Treatment of malignant gastrointestinal- and biliary obstructions with metal stents

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Abbreviations

APC	Argon plasma coagulation
ASA	American Society of Anesthesiologists
BTS	Bridge to surgery
EORTC	The European Organization for Research and Treatment of Cancer
GE	Gastric emptying
GEA	Gastro-entero-anastomosis
GI	Gastrointestinal
GOO	Gastric outlet obstruction
PEG	Percutaneous endoscopic gastrostomy
PRO	Patient reported outcome
PTBD	Percutaneous Transhepatic Biliary Drainage
QLQ	Quality of life questionnaire
QoL	Quality of life
SEMS	Self-expanding metal stent
$T_{50\%}$	Half emptying time
VAS	Visual analog scale

List of papers

Paper 1

Treatment of malignant gastric outlet obstruction with stents: an evaluation of the reported variables for clinical outcome.

Larssen L, Medhus AW, Hauge T.

BMC Gastroenterol. 2009 Jun 17;9:45. doi: 10.1186/1471-230X-9-45.

Paper 2

Patient-reported outcomes in palliative gastrointestinal stenting: a Norwegian multicenter study.

Larssen L, Medhus AW, Hjermstad MJ, Körner H, Glomsaker T, Søberg T, Gleditsch D, Hovde O, Nesbakken A, Tholfsen JK, Skreden K, Hauge T.

Surg Endosc. 2011 Oct;25(10):3162-9

Paper 3

Long-term outcome of palliative treatment with Self-expanding metal stents for malignant obstuctions of the GI tract

Lene Larssen MD, Asle W. Medhus MD, PhD, Hartwig Körner MD, PhD, Tom Glomsaker MD, Taran Søberg MD, Dagfinn Gleditsch MD, Øistein Hovde MD , Jan K. Tholfsen MD, Knut Skreden MD, Arild Nesbakken MD, PhD and Truls Hauge MD, PhD

Scand J Gastroenterol. 2012 Dec;47(12):1505-14

Paper 4

Stent treatment of malignant gastric outlet obstruction

- The effect on rate of gastric emptying, symptoms and survival

Lene Larssen MD, Truls Hauge MD, PhD and Asle W. Medhus MD, PhD

Surg Endosc. 2012 Oct;26(10):2955-60

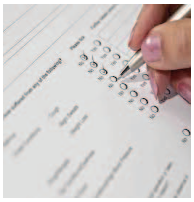
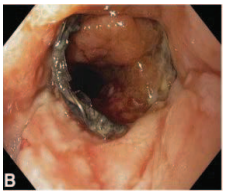
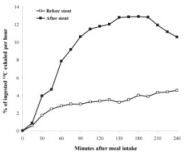
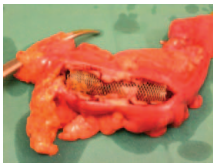
Paper 5

Stenting as a bridge to surgery is safe and effective in acute malignant left-sided large bowel obstruction

Lene Larssen MD, Asle W. Medhus MD, PhD, Hartwig Körner MD, PhD, Tom Glomsaker MD, PhD, Taran Søberg MD, Dagfinn Gleditsch MD, Øistein Hovde MD[1], Jan K. Tholfsen MD, Knut Skreden MD, Arild Nesbakken MD, PhD and Truls Hauge MD, PhD.[1,2]

Submitted

Thesis at a glance

	Aim	Patients and methods	Results		Conclusion
I	To review how is treatment outcome after gastroduodenal stents evaluated	Review of publications between 2000 and 2008 regarding palliative treatment of gastroduodenal obstruction with stents.	18 out of 45 publications had used a graded symptom scale to evaluate stent effect No studies had used PRO to evaluate effect. No studies had objectively evaluated stent effect.		Available reports do not provide sufficient relevant information of the clinical outcome of duodenal stenting.
II	To study how patients evaluate the clinical effect of palliative stent treatment by using PRO/QoL	162 patients treated with metal stents for gastrointestinal- and biliary obstruction at 9 Norwegian hospitals from 2006 until 2008 were included. QLQ were completed before and 2 weeks after treatment.	Significant clinical improvement in obstruction related symptoms and global health were found for all 4 stent locations. Physicians reported a larger improvement than the patients.		SEMS treatment is effective in relieving symptoms of malignant GI and biliary obstruction. Both according to patients and physicians, physicians reported the largest effect.
III	To evaluate long-term outcome after stent treatment , with special focus on need for reinterventions and rehospitalizations	219 patients palliatively treated with metal stents were followed for at least 6 months after treatment	33 % needed reinterventions, most often for reobstruction, esophageal stents most frequently. 72 % needed readmissions, only 25 % for stent complications.		Palliative stenting of malignant gastrointestinal obstruction is safe and effective.
IV	To study how gastroduodenal stents effects the gastric emptying rate	17 patients underwent gastric emptying test before and after treatment with gastroduodenal stents	Gastric emptying improved significantly. There was no correlation between survival and rate of gastric emptying before, after or change in rate of emptying.		SEMS treatment results in improved gastric emptying in most patients with GOO.
V	To evaluate the safety and efficiency of colonic stents as a bridge to surgery	46 patients with malignant colonic obstruction were included with intention BTS, 43 with left sided colon obstructions	34 patients underwent elective surgery after stent. Stenting as BTS was successful in 77 %, with procedure related bowel perforation rate of only 5 % and no mortality.		Emergency stenting of colorectal obstruction was safe and effectively prevented diverting stomas.

Introduction

Every year around 5000 new cases of gastrointestinal cancer (GI) are diagnosed in Norway, which accounts for 25 % of all cancer cases. The incidence rate of esophageal – and colorectal cancer is increasing, but the rate of non-cardiac gastric cancer is decreasing. Cancers located in other parts of the GI tract have more stable incidences [1]. The cancer survival rate has generally increased due to earlier detection and better treatment regimes, but still 40-80 % of patients have cancer at such advanced stages at the time of diagnosis that only palliative treatment can be offered [2-4].

Obstruction is a common problem in advanced stages of GI- and biliary cancers. Most patients with advanced esophageal cancer will develop some degree of dysphagia and 50 % of patients with will need a stent during the course of the disease [5]. Malignant gastric outlet obstruction (GOO) is commonly seen in patients with advanced gastric-, pancreatic-, duodenal, hepato-biliary or metastatic malignancies. GOO causes nausea and vomiting, and can lead to dehydration and cachexia, which severely reduces the patients' Quality of Life (QoL). Ten to 25 % of patients with pancreatic cancer will develop duodenal obstruction and 70-80 % biliary obstruction during the course of the disease [3;6-8].

Primary biliary duct cancer (cholangiocarcinoma) and other malignancies causing biliary obstruction (gallbladder cancer, metastatic cancer disease) are usually diagnosed at an advanced stage when only palliative treatment can be offered [9]. Obstruction of bile flow to the duodenum can lead to, itching and icteric discoloration of the skin that can be socially stigmatizing and serious infections.
Colorectal cancer have a debut with acute bowel obstruction in 10-30 % [10;11], whereas 20-50 % of patients with ovarian cancer experiences symptoms of large bowel

obstruction [12]. Complete obstruction of the large bowel is a life threatening condition that needs emergency intervention.

