Statistical analysis

Descriptive statistics were used. Analyses were performed on an intention-to-treat basis and included all patients. The GOOSS score before and 1 week after stent placement were analyzed using the Wilcoxon signed rank test. P values of less than 0.05 were considered to be statistically significant.
Results

A total of 62 consecutive patients (35 men, 27 women; mean age 69.9 years, range 37-103 years) who met the inclusion criteria were identified at the 15 centers. Obstruction was caused by pancreatic cancer in 40 patients (65%), gastric cancer in nine patients (15%), metastatic disease in five patients (8%), cholangiocarcinoma in three patients (5%), gallbladder cancer in three patients (5%), cancer of the ampulla in one patient (2%) and duodenal cancer in one patient (2%) (Table 2).

Before stent placement, all the patients suffered from inability to eat a low-residue diet and/or early satiety, nausea, and vomiting. The median length of the stenosis was 4 cm (range 1-15 cm): this was measured fluoroscopically in 36 patients (58%) and endoscopically in 26 patients (42%).

In total, 66 stents were placed in the first endoscopic procedure: 58 patients required one stent to transverse the obstruction; four patients required two stents, because of distal impaction against the duodenal wall (n=2), because of the length of the stenosis (n=1), or due to immediate migration of the first enteral stent (n=1). In all these four cases a second enteral stent was successfully placed during the same procedure. A 9-cm stent was placed in 45/62 patients (73%); one of these migrated during the procedure and was replaced by
another 9-cm stent. A 6-cm stent was placed in 9/62 patients (15%); two of these (22%) were extended by a 9-cm enteral stent because of distal impaction against the duodenal wall. A 12-cm stent was placed in 8/62 patients (13%); an additional (9-cm) stent was needed in one of these patients to transverse a 15 cm long stenosis.

Clinical success

Before stent placement 25 patients (40%) had no oral intake (GOOSS score 0), 24 patients (39%) were only tolerating liquids (GOOSS score 1), seven patients (11%) were able to tolerate soft solids (GOOSS score 2) and six patients (10%) could take a low-residue or full diet (GOOSS score 3) but had severe complaints of early satiety, and/or nausea, and/or vomiting. The GOOSS score after 1 week was recorded for 56 surviving patients (six patients died within 1 week, see section on complications). All the patients had resumed oral intake: of these 56 patients, seven patients (13%) were able to tolerate liquids only, 17 patients (30%) were able to tolerated soft solids, and 32 patients (57%) were able to tolerate a low-residue or full diet (Table 3). One week after stent placement, therefore, 49/62 patients (79%) had a satisfactory quality of diet (i.e. GOOSS score 2 or 3) (Figure 3). The GOOSS score did not deteriorate after stent placement in any of the patients. In nine patients the score did not improve: one patient stayed on liquids only, two patients remained able to tolerate soft solids only, and the other six patients had a maximum score prior to stenting. All the patients with a maximum score prior to stenting were relieved of the symptoms of gastric outlet obstruction after stent placement, however. Clinical success was therefore achieved in 53/62 patients (85%) 1 week after enteral stent

Table 2. Baseline demographic and clinical features of the 62 study patients.

<table>
<thead>
<tr>
<th>Mean age ± SD (range), years</th>
<th>69.9 ± 14.2 (37-103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>35 (56.5%)</td>
</tr>
<tr>
<td>Women</td>
<td>27 (43.5%)</td>
</tr>
<tr>
<td>Primary illness, n (%)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>40 (64.5%)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>9 (14.5%)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>5 (8.1%)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>Gallbladder cancer</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>Cancer of the ampulla of Vater</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Duodenal cancer</td>
<td>1 (1.6%)</td>
</tr>
</tbody>
</table>

SD, standard deviation.
placement: the GOOSS score improved by 1 point in 16 patients and by 2 points in 31 patients and symptoms of gastric outlet obstruction were alleviated in all six patients with a maximum GOOSS score prior to stenting. We assumed that none of the six patients who died within the first week would have had an increase in their GOOSS score 1 week after enteral stent placement. Comparing the GOOSS score before and 1 week after enteral stent placement.

Table 3. The gastric outlet obstruction scoring system (GOOSS) scores before and 1 week after stent placement.

<table>
<thead>
<tr>
<th>GOOSS score before stent placement</th>
<th>0 (no oral intake)</th>
<th>1 (liquids only)</th>
<th>2 (soft solids)</th>
<th>3 (low residue)*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>GoOSS score 1 week after stent placement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (no oral intake)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1 (liquids only)</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>2 (soft solids)</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>3 (low-residue)</td>
<td>8</td>
<td>13</td>
<td>5</td>
<td>6‡</td>
<td>32</td>
</tr>
<tr>
<td>Died within 1 week†</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>24</td>
<td>7</td>
<td>6</td>
<td>62</td>
</tr>
</tbody>
</table>

* Patients with this score at baseline suffered from early satiety, and/or nausea, and/or vomiting.
† These patients were relieved of early satiety, and/or nausea, and/or vomiting.
‡ We assumed that none of the six patients who died within the first week would have had an increase in their GOOSS score 1 week after enteral stent placement.

Figure 3. Bar graphs showing the gastric outlet obstruction scoring system (GOOSS) scores before stent placement (a) and 1 week after stent placement (b).
stent placement, a statistically significant improvement was seen ($P < 0.001$). Oral intake was possible after a median time of 1 day (range 0-8 days) after enteral stent placement. The median hospital stay was 6 days (range 1-27 days).

Complications

Of the 62 patients enrolled in the study, the 30-day follow-up was available for 60 patients; two patients were lost to follow-up. Perforations occurred during stent placement in two patients (3%): one perforation was stent-related and one was procedure-related (perforation by the scope). The patient with the stent-related perforation was treated conservatively, resumed oral intake 5 days after the perforation, and was discharged on day 7. Immediate surgical intervention was required in the other patient and this patient died due to sepsis 3 days after the stent procedure. Other severe complications that were possible procedure-related were pneumonia (n=3) and sepsis of unknown origin (n=1), all leading to death within 1 week after inclusion. One patient developed a fatal cholangitis 3 days after stent placement despite placement of a self-expanding metal biliary stent in the common bile duct 1 week before placement of the enteral stent. Minor complications were tumor ingrowth (n=1) for which a new enteral stent was placed 5 days after the initial stent placement; a self-limiting bleeding (n=1); and stent migration during initial stent insertion (n=1), which was managed by placement of an additional stent during the same procedure. In total, 10/60 patients (17%) suffered either a minor or a major complication within 30 days after enteral stent placement. One patient (2%) needed a re-intervention because of stent dysfunction within 30 days.

Discussion

Stenting has been used increasingly in recent years as a minimal invasive technique for palliative treatment of malignant gastric outlet obstruction. A recent systematic review of 32 case series by Dormann et al.\textsuperscript{16} showed a technical success rate of 97%, a clinical success rate of 89%, resolution of symptoms within a mean of 4 days, and a rate of severe complications of 1%. These data suggest that enteral stent placement is a safe and effective alternative to surgical gastrojejunostomy. Unfortunately, however, grade A evidence is very limited as only one randomized controlled trial has been published comparing surgical gastrojejunostomy with enteral stenting in patients with malignant gastric outlet obstruction.\textsuperscript{12} In this series, which was reported by Metha et al., 27 patients were included over a 3-year period. In total, 14 patients were randomized to undergo laparoscopic gastrojejunostomy and 13 patients to radiologic stenting of the duodenum. They found a significant difference in visual analog pain score, hospital stay and Short Form-36 questionnaire at 1 month, all in favor of duodenal stenting.\textsuperscript{12} Unfortunately,
they did not report the effects of the treatment on either symptom relief or on the GOOSS score.

We have described the initial European experience with the WallFlex enteral stent in patients with gastric outlet obstruction. The primary tumors responsible for this condition in our cohort were similar to those found by other investigators, with the majority of patients having advanced pancreatic cancer.\textsuperscript{1,16,19,20} The mean age and age range of the patients in our series were also very similar to those of other published reports.

Malignant gastric outlet obstruction occurs mainly in the elderly, but the reported range is extremely wide (23-103 years).\textsuperscript{16} In general, patients with gastric outlet obstruction due to advanced carcinomas have a poor prognosis, with a median survival of 12.1 weeks, according to the literature.\textsuperscript{16} Twelve patients (20\%) died during our short follow-up period of 30 days, which underlines the poor prognosis of these patients. This prognosis and the mean age of the patients make a nonsurgical, minimal invasive approach with a short hospitalization time very attractive.

The primary aim of this study was to investigate the clinical success and 30-days complications rate of the WallFlex enteral stent. The study population therefore consisted of patients in whom an enteral WallFlex stent placement was attempted after successful placement of a guide wire across the stenosis.

In our study, the majority of patients were able to tolerate oral intake 1 day after enteral stent placement; all patients resumed oral intake within 8 days; and the median time to discharge was 6 days. These results are comparable to those of previously published studies of enteral stent insertion for malignant gastric outlet obstruction with respect to clinical success, time to tolerance of oral intake, and time to discharge from hospital.\textsuperscript{16,17} Severe complications occurred in seven patients (11\%). One patient (2\%) developed a stent-related perforation and one patient (2\%) developed a procedure-related perforation (a scope perforation). With regard to the remaining 5 complications (three patients developed pneumonia, one developed sepsis of unknown origin, and one patient developed cholangitis), it was not possible to differentiate between procedure-related and underlying disease-related complications. We feel that most of these complications were not directly related to the stent design. We believe that the patients’ poor condition due to their advanced disease was the main factor contributor to their susceptibility for severe infections.

Our study revealed only three minor complications (5\%): tumor ingrowth in one patient, a self-limiting bleed in one patient, and stent migration in one patient. This number is, however, biased by the short follow-up period and the retrospective nature of our study. According to the literature, stent obstruction is the main cause of minor complications, usually occurring after a mean follow-up of over 90 days.\textsuperscript{16} Taking these results into consideration, the new designed stent appears to be as good as older stent designs with regard to clinical success, time to tolerance of oral intake, time
to discharge from hospital, and complications. A randomized comparison would be needed to prove any significant advantage of one design over another.

During our 30-day follow-up period, only one patient (2%) developed biliary problems; this incidence is similar to the incidence reported in the systematic review conducted by Dormann et al., in which 1.3% of the patients experienced biliary problems after the procedure. This review also revealed that up to 61% of the patients receiving a duodenal stent underwent placement of a biliary stent, either before (41%), at the same time as (18%), or after (2%) enteral stent placement. We believe that the standard of care expected nowadays mandates primary biliary evaluation with replacement of plastic endoprotheses by metal stents and preventive stent placement in patients with signs of biliary obstruction before duodenal stenting. In case dilatation is needed to reach the papilla, we prefer to place the duodenal stent during a second procedure 2-3 days later in order to minimize the risk of migration.

In patients who show no signs of biliary obstruction at the time of the gastric outlet obstruction, the chance that this will appear during the remaining life of the patient is very low (around 1%-2%). We therefore believe that there is no indication for preventive biliary stenting in this group of patients. Biliary re-intervention after metal stent placement can be undertaken either via the percutaneous route or endoscopically through the meshes of the stent.

Initial trials of minimally invasive surgical techniques for palliative management of gastric outlet obstruction have shown that laparoscopic gastroenterostomy associated with cholecystojejunostomy leads to a shorter hospital stay and a more rapid return to normal activity in comparison with open surgery. Although this new technique is promising, the randomized controlled trial by Metha et al. did not reveal any advantage of laparoscopic gastroenterostomy over duodenal stenting.

In conclusion, in this first European series, duodenal stenting with the WallFlex enteral stent appears to be effective and relatively safe for the palliative treatment of patients with malignant gastric outlet obstruction. In order to determine whether it is the treatment of choice in patients with malignant gastric outlet obstruction, prospective trials should be performed, preferably comparing enteral stent placement with surgical gastrojejunostomy.

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We wish to acknowledge the following participating hospitals for their efforts: U. Arnelo, Karolinska University Hospital, Huddinge, Sweden; G. Dorta, CHU Vaudois, Lausanne, Switzerland; R. Dumas, CH Princesse Grace, Monaco; A. El-Shabrawi, University Klinik Graz, Graz, Austria; B. Fox, Derriford Hospital, Plymouth, UK; F. Igea, Hospital Rio Carrión, Palencia, Spain; R. Laugier, CHU Timone, Marseille, France; P. Park, Östra Sjukhuset, Gothenburg,
Sweden; P. Siersema, Erasmus MC, Rotterdam, The Netherlands; J. Spicák, IKEM, Prague, Czech Republic; J. Vandervoort, Onze-Lieve-Vrouw Hospital, Aalst, Belgium.

Part of these data has been presented as a poster presentation at the United European Gastroenterology Week 2005, Copenhagen, Denmark and at the Digestive Disease Week 2006, Los Angeles, USA.
Reference List


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Efficacy and safety of the new WallFlex enteral stent in palliative treatment of malignant gastric outlet obstruction (DUOFLEX study): a prospective multicenter study

Jeanin E. van Hooft, Madeleen J. Uitdehaag, Marco J. Bruno, Robin Timmer, Peter D. Siersema, Marcel G. W. Dijkgraaf, Paul Fockens
Abstract

**Background:** Gastric outlet obstruction (GOO) is most commonly a complication of advanced distal gastric, periampullary or duodenal malignancy. Palliation of obstruction is the primary aim of treatment in most of these patients. Self-expandable metal stents have emerged as an effective treatment option.

**Objective:** Our purpose was to investigate the efficacy and safety of a newly developed enteral metal stent (WallFlex).

**Design:** Prospective multicenter cohort study.

**Setting:** Three tertiary referral centers (2 academic).

**Patients:** Fifty-one consecutive patients with symptomatic malignant GOO from January 2005 to February 2006.

**Intervention:** Placement of a self-expandable metallic stent (WallFlex).

**Main outcome measurements:** The primary end point was defined as improvement of the GOO scoring system for the remainder of the patients’ lives. Secondary end points focused on efficacy and safety and global quality of life.

**Results:** The Gastric Outlet Obstruction Scoring System score improved (P<.001), the body mass index decreased (P<.001) as well as the World Health Organization performance status (P =.002) when the score before stenting was compared with the mean score until death. Global quality of life did not improve. Technical and clinical success was achieved in 98% and 84% of the patients. Median survival was 62 days (75% alive at 35 days, 25% alive at 156 days). Median stent patency was 307 days (75% functional at 135 days, 25% functional at 470 days). Stent dysfunction was proven in 7 patients (14%), migration in 1 (2%), and tumor overgrowth or ingrowth in 6 (12%).

**Limitations:** Lack of a control group.

**Conclusion:** Placement of a WallFlex enteral stent in patients with nonresectable malignant GOO is safe and provides a statistically significant and clinically relevant relief of obstructive symptoms with a low need for reintervention.
**Introduction**

Patients with cancer of the periampullary area (head of the pancreas, distal bile duct, papilla of Vater) and with distal stomach or duodenal cancer are often seen with advanced-stage disease, with only 15% to 20% of patients having a resectable tumor at diagnosis. The majority of cases have locally advanced or metastatic cancer with a poor prognosis and a median survival of 3 to 6 months. These patients have significant morbidity, including pain, jaundice, and gastric outlet obstruction (GOO), which contributes to a progressive deterioration of a patient’s quality of life. Palliation of symptoms is the primary aim in these patients. Traditionally, for patients with intestinal obstruction who are fit for surgery, the therapy of choice has been a gastrojejunostomy combined with a biliary-digestive bypass in cases of concomitant biliary obstruction. Unfortunately, because of advanced disease and a poor general condition, surgical intervention in patients with malignant upper intestinal obstruction is associated with significant morbidity and mortality rates. It has been reported that delayed gastric emptying after gastrojejunostomy occurs in up to 57% of patients and leads to prolonged hospital stay.

Endoscopic placement of a self-expandable metal stent has emerged as an alternative minimally invasive treatment option in case of upper intestinal obstruction. Two recent review articles point to a technical success rate of 94% to 97%, a clinical success rate of 87% to 94%, no intervention-related deaths, a short procedure-related hospital stay, and resuming oral intake usually within 4 days after stent placement. Nonetheless, there are complications associated with endoscopic duodenal stent placement, such as pain, perforation, bleeding, reobstruction, or stent migration. Severe complications occur on average in 1% (0%-10%) of patients, whereas minor complications occur in 26% (0%-30%). Most published data relate to patients treated with an enteral Wallstent (Boston Scientific, Natick, Mass), a self-expanding stainless-steel woven stent. This stent is preloaded on a delivery system that can be introduced through the working channel of a therapeutic endoscope with subsequent deployment controlled by both fluoroscopic and endoscopic views. The limited flexibility of the metal wire mesh of the Wallstent might contribute to stent migration. Also, the sharp ends of the metal meshes of the Wallstent may injure the GI wall, leading to ulceration with the associated risk of bleeding and perforation. Recently, a new enteral stent (WallFlex, Boston Scientific) was introduced that is made of nitinol instead of stainless steel (Figure 1). This new stent has been constructed to provide an improved flexibility while maintaining lumen integrity, has looped ends to reduce risk of mucosal injury, and has a proximal flared end to minimize risk of stent migration. A previously published retrospective series revealed an excellent short-term clinical success rate. The purpose of this prospective single-arm observational study was to further investigate the efficacy and safety features of this new enteral stent.
Patients and Methods

The DUOFLEX study was designed as a multicenter, single-arm, prospective, observational clinical trial to evaluate the efficacy and safety of the WallFlex enteral stent in 3 large Dutch hospitals. The protocol was approved by the Medical Ethical Committee of the Academic Medical Center in Amsterdam. The study was conducted at the Department of Gastroenterology and Hepatology of the Academic Medical Center in Amsterdam, Erasmus Medical Center in Rotterdam and St Antonius Hospital in Nieuwegein. Written informed consent was obtained from each patient.

Patients

From January 2005 to February 2006, all consecutive patients more than 18 years of age with a histologically proven malignancy of the periduodenal area with symptoms compatible with GOO at 1 of the 3 participating Dutch hospitals, were considered for inclusion in this trial.

After exclusion of potentially curable disease, proximal stomach obstruction, pre-procedural evidence of additional strictures in the small bowel or colon, previous treatment with a self-expanding enteral metal stent for the same condition, inability to undergo upper GI endoscopy, or inability to complete quality-of-life questionnaires, patients were asked to participate in the study.

Data collection

Medical history, medication use, disease-specific information (primary tumor site, level of obstruction, biliary obstruction/drainage), severity of obstruction (symptoms compatible with GOO and GOO Scoring System [GOOSS] score), general condition (body mass index [BMI], World Health Organization [WHO] performance score), additional therapy
(biliary drainage, chemotherapy, radiotherapy), and pretreatment scores of quality-of-life questionnaires (European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 version 3, EQ-5D including the EuroQol visual analog scale [EQ-VAS]) were collected by the research nurse immediately after inclusion. Procedure-related data were collected by the treating physician. Follow-up data were obtained by mail and completed through telephone interviews by the research nurse. Follow-up included inquiries about adverse events, severity of obstruction, general condition, additional therapy and quality of life. Patients were followed up at 7 and 14 days (GOOSS score, WHO performance score), 4 weeks (GOOSS score, BMI, WHO performance score, EORTC QLQ-C30 version 3 and EQ-5D including the EQ-VAS), monthly (GOOSS score), and bimonthly (BMI, WHO performance score, EORTC QLQ-C30 version 3 and EQ-5D including the EQ-VAS), after stent placement. Patients were followed until death.

