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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

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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.[1;2] The majority of cases have locally advanced or metastatic cancer with a poor prognosis and a median survival of 3 to 6 months.[3-7] 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.[8] 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.[9;10] 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.[11-14] It has been reported that delayed gastric emptying after gastrojejunostomy occurs in up to 57% of patients and leads to prolonged hospital stay.[9;15-17]

Endoscopic placement of a self-expandable metal stent has emerged as an alternative minimally invasive treatment option in case of upper intestinal obstruction.[18-23] 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.[24;25] 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%).[24;25] Most published data relate to patients treated with an enteral Wallstent (Boston Scientific, Natick, Mass), a self-expanding stainless-steel woven stent.[24;25] 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.[26] 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.[27] The purpose of this prospective single-arm observational study was to further investigate the efficacy and safety features of this new enteral stent.
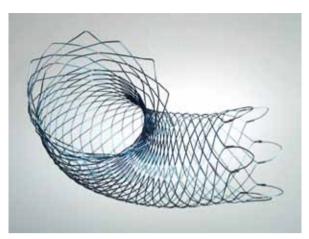
Duodenum

Figure 1. WallFlex duodenal 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

Duodenum

Table 1. Patient demographics and clinical characteristics at baseline.	
Number of patients, n	51
Age (y), (mean [SD])	67.6 (12.3)
Sex (male/ female)	25/26
Tumor characteristics, no. (%)	
Pancreatic cancer	35 (69)
Metastatic disease	5 (10)
Cholangiocarcinoma	3 (6)
Duodenal cancer	3 (6)
Gastric cancer	2 (4)
Gallbladder cancer	2 (4)
Cancer of the ampulla of Vater	1 (2)
Biliary tract, no. (%)	
Drained	
Metal stent	31 (61)
Plastic stent	3 (6)
Signs of obstruction	4 (8)
No signs of obstruction	13 (25)
Severity of obstruction	
GOOSS score, median (IQR)	1 (0-2)
0 No oral intake, no. (%)	18 (35)
1 Liquids only, no. (%)	19 (37)
2 Soft solids, no. (%)	4 (8)
3 Low residue or normal diet, no. (%)	10 (20)
General condition	
BMI, mean (SD)	22.7 (3.2)
WHO performance score, mean (SD)	2.06 (1.05)
WHO 0 – fully active, no. (%)	2 (4)
WHO 1 – cannot carry out heavy physical work, no. (%)	15 (29)
WHO 2 – up and about > 50% of the day, no. (%)	17 (33)
WHO 3 – up and about < 50% of the day, no. (%)	12 (24)
WHO 4 – bed or chair bound all day, no. (%)	5 (10)
Quality of life	
QLQ-C30 Global Health status (QL2), mean (SD)	44.5 (20.9)
EQ-VAS score, mean (SD)	42.5 (18.4)

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.[28] 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 proporties, 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 (version12.0.2) 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.[27] 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).
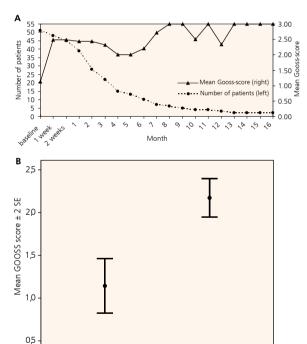

Figure 2. A, Mean GOOSS score over time. **B**, Mean GOOSS score at baseline versus total follow-up. Bars represent 2 times SE.

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).
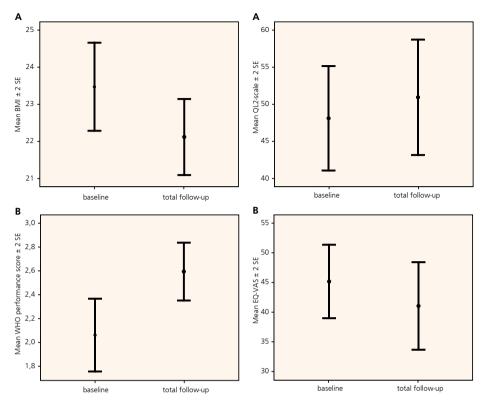
Figure 3. A, Mean BMI at baseline versus total follow-up. Bars represent 2 times SE. **B**, Mean WHO performance score at baseline versus total follow-up. Bars represent 2 times SE.

Figure 4. A, Mean QL2 at baseline versus total follow-up. Bars represent 2 times SE. **B**, Mean EQ-VAS at baseline versus total follow-up. Bars represent 2 times SE.

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.[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.[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%.[29]

In the current study, 13 of 51 patients (25%) did not have a biliary stent placed or cholestatic 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.[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%.[33] 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.[19] 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
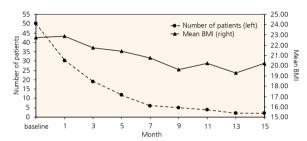

Figure 5. Mean BMI over time.

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).[34;35] 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.

Duodenum

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Duodenum