Palliative treatment of malignant GI-and biliary obstruction

Patients diagnosed with malignant GI obstructions often have advanced cancer which implies that curative treatment or prolongation of life no longer is possible. Effective palliation from distressing symptoms becomes pivotal for the patients when life expectancy is limited. Rapid relief from distressing symptoms, time outside hospital, and absence of complications are important factors that are believed to strongly influence the patients QoL. Several factors needs consideration in order to make decisions about the best palliative option: i.e. age, expected survival, co-morbidities, the patients' wishes, severity of symptoms, location of stenosis and available medical expertise. In clinical practice it is important to predict expected survival in order to choose the right palliative treatment. This can be difficult [13-15], but all the more important, since we should not expose patients with a short life expectancy to unnecessary procedures with potential serious complications.
A multidisciplinary approach, preferable early in the course of the disease, is believed to be an advantage [16]. The approach to palliative treatment of malignant GI obstructions has changed significantly over the last 20 years. Open surgical procedures have been replaced by endoscopic, interventional radiologic and laparoscopic surgical procedures and this has led to a significant decrease in procedure related morbidity and mortality, discussed in more detail below.

Patients with advanced esophageal cancer often experiences dysphagia which leads to nutritional deficiency. Palliative esophageal resections are rarely performed because of a high risk of complications [17]. For some patients a nasogastric feeding tube or a percutaneous endoscopic gastrostomy (PEG) can offer good palliation and maintain enteral nutrition for a shorter time period. For patients with longer life expectancy, however, will the inability to swallow, at least liquids and their own saliva be very

distressing, even if nutritional status is maintained though a tube or PEG. Therefore reestablishment of passage with self- expanding metal stent (SEMS) has become the first choice treatment for many patients with malignant esophageal obstructions. Radiation therapy (external or endoluminal) also is frequently used for palliation of malignant esophageal obstruction. Both methods have a well documented effect on dysphagia. SEMS have a more rapid effect on dysphagia while radiation therapy has a longer lasting effect [18;19]. The two treatment modalities are frequently used in combination; this is associated with an increased risk of esophago-tracheal fistula formation [20].

Gastric outlet obstruction (GOO) leads to nausea, vomiting, aspiration, pain and malnutrition which can severely affect quality of life. Simple aspiration of gastric contents by a nasogastric tube is often good palliative care for patients with a short life expectancy. For patients with longer expected survival the ability to maintain per oral nutrition is very important for the QoL, and we therefore usually attempt restoration of gastrointestinal passage. Endoscopic treatment of malignant GOO with SEMS has to a great extent replaced palliative surgery with gastro-entero-anastomosis (GEA). Studies comparing gastroduodenal stents with bypass surgery have shown that there are fewer serious complications[21], less need for care in intensive care units [22], the hospital stay is shorter [23;24] and the symptomatic relief is more rapid after SEMS treatment [8;25-28] compared to surgical palliation with GEA [3;29;30].

Palliative surgery for malignant biliary obstructions has been replaced by endoscopic- (ERCP) or interventional radiologic procedures. The bile can either be drained externally with Percutaneous Transhepatic Biliary Drainage (PTBD) or internally with placement of a stent to the duodenum by an endoscopic procedure, endoscopic retrograde cholangiopancreatography (ERCP). Internal drainage is preferable for mobile patients with expected survival beyond 3-4 weeks. Both plastic stents and SEMS are effective for biliary drainage. Plastic stents are less expensive, but SEMS have longer patency and therefore preferred for patients with expected survival > 3 months who otherwise would need repeated procedures every 3 months [31-34].

Primary colon cancers and metastatic malignancies may cause obstructions of the large bowel that can be life-threatening if complete obstruction occurs. Patients with very short life expectancy should receive palliative care with analgetics, anti-emetics, steroids, anti- cholinergic drugs or somatostatin [35]. Decompression with a nasogastric tube or a PEG can also offer palliation when endoscopic or surgical decompression of the colon not is possible. For patients with longer expected survival, however, reestablishment of bowel passage is usually attempted. Traditionally has palliative surgery with a colostomy been standard treatment for these patients. Emergency surgery in these often old and debilitated patents involves a high risk of peri- and post operative complications, with mortality rates between 12-25 % [36-39], even up to 40 % for patients with high surgical risk (ASA 4) [40]. Therefore palliative surgery to a large extent has been replaced by endoscopic with SEMS. The stents serve as permanent palliative treatment for patients with advanced disease, but can serve as a bridge to curative surgery for patients with more limited disease, described in more detail in a later section.

Self-expanding metal stents (SEMS)

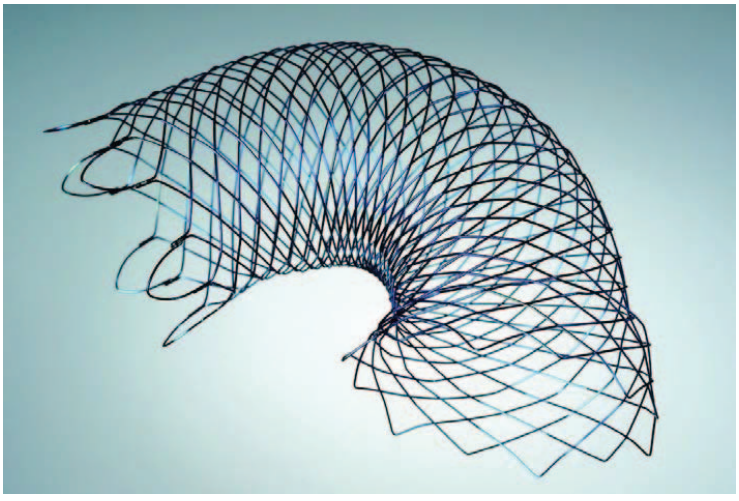


Figure 1: Uncoverd colonic SEMS

Taking advantage of the technology developed in endovascular stents, gastrointestinal stents were introduced in early the 1990 s. The first publications on biliary stents [41;42] were rapidly followed by publications where SEMS had been successfully applied in esophagus [43;44] , proximal small intestine [45] and colon [46;47]. The first metal stents were made of stainless steal, today most SEMS are made of nitinol (an alloy of nickel and titanium), which exhibit properties of shape memory and super elasticity that makes them more suitable for their purpose. SEMS are produced in different lengths and diameters and possesses different expanding forces, depending on the organ in which they are to be placed. Precise placement of uncovered stents is crucial since they quickly gets incorporated into the tissue and usually are not removable. Occlusion of stents by tumor in- and overgrowth though the nitinol mesh is a problem. SEMS that are partially or fully covered with a polyurethane membrane have been developed to prevent this, but these stents have a higher rate of migration [48]. Palliative treatment SEMS is regarded an advanced endoscopic procedure, usually performed by experienced endoscopists or radiologists, depending on local expertise.

Esophageal stents

Esophageal SEMS are used to relieve dysphagia due to malignant obstruction either by intrinsic or extrinsic compression of the esophagus. The stents can also be used to close malignant esophago-tracheal fistulas. They relieve dysphagia rapidly in 89- 99 % [49-52] of the patients, with an overall complication rate of 25- 50 % [5;49;53-59]. The most common complications are reobstruction, stent migration and esophago-tracheal fistula formation, which usually can be treated with a repeated endoscopic procedure[56;60]. Mortality directly related to the procedure is 0.5-2 % [61].

Biliary stents

Biliary SEMS are used in patients with malignant biliary obstruction caused either by primary biliary cancer or extrinsic compression by i.e. liver metastasis. Metal stents are preferred in patients with a expected survival > 3 months since these stents have a longer patency than plastic stents and hence reduce the need for repeated procedures [62;63]. Covered and partially covered biliary SEMS have been developed to

prevent tumor ingrowth, but do not seem to have increased patency compared to uncovered stents [64-66].