Definitions and end points

The primary end point of the study was defined as improvement of the GOOSS score (a 4-point scoring system; Table 1) for the remainder of the patients’ lives.18 Secondary end points were technical success (successful stent placement and deployment at the site of the stricture), clinical success (defined as relief of symptoms compatible with GOO or improvement of the GOOSS score 1 week after inclusion), median survival, time until regain of oral intake, procedure-related hospitalization time, stent patency, intervention-related complications including 30-day mortality rate, impact on general condition, and global quality of life reflected by the global health status (QL2) scale from the validated EORTC QLQ-C30 version 3 measure and the EQ-VAS. Symptoms compatible with GOO were defined as early satiety, nausea, and vomiting. In case of clinical suspicion of stent dysfunction (decrease in GOOSS score of 2 points), a small-bowel series or endoscopy were performed to investigate the underlying cause (tumor overgrowth or ingrowth, migration, compression, or food impaction), unless patients refused further investigations or interventions. If the enteral stent was shown to be patent and no secondary stricture was identified by endoscopy or small-bowel follow-through, disturbance of food passage was considered to be due to motility dysfunction, for example, peritonitis carcinomatosis or gastroparesis caused by neural involvement. Stent patency was defined as the period between initial stent placement and first stent dysfunction (migration, reobstruction).

Intervention

After inclusion, biliary patency was evaluated. If patients did not already have a biliary stent placed or cholestatic liver functions, enteral stenting was pursued without prior biliary drainage. Patients with a suspicion of biliary obstruction (cholestatic liver
### Table 1. Patient demographics and clinical characteristics at baseline.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n</td>
<td></td>
<td>51</td>
</tr>
<tr>
<td>Age (y), (mean [SD])</td>
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<td>67.6 (12.3)</td>
</tr>
<tr>
<td>Sex (male/ female)</td>
<td></td>
<td>25/26</td>
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<tr>
<td>Tumor characteristics, no. (%)</td>
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<td></td>
</tr>
<tr>
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<td>Metastatic disease</td>
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<td>Cholangiocarcinoma</td>
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<td>Duodenal cancer</td>
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<tr>
<td>Gastric cancer</td>
<td></td>
<td>2 (4)</td>
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<td>Gallbladder cancer</td>
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<tr>
<td>Cancer of the ampulla of Vater</td>
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<td>1 (2)</td>
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<td>Biliary tract, no. (%)</td>
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<tr>
<td>Drained</td>
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<td>Severity of obstruction</td>
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<td>General condition</td>
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<td>WHO 0 – fully active, no. (%)</td>
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<td>WHO 1 – cannot carry out heavy physical work, no. (%)</td>
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<td>WHO 2 – up and about &gt; 50% of the day, no. (%)</td>
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<td>17 (33)</td>
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<td>WHO 3 – up and about &lt; 50% of the day, no. (%)</td>
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<td>12 (24)</td>
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<td>WHO 4 – bed or chair bound all day, no. (%)</td>
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<td>5 (10)</td>
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<td>Quality of life</td>
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<td>QLQ-C30 Global Health status (QL2), mean (SD)</td>
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<td>44.5 (20.9)</td>
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<td>EQ-VAS score, mean (SD)</td>
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<td>42.5 (18.4)</td>
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</table>
functions) underwent biliary drainage by insertion of an expandable metal stent, either endoscopically or radiologically. If patients had already a plastic biliary stent in situ, this was replaced by an expandable metal biliary stent regardless of liver function test results. To prevent enteral stent migration, placement was not attempted within 48 hours after enteral stricture dilation had been performed for biliary stent placement. All patients in this study were treated with a WallFlex enteral stent (Boston Scientific, Natick, Mass). The enteral WallFlex stent was available with a diameter of 27 mm at the flared end and 22 mm at the body; lengths available for this study were 6 cm, 9 cm, and 12 cm. The stent is already preloaded on a 10 French delivery system and was Conformité Européenne approved at the time of the study.

Stent placement was done with the patient under conscious sedation (midazolam or fentanyl). A therapeutic endoscope (working channel ≥ 3.7 mm), either forward or side viewing, was used for placement of the through-the-scope WallFlex enteral stent. The length of the stricture was assessed either endoscopically or fluoroscopically. To avoid dilation of the stricture by advancing the endoscope through it, which might facilitate stent migration, the endoscope was only passed in case of no resistance; otherwise a catheter and a guidewire were used to pass the stricture. Subsequently, the guidewire was advanced into the horizontal part of the duodenum. The length of the stent had to exceed the stricture length for at least 2 cm, and, preferably, the flared proximal end of the stent was placed proximal to the pylorus. This was not based on any literature but on our believe that the anti-migration purpose of the flared end could be further prospered by doing so. After the required stent length was determined, it was advanced through the endoscope over the guidewire until it passed the distal end of the stricture; after this the stent was deployed under continuous fluoroscopic control. The stent was not repositioned once fully deployed. The position of the stent was confirmed endoscopically and fluoroscopically.

Statistical analysis
The expected number of eligible patients to be included at the participating hospital sites during a year was 50. Descriptive statistics were used for data of all included patients (intention-to-treat). Depending on distributional properties, Wilcoxon matched-pairs signed-rank test (GOOSS score) or paired-samples t tests (QL2, EQ-VAS, BMI and WHO performance score) were used to assess improvements from baseline, after calculating the average score per patient from available follow-up assessments until death, weighed for the length of the preceding time interval in between planned assessments. Stent patency was assessed by Kaplan-Meier analysis with stent dysfunction taken as event and death before stent dysfunction as censored observation. Kaplan-Meier analyses were also performed for times until oral intake, hospital discharge, and death. Statistics
were performed with the SPSS (version 12.0.2) software package (SPSS, Chicago, Ill). Statistical significance in all analyses was set at $P < .05$.

**Results**

Between January 2005 and February 2006, 51 patients (25 men, 26 women; mean age ± SD 67.6 ± 12.3 years) were included. Fourteen of the 51 patients had already been included in a previous multicenter European study reporting only short-term (30-day) results. Patients demographics and clinical characteristics are summarized in table 1.

**Primary end point**

The GOOSS score improved significantly ($P < .001$) when the score before stenting was compared with the mean score during follow-up until death (Figure 2).

**Secondary end points**

Stent placement was technically successful in 50 patients (98%). In 1 patient the proximal end of the stent was balloon dilated directly after stent placement because of insufficient deployment; during the completion of the follow-up there were no additional
complications. Two patients died within the first week, 1 from severe cholangitis and 1 from progressive malignant disease without procedure- or stent-related complications. Of the remaining 49 patients, clinical success was achieved in all but 6 patients (88%), resulting in overall clinical success after 1 week in 43 of 51 patients (84%). At the time of initial stent placement, 54 stents were placed. In total, in 48 patients 1 stent proved sufficient to cover the stricture, whereas 3 patients required 2 stents, either because of too distal placement of the first stent (n=2) or because of the presence of 2 strictures located too far from each other to be covered with one stent (n=1). In these patients, both enteral stents were placed during the same procedure. Of the 54 enteral stents, 40 (74%) were 9 cm, 8 (15%) 6 cm, and 6 (11%) 12 cm. The mean length of the stricture was 4.0 cm (SD ± 1.6 cm, range 2-8 cm). Median survival was 62 days (75% alive at 35 days, 25% alive at 156 days). Oral intake was resumed by 46 patients (90%) either at the day of or at the day after stent placement. The median procedure-related hospital stay was 3 days, 75% of the patients were discharged within 5 days after stent placement.

Clinical suspicion of stent dysfunction occurred in 12 of 51 (24%) patients. Three patients (6%) were terminally ill at the time of stent dysfunction and refrained from further treatment. Six patients (12%) had endoscopic evidence of tumor overgrowth or ingrowth (n=1 and n=5, respectively) at a median time interval of 121 days after stent placement; in another patient the enteral stent had migrated distally (2%) after 13 days. These 7 patients were successfully managed by the insertion of an additional enteral stent (1 patient received inadvertently a D-Weave Niti-S™ stent [Taewoong Medical, Seoul, Korea] instead of a WallFlex enteral stent). The 2 remaining patients (4%) with a patent enteral stent and no evidence of a downstream anatomical obstruction were classified as having motility dysfunction and were respectively treated with a duodenal feeding tube and gastroenterostomy. No incomplete stent expansions were seen. Median stent patency was 307 days (75% functional at 135 days, 25% functional at 470 days). Other complications included intermittent pain (n=2) directly after stent placement treated with analgesics, cholangitis (n=3) treated with antibiotics in 2 patients and percutaneous drainage in 1 patient, and bleeding (n=2) for which 1 patient was treated with radiotherapy and 1 patient endoscopically. Two of the 3 patients who had cholangitis had a metal biliary stent in situ. Eleven patients (22%) died within 30 days after stent placement: 1 had clinical symptoms of cholangitis and was unsuccessfully treated with antibiotics; all others died from progressive malignant disease, but without clinical signs of biliary or enteral obstruction.

Over time, the BMI decreased (P<.001) as well as the WHO performance status (P =.002) when the score before stenting was compared with the mean score until death (Figure 3). The QL2 scale and the EQ-VAS did not improve (P =.52 and P =.31, respectively) (Figure 4).
Discussion

Several studies have assessed clinical and technical success of endoscopic duodenal stenting in the palliative treatment of advanced periampullary, distal stomach, or duodenal cancer. Our prospective series is the first to focus on the duodenal WallFlex stent. The clinical and technical success rate (intention-to-treat) with this new enteral stent in the management of malignant duodenal strictures was 84% and 98%, respectively, which is in accordance with the recent literature.24,25 A more important observation was that after enteral stent placement the mean GOOSS score significantly improved for the remainder of the patients’ lives compared with pretreatment scores. In light of this observation, it is worth mentioning that 10 of our patients (20%) had already a maximum GOOSS score before stent placement. Despite a maximum GOOSS score these patients had symptoms compatible with GOO, particularly nausea and (intermittent) vomiting. Clinical success was achieved in 7 of these 10 patients. Importantly, this indicates that, when deciding...
on the necessity of duodenal stent placement in patients with incurable malignancy of the periduodenal region, not just the GOOSS score should be taken into account. There was a large difference between median stent patency (307 days) and median survival (62 days), suggesting that adequate resolution of the GOO is achieved with the WallFlex enteral stent in the majority of patients until death. Chemotherapy was of no significant influence because only 3 patients received chemotherapy in our series after enteral stent placement. Recent data of 2 larger series revealed that chemotherapy after stent placement was associated with an increase in maintenance of stent patency.\textsuperscript{29,30} Stent dysfunction was proven in 7 patients: migration in 1 (2\%) and tumor overgrowth or ingrowth in 6 (12\%). The low rate of stent migration may be partly explained by the stent design with a proximal large-diameter flare that was preferably positioned proximal to the pylorus. In addition, duodenal stricture dilatation to enable drainage of the bile duct, which might negatively affect migration rate of enteral stents when placed during the same session, was not done within 48 hours of stent placement. Stent reobstruction caused by tumor overgrowth or ingrowth occurred after a median of 121 days, which implies that enteral stent obstruction is a late complication. The longer the patients survive, the higher the risk of reobstruction from tumor overgrowth or ingrowth. With continuing efforts for a more effective palliative chemoradiotherapy regimen aiming for a longer survival, the prevention and management of reobstruction becomes an even more important topic. The use of covered duodenal stents would be one way of trying to avoid stent obstruction by preventing tumor ingrowth through the metal meshes. However, the observed migration rate of covered stents between 21\% and 26\% has withheld their routine use.\textsuperscript{31,32} A recently published large prospective series evaluating the use of fluoroscopically placed dual expandable nitinol stents, consisting of an inner uncovered and outer partially covered stent, revealed promising results. Migration occurred in 4\%, recurrent symptoms in 16\% (as opposed to 24\% in the current series) and minor bleeding in 1\%.\textsuperscript{29} In the current study, 13 of 51 patients (25\%) did not have a biliary stent placed or choledochal liver function at the time of enteral stenting. Only 1 patient developed biliary obstruction, presenting with cholangitis 21 days after enteral stent placement. Four patients (8\%) with GOO had concomitant biliary obstruction (cholestatic liver function) for which a metal biliary stent was inserted. The majority of patients (67\%) had already had biliary obstruction before GOO and had a good functioning biliary stent at the time of duodenal stent placement. These data are in accordance with the result of a large systematic review in which 41\% of the patients had biliary obstruction before, 18\% at the same time, and only 2\% after enteral stenting for GOO.\textsuperscript{18,24} An argument of a proactive approach with regard to drainage of the biliary duct before enteral stent placement has always been the expected difficulty in the placement of biliary (metal) stents through the meshes of a duodenal stent placed across the papilla. Recently Mutignani et al. published a study in which they were successful in placing a biliary stent through the meshes of
duodenal stents. After achieving biliary cannulation they either widened the meshes of the enteral stent with a pneumatic balloon or removed those covering the papilla with a rat-tooth foreign body forceps or argon plasma coagulation. They even treated patients with concurrent biliary and duodenal obstruction by initially placing a duodenal stent followed by a biliary stent, which was successful in 13 of 14 patients, 95%. These results provide evidence that enteral balloon dilatation of the duodenal stricture to reach the papilla for placement of a biliary stent before enteral stent placement is not a prerequisite, which potentially should avoid the risk of perforation. However, these results come from a single expert center and it remains to be established whether the same results can be achieved by others.

Our series reveal that patients with gastric outlet obstruction resulting from incurable periampullary, distal stomach or duodenal cancer have a poor quality of life (mean EQ-VAS ± SD: 42.5 ± 18.4, mean QL2 scale ± SD: 44.5 ± 20.9), compared with the general population (mean EQ-VAS ± SD: 79.7 ± 15.9, mean QL2 scale: 64.1). Unfortunately, we did not achieve a significant improvement of the global quality of life during the remainder of patients’ lives. It remains uncertain how the global quality of life would have developed without enteral stent placement because of the absence of a control group. It appears feasible that palliative treatment for these patients should absolutely not only be focused on food passage but also on other factors that might potentially decrease the quality of life, such as pain, deterioration of patient’s physical condition, and mental support. With regard to the general condition (BMI and WHO performance score) of patients, a similarity was observed: the BMI score significantly decreased (P< .001) as well as the WHO performance status (P =.002). Apparently the improved ability to pass food might have no influence on the general condition. As shown by figure 5, the mean BMI decreased gradually after one month of follow-up. These figures are even more striking when taken into account that, according to common practice in the Netherlands, the majority of patients expectedly have been seen by a nutritionist and given pancreatic enzyme supplementation when indicated. The weight loss would otherwise have been detrimental.
Conclusion

This single-arm prospective cohort study showed that placement of a WallFlex enteral stent in patients with nonresectable malignant GOO is safe and provides a statistically and clinically significant relief of obstructive symptoms until death.
Reference List


Chapter 6

Independent predictors of survival in patients with incurable malignant gastric outlet obstruction: a multicenter prospective observational study

Jeanin E. van Hooft, Marcel G.W. Dijkgraaf, Robin Timmer,
Peter D. Siersema, Paul Fockens

Abstract

Objective: Gastric outlet obstruction (GOO) is one of the late complications of a variety of malignancies. Palliation of symptoms of obstruction rather than cure is the primary aim of treatment in affected patients. Thus far prognostic information on life expectancy is lacking in these patients although it can be of importance when deciding upon their optimal treatment. The purpose of this study was to investigate whether baseline data in patients with incurable GOO can independently predict survival.

Patients and methods: In total, 105 consecutive patients with symptomatic GOO treated with duodenal stent placement were enrolled in this multicenter prospective observational study. Patients were followed until death or till 1 November 2008. The Cox proportional hazard regression model was used for both univariate and multivariate analyses of survival.

Results: Baseline data of 101 patients were completed. At the time of analysis, 95% of patients had died; median overall survival was 82 days (75% alive at 36 days, 25% alive at 156 days). The final prediction model revealed the dichotomized WHO performance status (HR: 2.63, 95%CI: 1.68 - 4.12, \( p < 0.001 \)), prescription of morphines stronger than tramadol (HR: 2.42, 95%CI: 1.38 - 4.25, \( p = 0.002 \)) and pain score of the EORTC QLQ-C30 (HR: 1.01, 95%CI: 1.00 - 1.01, \( p = 0.035 \)) as independent significant prognostic factors for short survival.

Conclusions: This study demonstrates clear predictors of poor outcome for patients presenting with symptomatic malignant GOO. The model may enhance the selection of optimal treatment for individual patients.
Introduction

Almost 20% of patients with gastric, duodenal or periampullary malignancies (including carcinoma of the head of the pancreas, distal bile duct or ampulla of Vater) will develop gastric outlet obstruction (GOO) in the late stage of their disease.\(^1\) This obstruction leads to significant morbidity with nausea, vomiting, inability to eat and weight loss. One of the aims for palliation of these patients is the relief of GOO symptoms.

A surgically performed gastrojejunostomy has been the standard palliative therapy for many decades. This treatment modality is associated with a good functional outcome and relief of symptoms in 72% of patients.\(^2\) However, it has also been reported to be associated with considerable morbidity and mortality.\(^3\)-\(^5\) Up to 57% of the patients have symptoms of delayed gastric emptying, which is defined as the inability to tolerate fluids for 8 days or more after treatment, often causing a prolonged hospital stay.\(^1;6;7\)

Endoscopic placement of a self-expandable metal stent has emerged as an alternative, minimally invasive treatment option in case of upper intestinal obstruction. Review articles as well as prospective studies on stent placement revealed a technical success rate of 94%-98%, a clinical success rate of 84%-94%, absence of intervention-related deaths, a short procedure-related hospital stay and resumption of oral intake in about 90% of the patients within 4 days after stent placement.\(^8\)-\(^10\) Nonetheless, there are complications associated with endoscopic duodenal stent placement such as perforation, bleeding, re-obstruction or stent migration and pain, leading to an overall complication rate of 26%.\(^8\)-\(^10\) A recently conducted systematic review comparing enteral stent versus gastrojejunostomy for the palliation of GOO suggested that stent placement may be associated with more favourable results in patients with a short life expectancy, whereas gastrojejunostomy is preferable in patients with a better prognosis.\(^2\) This conclusion has also been suggested by a recently published randomized controlled trial.\(^11\) On the basis of this information, prognostic information on life expectancy in patients with symptomatic malignant GOO seems to be of major importance for tailored care.

Recent literature suggests that patient-reported outcomes, like quality of life (QOL) questionnaires, reveal good prognostic significance with regard to survival.\(^12;13\) Combining patient-reported outcomes with predictors of survival related to a patient’s clinical and performance status might further improve the accuracy of prognostication. In an attempt to define the role of baseline measures as prognostic factor, we conducted an analysis of pooled data from two recent prospective studies in a large cohort of patients treated with endoscopic stenting for GOO. The main objective of this study was to evaluate whether baseline data in patients with symptomatic GOO can independently predict overall survival, which could help us to select the optimal treatment for an individual patient.
Methods

Study design
At the initiation of our prospective research program on duodenal stenting in patients with malignant GOO, we decided to collect data on quality of life and performance status to enable the analysis of predictors of survival in a large cohort. Thus far, data were prospectively collected during two multicenter studies on patients being treated for malignant GOO with either the Wallflex (Boston Scientific, Natick, MA, USA) or the D-Weave Niti-S™ (Taewoong Medical, Seoul, South Korea) enteral stent. The protocols of both studies were approved by the Medical Ethical Committee of the Academic Medical Center in Amsterdam and the local Ethical Committees of the other two participating centers (Erasmus MC, Rotterdam and Sint Antonius Hospital, Nieuwegein). Written informed consent was obtained from each patient. The protocols were identical with the exception of the type of enteral stent used. Data on efficacy and safety of one of the trials have been published elsewhere.10

Patients
Between January 2005 and September 2008 all patients over 18 years of age with a histologically proven malignancy of the peri-duodenal area, who presented with symptoms compatible with GOO at one of three Dutch hospitals, were considered for inclusion. After exclusion of potentially curable disease, proximal stomach obstruction, evidence of additional strictures distally in the small bowel or colon, previous treatment with a self-expanding metal stent, inability to undergo upper gastrointestinal endoscopy, or inability to complete quality of life questionnaires, patients were asked to participate in the two consecutive studies on duodenal stenting.