Gastroduodenal stents

Gastroduodenal SEMS are used to relieve malignant gastric outlet obstruction (GOO) caused by either distal gastric cancer, pancreatic cancer, periampullary cancers or metastatic cancer to this region. The stents offer good symptomatic palliation for close to 90 % of patients [6-8;24;67-70], with few serious complications. Around 20 % experiences reobstruction[8], but this can usually be treated with a repeated endoscopic procedure. Simultaneous obstruction of the biliary tract and the proximal small intestine is common and can be treated with double stenting. If there is sign of biliary obstruction should a biliary metal stent should be placed first if possible, since the papilla Vateri can be difficult to access after a duodenal stent has been inserted [7;71]. If biliary obstruction occurs after a duodenal stent have been placed, can a biliary stent be placed with the help of a combined radiologic- and endoscopic procedure (rendezvous technique) or with a EUS (endoscopic ultrasound) procedure [72;73].

Colonic stents

Colonic SEMS are used for permanent palliation of malignant colonic obstruction as a alternative to palliative surgery. Several studies and reviews have reported a high clinical success rate with an acceptable rate of complications [10;74-79]. Colonic stents can be placed in the whole length of colon, but preferably not closer to the rectum than 4-5 cm, since this is associated with fecal incontinence and pain. Perforation of colon is the most dreaded complication, and occurs in 5 % [10;74].

Evaluation of the clinical outcome of SEMS treatment

Short- and long-term outcome

Early studies concerning the outcome of SEMS treatment, whether randomized, comparative, or merely descriptive, focused on technical success (e.g. correct deployment of the stent), clinical success (restored passage), short-term complications and cost-effectiveness. Numerous studies demonstrated the feasibility, safety and cost- efficiency of stent treatment on a short term basis [8;33;34;54;68;74;80;81]. Few studies had applied a grading scoring of obstructive symptoms, which makes it difficult to draw conclusions concerning treatment effect and to compare results.

Modern multimodal treatment of GI cancer, i.e. chemotherapy, anti- angionetic drugs and surgery for metastases, have prolonged the survival for patients with advanced cancer, colorectal cancer in particular [82-84]. Accordingly, the number of patients experiencing late SEMS-related complications, e.g. stent occlusion and perforation of the colon may increase. Long- term outcomes like reobstruction rate/patency, late complications and re-hospitalizations are therefor important and needed evaluation[55;56]. Currently, available long-term data are limited, somewhat conflicting and still subject to debate[7;85;86].

Patient reported outcomes (PRO) measures

Traditionally, the physicians' clinical evaluation of symptomatic effect has been the main outcome measure of SEMS treatment. It is known form several studies in palliative medicine, however, that physicians' and patients 'evaluation differ, and underestimation of patients' symptoms by physicians is most common[87-93]. In clinical trials concerning palliative oncology there has been a gradual change from curative/non-curative towards patient reported QoL as the main ending point [94;95]. The same outcome measures should be used when evaluating the outcome of palliative endoscopic- and surgical procedures. In the planning of the present study few publications had applied PRO to assess clinical outcome of SEMS treatment [18;19;60;96-98].

Furthermore, no data comparing patients' and physicians' assessments of the clinical effect of SEMS treatment were available.

The term QoL or health related QoL is widely used, but not well defined. The term usually includes aspects of general health, physical functioning, physical symptoms, emotional and cognitive functioning and social functioning, but may vary between investigators. Many authors prefer the term patient-reported- outcomes (PRO), which suggest interest in the full range of outcomes form mental to physical symptoms. A vide variety of questionnaires developed and validated for the assessment of QoL are available [99]. Some are generic, which means that they can be used irrespective of condition, also for healthy people (SF 36, Euro-Qol/EQ-5D)[100;101]. Others are disease specific (EORTC QLQ-C30, EORTC disease- or treatment specific modules, Functional Assessment of Cancer Therapy (FACT)[102;103] or addressing specific aspects of QoL(HADS, McGill Pain Questionnaire (MPQ), Fatigue Inventory (MFI), Bartel Index of Disability (BI))[104-107]. Some are short, developed for everyday clinical practice, while others are more complex and extensive and best suited for use in clinical research. Often questionnaires are used in combination in order to evaluate different aspects of patients' physical- and psychic functioning. ECOG[108] and Karnofskys performance scale [109] are tools commonly used to assess patients physical functioning are, but these are not considered complete QoL instruments. Some authors develop their own questionnaires to fit their specific study population and design. This is generally not recommended; since standardized and validated forms must be used in order make the results from different studies comparable.

Objective evaluation of SEMS effect

The clinical effect of SEMS treatment is usually evaluated, as described above, by the physician or patients' assessments, by objective tests are not commonly performed. Normalization of s- bilirubin is a good objective measure of a clinical successful biliary SEMS placement. Passage of contrast is often used to verify reestablishment of

passage though gastroduodenal- and colonic SEMS, but scoring to clinical experience some patients may still experience symptoms even though passage is reestablished by a stent.

Placement of a gastroduodenal stent through the pylorus is likely to influence the complex interplay between the motility of the stomach and the duodenum. The functional consequence on gastric emptying has only been examined in one available study quantifying gastric emptying *after* stent treatment[110]. No studies have, however, estimated the effect of the stent by comparing the rate of gastric emptying before and after stent treatment with relation to patient reported effect on symptoms and survival.

Colonic stents as a bridge to elective surgery

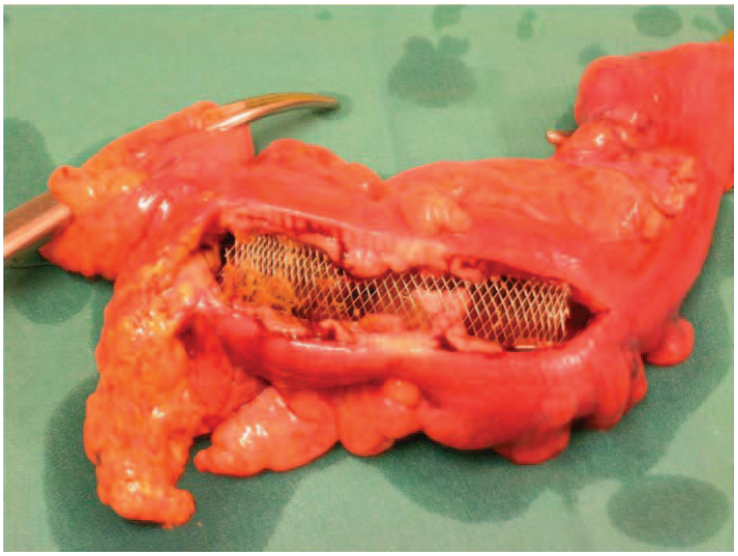


Figure 2: Bridge to surgery, resected tumor with stent in place

SEMS was primarily introduced as a method for permanent palliation, but the area of use has gradually been extended into several other indications. The use of colonic SEMS as a bridge to elective surgery for acute malignant left-sided colonic obstruction

(BTS) were introduced in the early 1990s [111]. Emergency surgery for malignant colonic obstruction has a high morbidity and mortality rate, particularly in elderly patients with comorbidities[39;40;112;113]. Furthermore, the surgery often has to be performed in two stages with a temporary stoma after the first operation [39;114;115]. Although planned to be temporary, many stomas are never closed [116] and permanent stomas are associated with complications and reduced patient reported QoL[117-119]. The use of SEMS to decompress the bowel followed by an elective one - stage resection of the tumour with primary anastomosis, the concept of BTS, is therefore an attractive alternative. Several observational studies and reviews have shown that SEMS as BTS decreases morbidity, mortality and the number of permanent stomas compared to emergency surgery [10;74;76;120-123].

There are, however, concerns about that the use of SEMS as BTS can adversely affect the oncologic outcome in patients treated with curative intent. It has been demonstrated that manipulation of cancers by colonoscopy and stenting increases the number of circulating tumour cells [124;125], but the clinical consequence of this is not known. The worries are that stent insertion or silent perforations might lead to tumor seeding and cancer dissemination. Publications on long-term outcome after stents as BTS are sparse and not conclusive [86]. Randomized trials and studies of long-term oncologic outcome are needed to clarify these issues.

Aims

The general aim of this thesis was to increase the knowledge about the clinical outcome of SEMS treatment for malignant GI-and biliary obstruction.

The specific aims were:

- To explore whether available reports on SEMS treatment for GOO provides sufficient data for evaluation of clinical outcome.

- To evaluate how patients assess clinical outcome of palliative SEMS treatment by using patient reported outcome measures (PRO).

- To compare patient/physician assessments of symptoms and outcome.

- To evaluate and compare the long-term outcome on four different stents locations after palliative treatment with SEMS with regard to complication rate, re-intervention rate and re-hospitalizations rate.

- To evaluate the effect of gastroduodenal stents on gastric emptying rate in patients with GOO.

- To study the relation between survival, gastric emptying and the effect on symptoms.

- To evaluate use of SEMS as a bridge to surgery (BTS) for acute malignant left-sided colonic obstruction with regard to complication rate and the rate of successful delayed surgical resections.

Patients and study design

Patients

Paper 2-5

Nine out of 11 Norwegian hospitals, 3 academic- and 6 community hospitals, accepted the invitation to participate in the inclusion of patients in this prospective observational multi-center study constituting paper 2-5. All participating centers performed stent procedures on a regular basis and had one or two dedicated physicians that identified eligible candidates for the study and administered the inclusion. The hospitals served catchment areas between 75000 and 300000.

Patients were included consecutively at all participating hospitals from November 2006 until April 2008 for the study of patient reported outcomes (paper 2), long-term outcomes (paper 3) and colonic SEMS as BTS (paper 5). Patients for the study of gastroduodenal SEMS and gastric emptying (paper 4) were recruited only at Oslo University Hospital, Ullevål with an extended inclusion period until May 2010.

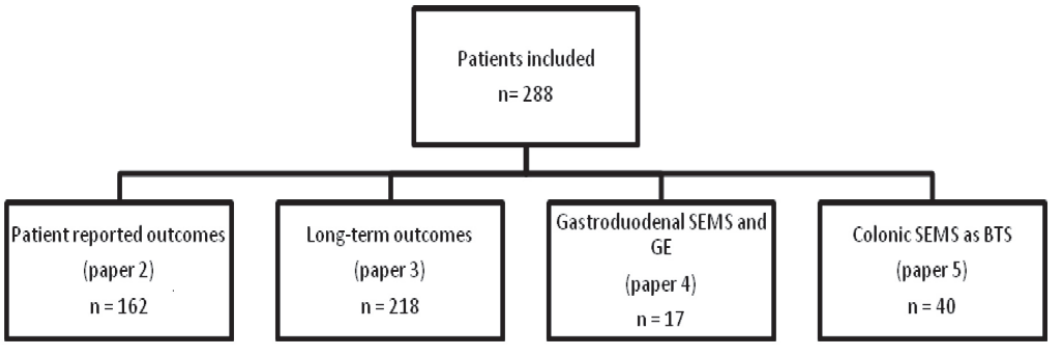


Figure 3: Flow chart illustrating the included patients' paper in 2-5. 288 patients were included totally at 9 participating centers.

Paper 2: Patient reported clinical outcome of SEMS treatment

The inclusion criteria for paper 2 were: 1. symptoms related to malignant GI obstruction; 2. indication for treatment with metal stents established; 3. fluency in oral and written Norwegian; 4. cognitive capability to complete the questionnaires; 5. completion of both quality of life questionnaires (QLQs). Patients treated with colonic stents as a BTS, who underwent subsequent bowel resection within two weeks, were not included in the analyses in paper 2.

Power calculations in paper 2 were based on a mean change in global health score of 10, which is considered a small - medium clinically noticeable change for the patients[126]. A SD of 15 of, with 90% power and a 5% level of significance, yielded a sample size of minimum 26 patients that had to complete both QLQs for each of the four stent locations.

Paper 3: Long-term outcomes after SEMS treatment

Patients treated with SEMS as permanent palliation, with their SEMS in place and long-term data available, were included in the study of long-term outcomes (paper 3).

Paper 4: Gastroduodenal SEMS and gastric emptying

Patients with endoscopically verified malignant obstruction of the proximal duodenum and planned SEMS treatment were recruited consecutively for paper 4. Patients with indications of complete gastroduodenal obstruction, or who had undergone endoscopic dilatation of the stricture during the last 4 weeks were not considered eligible for inclusion.

Change in $T_{1/2}$ (half emptying time) was used for sample size calculation in paper 4. To identify a 15 min-difference in $T_{1/2}$ with a SD of 18 and a standard difference of 1.67[127] with 90 % power and 5% level of significance, a minimum of 17 patients were required. A significant change in gastric emptying was defined as a change exceeding

20 % based on data on the expected intra- individual variance of the octanoic acid breath test [128;129].

Paper 5: Colonic SEMS as BTS

Patients treated with SEMS with the intention BTS for acute malignant left-sided colonic obstruction, were included in paper 5.

Study design

Paper 1

Paper 1 was a review of published literature from January 2000 until September 2007 regarding clinical outcome treatment for GOO with SEMS. The literature search was performed combining the following search terms: duodenal stent, malignant duodenal obstruction, gastric outlet obstruction, SEMS, and gastro-entero-anastomosis. The search was done in Pub Med, Embase, and Cochrane library.

Only papers that comprised ≥ 15 patients and were written in English were included. The identified studies were reviewed with regard to the following parameters: 1. the use of a graded scoring system to evaluate clinical outcome; 2. if PRO were used to assess clinical outcome; 3. if information on stent patency and survival were provided and 4. if objective criteria to evaluate the stent effect had been used.

Paper 2-5

The QoL questionnaires were administered to the study participants upon admission by the treating physician or a study nurse. The same questionnaire was given to the patients when leaving the hospital. The patients assessments in paper 2 were completed twice, at inclusion (-2 to +1 day before/after the procedure) and two weeks after treatment. The patients were instructed to complete the second questionnaire two weeks after stent treatment and return it by mail.

Data on long-term outcomes were retrieved by a retrospective review of the patients medical journals. Patients were followed until death, surgical intervention with removal of SEMS or until at least six months after treatment. Follow-up visits were performed only when needed since we did not want to burden these often severely ill patients with unnecessary hospital visits.

Patients included in paper 4 performed the octanoic breath test of gastric emptying (confer below) before treatment. Thereafter, on the same or the following day, patients were treated with a stent, and a new gastric emptying test was performed within one week.

Patients with acute malignant colonic obstruction, who required emergency treatment, in whom SEMS as BTS was found to be indicated, were eligible for inclusion in paper 5. Patients considered to be at high surgical risk were also included. After discharge from the hospital the patients were followed according to national guidelines for the treatment of colorectal cancer issued by the Norwegian Gastro-Intestinal Cancer Group (NGICG), which were the guidelines during the study period.