Data collection
Medical history, medication use, disease-specific information (primary tumor site, level of obstruction, biliary obstruction/drainage), severity of obstruction (symptoms compatible with GOO and GOO Scoring System [GOOSS] score), general condition (body mass index [BMI], World Health Organization [WHO] performance status) and additional therapy (biliary drainage, chemotherapy, radiotherapy) were obtained from medical records by the treating physician. Quality of life questionnaires (European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 version 3, EQ-5D including the visual analogue scale [EQ-VAS]) were completed by the patients before treatment. The questionnaires included instructions for patients on how to complete the questionnaire items. A research nurse could be contacted by the patients to clarify the instructions if
necessary. Patients were followed until death or till 1 November 2008. Date of death was either obtained from patient’s relatives or general practitioner.

**Aim and scoring systems**

The aim of this study was to investigate whether baseline measures could be identified that predict survival in patients with symptomatic malignant GOO. Older age, primary illness, BMI, WHO performance status, and the use of pain medication (paracetamol, non-steroidal anti-inflammatory drugs, tramadol or other morphines) were considered as likely clinical predictors of survival. In addition, the predictive value of sex was assessed.

The primary illness was clustered according to the histology in the following 4 groups: (1) gastric cancer, duodenal cancer and cancer of the ampulla of Vater, (2) cholangiocarcinoma and gallbladder cancer, (3) pancreatic cancer and (4) metastatic disease. In addition it was also clustered by anatomic location: gastric cancer, periampullary malignancies, metastatic disease.

The performance status was assessed by the treating physician during anamnesis using the WHO performance status, which assigns a point score depending on patient’s level of activity including self-care. This five point score ranges from normal activity (score 0) to completely disabled (score 4) (Table I). The EORTC QLQ-C30 is a patient-reported questionnaire, containing 30 questions that address various aspects of QOL. On the basis of the literature we decided to focus on the following scores: Global QOL, social functioning, fatigue and pain. Scores were derived from standard scoring algorithms and ranged from 0 to 100. For functional domains a higher score signifies a superior QOL; for other domains like Global QOL, fatigue and pain a lower score reflects a superior QOL. EQ-5D is a self-classifier with five questions (mobility, self-care, daily activities, pain/discomfort, mood); a visual analogue scale (EQ-VAS) is added offering a simple method for obtaining a score on overall self-rated health, with 0 being worst and 100 being best imaginable health state.

**Statistical analysis**

Overall survival was measured from the date of inclusion to the date of death (due to any cause). Patients who were alive on 1 November 2008, the time of analysis, were censored. The log-rank test following Kaplan-Meier survival analysis was used to assess survival differences between groups of patients (by sex, primary illness, WHO performance status, pain medication). In preparation of a Cox regression analysis of survival, Kaplan-Meier survival curves were visually inspected for violation of the proportional hazard assumption. The continuous factors age, BMI, Global QOL, social functioning, fatigue, pain and the EQ-5D VAS were univariately assessed in a Cox regression analysis. For all factors, a p-value below 0.10 was taken as the cut-off value for...
inclusion in a multivariate Cox regression model. A backward stepwise procedure based on significance of the Wald statistic was applied. A $p$-value below 0.05 was considered significant. Multicollinearity was taken into account by comparing alternative predictor sets among univariately significant predictors. Potential multicollinearity or strong associations among univariately significant factors were assessed by Pearson product-moment correlations (continuous factors), $T$-tests (categorical against continuous factors) or $\chi^2$-statistics (categorical factors). Eventually, the model with the highest reduction of the minus 2 log likelihood value was identified as the final prognostic model. The hazard ratios (HR) and the corresponding 95% confidence intervals (CI) of significant factors in this final model are reported. All data analyses were performed using SPSS (version15.0) software package (SPSS, Chicago, IL).

**Results**

A total of 105 patients were recruited into two consecutive multicenter prospective trials. With 101 patients the baseline data were complete. These patients constitute the cohort of the current study. Median age was 69 years (range 39-88), 53% of patients were male, 63% had pancreatic cancer (Table I). At the time of analysis, 95% of patients had died; the median overall survival was 82 days (75% alive at 36 days, 25% alive at 156 days).

**Univariate analysis**

Survival differences among groups of patients were assessed for sex, primary illness, WHO performance status and pain medication (Table II). No survival differences by sex or by the type of tumor were observed, not even after clustering by histology or anatomic location. Only when comparing a cluster consisting of all other tumor types to those having GOO due to metastasis, a trend to shorter survival ($p=0.057$) among those with metastatic GOO was seen. Dichotomized WHO performance status, based on either complete self-care (score 0-2) or incomplete self-care (score 3-4), was prognostic for survival ($p<0.001$). Prescription of morphinomimetics stronger than tramadol revealed a significantly shorter survival ($p<0.001$).

Among the continuous factors (Table II), Global QOL ($p<0.001$), social functioning ($p=0.026$), fatigue ($p<0.001$), pain ($p=0.025$), and the EQ-5D VAS ($p<0.001$), all had significant prognostic impact on survival; age and BMI did not show any association with survival in this study population.

**Multivariate analysis**

Cox regression was performed to assess which factors were independent prognostic parameters for survival. The candidate parameters for the multivariate model contained
Table I. Patient demographics and clinical characteristics at baseline.

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n</td>
<td>101</td>
</tr>
<tr>
<td>Median age, years</td>
<td>69</td>
</tr>
<tr>
<td>Range</td>
<td>39-88</td>
</tr>
<tr>
<td>Sex: male; female, n</td>
<td>54; 47</td>
</tr>
<tr>
<td>Mean body mass index (SD)</td>
<td>22.3 (3.9)</td>
</tr>
<tr>
<td>Primary illness, n (%)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>64 (63%)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>Duodenal cancer</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Gallbladder cancer</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Cancer of the ampulla of Vater</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Pain medicationa, n (%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>57 (57%)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>34 (34%)</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Other morphines</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>WHO performance state, n (%)</td>
<td></td>
</tr>
<tr>
<td>WHO 0 – fully active</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>WHO 1 – cannot carry out heavy physical work</td>
<td>26 (26%)</td>
</tr>
<tr>
<td>WHO 2 – up and about &gt; 50% of the day</td>
<td>35 (35%)</td>
</tr>
<tr>
<td>WHO 3 – up and about &lt; 50% of the day</td>
<td>29 (29%)</td>
</tr>
<tr>
<td>WHO 4 – bed or chair bound all day</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
</tr>
<tr>
<td>QLQ-C30, mean (SD)</td>
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</tr>
<tr>
<td>Global QOL</td>
<td>45.0 (20.3)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>62.9 (32.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>62.4 (28.1)</td>
</tr>
<tr>
<td>Pain</td>
<td>36.5 (35.0)</td>
</tr>
<tr>
<td>EQ-VAS score, mean (SD)</td>
<td>43.1 (18.5)</td>
</tr>
</tbody>
</table>

*aTwenty-one patients used a combination of pain medication*
two clinical parameters (metastatic GOO, prescription of morphinomimetics stronger than tramadol), one performance status (dichotomized WHO) and five QOL scores (Global QOL, social functioning, fatigue, pain and the EQ-5D VAS). Several strong associations indicating potential multicollinearity were observed among these univariately significant factors (dichotomized WHO against global QOL, social functioning, fatigue and EQ-5D VAS; metastatic GOO against global QOL, pain and dichotomized WHO; global QOL against EQ-5D VAS). Taking this into account the final prediction model revealed morphinomimetics stronger than tramadol, dichotomized WHO performance status,
and pain score of the EORTC QLQ-C30 (Table III) as independent significant prognostic factors for survival.

**Discussion**

One of the aims in the palliative treatment of patients with malignant GOO is relief of obstructive symptoms and improvement of food intake. The optimal palliative treatment for GOO is subject of debate. Every treatment option has specific advantages and disadvantages. Prognostic information on life expectancy therefore seems to be important to choose the best treatment for the individual patient. The main objective of our study was to evaluate whether baseline data can independently predict survival.

The results of our study show that some baseline data are indeed significant independent prognostic indicators in patients with symptomatic malignant GOO. For instance, in case a patient uses morphinomimetics stronger than tramadol at baseline the prognosis is significantly poorer than without.

Patients with incomplete self-care, reflected by WHO performance status 3-4, also have a significantly decreased 3 months survival rate of 26.3% compared with 60.1% for patients with complete self-care (Figure 1). Another prognostic indicator is the EORTC QLQ-C30
pain score which also remained significant after multivariate analysis. A higher pain score reflects a shorter survival; patients with a pain score in the highest two categories (score $\geq 83$) had a three months survival rate of only 37.6% in our study (Figure 1).

Even more striking is the 30 days survival chance below 10% for patients who have all three prognostic indicators combined ((1) use morphinomimetics stronger than tramadol, (2) have incomplete self-care, and also (3) have a pain score of $\geq 83$ at baseline) (Figure 1).

The significant prognostic indicators that we found in our patient cohort are all relatively easy to obtain, consist each of maximal two questions (EORTC QLQ-C30 pain score) and lack complex calculations.

Our study has some shortcomings. The data were not corrected for confounding factors like social-economic status, having (grand)children or psychiatric disease in patients’ previous history: all factors which might influence survival. We decided not to take these factors into account because they were, among others, difficult to obtain from the patient’s medical record. In addition our data were collected just before an intervention which might have influenced the mood of the patients: some might have been frightened, others hopeful and as a consequence rather optimistic.

Our dataset also lacked information on the presence of metastasis (other than those causing GOO) of the primary illness at baseline, while this is known to be a prognostic factor in patients with nonresectable pancreatic adenocarcinoma. Besides good data on the nutritional status of the patient, for instance reflected by serum albumin levels or weight loss before baseline, were unfortunately not consistently available. However the BMI, also an indicator of nutritional status, showed no association with survival.

It has to be stressed that our model is a predictor of survival rather than a suggestion which treatment modality is best used in these patients. It may however be of value in the discussion with the patient on the selection of an intervention. Being informed on expected survival may help patients and family members to decide on a tailor-made treatment, which may result in a purely supportive treatment, excluding interventions in individual cases. Knowing the rather sad prognosis may also help physicians to get away from intervention-driven support to more mental support.

Although our patients were all referred for endoscopy and therefore were probably already selected as poor candidates for surgery, 94 out of 101 patients fulfilled the inclusion and exclusion criteria as used in a multicenter study in which surgical gastrojejunostomy was compared to endoscopic stent placement for the palliation of malignant GOO. Although we realize the presence of a potential bias it would be of interest to know if our model would also be of value for incurable patients having GOO who are on the brink to decide to undergo a surgical bypass. In those patients for whom the model predicts poor prognosis, adjustment of the strategy may potentially decrease hospital stay and avoid postoperative morbidity and mortality, adding QOL in a short-term palliative situation. As suggested in previous reports, such a calculated and evidence based approach may not
only aid individual ethical patient management but would also be more cost effective for the health system as a whole.19
In conclusion, this study demonstrates clear predictors of poor outcome for patients presenting with symptomatic malignant GOO. Being informed on expected survival may help patients, family members and physicians in better deciding on a tailor-made treatment.
Reference List


Chapter 7

Endoscopic magnetic gastroenteric anastomosis for palliation of malignant gastric outlet obstruction: a prospective multicenter study

Jeanin E. van Hooft, Frank P. Vleggaar, Olivier Le Moine, Alessandra Bizzotto, Rogier P. Voermans, Guido Costamagna, Jacques Devière, Peter D. Siersema, Paul Fockens

Gastrointestinal Endoscopy 2010; 72: 530-535
Abstract

**Background:** Palliation of malignant gastric outlet obstruction remains challenging. Although there are 2 established treatment options, ie, surgical gastrojejunostomy and endoscopic duodenal stent insertion, there is an ongoing search for a technique that would combine the safety and rapid effect of duodenal stent placement with the long-term efficacy and low reintervention rate of a surgical gastrojejunostomy.

**Objective:** To investigate the safety and success rate of endoscopic creation of a gastroenteric anastomosis formed by magnetic compression and stent placement.

**Design:** Prospective, multicenter cohort study.

**Setting:** Four referral centers.

**Patients:** The expected number of patients with symptomatic malignant gastric outlet obstruction to be included at the participating hospitals during a year was 40. Because of a serious adverse device event, the study was terminated after inclusion of 18 patients.

**Intervention:** Creation of an endoscopic gastroenteric anastomosis by using the Cook Magnetic Anastomosis Device with transanastomotic deployment of a self-expandable stent.

**Main outcome measurements:** Primary endpoints were safety and success rate associated with the creation of an endoscopic gastrojejunostomy by using a magnetic anastomotic device with transanastomotic deployment of a self-expandable stent.

**Results:** Because of a serious adverse event, the study was terminated prematurely. A success rate of 66.7% (12 of 18 patients) was achieved; 1 serious adverse event (stent perforation) occurred leading to the death of the patient. Three patients (25%) experienced an adverse device effect (stent migration).

**Limitations:** Small sample size, lack of control group.

**Conclusion:** Endoscopic creation of a gastroenteric anastomosis by magnetic compression is feasible and safe; however, the necessity of a stent led to serious morbidity and even mortality in this study. The current system can therefore not be recommended for clinical use.
Introduction

Malignant gastric outlet obstruction (GOO) is often caused by advanced gastric, duodenal or periampullary malignancies.\(^1\)\(^-\)\(^3\) GOO leads to significant morbidity, including nausea, vomiting, inability to eat, and weight loss. The aim of treatment is resolution of these debilitating symptoms.

A surgical gastrojejunostomy has long been the standard palliative therapy for these patients, but it carries considerable morbidity and even mortality.\(^4\)\(^-\)\(^6\) As many as 57% of the patients have symptoms of delayed gastric emptying, often causing a prolonged hospital stay.\(^7\)\(^-\)\(^9\) Once the gastrojejunostomy is functioning, recurrent obstruction is rare.\(^10\) Endoscopic placement of self-expandable metal stents has emerged as an alternative, minimally invasive treatment option. This endoscopic procedure leads to resumption of oral intake in about 90% of the patients within 4 days after stent placement, and it has a short procedure-related hospital stay and no intervention-related mortality.\(^1\)\(^-\)\(^3\),\(^11\) One of the most feared complications of enteral stent placement remains recurrent obstruction, caused by either stent migration or tumor infiltration.\(^1\)\(^-\)\(^3\) A recently published randomized, controlled trial clearly underlined the previously cited shortcomings of the currently available techniques.\(^12\) Promising data on a new minimally invasive technique were reported by Chopita et al., who successfully created an endoscopic gastroenteric anastomosis by using magnetic compression. Based on these and other recent results of creation of an anastomosis with magnetic compression, the Magnetic Anastomosis Device (Cook Endoscopy Inc, Winston-Salem, NC) was developed.\(^13\)\(^-\)\(^15\) This multicenter study was designed to evaluate the safety and technical success of the creation of a gastroenteric anastomosis with the Magnetic Anastomosis Device followed by transanastomotic deployment of a self-expandable stent as palliative treatment of malignant GOO.

Patients and Methods

Study design

The protocol of this multicenter, prospective, observational clinical trial (NCT00487552: Magnetic Anastomosis Device Relief of Malignant Gastric Outlet Obstruction [MAD]) was approved by the Medical Ethical Committee of the Academic Medical Center in Amsterdam and the local ethical committees of the other 3 participating centers (University Medical Center Utrecht; Hôpital Erasme, Brussels; and Catholic University, Rome). All participants provided written informed consent.
Patients
Between January 2008 and February 2009, patients older than 18 years of age with a histologically proven malignancy of the periduodenal area, who presented with symptoms compatible with GOO (GOO Scoring System [GOOSS] score \( \leq 2 \)) and a Karnofsky Performance Scale score of at least 60 (requires not more than occasional care for most needs) were considered for this study. Exclusion criteria were the inability to give informed consent, pregnancy, implanted cardiac device, coagulopathy, use of medication impairing wound healing, small-bowel strictures, and surgically altered gastrojejunal anatomy.

Material and Interventions
All endoscopic procedures were performed with the patient under conscious sedation or general anesthesia. Standard gastroscopy was performed to assess whether the endoscope could be passed through the obstruction. If this was not possible, a guidewire and a 5 French catheter were advanced through the endoscope and manipulated through the narrowed bowel lumen with fluoroscopic guidance. The malignant stricture was dilated to at least 16.5 mm with a through-the-scope balloon dilator (CRE balloon; Boston Scientific, Natick, Mass).

After dilation a guidewire was passed beyond the ligament of Treitz under fluoroscopic control, and the endoscope was removed. The jejunal magnet (14-mm diameter) was mounted on a catheter and advanced over the guidewire to the horizontal part of the duodenum under fluoroscopic guidance. Finally, the gastric magnet (16-mm diameter) was inserted in the stomach attached to the endoscope with a forceps and manipulated under fluoroscopic guidance until mating with the previously placed jejunal magnet occurred. The location of the magnet was marked with an endoscopic clip (Figure 1) or with India ink, to easily identify the location of the placement should the magnets be passed into the intestine.

Approximately 8 to 10 days after magnet placement, a gastroscopy was repeated to identify the gastroenteric fistula and to remove the magnet pair by the retrieval suture if the magnets were free in the stomach. In case the magnets were still attached to the wall, gastroscopy was repeated 2 to 4 days later at the discretion of the endoscopist. Once the magnets had been removed or had passed into the small bowel, a self-expanding metal stent with a 15-mm body and wide flanges (Figure 2) was delivered through the gastroenteric fistula (Figure 3) by using direct vision and/or fluoroscopy. The stent’s proximal flanged edge (Figure 4) was positioned in the gastric lumen to prevent migration.

Data collection
After obtaining informed consent, the GOOSS (a 4-point scale with 0 being the inability to intake orally and 3 the ability to eat a low-residue or full diet) scores were determined
Patients were followed up by telephone between magnet and stent placement and 24 hours after stent placement. The GOOSS score was determined before and 24 hours after stent placement. Thereafter, the patients were contacted every 5 to 7 days during the initial 3 weeks and every 25 to 30 days thereafter to assess the GOOSS score and to detect any adverse events or adverse device effects until an endpoint was reached. Patients returned 4 weeks after stent placement (25–30 days) for physical evaluation and an abdominal radiograph to check the position of the stent. Patients were followed for 180 days or until stent occlusion, recurrence of GOO, or death. Procedure-related data such as endoscopic difficulty of placement, technical difficulties and immediate post-placement complications were also assessed.
Definitions and endpoints

Safety and the technical success rate associated with the creation of a gastroenteric anastomosis by using the Cook Magnetic Anastomosis Device with transanastomotic deployment of a stent was the primary endpoint. Safety was defined as the absence of serious adverse events, serious being defined as those events leading to death, life-threatening situations, hospitalization, or prolongation of hospital stay. Technical success was defined as placement of the gastric and jejunal magnets, creation of the anastomosis, and deployment of a stent through the anastomosis. Possible adverse device effects included perforation of interposed organs or tissue, proximal or distal migration of the gastrojejunal stent, small-bowel obstruction because of failure of the magnets to pass a distal intestinal stricture, and any adverse event occurring during endoscopic placement. Secondary endpoints were improvement in tolerance of oral feeding by using the GOOSS score, the rate of stent migration, and the duration of patency of the stented anastomosis. Technical difficulties were defined as the inability to dilate the stricture, inability to successfully fuse the magnets or to deploy the stent, and failure of any component of the delivery system for the magnet or stent. Ease of placement of magnets and the stent was graded on an analogue 5-point scale (1 being very easy and 5 being very difficult).