Methods

Patient reported Quality of life

The European Organization for Research and Treatment of Cancer (EORTC) questionnaires were chosen as our tool for assessing patient reported outcomes after consulting with a research group that possesses extensive experience with the development, use and interpretation of patient reported outcome measures in palliative oncology. EORTCs QLQs are developed, validated and frequently used in study populations similar to ours and were found to be well suited for the study purposes.

The EORTC QLQ-C30 [102] is a cancer specific 30-item self-reporting questionnaire consisting of both multi-item scales and single-item measures that has been validated in Norwegian [130]. These include five functional scales (i.e. physical, role, cognitive, emotional, and social), three symptom scales (i.e. fatigue, nausea/vomiting, and pain), and six single items (i.e. dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems), as well as two questions where the patients assessed their overall health and QoL on a scale from 1-7. A combination of these two scores results in a global health score.

EORTC has in addition to the core questionnaire C30 developed a series of organ/cancer specific questionnaires and it is recommended that they are used in combination with the core questionnaire C30. For the purpose of the present study, a selection of questions was made from the relevant organ specific modules to reduce the respondent burden for these often severely ill and old patients and thereby increases compliance and response rate. Questions to be answered by the patients receiving esophageal, biliary, and colonic stents were selected from the stomach module, EORTC QLQ-STO22;[131] the pancreatic, EORTC QLQ-PAN26;[132] and the colorectal module, EORTC QLQ-CR38,[133] respectively. Patients receiving gastroduodenal stents did not answer any additional questions as their main obstruction related symptoms, nausea and vomiting, were specifically addressed by the core questionnaire. The questionnaire used in paper 2 consisted of 38 questions: EORTC C-30 + 8 organ specific questions (appendix 2).

Higher scores on the symptom scales and single items from the core questionnaires and the organ-specific modules indicated more severe symptoms, while higher scores on the functional scales indicate better functioning. All items were to be answered on an ordinal scale ranging from 1 (“Not at all”) to 4 (“Very much”), except for the two modified visual analogue scales assessing global health and QoL, which ranged from 1 to 7. The time frame was the past seven days. Scale and item scores were transformed into a continuous scale from 0 to 100, as described in the EORTC Scoring Manual.[134]

A mean score difference of 5-10 is usually regarded as a small but clinically noticeable change for the patients, a change from 10-20 as moderate, and >20 as a large clinical change [126;135]. Results are estimated and reported as a mean effect on a group level.

Physician reported outcome

The physicians assessed the same organ specific symptoms as the patients; at inclusion and the second assessment at hospital discharge or two weeks after stent treatment if the patient was still hospitalized.

Endoscopic procedure

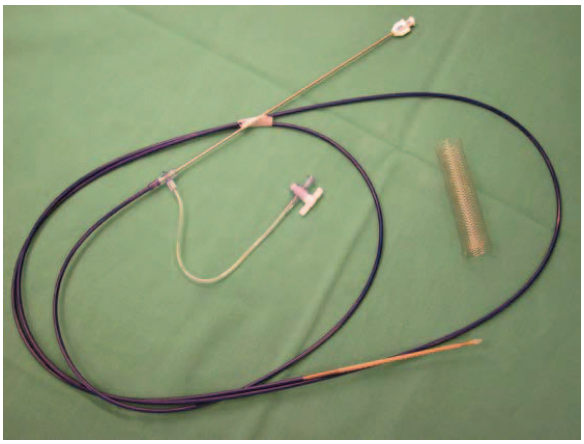


Figure 4: A introducer set with a preloaded stent.

The stent procedures were performed by experienced endoscopists. Most stents were placed with a combined endoscopic and radiologic procedure, with the exception of 5 esophageal stents placed only by endoscopic guidance. Most procedures were performed under conscious sedation using titrated doses of midazolam, pethidine or a short acting opioid (alfentanil or fentanyl). A few procedures required anesthesiology assisted Propofol® sedation. Firstly the stricture was identified and visualized endoscopically or with radio contrast. The length of the stricture was measured either

by direct vision, with the help of an ERCP-balloon, if the stricture not could be passed by the endoscope. Esophageal strictures were marked either by external radio opaque markers, internal metal clips or injection of radio opaque marker Lipoidol®. Dilatation of malignant strictures is associated with increased risk of perforation, but was however sometimes necessary in esophageal strictures to allow passage of the introducer system through the stricture. A *stiff* guidewire was then inserted through the working channel of the endoscope and through the stricture at least 20 cm beyond the stricture. SEMS are preloaded onto a delivery system that can be introduced though the working channel (TTS) of the endoscopes (with the exception of esophageal stents). Finally the introducer set could be passed over the guidewire, through the stricture into the correct position and deployed. After deployment the SEMS will try to expand back to its original shape and size, this happens gradually over 1-2 days., Some patients can go home after a few hours observation, others are kept in hospital for a day or two, depending on the patients health status prior to treatment and degree of discomfort after the procedure.

Octanoic acid gastric emptying breath test

Figure 5: The octanoic breath test meal consisting of C13 marked egg yolk and bread with butter

The rate of gastric emptying was measured by administering a solid meal of 1050 kJ consisting of 60 g of white bread, 5 g margarine, a one-egg omelet, and 150 ml water. The egg yolk included in the meal contained 91 mg ^{13}C-octanoic acid as marker of gastric emptying. Breath samples were collected every 15 min until 240 min after meal intake and ^{13}C-content was determined by gas chromatographic purification isotope ratio mass spectrometry. Variables of gastric emptying were estimated according to Ghoos et al[136].

Patients scored their sensation of hunger, satiety and nausea on a visual analogue scale (VAS) before meal and every 60 min until 240 min after intake [127]. They were also asked to grade their symptoms related to obstruction (nausea, vomiting, bloating, stomach pain, problems eating solid- or soft food or drinking liquids), before and two weeks after treatment. The symptoms were selected from EORTCs quality of life questionnaires EORTC QLQ-C30 [102]and EORTC QLQ-STO22 [131].

Statistical methods

The results in paper 3 were reported as median (range) for continuous variables, since the data were non-normally distributed. In overall survival analyses, deaths from all causes were registered as events, and patients were censored at study closure. In stent patency analyses, the first reintervention due to stent failure was registered as an event, and patients with functioning stents were censored at death or study closure.

Non-parametric tests were used for comparison of grouped data, Wilcoxon test for two related samples and Mann-Whitney U test for independent samples. Kruskal-Wallis test was used for comparing more than two independent samples, and Fisher exact test for analysis of contingency tables. Correlation analyses were performed by Spearman correlation. Time- dependent events were calculated using the Kaplan- Meier (KM) method, and log rank test was used to compare groups. The level of statistical significance was set at $p < 0.05$ for all analyses. Results were given as median with 10 and 90 percentiles in brackets unless otherwise stated.

Statistical analyses were performed with the at the time latest version of the SPSS software package (IBM - SPSS Inc. New York, US).

Ethics

The study was approved by the Regional Committee for Medical Research Ethics in Southern Norway and the Data Protection Supervisor at Oslo University Hospital, Ullevål. All patients received oral and written information about the study. Written informed consent was obtained from all participants before inclusion in the study.

Summary of papers

Paper 1:

Treatment of malignant gastric outlet obstruction with stents: an evaluation of the reported variables for clinical outcome.