Statistical analysis

We expected to be able to include 40 patients at the participating hospitals during 1 year. This was based on 2 recently concluded prospective studies on duodenal stent placement including 20 patients per year in the Amsterdam Medical Center, combined with the assumption that half of these patients might not meet the more strict entry criteria of the current study. All participating centers were expected to have a similar patient recruitment. Descriptive statistics were used for data of all included patients (intention to treat), except for those patients who died between the time of providing informed consent and the first endoscopic procedure. Wilcoxon matched-pairs signed-rank test was used to assess improvements from baseline (GOOSS score), after calculating the average score per patient from available follow-up assessments until death, weighed for the length of the preceding time interval between planned assessments. Duration of patency of the stented anastomosis was defined as time to first occlusion and was assessed by Kaplan-Meier analysis with stent dysfunction taken as event and death before stent dysfunction as censored observation. The date of occlusion was judged from the date of first reported symptoms. Statistics were performed using the SPSS (version 16.0) software package (SPSS, Inc, Chicago, Ill). Statistical significance in all analyses was set at $P < .05$. A data safety monitoring board consisting of independent physicians convened on a regular basis to evaluate study progress and review adverse events and adverse device effects.
Results

Inclusion of patients started in January 2008. In July 2008, after the inclusion of 12 patients, the study was placed on hold because of 2 adverse device effects both of which were stent migration. The study was reopened in November 2008 after approval of the medical ethical committees to continue with a different stent. In February 2009, the enrollment was suspended by the data safety monitoring board because of a serious adverse event leading to the death of a patient. Until this suspension, 18 patients with malignant GOO had been included.

Patient demographics and clinical characteristics are summarized in table 1.

Table 1. Patient demographics and clinical characteristics at baseline.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (y), mean (SD)</td>
<td>68.8 (11.0)</td>
</tr>
<tr>
<td>Sex: male/female, no.</td>
<td>15 / 3</td>
</tr>
<tr>
<td>Tumor characteristics, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Duodenal cancer</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Severity of obstruction</td>
<td></td>
</tr>
<tr>
<td>GOOSS score, no. (%)</td>
<td></td>
</tr>
<tr>
<td>0: No oral intake</td>
<td>11 (61.1)</td>
</tr>
<tr>
<td>1: Liquids only</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>2: Soft solids</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>General condition</td>
<td></td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>21.8 (3.5)</td>
</tr>
<tr>
<td>Karnofsky Performance Scale score, mean (SD)</td>
<td>72.2 (9.4)</td>
</tr>
</tbody>
</table>

GOOSS, Gastric outlet obstruction scoring system; SD, standard deviation.

Primary endpoint

In 3 of the 18 patients, adequate alignment of the magnets could not be achieved. Two patients died 2 and 10 days after magnet placement and before stent placement. Autopsy on both patients did not show a stent-related cause of death, and disease
progression was considered the most likely cause of death. In 13 patients, placement of a stent through the gastroenteric fistula was attempted. This procedure took place a median of 10 days (range 8-21 days) after magnet placement. Stent placement failed in 1 patient because of technical difficulty to release the stent from the delivery system. Placement of the stent was therefore successful in 12 out of 13 patients with a magnetic anastomosis (92%) and 12 out of the 18 original patients (66.7%).

During follow-up, adverse device effects occurred in 3 patients (25%), all being stent migrations, proven by radiography at 7, 11 and 81 days after stent placement. These patients were all treated with either a new gastrojejunal stent through the anastomosis (2 patients) or a duodenal stent (1 patient). Stents that had migrated were left and did not lead to symptoms. In 1 patient, a serious adverse event (free peritoneal perforation of the stent) occurred 7 days after stent placement, used in the second part of the study. The perforation was located in the jejunum at the distal margin of the stent, leading to fatal sepsis. Because of this serious adverse event further enrollment was suspended.

Secondary end points

Because of the limited number of patients and follow-up assessments, the improvement from baseline of the GOOSS score and duration of patency of the stented anastomosis were not calculated. Failure of the stented anastomosis occurred twice after 7 days (1 perforation, 1 migration), once after 11 days (migration), and once after 81 days (migration). Seven patients died while having a functional anastomosis. One patient completed the follow-up of 180 days with a functional anastomosis.

The magnet placement procedure took a median of 48 minutes (range 21-168 minutes). In 12 of 18 patients the duodenum had to be dilated with a balloon to pass the jejunal magnet. Difficulty of placement was graded a median 4 out of 5 (difficult) for the jejunal magnet, 2 out of 5 (easy) for the stomach magnet, and 2 out of 5 for the entire procedure. Stent placement took median 30 minutes (range 15-93 minutes); the magnets were retrieved in 6 patients, and in 7, the magnets had migrated distally. In 1 patient, the anastomosis appeared to be immature and a second procedure took place 2 days later, 12 days after magnet placement. Difficulty of stent placement was graded a median 2 out of 5.

Discussion

Palliation of malignant GOO remains challenging. There seems to be a need for a technique that combines the safety of the duodenal stent with the long-term efficacy of a surgical bypass.

Our study revealed that the use of magnets to create an anastomosis between the stomach and jejunum is feasible and safe. None of the adverse events was related to the
magnets. It can, of course, not be excluded that the first endoscopic procedure to place the magnets may have worsened the condition of the 2 patients who died before stent placement.

Alignment of the magnets was not always easy and failed in 17% of the patients. Nevertheless, the overall magnet placement procedure was graded easy and took a median 48 minutes.

In the first instance, a specially designed fully covered "yo yo"-shaped stent was used. This stent was fully covered to minimize the risk of leakage of the anastomosis. Because of the well-known risk of migration of covered stents, wide horizontal flanges had been added at both sides of the relatively short body (15 mm). During the study, it appeared that this special stent caused some difficulties: mounting it on the delivery system, releasing it accurately, and migration in 3 of 7 (42.8%) successful placements. Mainly because of the high migration rate it was decided to switch to the commercially available non-covered, 6-cm nitinol duodenal stent (Evolution Duodenal Stent, Cook Endoscopy Inc). This stent was successfully placed in 5 patients without migration but led to a fatal perforation in the last patient. This perforation probably occurred because of the distal end of the stent impinging on the opposite jejunal wall.

The median period of 10 days (range 8-21 days) between magnet placement and stent placement is a point of concern. We hypothesized that dilating the stricture at least 15 mm, which was needed to pass the 14 mm diameter magnet, would be sufficient for at least a liquid diet until stent placement.

As a consequence of the limited number of patients and follow-up assessments, we concluded that the data were insufficient to do a formal calculation of the secondary endpoints. Fifty percent of our patients either had a stent failure or died within 1 month after stent placement.

There is only 1 other clinical study on the creation of a gastroenteric anastomosis by using magnets for the palliation of malignant GOO. In this single-center, prospective study, 15 patients were included; in 2 the procedures failed, 1 because of the inability to sufficiently dilate the stricture to allow passage of the duodenal magnet and the other because of a perforation that occurred as a result of manipulation of the fresh gastroenteric anastomosis, making emergency surgery necessary. During follow-up, 3 stent migrations and 1 stent obstruction occurred. All patients maintained oral intake of solids until death. As in our study, the procedural concept appears to be in order, but the design of the stent seemed to be one of the limitations. It is also interesting to note that in this single-center study no failures of alignment of the magnets were mentioned, indicating that a learning curve effect may have contributed to our 3 failures.

The current available data seem to justify further development of this innovative technique. Research could focus on improvement of the design of the stent, creating, for example, a "yo yo"-shaped, partially covered stent with larger flanges and a shorter body to prevent migration or an uncovered stent approximately 3 cm in length with flanges at
both sides. Ideally, an endoscopic magnetic bypass would not need any device to keep it open. Maturation of the anastomosis would preferably occur in 2 to 3 days or the magnets should have a central lumen that could be used to place a temporary feeding tube. Finally the option of combined placement of a duodenal stent for short-term palliation and creation of a gastroenteric anastomosis for long-term palliation could be considered.

The attractiveness of the concept of a compression magnetic anastomosis is underlined by recent studies on the creation of a choledochoduodenostomy, Roux-en-Y gastric bypass, and colonic anastomosis. In our opinion, the endoscopic magnetic gastroenteric anastomosis is a very interesting and feasible concept. However, in this study, the necessity of a stent led to serious morbidity and even mortality. The current system can therefore not be recommended for clinical use, and further research is needed to make this technique safe as well as feasible.

**Acknowledgments**

The authors wish to thank Marcel G. Dijkgraaf, PhD, for statistical assistance and Cook Endoscopy for logistic and administrative support.
Reference List


Chapter 8

Premature closure of the Dutch Stent-in I study

J.E. van Hooft, P. Fockens, A.W. Marinelli, P.M. Bossuyt, W.A. Bemelman,
on behalf of the Dutch Stent-in study group

Lancet 2006; 368: 1573-1574
We would like to draw your attention to the following. On Jan 18, 2006, the Dutch Stent-in I study (ISRCTN01790428) had to be terminated prematurely because of a high number of serious adverse events. This study was a multi-centre, prospective, randomised controlled trial to assess the potential benefit of endoluminal stenting with the WallFlex colonic stent (Boston Scientific, Natick, MA, USA) compared with surgery in patients with incurable colorectal cancer.

When the study was stopped on the advice of the Safety Monitoring Committee, 21 patients had been included. 11 patients were assigned stenting: of those, 10 were treated accordingly. During follow-up four patients had a stent perforation, respectively 12, 12, 44 and 106 days after stent placement. Three of these patients died as a result of this complication. This high number of late perforations was unexpected because published data revealed a much lower incidence (4%) of perforations, mostly early and associated with stent placement.1,2
In one patient the perforation was located at the right side of the colon and was thought to be caused by a blowout due to stent obstruction. In three patients the perforation occurred at the site of the stent, apparently because of erosion of the stent through the bowel wall, since the pathology did not show malignant tissue at the site of perforation (Figure). In two of these, the perforation was at the proximal edge of the stent. In the fourth patient, who was on chemotherapy, the exact location remained unclear due to peritonitis at the outside of the colonic wall.

We cannot tell whether this high complication rate is caused by the design of this new enteral stent or is a chance phenomenon. There are no published data on the safety of this new stent. We can only point out that changes in the stent design could have contributed to the perforations: the stent has a larger diameter at the proximal end (30 mm), where the perforation occurred in two, and possibly three, of the four patients. Additionally, the stent is made from braided nitinol instead of stainless steel (as for the enteral Wallstent [also Boston Scientific]). This might affect the force applied to the colonic wall. As long as the cause of the high incidence of late perforations remains unclear, we feel that it is of paramount importance that patients being or having been treated with this new type of colonic stent are prospectively followed in a registry, since the WallFlex colonic stent is still commercially available.
Reference List


Early closure of a multicenter randomized clinical trial of endoscopic stenting versus surgery for stage IV left-sided colorectal cancer

J.E. van Hooft, P. Fockens, A.W. Marinelli, R. Timmer, A.M. van Berkel, P.M. Bossuyt, W.A. Bemelman, on behalf of the Dutch Colorectal Stent Group

Endoscopy 2008; 40: 184-191
Abstract

Background and study aims: The introduction of self-expandable metal stents has offered a promising alternative for palliation of malignant left-sided colonic obstruction. This randomized clinical trial aimed to assess whether a nonsurgical policy, with endoluminal stenting, is superior to surgical treatment in patients with stage IV left-sided colorectal cancer and imminent obstruction.

Patients and methods: Patients with incurable left-sided colorectal cancer who fulfilled the study criteria were randomly assigned to nonsurgical or surgical treatment. The primary outcome measure was survival in good health out of hospital (World Health Organization performance scores 0 or 1).

Results: A high number of serious adverse events in the nonsurgical arm led to premature closure of the trial. Ten patients were allocated to surgical treatment and 11 patients to nonsurgical palliation. The median survival in good health out of hospital during the first year was 56 days (interquartile range 7.5 – 338.5 days) in the surgical arm vs. 38 days (interquartile range 5.25 – 288.75 days) in the nonsurgical arm (P = 0.68). Eleven adverse events (six perforations) occurred in the nonsurgical arm vs. one adverse event in the surgical arm (P < 0.001). Of the six perforations, two were stent-related because they occurred at the proximal edge of the stent by erosion through a normal colon wall; one was probably stent-related (it was located in the region of the proximal half of the stent); one was a colon blowout; and two were late tumor perforations in patients on chemotherapy.

Conclusions: The unexpected high rate of perforation in the nonsurgical arm might be specifically WallFlex-related or enteral stent-related in patients on chemotherapy and warrants attention.
Introduction

Colorectal cancer is the fourth most commonly diagnosed malignancy worldwide, with an estimated 1,023,000 new cases and 529,000 deaths each year. In The Netherlands, colorectal cancer is the second most common cancer in women and the third most common cancer in men, with an incidence of 9898 new cases in 2003. Surgical resection of the tumor, either as initial treatment or after neoadjuvant radiotherapy in cases of rectal cancer, combined with adjuvant chemotherapy if indicated, is the only curative treatment strategy. Unfortunately, 20% of patients present with incurable disease because of metastases or locally advanced colorectal cancer (stage IV). For these patients, a palliative resection or fecal diversion and stoma creation are the standard procedures if the patient is fit enough to undergo surgery. Morbidity associated with surgery can jeopardize successful palliation of obstruction and bleeding, however. Recent studies have demonstrated that palliative chemotherapy in patients with metastatic disease significantly prolongs survival and enhances quality of life, but recovery from surgery after discharge from hospital can delay or even exclude palliative chemotherapy.

Colonic stenting was introduced in the early 1990s as a tool to treat malignant colonic obstruction. Colonic stenting was demonstrated to be useful in acute malignant colonic obstruction, enabling one-stage curative surgery at a later stage or serving as a permanent treatment in those patients who appeared to be incurable after diagnostic work-up. A systematic review by Sebastian et al. showed an overall rate for relief of obstruction of 84%–94% and a rate of 72% when stent placement was used as a bridge to surgery. However, these success rates are observed at the expense of complications such as perforation (4%), stent migration (10%–12%) and reobstruction (7%–10%), causing a cumulative mortality of 1%.

Although several promising studies have been published on colonic stenting in different situations, there is little evidence available comparing endoscopic stenting with elective surgery as palliative treatment in patients with grade IV left-sided colorectal cancer. So far, there has only been one small randomized clinical trial (which lacked long-term follow-up) and one small retrospective cohort study. Few data have been published on the safety of endoluminal stenting in patients receiving different forms of chemotherapy, which can include angiogenetic inhibitors such as bevacizumab, which has been reported to cause enteral perforations (though the mechanism for this is unclear). This is important because bevacizumab has recently been added to the initial chemotherapeutic regime for patients with advanced colorectal cancer.

The current tendency to accept colonic stenting as the palliative treatment of choice for patients with left-sided colonic obstruction due to stage IV colorectal cancer does not accord with the sound principles of evidence-based medicine. For this reason, a randomized trial was designed to compare a nonsurgical policy of endoluminal stenting
with surgical treatment in patients with stage IV left-sided colorectal cancer and imminent obstruction.

**Patients and methods**

The Dutch Stent-in I study (ISRCT01790428) was designed as a multicenter, prospective, randomized clinical trial to evaluate the effectiveness of a policy of endoscopic stenting in patients with imminent obstruction (the nonsurgical arm) vs. surgery (the surgical arm) in patients with stage IV left-sided colorectal cancer. The protocol was approved by the Medical Ethical Committee of the Academic Medical Center (AMC) in Amsterdam and by the local ethical committees of the 29 participating centers. All participants provided written informed consent. An independent data and safety monitoring committee monitored the safety of the participants.

**Patients**

Men and women over the age of 18 years with left-sided colorectal cancer who presented at one of the 29 participating Dutch hospitals were considered for inclusion in the trial, starting in December 2004. Routine work-up included endoscopy, pathological confirmation of malignancy, and, preferably, computed tomography of the abdomen and chest or thoracic radiography and ultrasound of the liver. The patient’s disease was considered to be incurable when curative resection of metastatic disease was impossible, either because of the features of the liver metastases (bilobar multiple lesions, involvement of the hilum or of three major hepatic veins, remnant liver volume <30% after hepatectomy) or because of the presence of extrahepatic disease. Patients with incurable left-sided colorectal cancer were eligible for inclusion in the study if the tumor was localized between the splenic flexure and the proximal rectum (distal margin at least 10 cm from the anal verge). A second colonic tumor had to be excluded by complete colonoscopy, gastrografin enema study, or abdominal computed tomography. Exclusion criteria were ileus, a Karnofsky performance status (KPS) of less than 50% or an American Society of Anesthesiologists (ASA) class of IV or V. Eligible patients were invited to participate in the study and were asked for signed informed consent.

**Randomization**

Participants were randomly assigned by computerized randomization to either the surgical or the nonsurgical arm. The randomization for the study was done centrally in the AMC Amsterdam, with only stratification per center. Immediately after inclusion in the study, the research nurse collected patients’ demographic and general clinical data (sex, age, tumor location, metastatic spread), and
data on the severity of obstruction (symptoms and endoscopic scoring), general condition (body mass index [BMI], World Health Organization [WHO] performance score, KPS), adjuvant chemotherapy or radiotherapy, and the results of quality-of-life questionnaires (the European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 version 3 measure, the EuroQol 5 dimensions [EQ-5D], and the EuroQol visual analog scale [EQ-VAS] questionnaires). The nurse carried out a monthly follow-up by telephone, inquiring about obstructive symptoms, general condition, additional therapies, quality of life, and adverse events. Patients were followed until death or until at least 1 year after inclusion.

End points and definitions
As the primary outcome measure we chose a parameter that combined mortality, morbidity, and functional health status in an objective way. As hospital stay is a good and reliable proxy measure for serious morbidity and because the WHO performance score is a reflection of functional health status, we decided to consider survival out of hospital ("hospital-free") and in good health as the primary outcome measure of the study. Good health was defined as a WHO performance score of 0 or 1, which corresponds to normally active (WHO 0) or slightly less active but able to perform activities of daily living (WHO 1).
Additional outcome measures were effectiveness of palliation, quality of life, adverse events, costs, and procedural morbidity and mortality. Effectiveness of palliation was defined as long-term relief of obstructive symptoms. Health-related quality of life was assessed using the oncology-specific EORTC QLQ-C30 version 3 measure, the EQ-5D, and the EQ-VAS questionnaires.21,22
Serious adverse events were defined as events leading to surgical re-intervention, or events requiring patient admission to the intensive care unit (ICU) for more than 48 hours or causing death. Mild adverse events were events that led to hospital admission or prolonged hospital stay, but which did not fulfil the criteria for severe adverse events. Clinical suspicion of imminent obstruction was based on changes in the symptoms and signs of nausea, vomiting, abdominal discomfort, abdominal distension, or diarrhea, assessed on a three-point symptom score (never, sometimes, or daily). Where there was suspicion of imminent obstruction (at least one symptom daily), an endoscopy was performed. The obstruction was considered imminent when it was not possible to pass a normal colonoscope (diameter >12.5 mm).