The published literature regarding treatment of malignant GOO with stents from 2000-2007 were reviewed to reveal whether the information provided is sufficient to evaluate the clinical effects of this treatment.

45 original papers in English were identified. In 18 out of 45 studies some sort of graded scoring system was used. No studies used standardized QoL- questionnaires to evaluate the clinical outcome of stent treatment.

35/45 studies reported on stent patency and 11/45 had performed an oral contrast examination after stent placement. No studies had used objective quantitative tests of gastric emptying to evaluate stent effect.

Our review indicated that the available reports at that point in time did not provide sufficient relevant information of the clinical outcome of duodenal stenting. Graded scoring of symptoms, patient reported outcome and objective assessment of the stent effect should be applied to improve the evaluation of stent treatment.

Paper 2:

Patient-reported outcomes in palliative gastrointestinal stenting: a Norwegian multicenter study.

We evaluated clinical outcome in 162 patients palliatively treated with SEMS for malignant gastrointestinal (GI) – and biliary obstructions. This was done by patient

reported outcome measures/ QoL, and by a graded scoring of the obstruction related symptoms. Differences in outcome evaluation between the four outcome locations and between patients and physicians were compared.
A significant improvement in the mean global health score was observed after two weeks (from 9 – 18 on a 0-100 scale, $p<0.03$) for all stent locations. Both patients and physicians reported a significant reduction in all obstruction related symptoms (>20 on the 0-100 scale, $p<0.006$) after SEMS treatment. The physicians reported a larger mean improvement in symptoms than the patients, mainly due to reporting more severe symptoms before treatment.

To conclude, SEMS treatment is effective in relieving symptoms of malignant GI and biliary obstruction, as reported by patients and physicians. Physicians and patients evaluate treatment effects differently and thereby illustrate the importance of taking patient reported outcomes into account when evaluating clinical palliative interventions.

Paper 3:

Long-term outcome of palliative treatment with Self-expanding metal stents for malignant obstructions of the GI tract

Long-term outcome after palliative stent treatment for malignant esophageal, gastroduodenal, biliary and colonic obstructions was evaluated in 219 patients. Patients were followed for at least six months with respect to stent patency, reinterventions, complications and readmissions to hospital.
72 patients (33%) needed reinterventions. Stent occlusions or migrations (92 %) were the most common reasons. Eighty percent of reinterventions were repeated endoscopic procedures that successfully restored patency. Esophageal stents required reinterventions most frequently (41%), and had a significantly ($p= 0.02$) shorter

patency (median 152 days) compared to other locations (gastroduodenal, 256 days; colon, 276 days; biliary, 460 days).

Readmissions were required for 156 (72%) patients. Progression of the underlying cancer was the most common reason, whereas 24 % were readmitted due to stent complications.

The overall median survival was 98 days (1-793): 64 (1-104) days after gastroduodenal, 98 (7-793) days after esophageal, 127 (6-594) days after biliary and 140 (8-630) days after colonic stenting. Patients with gastric cancer had the shortest survival (median, 54 days), significantly shorter than patients with pancreatic cancer (median, 98 days, p=0.001), esophageal cancer (median, 102 days, p=0.005) and colon cancer (median, 172 days, $p < 0.001$). Patients with longer survival had more reinterventions and needed hospital readmissions more frequently.

In conclusion, long-term outcome after palliative treatment with SEMS for malignant GI- and biliary obstruction shows that 70 % had a patent stent until death, and that most reobstructions could be solved endoscopically. Hospital readmissions were mainly related to progression of the underlying cancer disease.

Paper 4:

Stent treatment of malignant gastric outlet obstruction
- The effect on rate of gastric emptying, symptoms and survival

Gastric emptying rate, symptoms and survival were evaluated in 17 patients with malignant gastric outlet obstruction (GOO) treated with duodenal stents.

Following stent treatment, 13 patients (76%) had improved rate of gastric emptying, whereas four had unchanged or worsening in rate of empting. There was a significant improvement in the symptoms nausea (p=0.046), vomiting (p=0.002) and problems swallowing solid food (p=0.007) after treatment.

There was no correlation between survival and gastric emptying or between survival and symptoms.

In conclusion, treatment with SEMS results in improved gastric emptying in most patients with GOO, which corresponds with a reduction in self-reported obstructive symptoms.

Paper 5:

Stenting as a bridge to surgery is safe and effective in acute malignant left-sided large bowel obstruction

Forty patients with acute malignant obstruction of the left colon (n=26) or rectum (n=14) underwent stent treatment as a bridge to surgery (BTS).

Successful stent placement with adequate decompression of the bowel was obtained in 34 (85%) patients, whereas emergency surgery was necessary in 6 patients, i.e. 15 % initial failures. Stent placement failed in two patients and in two patients adequate decompression was not achieved despite successful placement of the stent. Two patients experienced bowel perforation in relation to the stent procedure. There was no procedure related mortality.

Tumour resection with primary anastomosis was performed in 32 of the 40 patients (70%). Four of the patients with rectal resections with a low anastomosis on the pelvic floor level had a routine protective loop ileostomy in an elective setting, and these cases were consequently not considered failures.

In conclusion, stenting as bridge to surgery was successful in 77% of the patients who then underwent the same surgical procedure, as would have been performed in an elective setting.

General discussion

Methodological considerations

Patients

Patients were included unselected and consecutively in this observational study. As in all non- randomized studies, we can not exclude the risk of selection bias by missed inclusions of failed procedures, but the risk is reduced since patients were included prospectively.

Study design

The decision to perform a multi-center study was made because palliative treatment with SEMS is a decentralized procedure in Norway, and this would make the results applicable in everyday clinical practice. This study design also made it possible to include the sufficient number of patients within a limited time period, and thereby avoid the influence of changes in clinical practice that occurs frequently in this rapidly developing field. The disadvantage of a multi-center design was that the inclusion and stent procedures were performed by a variety of clinicians in a variety of hospital with little control over variations in technique among different hospitals.

RCTs are the gold standard when evaluating new treatment methods. We considered the to conduct a RCT comparing the outcomes after emergency surgery to SEMS as BTS, but found that it would be very difficult to include the sufficient number of patients given the population in Norway. The lack of randomization is a limitation in the study of colonic SEMS as BTS (paper 5), but the prospective collection of data limited the risk of selection bias and the results may add important knowledge.

Patient reported outcomes

Non-responders represent a problem in QoL studies and might influence results in both directions[137]. It has been argued that if the rate of non-responders exceeds 20 %, it poses a significant risk of bias to the results[138]. A 100 % response-rate is impossible to achieve in a study population like ours. Missing responses have different causes; hence, the reasons for missing questionnaires must be recorded, in order to evaluate the risk of possible selection biases.

We achieved 68 % compliance for completing both QLQs, which is considered acceptable in this patient population and in accordance with comparable studies. Response rates are known to fall with increasing age and as patients come closer to death[139-142]. Seventy-six patients, that had completed QLQ 1, did not return the second questionnaire, 27 for unknown reasons.

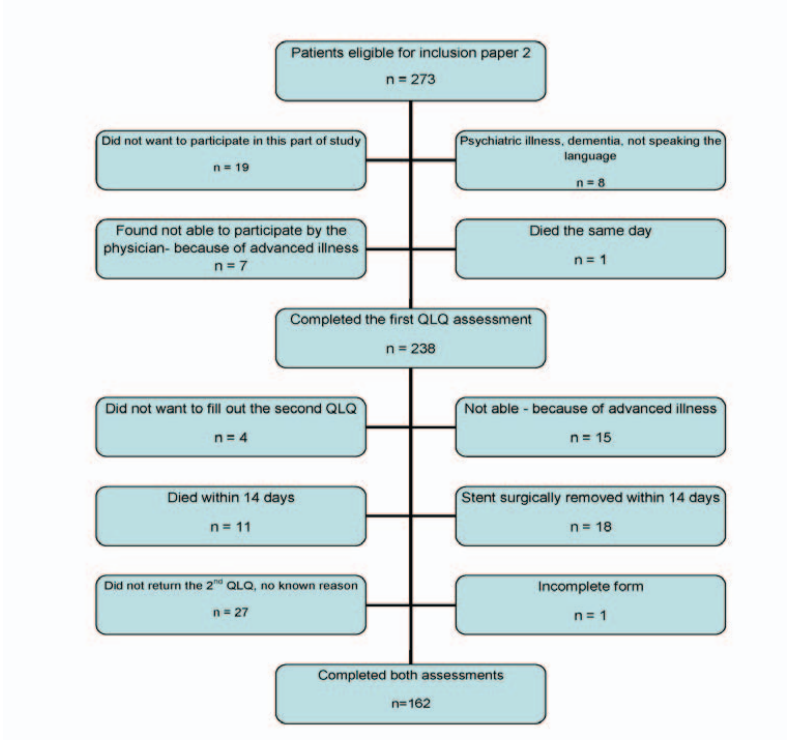


Figure 6: flow-chart illustrating the selection of the 162 patients included in paper 2.

This represents a possible risk of selection bias, however, but we know that these patients did not differ in age, pre-treatment global health, or survival compared to the 162 repliers, which reduces the likelihood. Three of the 27 non-responders experienced stent dysfunctional and needed re-interventions during the first two weeks, which might have influenced their opinion of stent function. We might have overestimated the clinical effect of SEMS treatment if patients without the expected effect chose not to return the 2nd questionnaire.

Instruments used in the assessment QoL/PRO must have a high validity, which means that they measure what they are supposed to measure, for the purpose of this study: changes in QoL. If the questions assessed have no relevance to the patients, we will not be able to measure and detect changes in the patients QoL. Our 38- item questionnaire was feasible and well functioning for most patients, based on the response rate and the low number of missing items. However, 15 patients in a more terminal face of their cancer disease declined to complete the QLQ because it was too extensive. The selected organ specific questions turned out to be well suited since the majority of patients reported having the assessed symptoms to some degree. The exception was the symptom itching that only 50 % of patients with biliary SEMS reported before stent treatment.

To reduce the influence of recall bias, the patients had to complete the initial questionnaire no later than the day after the procedure and the second questionnaire no later than 3 weeks after treatment. Sixty-four patients (40%) completed the first assessment the day after stent insertion, due to emergency stent treatment or pronounced symptoms before treatment. The scorings from patients who completed the pre-treatment questionnaire prior to treatment were similar to patients who completed this the day after treatment, but the risk of recall bias can not be eliminated.

The two-week time span between assessments was chosen to reach the maximum effect of the stent and reduce the impact of disease progression. We decided not to repeat QoL assessments beyond week two because we primarily wanted to study short term outcome of SEMS. We believed that repeated assessment beyond the second week not would add further information and that the influence of the progressive

cancer disease would make the results difficult to interpret. In retrospect, however, we know that repeated assessments would have been possible for many patients and could have added important information about long-term outcomes.

Physician reported outcomes

The physicians assessed the same organ specific symptoms as the patients, first at inclusion and then at hospital discharge or two weeks after stent treatment if the patient was still hospitalized. The study protocol did not require a scheduled follow-up after stent treatment. The patients were often severely ill, with long travelling distance to hospital, and an extra hospital visit to allow the physician to perform a symptom assessment was hence not included in the follow-up. As the hospital stay related to the stent procedure usually was of short duration, the physicians scoring often had to be performed at discharge from the hospital. This led to that the physicians' second assessments were performed earlier than day 7 for 81% of the patients while the patients assessed their symptoms between days 7-14. It is difficult to predict the possible influence of this discrepancy, but physicians might have performed the second assessment before full clinical effect was achieved, and thereby underestimated the clinical effect. However, it is likely that the questionnaire's one week time format (symptoms during the last week are assessed) reduced the influence of the discrepancy between physicians' and patients' second assessment.

Long-term outcomes

Long- term data were collected by a review of the medical journals. Follow-up visits were performed only when needed for the palliatively treated patients since we did not want to burden these often severely ill patients with unnecessary hospital visits. The retrospective collection of data might have led to that minor complications were missed, and that the correct complication rate is higher than estimated. It is unlikely

that major SEMS complications were overlooked since they would have resulted in referral to a public hospital in Norway. The prospectively inclusion of patients improves the data quality compared to retrospective materials.

Power calculations were based on detecting clinically significant changes in the EORTC C-30 global health score, not on detecting significant differences in complications and long-term outcomes. We were able to demonstrate significant differences for several long-term outcomes, but significant differences might have been missed if the included number of patients were too small.

The study population was heterogeneous with regard to cancer type, location of obstruction (proximal-distal) and stage of the cancer disease. This might have influenced the results, but are in accordance with most comparable literature and therefore makes the results comparable [74;143-145]. Furthermore is it likely SEMS as palliative treatment principle can be evaluated independently of cancer type, stage and locations for many outcomes.

The octanoic acid breath test of gastric emptying

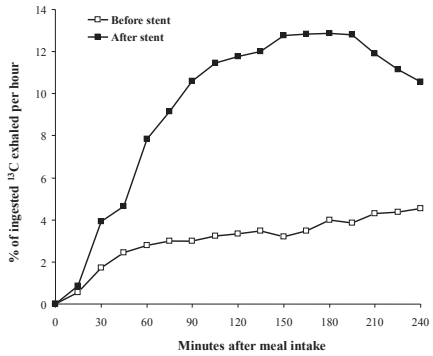


Figure 7: Typical example of the gastric emptying breath curve before and after stent

Scintigraphy is the gold standard to study gastric emptying [146;147], but for the present study, the use of the octanoic breath test was considered more suitable. For patients with advanced cancer disease was it fortunate to perform the test in a sitting position in bed or a comfortable chair, instead in front of a gamma camera. We decided to use a gastric emptying test with a solid meal which is more challenging for the stomach to grind and empty, than a liquid meal, and therefore more comparable to a normal diet. Furthermore, the octanoic breath test is reliable for the study of variation in gastric emptying within subjects[128]. Patients with the most severe symptoms and complete obstruction were not included in the study. According to clinical observations, these patients can expect the best clinical effect of stenting. We do not know whether this has influenced the results, but our patients' selection might have contributed to a underestimation of stent effect on a group level.

Discussion of results

Patient reported outcomes

One of this study's main findings is that the majority of patients reports a significant clinical effect on obstructive symptoms and an improved global health score two weeks after SEMS treatment (paper 2). These finding correspond with studies by Madusudhan[148] (33 patients were treated with esophageal stents) and van Hooft [149] (52 patients treated with gastroduodenal stents). Other comparable studies have not been able to identify improvement in global health, despite a significant clinical improvement in obstructive symptoms [18;19;97;98;150]. It is somewhat unexpected that relief from distressing obstructive symptoms not significantly influences global health score. Patients with advanced cancer have several health issues that can influence the global health score negatively. A review of the medical charts revealed that absence of improvement the scorings often could be explained by dysfunctional stents, migrations, infections, pain, or intercurrent diseases during the first two weeks, but these patients were included in analysis. Ongoing treatment with other modalities (e.g.

chemotherapy) can potentially influence global health negatively, but we found no significant difference in scorings for the 25 patients who received chemo- and/or radiation therapy during the assessment period.