Interventions
In the surgical arm, palliative surgery had to be carried out within 3 weeks after randomization. The decision on whether a palliative resection or fecal diversion was performed (open or laparoscopic) was made at the discretion of the surgeon. Bowel
preparation and preoperative prophylactic antibiotics were given according to the local hospital guidelines. Patients received a regular diet as soon as possible.

In the nonsurgical arm, patients were referred to a medical center with an experienced endoscopist for colonic stent placement if obstruction was imminent. Endoscopists were considered to be experienced if they had placed a minimum of 20 colonic or duodenal stents.

Patients were treated with the recently introduced WallFlex colonic stent (Boston Scientific, Natick, Massachusetts, USA) (Figure 1). The WallFlex colonic stent used in the study is a through-the-scope, self-expandable metallic stent with a length of 6 cm, 9 cm, or 12 cm, and a diameter of 30 mm at the flared end and 25 mm in the body section. The stent was preloaded on a 10-Fr delivery system and was CE-approved. After preparation of the distal colon with an enema, the colonoscope was introduced up to the site of the obstruction. In cases where the colonoscope was not able to pass, a double-lumen catheter with a guide wire and contrast was used to pass the stenosis. The length of the stenosis was then assessed fluoroscopically. A stent was chosen which was at least 3 cm longer than the stenosis (1.5 cm at either end). The selected stent was advanced through the endoscope over a guide wire until it passed the proximal end of the stricture; after this the stent was deployed under continuous radiographic control. If the stent did not cover the entire length of the tumor, a second overlapping stent was placed. The correct position of the stent was confirmed using fluoroscopy. The stenosis was not dilated before or directly after stent placement.

Patients were observed for a minimum of 4 hours and, if possible, were discharged the same day. Instructions on the importance of keeping their stools soft and on how to use the prescribed laxatives were given to the patients. All patients were offered palliative
chemotherapy, which was started as soon as possible after surgical resection or after inclusion in the nonsurgical arm, the regimen at the discretion of the oncologist.

Statistical analysis
The mean log-transformed hospital-free survival in good health was calculated and differences tested with the t test statistic. We assumed that patients with stage IV colonic cancer had a mean ± standard deviation (SD) survival of 40 ± 6 weeks and anticipated a difference in hospital-free survival in good health between the two arms of 3 weeks in favor of the nonsurgical arm. It was calculated that a group size of 85 patients per arm would then be necessary to detect a significant difference (alpha 0.05, beta 0.1).

A data and safety monitoring committee periodically looked at safety and effectiveness. An interim analysis was planned after inclusion of 100 patients.

All analyses were performed on an intention-to-treat principle and included all randomized patients. Statistical analyses were performed using the SPSS (version 12.0.1) software package. Statistical significance in all analyses was set at \( P < 0.05 \).

Results
The study started including patients in December 2004. In January 2006 inclusion was discontinued because of an unusually high number of serious adverse events in the nonsurgical arm – a possible stent-related perforation had occurred in three of the nine stented patients. After carefully studying all the serious adverse events, the safety monitoring committee advised us to close the study prematurely, from 8 March 2006. The Medical Ethical Committee of the coordinating center approved this closure and all participating hospitals and patients were informed.

At the time the study was closed a total of 48 patients had been screened for eligibility. Six of these did not meet all the inclusion criteria. Of the 42 patients who met the inclusion criteria, 21 declined to participate, mainly because they preferred surgery or only wanted chemotherapy and no intervention at all. In total, 21 patients were enrolled in the study (Figure 2). The patients were well matched with respect to baseline demographic features and clinical characteristics (including all 15 scales of the QLQ-C30 version 3, though only the Global Health score data are given) (Table 1).

Treatment in the surgical arm
Ten patients were randomly allocated to the surgical arm. One patient suffered from a myocardial infarction 7 days after inclusion and so could not be treated surgically within 3 weeks after randomization. Because this patient had clear symptoms of obstruction
### Table 1. Patient demographics and clinical characteristics at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Surgical arm (n = 10)</th>
<th>Nonsurgical arm (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Mean age ± SD (range)</td>
<td>67.8 ± 12.3 (46 - 81)</td>
</tr>
<tr>
<td><strong>Sex, male/female</strong></td>
<td>7/3</td>
<td>4/7</td>
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<tr>
<td><strong>Tumor characteristics, n (%)</strong></td>
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<td>Site of obstruction</td>
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<td>Rectosigmoid</td>
<td>9 (90%)</td>
<td>7 (64%)</td>
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<td>Descending colon</td>
<td>1 (10%)</td>
<td>4 (36%)</td>
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<td>Site of metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>2 (20%)</td>
<td>6 (55%)</td>
</tr>
<tr>
<td>Liver</td>
<td>10 (100%)</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Bone</td>
<td>1 (10%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>0</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>1 (9%)</td>
</tr>
<tr>
<td><strong>General condition, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO performance score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO 0</td>
<td>3 (30%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>WHO 1</td>
<td>5 (50%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>WHO 2</td>
<td>2 (20%)</td>
<td>5 (46%)</td>
</tr>
<tr>
<td>WHO 3</td>
<td>0</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Karnofsky performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (range)</td>
<td>79.0 ± 13.7 (60 - 100)</td>
<td>79.1 ± 17.0 (50 - 100)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (range)</td>
<td>23.0 ± 2.5 (17.8 - 26.0)</td>
<td>25.5 ± 4.4 (19.0 - 32.7)</td>
</tr>
<tr>
<td><strong>CEA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>26.5 (6.18 - 72.15)</td>
<td>15.0 (7.15 - 663.50)</td>
</tr>
<tr>
<td>QLQ-C30 Global Health score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>54.2 (16.67 - 77.08)</td>
<td>50.0 (41.67 - 83.33)</td>
</tr>
<tr>
<td>EQ-5D index score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (range)</td>
<td>0.71 ± 0.29 (0.11 - 1.0)</td>
<td>0.65 ± 0.31 (-0.05 to +1.0)</td>
</tr>
<tr>
<td>EQ-5D VAS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>57.5 (20.00 - 72.50)</td>
<td>60.0 (40.00 - 76.25)</td>
</tr>
</tbody>
</table>

BMI, body mass index; CEA, carcinoembryonic antigen; IQR, interquartile range; SD, standard deviation; WHO, World Health Organization.
he underwent endoscopic stenting. Another patient died prior to surgery as a result of a myocardial infarction.

A total of eight patients therefore underwent surgical palliation (Table 2). Of these, six underwent a resection with a primary anastomosis. One patient had to be treated in the ICU postoperatively for 2 days. Oral intake was possible after a median period of 4 days (interquartile range [IQR] 1 – 9 days) after surgical intervention. The median hospital stay after surgery was 12 days (IQR 5.75 – 16.75 days). One patient suffered from a postoperative ileus for 13 days, lengthening the hospital stay.

There were two late complications (≥30 days after the operation) that were not related to the surgical procedure: one patient developed cholangitis due to massive liver metastases; and one patient developed a pneumothorax after placement of a Port-a-Cath. Six of the eight patients began chemotherapy after surgery; two patients declined this treatment. Three patients were still alive at the end of follow-up, on 1 December 2006.

* This patient had a myocardial infarction, preventing surgery within 3 weeks

** Inability to pass a guide wire beyond the tumor.

Figure 2. Trial profile.
Eleven patients were allocated to endoscopic stenting in the event of imminent obstruction. One patient did not develop imminent obstruction and did not therefore undergo colonic stenting. Endoscopic stenting was attempted in 10 patients. This was unsuccessful in one patient because it was not possible to pass a guide wire beyond the tumor. This patient then received surgical palliation, without complications. The other nine patients underwent successful endoscopic placement of a stent a median of 6 days after inclusion (IQR 2.00 – 55.5 days) (Table 3). In this group, oral intake was possible a median of 0 days (IQR 0 – 1.5 days) after stent placement. The median hospital stay after stent placement was 0 days (IQR 0 – 11.5 days).

---

**Table 2. Features of the surgical procedures in the patients in the surgical arm who underwent intervention (n = 8).**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic prophylaxis, n (%)</td>
<td>7 (88%)</td>
</tr>
<tr>
<td>Laparoscopy, n (%)</td>
<td>3 (38%)</td>
</tr>
<tr>
<td>Laparotomy, n (%)</td>
<td>5 (63%)</td>
</tr>
<tr>
<td>Primary anastomosis, n (%)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Definitive colostomy, n (%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Blood loss &lt; 500 ml, n (%)</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>Mean ± SD duration of operation (range), minutes</td>
<td>122 ± 62 (51 - 215)</td>
</tr>
</tbody>
</table>

**Table 3. Features of the endoscopic procedures (n = 9).**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation, n (%)</td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Bowel preparation</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>Sedation</td>
<td>7 (78%)</td>
</tr>
<tr>
<td>Stent placement*</td>
<td></td>
</tr>
<tr>
<td>Type of stent, n (%)</td>
<td></td>
</tr>
<tr>
<td>WallFlex 6 cm</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>WallFlex 9 cm</td>
<td>6/10 (60%)</td>
</tr>
<tr>
<td>WallFlex 12 cm</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>No. of stents required for successful placement</td>
<td></td>
</tr>
<tr>
<td>One stent</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>Two stents</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

* One patient had two stents placed.
There were two perforations, both 12 days after stent placement. One of these patients developed severe sepsis as a result of the perforation and the other patient refused any further treatment. They both died within 30 days after stent placement (Table 4). The pathology reports of both patients reported ulceration and perforation at the proximal end of the colonic stent without tumor at the site of perforation (Figure 3).

There were two other events within 30 days after stent placement: one patient was admitted with an episode of severe diarrhea immediately after stent placement that caused electrolyte disturbances and which lasted for 4 days; another patient developed severe pain 1 day after stent placement and required hospital admission. In this patient no signs of perforation could be detected and his complaints lessened spontaneously after 6 days. There were four late (≥30 days after stent placement) colonic perforations at day 44, day 106, day 351, and day 355 after stent placement; one of these four patients died as a result, after refusing surgery (Table 4). The pathology reports described the perforations as: in the proximal half of the colonic stent (n = 1), a proximal colon blowout (n = 1), and a perforation at the height of the tumor (n = 2).

Stent obstruction was observed in two patients, in one patient due to fecal impaction and in the other patient caused by tumor ingrowth into the stent. Both patients had a second stent placed through the first stent and recovered well. There was one case of stent migration 390 days after placement. This patient also received a new colonic stent. Of the 11 patients in the nonsurgical arm, nine received chemotherapy (the two patients who died early on did not receive any chemotherapy). Of the seven stented patients who were treated with chemotherapy, four developed a perforation: two of these patients were treated with a regime containing oxaliplatin, infusional fluoracil and leucovorin (FOLFOX); one patient was treated with a regime containing cetuximab, capecitabine,
oxaliplatin, and bevacizumab (CAIRO II); and one patient received irinotecan. The perforations occurred 3 days and 24 days after the last cycle of chemotherapy in the patients receiving the FOLFOX treatment, 16 days after the last treatment in the patient on the CAIRO II regime (including bevacizumab) and 14 days after the last treatment in the patient receiving irinotecan chemotherapy.

On 1 December 2006, at the end of the follow-up period, two patients in this group were still alive, one with a stent in situ.

**Analysis**

The median hospital-free survival in good health (WHO 0 or 1) during the first year after inclusion was 56 days (IQR 7.5 – 338.5 days) in the surgical arm vs. 38 days (IQR 5.25 – 288.75 days) in the nonsurgical arm ($P = 0.68$) (Table 5). The median total time in hospital (for initial treatment and treatment of adverse events) was 11 days (IQR 6.25 – 17.25 days) in the surgical arm vs. 12 days (IQR 7.00 – 19.00 days) in the nonsurgical arm ($P = 0.46$). In total, there were 2 days of ICU stay among the surgical group patients and 21 days of ICU stay among the nonsurgical group patients. The median time spent in ICU was 0 days in both groups ($P = 0.30$). The median period of follow-up between randomization and death or 1 December 2006 was 173 days (IQR 129.5 – 512.25 days) for the surgical arm and 360 days (IQR 86.00 – 593.00 days) for the nonsurgical arm ($P = 0.67$). In total, there were 11 adverse events in the nonsurgical arm vs. one adverse event

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex, age</th>
<th>Complications &lt;30 days after stent placement</th>
<th>Complications ≥30 days after stent placement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mild adverse events</td>
<td>Severe adverse events</td>
</tr>
<tr>
<td>1</td>
<td>M, 64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F, 66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M, 53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F, 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>F, 88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>F, 56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>F, 56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>F, 57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>F, 50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Adverse events after endoscopic treatment.
in the surgical arm (\(P < 0.001\)). There was a significant difference between the two arms with respect to serious adverse events (\(P < 0.001\)). Of the 11 patients in the nonsurgical arm, eight suffered one or more adverse events; only one patient from the group of 10 patients in the surgical arm suffered one or more adverse events (\(P = 0.008\), relative risk 7.2). There were no significant associations between perforation and WHO performance score or the length of the stent (Fisher’s exact test), nor between perforation and the location of the tumor. Because of the high number of adverse events and the early discontinuation of the study, the quality-of-life questionnaires were not analyzed.

On 1 May 2007, five patients were still alive, three from the surgical group and two from the nonsurgical group. The one patient in the nonsurgical group with a stent still in situ suffered a stent obstruction 438 days after stent placement. Surgical palliation was needed because it was not possible to pass a guide wire beyond the tumor (this was not included in the study results analysis because follow-up for the purposes of analysis ended in December 2006).

**Discussion**

This randomized controlled trial comparing a nonsurgical policy of endoluminal stenting with surgical treatment for patients with stage IV left-sided colorectal cancer who showed signs of imminent obstruction had to be stopped early because of an unexpected high rate of adverse events in the nonsurgical arm. The development of three colonic perforations prompted us to discontinue the study.\(^{23}\) By the end of the follow-up period, perforation had occurred in another three patients. In total, six out of nine stented patients had a perforation and had surgical re-intervention and/or died. The overall complication rate for colonic stent placement and stent-related mortality (3/9) was considerably higher in the present study than had been reported until then in the

<table>
<thead>
<tr>
<th>Table 5. Results according to randomization.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Surgical arm (n = 10)</td>
</tr>
<tr>
<td>Nonsurgical arm (n = 11)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
</tr>
<tr>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Median hospital-free survival in good health (IQR), days</td>
</tr>
<tr>
<td>Median total time in hospital (IQR), days</td>
</tr>
<tr>
<td>Median total time on ICU (IQR), days</td>
</tr>
<tr>
<td>Median total follow-up time (IQR), days</td>
</tr>
<tr>
<td>No. of adverse events</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; IQR, interquartile range.
literature. Perforations are reported to occur in around 4% of patients, often associated with predilation of the obstructing tumor, and occur within 30 days after stent placement in the vast majority of patients. In our series none of the perforations were caused by the stent insertion itself, perhaps because all the stents were placed by senior staff members who were specialized in performing such interventions in high-volume centers: AMC, Amsterdam (six stent placements, four perforations), Medical Center Haaglanden, Den Haag (two stent placements, one perforation), and St. Antonius Hospital, Nieuwegein (one stent placement, one perforation).

In the present study the majority of the perforations appeared more than 30 days after stent placement. Because the site of the perforation was stent-related in two cases (at the proximal edge of the stent, by erosion through a normal colon wall) and possibly stent-related in one other patient (the perforation was located in the proximal half of the stent), an association between perforation and the design of the new colonic stent could not be excluded.

We chose to use the new CE-approved WallFlex colonic stent, a modification of the most frequently used enteral stent, the Boston Scientific Wallstent, for a number of reasons. Firstly, the new stent has an improved flexibility due to the use of nitinol and modification of the mesh structure. Secondly, the new stent exhibits excellent radiopacity of the complete mesh structure. Thirdly, the stent is repositionable up to 70% stent deployment (the point of no return), allowing easy repositioning and improving control. Fourthly, it has a flared end proximally, which minimizes the risk of migration, and looped ends, which reduces the chance of tissue injury. Because of these modifications, a further reduction in stent-related complications appeared to be a realistic expectation, although no literature on this was available.

In retrospect, the large proximal diameter of the WallFlex colonic stent (30 mm), which is 8 mm greater than the most commonly used Wallstent, might have led to increased pressure on the colonic wall; the different material used in the WallFlex stent might also have affected the pressure on the colonic wall. Unfortunately there are no data on the influence of diameter, stent design, or stent material on the radial and longitudinal forces exerted by enteral stents. The existing data have mainly been collected in studies using endovascular stents. The change from sharp ends to looped ends could also have had an effect, as sharp ends tend to lead to scar formation on the normal colon wall, while looped ends seem to lead to slow erosion of the wall.

Besides the probable adverse effect of the stent design, the administration of chemotherapy might also have influenced the risk of perforation. In our series two perforations occurred nearly 1 year after insertion of the stent in patients on long-term chemotherapy. A recently published study by Karou et al. focusing on the influence of colonic stents in the management of chemotherapy in patients with stage IV colorectal cancer revealed two patients on chemotherapy (6%) who developed a late perforation,
occurring 3 months and 14 months after stent insertion. They concluded that the risk of tumor perforation in patients receiving chemotherapy deserves attention. This is important because the availability of modern chemotherapy has improved the median survival in patients with stage IV colorectal cancer from around 11 months with conventional regimes to over 20 months with modern chemotherapeutic regimes. It seems likely, therefore, that the incidence of stent-related complications will increase as patient survival times lengthen.

Two other interesting articles have been published recently on the effect of primary tumor resection on survival in patients with stage IV colorectal cancer. These papers both concluded that palliative resection of primary colorectal cancer should be pursued in patients with irresectable distant metastasis as this prolongs survival for the majority of patients. The Costi et al. study found no benefit for patients with carcinomatosis, however, and Konyalian et al. found less benefit for patients with more than 75% metastatic liver involvement. We do realize that this is a re-opening of an old debate, but an increasing number of studies do demonstrate a longer median survival time after resection of the primary tumor in stage IV colorectal cancer.

We also considered the anatomical location of the stent as a probable explanation for the high number of perforations. We would have predicted that the curved sigmoid colon would be more prone to perforations. There are data in the literature supporting this possible explanation: a large review article revealed that most perforations occurred in the rectosigmoid area. In our series, however, four of the six perforations occurred in the descending colon, with the proximal end of the stent positioned several centimeters below the splenic flexure.

In contrast, the surgically treated patients in our study did very well. Only one intervention-related complication occurred in the surgical group. The complication rate in surgically palliated patients is reported in the literature to be between 14% and 30%. The cost implications of shifting to endoscopic stenting in the management of left-sided colorectal cancer are mainly determined by a shorter hospital stay, fewer days spent in ICU, and fewer re-interventions. In our study the median hospital stay after the initial procedure was, in accordance with the literature, shorter in the nonsurgical arm. Because of the high number of re-interventions due to complications, however, there was no overall difference in total hospital stay. The total number of days in ICU was higher in the nonsurgical arm as a consequence of the complications, making a cost reduction by shifting to stenting highly unlikely.

The unexpected high rate of perforations in the nonsurgical arm (which could be specifically WallFlex-related or enteral stent-related) in patients on chemotherapy warrants attention. These findings, combined with the data from recent literature on primary tumor resection in stage IV colorectal cancer might support the recommendation that fit patients who are able to undergo surgery and who are candidates for postoperative chemotherapy
should be treated by surgical resection. Only another randomized prospective study, with a large number of patients, would help to confirm this recommendation.

Acknowledgments

We are grateful to the following for their support in this study: Dr. D. A. Legemate, Dr. D. W. Meijer, and Dr. D. J. Richel for their role in the safety analysis; and to I. Peute, RN, for her substantial contribution to the collection and maintenance of the research data. Finally the authors would like to thank all investigators of the Dutch Colorectal Stent Group (see Appendix).

These data were presented in part as poster presentations at the United European Gastroenterology Week 2005, Copenhagen, Denmark, at Digestive Disease Week 2006, Los Angeles, USA, and at Digestive Disease Week 2007, Washington, USA.

A governmental subvention (ZonMW) for overhead costs was obtained for this study.

Appendix

The Dutch Colorectal Stent Group investigators
Reference List


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Chapter 9

Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial (Stent-in 2 study)

J.E. van Hooft, W.A. Bemelman, B. Oldenburg, A.W. Marinelli, M. Lutke Holzlik, M.J. Grubben, M.A. Sprangers, M.G. Dijkgraaf, P. Fockens for the collaborative Dutch Stent-In study group
Abstract

**Background:** Colonic stenting as bridge to elective surgery is becoming an increasingly popular alternative for emergency surgery as treatment of acute malignant colonic obstruction. We undertook a multi-centre randomised trial comparing colonic stenting with emergency surgery in patients with acute obstructive colorectal cancer.

**Methods:** Twenty-eight hospitals in the Netherlands participated. Patients were eligible if presented with obstructive symptoms existing less than one week and imaging compatible with a left-sided colorectal cancer. After informed consent patients were randomised to either endoscopic stent placement or emergency surgery. The primary outcome parameter was global health status during six months follow-up. Secondary outcome parameters were disease-specific and generic quality of life, morbidity, mortality and stoma rate. Group size was calculated based on the primary outcome parameter. Using a two-group t-test with a 0.05 two-sided significance level, 60 patients per arm were needed to detect an effect size of 0.5 on the EORTC QLQ-C30 global health scale with 80% power. Analysis was by intention-to-treat.

**Results:** Between March 2007 and September 2009, 98 patients with acute left-sided malignant colonic obstruction were randomly assigned to stent placement (n=47) or emergency surgery (n=51). Treatment was initiated within 24 hours after randomisation. The study was terminated early, following advice of the Data Safety Monitoring Committee (DSMC) because of an absolute risk increase of morbidity in the stent arm. At study termination 98 of the planned 120 patients had been randomised. No differences between emergency surgery and colonic stenting in response to treatment were observed regarding global health status (-4.7, p=0.36), 30 days mortality (Chi2=0.02, p=0.89), overall mortality (Chi2=0.04, p=0.84), morbidity (Chi2=0.64, p=0.43) and stoma rates at latest follow-up (Chi2=0.87, p=0.35). The only differences observed were a lower stoma rate directly after initial intervention (Chi2=5.8, p=0.016) and more frequently reported stoma-related problems (-12, p=0.046) in the colonic stenting group.

**Interpretation:** Colonic stenting as bridge to surgery has no decisive clinical advantages to emergency surgery in colorectal cancer patients with acute left-sided colonic obstruction. A persistent trend of increased 30 days morbidity in the colonic stenting group urged the DSMC to stop the trial prematurely. (ISRCTN46462267)
Introduction

Colorectal cancer is the third most common cancer in men and the second most common cancer in women in Europe, with a total of 412,900 new cases and 207,400 deaths in 2006. Between 7 and 29% of patients with colorectal cancer will present with a sub-total or total bowel obstruction. Conventionally these patients are treated with emergency surgery to restore luminal patency. Emergency operations, involving an unprepared and obstructed bowel, are reported to have a mortality rate of 15-34% and a morbidity rate of 32-64% despite advances in perioperative care. A variety of surgical techniques is applied to treat this condition. Mostly, an ostomy is fashioned. In many patients the ostomies will not be closed. Patients with a permanent stoma do frequently report complications and lower health-related quality of life than comparable patients without colostomy; in addition they require costly stoma materials. Since the early 1990s colonic stenting has been introduced to restore luminal patency in patients with malignant obstruction of the left-sided colon. Stenting can be applied as a preoperative treatment to prepare patients for elective surgery as well as a definitive palliative procedure in patients with incurable disease or inoperable patients. In uncontrolled studies stent placement before elective surgery (also known as “bridge to surgery”) has been suggested to improve the patients’ clinical condition and to decrease mortality, morbidity and number of colostomies. Additionally this temporary procedure gives the opportunity to perform accurate tumour staging, leading to avoidance of surgery in patients with disseminated disease or unacceptable surgical risk. In these patients the colonic stent may serve as permanent palliation. A systematic review by Sebastian et al. of 54 uncontrolled trials and case reports on placement of self-expandable metal stents revealed a technical success rate of 68-97% and a clinical success rate of 71.7% when used as bridge to surgery. Major complications related to stent placement included perforation (4%), stent migration (11.8%) and re-obstruction (7.3%), causing a cumulative mortality of 0.58%. It has to be underlined that stent perforation is not only a severe acute complication but may also lead to peritoneal tumour spill, changing a potentially curable disease in an incurable one.

It is important to realise that stenting so far has mainly been done by experts in tertiary centres and the published results are mostly retrospective and/or uncontrolled, subject to selection bias and not including learning curves. Notwithstanding a growing body of literature data, at the present a randomised prospective trial comparing the efficacy of treatment with colonic stenting before elective surgery against emergency surgery for malignant acute colorectal obstruction is lacking. The objective of this multicentre randomised trial was to finally get grade A evidence and confirm the promising data of uncontrolled series. We compared both treatment strategies in a randomised fashion with respect to global health, disease-specific and generic quality of life, morbidity, mortality and stoma rate. The study was performed by the Dutch Stent-In study group.
who previously reported a randomised study on colonic stenting in incurable malignant colonic obstruction.\textsuperscript{19}

**Methods**

**Patients**

The study population consisted of patients presenting with an acute left-sided colorectal obstruction presumably caused by a colonic malignancy. Inclusion criteria were: clinical signs of severe colonic obstruction existing less than one week with dilation of the colon on either plain abdominal radiograph and typical abnormalities on a gastrografin enema study or contrast enhanced CT-scan. The imaging modalities had to be compatible with a (sub)total malignant colonic obstruction. The obstruction had to be located in the left side of the colon (descending colon, sigmoid or rectum); patients had to be 18 years of age or older and had to sign informed consent. Exclusion criteria were: signs of peritonitis, perforation, fever, sepsis or other serious complications demanding urgent surgery; American Society of Anesthesiologists (ASA) classification IV or V; obstruction caused by a non-colonic malignancy or a benign disease; distal tumour margin less than 10 cm from the anal verge; inability to complete self-report quality of life questionnaires. Recruitment started after approval of the study by the Medical Ethical Committee of the Academic Medical Centre (AMC) in Amsterdam and the local Medical Ethical Committees of every participating centre.

**Study design and randomisation**

The study was designed as a multi-centred randomised clinical trial in 28 hospitals in the Netherlands comparing the effectiveness of colonic stenting as a bridge to elective surgery with emergency surgery (standard treatment) during a follow-up period of 6 months. The trial was notified to the Current Controlled Trials register under ISRCTN46462267.\textsuperscript{20} Upon informed consent randomisation was performed centrally at the Academic Medical Centre using computer-generated lists prepared by the Department of Clinical Epidemiology and Biostatistics. Lists were constructed with randomly permuted blocks sized 4 or 6 per stratum, in which strata were defined by centre (participating hospital). Treatment was initiated within 24 hours of randomisation in both arms.

**Interventions**

Colonic stenting was performed by experienced therapeutic endoscopists, having a track record of at least 20 enteral stents, 10 of which being colonic stents. Before colonic stenting was attempted the distal colon was prepared with an enema. In case a standard colonoscope or sigmoidoscope could traverse the lesion or the lesion appeared to be
Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction

benign, stent placement was considered not to be indicated. Because of our intention-to-treat principle these patients were neither crossed over, nor excluded. In case of a significant, probably malignant obstruction a guide wire was passed through the stricture into the proximal colon under fluoroscopic control. Thereafter an uncovered metallic self-expandable stent, 6 or 9 cm long, with a diameter of 22 mm (Enteral Wallstent™ (Boston Scientific, Natick, MA)) was advanced over the guide wire and released. Stents were selected to be approximately 3 cm longer than the lesion (1.5 cm at both sides). Dilation of the obstructive lesion prior to stent placement was not allowed in order to minimise the risk of perforation. If the stent did not cover the entire length of the tumour, a second overlapping stent was placed. Correct positioning of the stent was confirmed by fluoroscopy and endoscopy. If stent placement failed or symptoms of colonic obstruction did not resolve within 3 days, patients were treated surgically, but remained in the stent arm for intention-to-treat analysis. The self-expandable stent served as definitive palliative therapy if any of the following conditions appeared in the diagnostic work-up: patients at high surgical risk because of persistent co-morbidity, advanced local disease and/or incurable metastatic disease. Candidates for elective surgery were operated according to the protocol preferably between day 5 and 14 after inclusion. Type and extent of surgery was at the discretion of the treating surgeon.

In the emergency surgery arm of the study, patients were operated according to conventional standards. Whether a loop colostomy, resection with primary anastomosis with or without ostomy, Hartmann’s procedure, (sub)total colectomy with ileostomy or ileorectal anastomosis was performed, was at the discretion of the treating surgeon. After emergency surgery further diagnostic work-up was performed. The colostomy served as a definitive solution if the patient refused re-operation, in case of incurable metastatic disease or when a re-operation was judged to carry an unacceptable risk (ASA class IV or V). In case of a primary colostomy, an attempt at restoration of bowel continuity was performed, preferably within 3-6 months after the initial intervention. After preoperative bowel preparation and administration of antibiotics, according to the individual hospital’s protocol, stoma closure was performed in accordance with conventional surgical standards.

**Outcomes measures and assessments during follow-up**

The primary outcome parameter was global health status according to the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (EORTC QLQ-C30). Secondary outcomes included mortality, morbidity, quality of life other than global health and stoma rate. Stoma rate was added to the secondary outcome parameters after publication of the protocol as it had been omitted in the initial protocol but nevertheless considered important. Mortality was assessed as procedure-related mortality within 30 days post-intervention and as overall mortality including
mortality during follow-up. For morbidity the definition of serious adverse event was used: any event leading to hospital admission or prolonging hospital stay. Complications were defined as all unwanted events, thus including morbidity and other adverse events that did not cause admission or prolonged hospital stay. Oncology-specific and colon cancer-specific quality of life aspects were assessed with respectively the EORTC QLQ-C30 and EORTC QLQ-CR38. Higher scores on the global health and functional scales indicate higher quality of life; higher scores on the symptom scales indicate lower quality of life. In addition, the EQ-5D visual analogue scale was used to assess patients’ self-evaluation of health status, with higher scores indicating a better health status. Finally, the EQ-5D health status scoring profiles over time were used to derive estimates of quality-adjusted survival. To this end, published health utility scoring algorithms based on time trade-off elicitation techniques for health status preferences in the general population were used to calculate the number of quality-adjusted life years (QALY). It was assumed that observed health states reflected the health states during the period in-between (the actual and preceding) measurements. Six months of follow-up in perfect health equalled 0.5 QALY.

Stoma rates were assessed after completion of the initial treatment (emergency surgery or colonic stent placement followed by surgery), at 30 days and at latest follow-up. Quality of life, morbidity, mortality and stoma rates following the two interventions were assessed until latest follow-up, either death (for exceptions: see below), withdrawal of informed consent or 6 months follow-up, whichever came first. During follow-up patients completed the quality of life questionnaires on weeks 4, 12, and 24 after inclusion. The questionnaires were sent to the patients by post. Collection was done by a research nurse. The research nurse contacted the patients by telephone every two weeks to assess complications, re-interventions, re-admissions, visits to the outpatient clinic and missing items of the collected quality of life questionnaires.

Sample size and statistical analysis

The sample size calculation was based on the EORTC QLQ-C30 global health status as the primary outcome parameter. Using a two-group t-test with a 0.05 two-sided significance level, 60 patients per arm (or a total of 120 patients) were needed to detect with 80% power an effect size of 0.5 on the EORTC QLQ-C30 global health scale. An effect size of 0.5 was chosen because a recent systematic review, based on 38 studies, indicated a "remarkable universality" among estimates of clinical significance that centred around 0.5 effect size. The authors recommend an effect size of 0.5 to serve as a default value for clinically significant change on quality of life measures used with chronic disease patients, when more specific information is missing, as is the case in patients with malignant colonic obstruction. Sloan et al. argue that a 0.5 effect size is even a conservative estimate that is likely to be clinically meaningful. Based on these data an effect size of 0.5 in the present group of patients seemed realistic. Analyses
were undertaken on an intention-to-treat basis. Quality of life scores during follow-up were averaged per patient, weighted by the length of the preceding period in-between measurements. Missing follow-up data were considered to be missing at random. Deceased patients were assigned EQ-5D VAS and health utility scores with value of zero until 6 months post intervention. Unless otherwise stated, differences in (weighted) quality of life scores between the emergency surgery and colonic stenting groups were assessed for statistical significance by analysis of covariance to adjust for baseline scores. Difference in procedure-related (30 days) mortality, overall mortality and stoma rates were assessed by the chi-square test. Differences in survival were assessed by the Kaplan Meier log rank test. All reported p-values are two-sided and considered significant if below 0.05. Analyses were performed with SPSS version 18.0 (SPSS, Chicago, Illinois).

A Data Safety Monitoring Committee (DSMC) safeguarded the patients in the trial regarding safety and effectiveness data. Every serious adverse event defined as an event leading to hospital admission or prolonging hospital stay (further addressed as morbidity) and mortality in the experimental arm (colonic stenting) was reported to the DSMC on short notice. An interim analysis was scheduled following the completion of 30 days of follow-up after treatment of the first 60 patients. No formal stopping rule was formulated beforehand.

Results

Enrollment and termination of the trial

Between March 2007 and February 2009, a total of 60 patients had been included. Before the planned interim analysis of these data had been completed, numerous morbidity and some mortality occurred in the colonic stenting arm in the next 30 patients leading to a request of the DSMC to finish the interim analysis of the first 60 patients promptly and prepare an additional analysis as soon as 90 patients had completed the first month of their follow-up. The 90th patient was included in July 2009. After finishing the interim reports, the study was put on hold at the suggestion of the DSMC in September 2009 when the first preliminary data suggested a higher morbidity in the colonic stenting arm. At the time of pausing the study a total of 98 patients had been included. An independent statistician together with the primary investigator analysed the data limited to 30 days of follow-up with regard to procedure-related and in-hospital mortality, complications (including morbidity), and overall morbidity. The causality of all events (mortality and complications) was graded definitely because they occurred within a follow-up of 30 days.

Neither the analysis after 60 patients nor the analysis after 90 patients revealed a significant difference with regard to in-hospital mortality nor 30 days mortality.
However, the number of patients with events graded as morbidity showed a persistent trend against the colonic stenting arm with an absolute risk increase of 0.19 (95% CI -0.06 to 0.4) in the first interim analysis of 60 patients (14/28 colonic stenting patients versus 10/32 emergency surgery patients) and 0.19 (95% CI -0.01 to 0.37) in the second interim analysis of 90 patients (23/47 colonic stenting patients versus 13/43 emergency surgery patients). In addition, when specifically looking at the subgroup of colonic stenting patients who underwent elective surgery a relatively high number of complications was observed. Fourteen out of 26 of these patients experienced one or more complications, 11 of them had at least one event graded as morbidity including 6 patients with anastomotic leakage.

Although the DSMC was well aware of the importance of a completed RCT, particularly because many consider colonic stenting as bridge to surgery the preferred therapy while high grade evidence is lacking, they felt obliged, after counselling an independent external expert, to advice stopping the trial definitely. The trial was officially terminated in March 2010; at that moment all 98 patients had reached an endpoint.

**Figure 1.** Trial profile.
Table 1. Demographic and clinical characteristics of patients at baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Emergency surgery N=51</th>
<th>Colonic stenting N=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean [SD])</td>
<td>71.4 (9.7)</td>
<td>70.4 (11.9)</td>
</tr>
<tr>
<td>Men/women</td>
<td>27/24</td>
<td>24/23</td>
</tr>
<tr>
<td>ASA classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>unknown, no. (%)</td>
<td>1 (2)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>1, no. (%)</td>
<td>17 (33.3)</td>
<td>16 (34)</td>
</tr>
<tr>
<td>2, no. (%)</td>
<td>27 (53)</td>
<td>24 (51.1)</td>
</tr>
<tr>
<td>3, no. (%)</td>
<td>6 (11.8)</td>
<td>6 (12.8)</td>
</tr>
<tr>
<td>Severity of obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown, no. (%)</td>
<td>1 (2)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Incomplete*, no. (%)</td>
<td>14 (27.5)</td>
<td>13 (27.7)</td>
</tr>
<tr>
<td>Complete*, no. (%)</td>
<td>36 (70.6)</td>
<td>33 (70.2)</td>
</tr>
</tbody>
</table>

*Demonstrated by clinical signs of ileus but able to pass flatus.
^Demonstrated by inability to pass flatus during the last 24 hours before inclusion.

Patient characteristics

Between March 2007 and September 2009 a total of 98 patients (median age ± SD 71 ± 10.8, 51 male) were included in 25 centres. The flow chart of the study is presented in figure 1 with 51 patients randomised to emergency surgery and 47 to colonic stenting. Two protocol violations occurred, one patient refused emergency surgery and one endoscopist refused endoscopy because of uncertainty about the malignant nature of the stricture. The patient that refused emergency surgery was treated with a colonic stent followed by uneventful elective surgery. The other patient, though randomised to colonic stenting, underwent emergency surgery which was complicated by three events, two of which were graded as morbidity, the pathology report revealed a malignant obstruction. The characteristics of the 98 patients included in the intention-to-treat analysis are presented in table 1.

Global health and disease-specific quality of life

Table 2 shows the cancer-specific quality of life results at baseline and follow-up for the emergency surgery and colonic stenting groups respectively. Overall global health and function scores at baseline were somewhat lower and symptoms scores were slightly higher in the colonic stenting group. Both groups however responded equally well to treatment without significant differences in follow-up scores after correction for baseline scores. Table 3 shows the colon cancer-specific results. Colonic stenting patients more
frequently reported stoma-related problems during follow-up compared to emergency surgery patients. No differences were noted for other colon cancer-specific dimensions after correction for baseline.

**Self-assessed health status, health utility and quality-adjusted life years**

Table 4 shows that emergency surgery and colonic stenting patients rated their health equally high after the intervention and both interventions generated about 0.3 QALY of the maximum attainable 0.5 during the follow-up period. For 18 patients, EQ-5D VAS and health utility scores with a value of zero were imputed after their death.
Mortality and morbidity

No differences in mortality and morbidity were observed between emergency surgery and colonic stenting. In each group, 5 patients died within 30 days of the intervention (Chi²=0.02, p=0.89) and 9 patients died during the full follow-up period (table 5). Patients in the emergency surgery and colonic stenting group on average survived at least 156 days (95% CI: 140–173) and 153 days (95% CI: 135–170) respectively, the difference being non-significant (log rank statistic=0.03, p=0.86).

During the follow-up period 23 out of 51 emergency surgery patients experienced a prolonged hospital stay or additional hospital admission at least once against 25 out of 47 patients in the colonic stenting group (Chi²=0.64, p=0.43).
Stoma rates
After the initial intervention 38 patients (74.5%) in the emergency surgery group and 24 patients (51.1%) in the colonic stenting group had a stoma (Chi2 5.8, p=0.016). Of these stomas respectively 12 and 7 were definitive. Anastomotic leakage led to one additional stoma in the emergency surgery group (n=39) and 5 additional stomata in the colonic stenting group (n=29) within 30 days after the initial intervention. During the further follow-up restoration of bowel continuity was achieved in 4 patients in the emergency surgery group and in 1 patient in the colonic stenting group. At latest follow-up respectively 35 patients (68.6%) versus 28 (59.6%) had still a stoma (Chi2 0.87, p=0.35).

Discussion
Over the years, a number of comparative non-randomised studies have reported that stoma rate, total hospital stay and stay on the intensive care unit were significantly shorter

<table>
<thead>
<tr>
<th>EORTC QLQ-CR38 dimension</th>
<th>Emergency Surgery (ES)</th>
<th>Colonic Stenting (CS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (SD) (Nmax*40)</td>
<td>Follow-up (SD) (Nmax=44)</td>
</tr>
<tr>
<td>Functional scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodily image</td>
<td>73.0 (30.8)</td>
<td>74.6 (24.8)</td>
</tr>
<tr>
<td>Future perspective</td>
<td>41.9 (34.8)</td>
<td>59.4 (27.9)</td>
</tr>
<tr>
<td>Sexual functioning</td>
<td>12.0 (20.8)</td>
<td>10.6 (15.8)</td>
</tr>
<tr>
<td>Sexual enjoyment*</td>
<td>36.7 (36.7)</td>
<td>28.8 (31.6)</td>
</tr>
<tr>
<td>Symptom scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micturition problems</td>
<td>22.5 (20.8)</td>
<td>27.1 (14.0)</td>
</tr>
<tr>
<td>Chemotherapy side-effects</td>
<td>35.3 (20.8)</td>
<td>25.2 (19.4)</td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>40.9 (20.1)</td>
<td>15.7 (13.4)</td>
</tr>
<tr>
<td>Male sexual functioning</td>
<td>34.4 (42.5)</td>
<td>40.7 (36.3)</td>
</tr>
<tr>
<td>Female sexual functioning**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defaecation problems*</td>
<td>22.7 (15.6)</td>
<td>9.2 (6.4)</td>
</tr>
<tr>
<td>Stoma-related problems</td>
<td>-</td>
<td>28.6 (19.6)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>37.6 (35.2)</td>
<td>25.0 (22.6)</td>
</tr>
</tbody>
</table>
in patients treated with a colonic stent as bridge to surgery. In addition several non-comparative series on colonic stenting revealed high technical and clinical success rates as well as acceptable morbidity and very low mortality rates. This was reason to perform this randomised clinical trial. Although we expected and even hoped to confirm these data, our results appeared to be different. Our study had to be terminated early because of patient safety concerns. The DSMC concluded that a persistent trend existed towards an increased morbidity in the group of patients randomised to colonic stenting in the 30 days follow-up after inclusion. This trend could however not be confirmed for the total follow-up period of 6 months of the 98 patients finally included. In the end our multi-centred trial revealed no benefits with regard to mortality, morbidity, quality of life and stoma rates for neither colonic stenting nor emergency surgery in patients with acute left-sided malignant colonic obstruction.

We might have selected a population at a higher risk for complications than the non-randomised studies published previously. In our series 70% of the patients presented...
with a complete obstruction which is high in comparison to the existing literature.\textsuperscript{29} Patients with a total obstruction are probably more difficult to stent, might be less easily decompressed and could still be in a marginal condition when going to surgery, resulting in a relatively high leak rate if resection without a stoma is attempted. In a recently published retrospective study from a renowned tertiary referral centre, complete obstruction was identified as a risk factor for complications.\textsuperscript{29}

Our findings could in part also result from our meticulous survey of complications with telephone calls every 2 weeks during a 6 months period and a strict definition of morbidity. We included not only the complications of the initial intervention, colonic stenting combined with elective surgery or emergency surgery, but also the complications that occurred because of restoration of bowel continuity and all events that led to readmission within 6 months follow-up. The fact that most published studies

<table>
<thead>
<tr>
<th>EQ-SD</th>
<th>Baseline (SD) (Nmax*=45)</th>
<th>Follow-up (SD) (N=50)</th>
<th>Baseline (SD) (Nmax=41)</th>
<th>Follow-up (SD) (Nmax=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual analogue scale</td>
<td>35.8 (24.8)</td>
<td>52.4 (27.7)</td>
<td>36.6 (21.2)</td>
<td>52.7 (30.5)</td>
</tr>
<tr>
<td>Health utility/quality adjusted life-years**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK preferences</td>
<td>0.41 (0.43)</td>
<td>0.30 (0.17)</td>
<td>0.18 (0.42)</td>
<td>0.28 (0.20)</td>
</tr>
<tr>
<td>NL preferences</td>
<td>0.48 (0.37)</td>
<td>0.32 (0.17)</td>
<td>0.31 (0.35)</td>
<td>0.29 (0.19)</td>
</tr>
</tbody>
</table>

Table 4. Differences between emergency surgery and colonic stenting for health status during follow-up, based on available data and corrected for differences at baseline.

<table>
<thead>
<tr>
<th>Outcome parameter</th>
<th>Emergency surgery N=51</th>
<th>Colonic stenting N=47</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days mortality, no. (%)</td>
<td>5 (9.8)</td>
<td>5 (10.6)</td>
<td>0.89</td>
</tr>
<tr>
<td>Overall mortality, no. (%)</td>
<td>9 (17.6)</td>
<td>9 (19.1)</td>
<td>0.84</td>
</tr>
<tr>
<td>Morbidity, no. (%)</td>
<td>23 (45.1)</td>
<td>25 (53.2)</td>
<td>0.43</td>
</tr>
<tr>
<td>Stoma rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Directly after initial intervention, no. (%)</td>
<td>38 (74.5)</td>
<td>24 (51.1)</td>
<td>0.016</td>
</tr>
<tr>
<td>At latest follow-up, no. (%)</td>
<td>35 (68.6)</td>
<td>28 (59.6)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Table 5. Secondary outcome parameters.
had a less strict follow-up will probably explain an underestimation of the morbidity in the previous studies.

Especially with regard to colonic stenting as bridge to surgery the existing data focus on technical success, clinical success, stent procedure-related (placement of the stent) and stent-related (presence of the stent in the colon) complications. Our technical success rate of colonic stent placement was rather low (70%; 33 of 47) compared to the literature. Though we did request a certain experience with regard to stent placement in 8 out of 47 patients (17%) a guide wire could not be passed along the colonic stricture. This while all these endoscopists were experienced in pancreaticobiliary endoscopy, who are according to the literature more proficient colonic stenters.

Our relative high number of patients with a complete obstruction might have played a role: it is well recognized that stent placement in patients who present with a complete obstruction is a relatively difficult procedure. One could plead for restriction of the numbers of centres or endoscopists executing this procedure but this might lead to challenging logistic consequences. None of the patients that did receive a colonic stent had to be operated because the symptoms of colonic obstruction did not resolve, leading to a clinical success of 70% which is in accordance with the literature.

With regard to the stent procedure-related and stent-related complications the literature reveals a complication rate varying between 5% and 23.1%, of which on average 5% stent-related perforations. In our population procedure-related or stent-related complications occurred in 6 patients (12.8%): in 2 patients a guide wire perforation was made in an attempt to traverse the stricture, in 4 patients (8.5%) the stent led to a

---

<table>
<thead>
<tr>
<th>Corrected follow-up difference</th>
<th>Difference (95% LCL;UCL)^</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Nmax=45 ES / 39 CS)</td>
<td></td>
</tr>
<tr>
<td>-3.8 (-16.2; 8.6)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>-0.03 (-0.11; 0.05)</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>-0.04 (-0.11; 0.04)</td>
<td>0.35</td>
<td></td>
</tr>
</tbody>
</table>

* Number of patients with available (i) baseline, (ii) follow-up and (iii) baseline and follow-up data ranges from 43 to 45, 50 to 50, and 43 to 45 in the emergency surgery group and from 41 to 41, 44 to 44, and 39 to 39 in the colonic stenting group, respectively.

** Baseline data represent health utility values at the time of measurement. Follow-up data represent the number of quality adjusted life-years during the first half-year post-intervention while assuming that a patient’s health status at the time of measurement represents the health status in-between the actual measurement and the preceding one or baseline, whichever is appropriate. Applied scoring algorithms were available from the literature and were derived from time trade-off based elicitation techniques of health state preferences from the general public of the United Kingdom (UK) or, alternatively, the Netherlands (NL). See also Methods section.

^ Difference ES follow-up minus CS follow-up based on estimated marginal means with baseline EQ-SD VAS or baseline health utility as covariate; LCL: lower confidence limit; UCL: upper confidence limit.
perforation after 1, 7, 14 and 17 days respectively. Three of these perforations must be considered stent-related rather than procedure-related as they occurred a week or more after the stent placement. In addition 3 out of 26 colonic specimens retrieved showed signs of silent colonic perforation by the prosthesis. This leads to a total percentage of perforations of almost 20% of our patients. The problem of silent perforations has recently been underlined in another study thus far only published as abstract. They found 2 stent perforations and 8 silent perforations in 30 patients randomised to colonic stent as bridge to surgery.\textsuperscript{31;32} The oncological consequences of potential tumour dissemination caused by these silent perforations are unclear but the phenomenon is worrying and we feel strongly that these silent perforations cannot be disregarded.\textsuperscript{32} A hint of the influence of dissemination could potentially be derived from survival data. These data are however inconsistent, ranging from no difference between the treatment modalities to a significantly lower 5 year survival rate for patients treated with colonic stenting before elective surgery, all in non-randomised studies.\textsuperscript{6;33}

Another outcome parameter often used in the existing literature is the number of ostomies.\textsuperscript{4;5;14} These studies revealed a significantly lower ostomy rate in the colonic stenting group.\textsuperscript{4;5;14} Also our study revealed a significantly lower ostomy rate in the colonic stenting group after the primary intervention. However at the end of the six months follow-up the number of ostomies did not differ between the groups. Anastomotic leakage led to extra stoma creation in five patients from the colonic stenting group versus one in the emergency surgery group. Additionally a higher closure rate was achieved in the emergency group. Patients in the emergency surgery group did report significant less problems with their ostomies than the patients of the colonic stenting group. Disappointment of still having a stoma while being treated with a modality which was predicted to reduce the chance of stoma creation might explain this.

Our study obviously has some shortcomings; among these is the large number of participating hospitals, 25 hospitals out of the 28 hospitals actively included patients ranging from 1 to 17 patients. When designing the study we considered limited inclusion and endoscopic treatment to tertiary referral centres but this would introduce bias to the real life situation. This bias could be one of the reasons for the better results in the non-randomised studies. In addition patient accrual would be severely hampered and this kind of study can only be done with a large network of participating hospitals. Next to the study design also the execution of the study had its shortcomings. In the emergency surgery group all but one of the patients received the allocated treatment. In the colonic stenting group however several patients appeared not to have an indication for stent placement (6 patients): figure 1 depicts the exact reasons. In 4 patients (9%) stent placement was not performed because of an endoscopically benign appearing stricture. While designing this study we were well aware of this possibility and its potential influence on our intention-to-treat analysis but we found it unethical to perform
a diagnostic endoscopy before inclusion and only after confirmation of malignancy randomise the patient to either study arm. Our study also had some methodological limitations which might have influenced our results. First, we included the coloncancer-specific EORTC QLQ-CR38 questionnaire validated for the Netherlands after consultation of the EORTC. At the time of analysis however, the alternative EORTC QLQ-CR29 version had become more popular for its superiority in comparing patients with and without stoma. Because the two questionnaires overlap only partially one should be cautious when comparing the results of table 3 with results from other studies based on the EORTC QLQ-CR29. Second, the study protocol foresaw the application of the extended Q-TWIST method to the quality of life data in order to estimate differences in quality-adjusted survival between groups.\textsuperscript{20} However, with only 18 deceased patients, 10 of whom died before the first follow-up, insufficient data were available to perform the analysis as planned. Instead, an alternative method with similar information yield has been applied by deriving quality-adjusted life years after imputation of scores representing the state of death (i.e. health utility equals zero) in case patients died before the next measurement(s). Third, a cost-effectiveness analysis was planned alongside this randomised trial. Considering the advice by the DSMC however, we decided to refrain from judgement on the economic viability of colonic stenting when safety was possibly at stake. Fourth, though our trial was terminated early implying a loss of patients and hence, loss of statistical power, the very similar responses to treatment in both groups in terms of disease-specific and generic quality of life, mortality, morbidity and stoma rates suggest that the probability of colonic stenting becoming more effective than emergency surgery is negligible.

How should our outcomes be dealt with? As long as there are no other randomised trials either confirming or refuting our findings, we feel that colonic stenting as bridge to elective surgery should only be performed in randomised controlled settings with a stringent follow-up focussing on specific groups of patients who might benefit from either one of the treatment modalities, like recently initiated by Small et all.\textsuperscript{29} In addition we should be very keen on acquiring more information on (micro-)perforations and their possible consequences on the prognosis of patients.

At the moment we can only state that this first randomised controlled trial did not reveal any advantage with regard to quality of life, mortality, morbidity or stoma rates of colonic stenting as bridge to surgery in patients with left-sided colonic obstruction and can therefore not replace emergency surgery as standard treatment. Oncologic concerns of overt and silent perforations of stenting cannot be disregarded, particularly since no clear benefits of stenting as bridge to surgery could be shown.
Collaborative Dutch Stent-In study group

Centres (numbers of patients), departments, and investigators

**Academic Medical Centre, Amsterdam** (n=17): Department of Gastroenterology and Hepatology: J E van Hooft, P Fockens; Department of Surgery: W A Bemelman; Clinical Research Unit: M G Dijkgraaf; Department of Medical Psychology: M A Sprangers.

**Medical Centre Haaglanden, Den Haag** (n=12): Department of Surgery: A W Marinelli; Department of Gastroenterology: L Perk. 

**Medisch Spectrum Twente, Enschede** (n=9): Department of Gastroenterology: J E van Hooft; Department of Surgery: M Lutke Holzik.

**St Elisabeth Hospital, Tilburg** (n=5): Department of Gastroenterology: M J Grubben; Department of Surgery: J Heisterkamp. 

**Catharina Hospital, Eindhoven** (n=4): Department of Gastroenterology: L P Gilissen; Department of Surgery: G A Nieuwenhuizen. 

**Martini Hospital, Groningen** (n=4): Department of Gastroenterology: L A van der Waaij; Department of Surgery: P C Baas. 

**Onze Lieve Vrouwe Gasthuis, Amsterdam** (n=4): Department of Gastroenterology: J M Jansen; Department of Surgery: M F Gerhards.

**St Antonius Hospital, Nieuwegein** (n=4): Department of Gastroenterology: R Timmer; Department of Surgery: B van Ramshorst. 

**University Medical Centre, Utrecht** (n=4): Department of Gastroenterology: B Oldenburg; Department of Surgery: R van Hilligersberg.

**Atrium Hospital, Heerlen** (n=3): Department of Gastroenterology: C M Bakker; Department of Surgery: M Sosef. 

**Gelderse Vallei Hospital, Ede** (n=3): Department of Gastroenterology: P Witteman; Department of Surgery: Ph Kruyt.

**Groene Hart Hospital, Gouda** (n=3): Department of Gastroenterology: W R ten Hove; Department of Surgery: L N Tseng.

**Medical Centre Leeuwarden, Leeuwarden** (n=3): Department of Gastroenterology: K van der Linde; Department of Surgery: S A Koopal.

**Slotervaart Hospital, Amsterdam** (n=3): Department of Gastroenterology: A C Depla; Department of Surgery: E Derksen.

**TerGooi Hospitals, Hilversum** (n=3): Department of Gastroenterology: A H Naber; Department of Surgery: A A van Geloven. 

**Diaconessenhuis, Utrecht** (n=2): Department of Gastroenterology: R Breumelhof; Department of Surgery: P H Davids.

**Gelre Hospitals, Apeldoorn** (n=2): Department of Gastroenterology: H Akol; Department of Surgery: E van der Zaag. 

**Isala Hospitals, Zwolle** (n=2): Department of Gastroenterology: E Schenk; Department of Surgery: G A Patijn. 

**Leiden University Medical Centre, Leiden** (n=2): Department of Gastroenterology: R A Veenendaal; Department of Surgery: R A Tollenaar. 

**Rode Kruis Hospital, Beverwijk** (n=2): Department of Gastroenterology: A. van Berkel; Department of Surgery: H Cense. 

**St Lucas Andreas Hospital, Amsterdam** (n=2): Department of Gastroenterology: P Scholten; Department of Surgery: B van Wagensveld. 

**University Medical Centre Groningen, Groningen** (n=2): Department of Gastroenterology: J J Koornstra; Department of Surgery: K Havenga. 

**Amphia Hospital, Breda** (n=1): Department of Gastroenterology: M van Milligen de Wit; Department of Surgery: A M Rijken. 

**Bronovo Hospital, Den Haag** (n=1): Department of Gastroenterology: M Cazemier; Department of Surgery: O R Guicherit. 

**Haga Hospitals, Den Haag** (n=1): Department of Gastroenterology: M H Houben; Department of Surgery: W H Steup.
Reference List


Chapter 10

Summary and future perspective
Summary and future perspective

In this thesis we focused our research on new treatment modalities for gastrointestinal strictures. Some research projects took place very early in the development of a technique and addressed primarily safety and feasibility. Other research projects concerned prospective cohort studies investigating on new materials in an established technique and prospective randomized studies designed to incorporate the technique in an evidence-based treatment algorithm.

Chapter 2 describes a feasibility cohort study for the treatment of benign postsurgical esophagogastric anastomotic strictures. These strictures are a cumbersome complication requiring repetitive endoscopic intervention before remission can be achieved. The efficacy and safety of a biodegradable uncovered expandable stent was studied in 10 patients with dysphagia caused by such a benign postsurgical esophagogastric anastomotic stricture. In 6 out of the 10 patients the biodegradable stent proved an effective single-step treatment modality during 6 months of follow-up. Although we were concerned that the large diameter of the stent and its position high in the proximal esophagus might be uncomfortable to the patients, it appeared that the stent was well tolerated. The main adverse event was tissue hyperplasia, which was the primary reason for re-intervention. Placement of a biodegradable stent is a promising technique, however randomized studies comparing the new technique with the current gold standard have to be conducted to determine its position in the treatment algorithm for benign cervical anastomotic strictures. The reason to perform the study mentioned above actually arose due to the results of a study for the same clinical problem, described in chapter 3. In this prospective, randomized, multicenter study, the efficacy and safety of dilation by Savary bougienage was compared with electrocautery incision of the stricture. Sixty-two patients were included and followed for 6 months. A significant difference between electrocautery incision and Savary bougienage with respect to the mean number of treatment procedures and success rate was absent. Both treatments were similar with regard to safety: no patients from either group suffered complications. While considered very promising in uncontrolled studies, electrocautery incision appeared not to decrease the number of interventions, which is considered the most important disadvantage of the current gold standard: Savary bougies dilation.

Future perspectives for the treatment of benign postsurgical esophagogastric anastomotic strictures might come from combining the gold standard with another technique such as intralesional triamcinolon injections. This is currently investigated in a multicenter randomized trial. It seems likely however, that it will not diminish the mean number of interventions from seven to one or two per patient. Therefore further studies with the biodegradable stent as studied in chapter 2 have to be initiated. One could also consider to focus on prevention because risk factors that contribute to the development
of benign anastomotic strictures are known. Most risk factors cannot be prevented but postoperative anastomotic leakage probably could. It is therefore even conceivable that one day, every patient undergoing an esophagectomy will receive a fully covered biodegradable stent at the end of the surgical procedure.

Malignant gastric outlet obstruction is one of the late complications of a variety of cancers in the upper GI-tract. It causes nausea and vomiting and influences the patients’ ability to eat. In chapter 4 we investigated a new enteral stent, made of nitinol, for palliation of this complication. In a multicenter retrospective fashion the short-term (30 days) clinical success and complication rate of 62 patients were assessed. The results showed a clinical success rate of 85% on intention-to-treat basis, a significant improvement of the patients’ ability to eat and return to oral intake, on average, 1 day after stent placement. Severe complications appeared in 11% of patients; in our opinion most complications were not directly related to the stent design but rather to the patients’ poor condition and susceptibility to severe infections. We therefore concluded that the new stent appears to be effective and relatively safe. We felt encouraged and subsequently conducted a prospective multicenter cohort study to further investigate its influence on patients’ ability to eat, efficacy, safety and global quality of life (chapter 5). Fifty-one consecutive patients with symptomatic malignant gastric outlet obstruction were included and followed until death. The effect on patients’ ability to eat, the rapid resumption of oral intake and the high clinical success rate were confirmed. Another important finding was the large difference between median stent patency (307 days) and median survival (62 days), suggesting that for most patients adequate resolution of the gastric outlet obstruction was achieved until death with this new stent. Unfortunately, the improved ability to pass food could not prevent deterioration of the patients’ general condition, neither did it improve the patients’ quality of life. Given the study design, we cannot tell how the general condition and the global quality of life would have developed without enteral stent placement, but presumably, patients might have deteriorated even faster.

In chapter 6 results are reported from an observational study on 105 consecutive patients with symptomatic gastric outlet obstruction who were treated with duodenal stent placement. In this group univariate and multivariate analyses of baseline data were performed to search for independent prognostic factors for survival. Clear predictors of poor outcome could be demonstrated. These findings might help patients and physicians in better deciding on a tailored palliative treatment.

A recently published randomized controlled study of endoscopic enteral stenting and surgical gastrojejunostomy revealed that despite slower initial symptom improvement the gastrojejunostomy was associated with better long-term results. Building on these results we investigated a new technique to construct an endoscopic gastrojejunostomy. This would potentially combine the rapid effect of duodenal stent placement with the long-term efficacy of a surgical gastrojejunostomy. In a prospective, multicenter cohort
study (chapter 7) the safety and success rate of endoscopic creation of a gastroenteric anastomosis formed by magnetic compression and maintained by stent placement were investigated. The endoscopic creation of a gastroenteric anastomosis by magnetic compression appeared to be feasible and safe. However, the stent needed to keep the anastomosis open led to morbidity and even mortality. Therefore, the current system cannot be recommended for clinical use.

**Future perspectives:** enteral stenting for the treatment of malignant gastric outlet obstruction appears to be safe and effective in the majority of patients, although for patients with a long survival a gastrojejunostomy might be more appropriate as it leads to less re-interventions. A technique that would combine the safety and rapid effect of duodenal stent placement with the long-term efficacy of a surgical gastrojejunostomy warrants further elaboration. At this point we should probably widen our horizon and have a closer look at the recently developed minimal invasive treatment options for obesity, as the technique of bypassing a part of the intestine is often applied during these treatments.

In chapters 8a and 8b results are reported of a randomized clinical trial investigating whether a nonsurgical policy with endoluminal stenting is superior to surgical treatment in patients with stage IV left-sided colorectal cancer and imminent obstruction. In this study a surprisingly high number of perforations in the nonsurgical arm was found. Because we were not able to exclude a relation with the applied newly designed enteral stent and the clear advantage of surgical treatment, the trial was prematurely terminated. At termination 10 patients had been allocated to the surgical and 11 patients to the nonsurgical arm and one versus eleven adverse events occurred respectively, including six perforations. It can not be excluded that the use of concomitant chemotherapy also played a role in the unexpected findings.

In chapter 9 the results of a randomized comparison of colonic stenting as bridge to elective surgery versus emergency surgery in patients with acute obstructive colorectal cancer are described. This study was also terminated early because of patient safety concerns. The Data Safety Monitoring Committee concluded that a persistent trend existed towards an increased morbidity in the group of patients randomized to colonic stenting in the 30 days of follow-up after intervention. This trend could however not be confirmed for the complete follow-up period of 6 months of the included 98 patients. Final analysis of this multicenter trial revealed no benefits with regard to mortality, morbidity, quality of life and stoma rates for colonic stenting relative to emergency surgery in patients with acute left-sided malignant colonic obstruction. Because of a lack of evidence we should refrain from replacing emergency surgery as standard treatment by colonic stent as bridge to surgery.

**Future perspectives:** concerning the treatment of malignant colonic obstruction, one should obviously focus on obtaining grade A evidence for stenting. The temptation
to implement colonic stenting as the therapy of choice should be resisted as long as there is no grade A evidence. Properly executed randomized controlled trials should be performed before guidelines can be adapted. We may have to return to the main reason that stenting was attempted in patients with malignant obstruction of the left-sided colon. Do emergency operations, involving an unprepared and obstructed bowel, still have a high risk of mortality and morbidity as was previously the case? And if so, are there specific groups of patients particularly vulnerable under emergency conditions? Investigations focussed on these groups might give new insights.

This thesis tried to provide answers to relatively common problems in therapeutic endoscopy. The results of the different studies were at times surprising and confronting. We will need additional evidence through well-designed studies to establish evidence-based endoscopic therapy for gastrointestinal strictures.
Chapter 11

Samenvatting en toekomstperspectief
Samenvatting en toekomstperspectief

Het in dit proefschrift beschreven onderzoek richt zich op nieuwe behandelmogelijkheden van gastro-intestinale stricturen. Enkele onderzoeksprojecten vonden plaats tijdens de ontwikkelingsfase van een techniek waarbij met name gekeken werd naar veiligheid en haalbaarheid. Andere onderzoeksprojecten betroffen prospectieve studies waarbij nieuw materiaal gebruikt werd bij een reeds geaccepteerde behandeling én prospectieve gerandomiseerde studies om technieken op te kunnen nemen in een evidence-based algoritme.

Hoofdstuk 2 beschrijft een cohortstudie naar de haalbaarheid van behandeling van benigne postoperatieve oesophagogastrische anastomotische stricturen. Deze vernauwingen vormen een hinderlijke complicatie die herhaalde endoscopische interventies vereist voordat er een remissie is. De effectiviteit en veiligheid van een biologisch afbreekbare stent werden bestudeerd bij 10 patiënten met dysphagie die werd veroorzaakt door zo’n benigne postoperatieve oesophagogastrische anastomotische structuur. Bij 6 van de 10 patiënten bewees de plaatsing van een biologisch afbreekbare stent een effectieve één-staps behandelwijze te zijn bij een follow-up van 6 maanden. Hoewel we bang waren dat de grote diameter van de stent en de positie hoog in de proximale oesophagus oncomfortabel zou kunnen zijn voor de patiënten, bleek de stent goed verdragen te worden. De belangrijkste complicatie was weefselhyperplasie; dit was de hoofddreden voor hernieuwde dilatatie. Plaatsing van een biologisch afbreekbare stent is een veelbelovende techniek, maar gerandomiseerde studies waarbij de nieuwe techniek vergeleken wordt met de huidige gouden standaard moeten nog uitgevoerd worden om de plaats in het behandelalgoritme voor benigne cervicale anastomose nader te kunnen bepalen.

De stimulans om de eerder genoemde studie uit te voeren kwam voort uit onderzoeksresultaten van een studie naar hetzelfde klinische probleem, beschreven in hoofdstuk 3. In deze prospectief gerandomiseerde multicentrische studie werd Savary bougie dilatatie op effectiviteit en veiligheid vergeleken met incisie door electrocauterisatie als behandeling van een structuur. Tweeënzestig patiënten werden geïncludeerd en gevolgd gedurende 6 maanden. Er bleek geen significant verschil te zijn tussen electrocauterisatie incisie en Savary bougie dilatatie met betrekking tot het gemiddeld aantal behandelprocedures en het succespercentage. Beide behandelingen bleken even veilig; geen van beide leidde tot een complicatie.

Hoewel beschouwd als veelbelovend in ongecontroleerde studies bleek electrocauterisatie incisie niet het aantal interventies te verlagen, terwijl dit als grootste nadeel van de huidige standaard, Savary bougie dilatatie, wordt gezien.
Toekomstperspectieven voor de behandeling van benigne postoperatieve oesophageogastrische anastomotische stricken zouden kunnen komen van het combineren van de gouden standaard met een andere techniek zoals intra-oesophageale triamcinolon injecties. Dit wordt momenteel onderzocht in een gerandomiseerde multicentrische studie. Het is echter niet aannemelijk dat dit het gemiddelde aantal interventies zal doen afnemen van zeven tot één à twee per patiënt. Daarvoor moeten aanvullende studies met de biologisch afbreekbare stent, zoals beschreven in hoofdstuk 2, geïnitieerd worden. Men zou ook kunnen overwegen om zich meer te richten op preventie aangezien de risicofactoren die bijdragen aan het ontstaan van een benigne anastomotische stricuur bekend zijn. De meeste van deze factoren kunnen niet voorkomen worden, maar postoperatieve anastomotische lekkage misschien wel. Het is daarom aannemelijk dat op een gegeven moment alle patiënten die een oesophagus-resectie ondergaan, een volledig beklede biologisch afbreekbare stent geplaatst krijgen aan het eind van de chirurgische procedure.

Maligne maaguitgangstenose kan een late complicatie zijn van een variëteit aan maligniteiten in het bovenste deel van de tractus digestivus. Het veroorzaakt misselijkheid en braken en beïnvloedt de mogelijkheid van de patiënt om te eten. In hoofdstuk 4 onderzochten we een nieuwe enterale stent, gemaakt van nitinol, voor de palliatie van deze complicatie. Met een multicentrische retrospectieve studie werden korte termijn (30 dagen) klinisch succes en het aantal complicaties van 62 patiënten in kaart gebracht. De resultaten toonden op basis van intentie tot behandelen een klinisch succespercentage van 85% aan, een significante verbetering van de mogelijkheid van de patiënt om te eten en bovendien was orale belasting gemiddeld 1 dag na stentplaatsing weer mogelijk. Ernstige complicaties traden op bij 11% van de patiënten; de meeste complicaties waren naar ons idee niet direct gerelateerd aan de stentplaatsing, maar eerder aan de slechte conditie van de patiënten waardoor ze vatbaar waren voor ernstige infecties. Daarom concludeerden wij dat de nieuwe stent effectief en relatief veilig is. Deze resultaten stimuleerden ons om aansluitend een prospectieve multicentrische cohortstudie op te zetten om nader onderzoek te doen naar de invloed op de mogelijkheid van de patiënten om te eten, effectiviteit, veiligheid en algemene kwaliteit van leven (hoofdstuk 5).

Eenenvijftig opeenvolgende patiënten met symptomen passend bij een maligne maaguitgangstenose werden geïncludeerd en vervolgd tot aan het overlijden. Het effect op de mogelijkheid van de patiënt om te eten, de snelle hervatting van orale belasting en een hoog klinisch effectpercentage werden ook nu gevonden. Een andere belangrijke bevinding was het grote verschil tussen de mediane duur van de stentfunctie (307 dagen) en de mediane overleving (62 dagen). Dit suggereert dat een adequate oplossing voor de maaguitgangstenose werd bereikt bij de meerderheid van de patiënten tot aan het overlijden. Helaas kon deze verbeterde mogelijkheid om voedsel te laten passeren verslechtering van de algemene conditie van de patiënten niet voorkomen,
noch verbeterde het de kwaliteit van leven. De gebruikte studiemethode maakt het niet mogelijk om een uitspraak te doen over de ontwikkeling van de algemene conditie en de globale kwaliteit van leven als er geen entereal stent geplaatst zou zijn, maar het is aannemelijk dat patiënten dan nog sneller achteruit zouden zijn gegaan.

In hoofdstuk 6 worden resultaten van een observationele studie met 105 opeenvolgende patiënten beschreven. Deze patiënten hadden symptomen passend bij een maaguitgangstenose waarvoor ze behandeld waren met een duodenale stent. Binnen deze groep werden univariate en multivariate analyses van baseline gegevens uitgevoerd om onafhankelijke prognostische factoren voor overleving te kunnen detecteren. Duidelijke voorspellers van een slechte uitkomst konden worden geïdentificeerd. Deze bevindingen zouden patiënten en artsen kunnen helpen bij het bepalen van een voor een individu zo optimaal mogelijke palliatieve behandeling.

Een recent gepubliceerde gerandomiseerde studie waarbij entereal stentplaatsing werd vergeleken met een chirurgisch aangelegde gastrojejunostomie liet zien dat ondanks langzame initiële symptoomverbetering de conventionele gastrojejunostomie geassocieerd was met betere resultaten op de lange termijn. Voortbordurend op deze resultaten onderzochten wij een nieuwe techniek om een endoscopische gastrojejunostomie aan te kunnen leggen. Deze zou in potentie het snelle effect van duodenale stentplaatsing met de effectiviteit op lange termijn van een chirurgische gastrojejunostomie kunnen combineren. In een prospectieve multicentrische cohortstudie (hoofdstuk 7) onderzochten we de veiligheid en het succespercentage van een endoscopisch aangelegde gastro-enterale anastomose. Deze anastomose werd gevormd door magnetische compressie en opengehouden door vervolgens een stent in de anastomose te plaatsen. Het endoscopisch aanleggen van een gastro-enterale anastomose door magnetische compressie bleek haalbaar en veilig te zijn. De noodzaak van een stent om de anastomose open te houden leidde echter tot ernstige morbiditeit en zelfs mortaliteit.

Het huidige systeem kan daarom niet aanbevolen worden voor klinische toepassing.

Toekomstperspectieven: entereal stentplaatsing voor de behandeling van maligne maaguitgangstenose blijkt veilig en effectief in de meerderheid van de patiënten te zijn, hoewel voor patiënten met een lange overleving een gastrojejunostomie beter zou kunnen zijn vanwege vermindering van het aantal interventies. Een techniek die de veiligheid en het snelle effect van duodenale stentplaatsing combineert met de effectiviteit op lange termijn van een chirurgische gastrojejunostomie dient verder onderzocht te worden. Hiervoor moeten we misschien onze horizon verruimen en de recente ontwikkelingen binnen de minimaal invasieve behandelingen voor obesitas nauwkeurig bestuderen, omdat daarbij frequent maag-dunnedarm bypasses aangelegd worden.

In hoofdstukken 8a en 8b wordt een gerandomiseerde klinische trial beschreven die als doel had om vast te stellen of een niet-chirurgisch beleid, met entereale stenting, superieur
is ten opzichte van chirurgische behandeling bij patiënten met een stadium IV linkszijdige colorectale maligniteit en dreigende obstructie. In deze studie deed zich een onverwacht hoog aantal perforaties in de niet-chirurgische arm voor. Omdat we een relatie met de nieuw gebruikte enterale stent niet konden uitsluiten en er een duidelijk voordeel was van de chirurgische behandeling, werd de trial voortijdig gestopt. Op het moment van sluiten waren 10 patiënten gerandomiseerd voor de chirurgische arm en 11 patiënten voor de niet-chirurgische arm. Er deden zich respectievelijk één versus 11 bijwerkingen voor, inclusief 6 perforaties. Het is niet uit te sluiten dat de gelijktijdige toepassing van chemotherapie ook een rol heeft gespeeld bij de onverwachte bevindingen.

In hoofdstuk 9 worden de resultaten van een gerandomiseerde vergelijking van colonstenting als overbrugging naar electieve chirurgie versus spoedchirurgie bij patiënten met een acute obstructieve colorectale maligniteit beschreven. Deze studie moest ook vroegtijdig gestaakt worden vanwege bezorgdheid over patiëntenveiligheid. De “Data Safety Monitoring Committee” concludeerde dat er een persisterende trend richting een toegenomen morbiditeit binnen 30 dagen na interventie was in de groep patiënten die gerandomiseerd was voor stentplaatsing in het colon. Deze trend kon echter niet bevestigd worden met data van de totale follow-up periode van 6 maanden van de 98 geïncludeerde patiënten. Uiteindelijk toonde de multicentrische trial geen voordeel betreffende mortaliteit, morbiditeit, kwaliteit van leven en stoma aantallen voor noch colonstentplaatsing noch spoedchirurgie bij patiënten met acute linkszijdige maligne colonobstructie. Wegens gebrek aan bewijs zouden we moeten afzien van het vervangen van spoedchirurgie als standaardbehandeling door een colonstent als overbrugging naar operatie.

Toekomstperspectieven: betreffende de behandeling van maligne colonobstructie zou men zich duidelijk moeten concentreren op het verkrijgen van graad A bewijs voor stentplaatsing. De verleiding om stentplaatsing in het colon te implementeren als de voorkeursbehandeling moet weerstaan worden zolang er geen graad A bewijs is. Correct uitgevoerde gerandomiseerde studies zijn nodig alvorens men de richtlijnen kan aanpassen. Misschien moeten we terug gaan naar de reden waarom stentplaatsing ingang heeft gevonden bij de behandeling van maligne obstructie in het linkszijdige colon. Hebben spoedoperaties, bij een onvoorbereid en geobstrueerd colon, nog steeds zo’n hoge mortaliteit en morbiditeit als vroeger? En als dat zo is, zijn er dan specifieke groepen patiënten die extra kwetsbaar zijn onder spoedeisende omstandigheden? Onderzoek gericht op deze groep zou tot nieuwe inzichten kunnen leiden.

Het doel van dit proefschrift was om antwoorden te geven op relatief veel voorkomende vraagstukken binnen de therapeutische endoscopie. De resultaten van de verschillende studies waren soms onverwacht en confronterend. We hebben aanvullend bewijs nodig van goed ontworpen studies om tot evidence-based endoscopische behandeling te komen voor gastro-intestinale stricturen.
Dankwoord en Curriculum Vitae
Dankwoord

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Curriculum Vitae

Jeanin Elise van Hooft was born on January 17, 1973, in Nijmegen, the Netherlands. She attended high-school at the Liemers College in Zevenaar from which she graduated in 1991. In the same year she started her medical studies at the University of Groningen. During university she was a member of the international board of AEGEE (L’Association des États Généraux des Étudiants de l’Europe) and was an exchange student at the Free University of Berlin, Germany. In addition to medicine she also attended classes on law and economy. She obtained her Master of Science in medicine in 1996 and her qualification as Medical Doctor in 1998. From 1999 till 2003 she worked as a resident in Internal Medicine at the Deventer Hospitals, Deventer (dr. H.E. Sluiter). In that period the gastroenterology in the aforementioned hospital bloomed and came to the author’s attention.

She transferred to gastroenterology in 2003 and started her fellowship at the Academic Medical Center, Amsterdam (prof. dr. P. Fockens). During her fellowship she was secretary of the junior affiliation of the Dutch Gastroenterology association. In 2004 she started doing clinical research into gastrointestinal strictures. In 2006 she finished her training and became a consultant gastroenterologist at the Medical Spectrum Twente, Enschede. Her research expanded and in 2009 she rejoined the Department of Gastroenterology and Hepatology of the Academic Medical Center in Amsterdam. Her fields of interest are therapeutic endoscopy, oncology and in particular pancreatico-biliary issues. She is coordinator of the pancreatico-biliary research group.