Despite that the importance of QoL/PRO measures frequently is emphasized, surprisingly few publications have contributed to increased knowledge in this field in recent years. There can be several explanations for this, but most likely is the reasons that the use of QLQs are time consuming and the results are difficult to interpret without special knowledge of the questionnaire used. The mean effect for whole group of patients is not easily transferred into clinical decision making for each individual patient. Several efforts have been made to make the results from QoL studies more accessible to clinicians [151-153], and their frequent use in clinical research will increase the understanding over time.

Another argument for the incorporation of PROs in clinical studies is that physicians and patients evaluate symptoms severity differently, underestimation of patients' symptoms by physicians being more common [87-91;154;155]. This trial was the first to compare physicians and patients' assessment of symptoms related to GI-obstruction and the clinical effect of SEMS treatment. We found that physicians reported a significantly better treatment effect compared to the patients. The main reason was that they evaluated the symptoms before treatment as more pronounced than the patients ($p< 0.02$). We do not know the reasons for the discrepancies in scoring found in the present study; but one plausible explanation may reflect the enthusiasm of the physicians performing these procedures and their needs to justify the indication. The evaluation of clinical outcome in clinical trials should preferably be assessed by PROs and a graded scoring by the physicians, since different aspects of the clinical effect is evaluated. This dual assessment can help anchor the PRO results to clinical changes that are more familiar to the physicians.

Long –term outcomes

Short- term outcomes after palliative stent treatment were well documented when we planned this study, but publications on long-term outcomes were sparse. The need for repeated, unpleasant procedures and re-hospitalizations will negatively influence the QoL of patients with limited life expectancy. Knowledge about clinical outcomes measurements beyond the initial technical- and clinical success is hence essential when making decisions about palliative treatment options. We evaluated long-term outcome for 218 patients palliatively treated for malignant GI-obstructions and found that overall 67% had a patent stent without the need of reinterventions their remaining life-time (paper 3). Reobstruction was the most common reason for stent failure (80 %), but stent patency could usually be reestablished with a repeated endoscopic procedure. There were significant differences in outcomes between locations, and factors that might have contributed to this are discussed for each location.

Esophageal stents

Esophageal stents had the highest reintervention rate (41%), which is in accordance with previous literature [156-162]. The esophagus is the "first stop" for food passing through the GI tract, and food-bolus impaction was the reason for 29 % of the reinterventions. Small diameter stents (18 mm) was most commonly used during the study period and can in part explain this finding. Larger diameter and covered SEMS have been developed and have shown to reduce the risk of reobstruction by food or tumor ingrowths[145;163;164] , but fully covered stents are encumbered with a high risk of migration [49;164]. A partially covered SEMS with medium expansive force, diameter 20-23 mm may better serve as a basic stent.

Gastroduodenal stents

Patients treated with gastroduodenal stents had significantly shorter survival compared with the other locations. The reason was that two-thirds of these patients had

advanced gastric (34%) or pancreatic cancer (32%), which often entails short life expectancy. There are studies suggesting that surgical GEA should be considered as an alternative treatment option for patients with longer life expectancy expected survival, due to a lower re-obstruction rate [27;165]. The finding, that 75 % of patients with gastroduodenal stents did not need any re-intervention, suggests that SEMS was an appropriate palliative treatment option for the majority of the patients.

Biliary stents

Biliary SEMS have a longer patency than plastic stents [62] and are usually recommended for patients with an expected survival of more than three- four months [63;166], in order to avoid repeated procedures. Mainly uncovered biliary SEMS were used in the present study, and 70% stayed patent during the remaining lifetime of the patients which was a median of 128 days. Fifty per cent of patients treated with biliary SEMS who were still alive after six months had well functioning stents. This demonstrates that the patient selection was appropriate.

Partially covered- and fully covered biliary SEMS have been introduced to further prolong patency, but the results have not been unequivocal. Early results were promising with regard to increased patency[167;168], but two large RTCs published in 2010 found similar re-intervention rates between covered and uncovered biliary SEMS [169;170]. The initial worries for increased risk of cholecystitis and pancreatitis have not been confirmed [171]. If the problem with migration of covered SEMS can be solved they will become first choice treatment for malignant biliary obstruction.

Colonic stents

As patients with advanced colorectal cancer live longer with the help of modern multimodal treatment of GI cancer, i.e. chemotherapy, anti-angionetic drugs (Bevacizumab) and surgery for metastases, [83;172;173], the number of patients experiencing SEMS-related complications, e.g. stent occlusion and perforation of the colon expected will increase accordingly [143;174-178]. In the present study, long-term

clinical failure was 33 % for 45 patients palliatively treated with colonic SEMS. This is comparable to the failure rates found by Small et al (24 %) [143], Meisner et al (32 %) [78] and other authors [74;177;179-181]. Fernandez-Esparrach et al [182] reported a 51% long-term clinical failure rate, mainly due to migrations and reobstructions. This study, however, has several weaknesses, as 40 % of the obstructions could be passed with the endoscope, and therefore had a questionable indication for stenting and thus a high failure rate due to stent migration.

Colonic perforation is a serious complication to SEMS treatment. The clinical perforation rate in the present series was 5 %, including one late colonic perforation, which is in accordance with comparable literature [143;177;183;184]. There was no perforation related mortality. A literature review by Datye et al[185] evaluated the outcome for patients that experienced perforations related to colonic SEMS. The mortality directly related to the perforation was 0.8 %, and the overall mortality was 16.2 %, which is far less than after emergency surgery for colonic obstruction.

The outcomes after palliative colonic stenting are often reported being better for primary colonic malignancies than extra- colonic malignancies causing colonic obstruction [180;186-188]. The reasons are lower technical success rates, higher rates of clinical failures and complications. The study population consisted of only 8/45 patients with obstructions caused by extra- colonic malignancies, and the outcomes were similar to the main study population. According to personal experiences with complications after stenting of strictures in patients with carcinomatosis and adherent bowel, we have adopted a more reluctant approach to colonic stenting in this group of patients. Our conclusion is nevertheless that palliative treatment with SEMS is a better option than palliative surgery if possible. Our conclusion is strengthened by the fact that patients in this study were included and treated at small local centers, not large expert centers.

Survival

The overall survival in the present study was three months, which is in line with previous publications [5;8;68]. Patients with a short life expectancy should not be exposed to unnecessary procedures with potential serious complications. Therefore, is an estimation of expected survival highly important when making decisions about palliative treatment, but can be very difficult [13-15;189-192]. In retrospect, we treated and included several patients with either very short or very long survival that not were optimal candidates for SEMS and should have been treated with a different palliative option. On the other hand, SEMS treatment was effective palliation to many patients with relatively short survival. Our experience is that several of these patients could have benefitted from an earlier referral for SEMS treatment. A multidisciplinary approach would ensure that palliative cancer patients receive the right palliative treatment, at the optimal time.

Gastroduodenal stents effect on gastric emptying

Our initial review (paper 1) reviled that only 24 % of the publications included had used objective methods to evaluate the GI- function following stent treatment (oral contrast examination), and no studies had performed quantitative tests of gastric emptying.

We found that almost 80% of the patients had a significant improvement in the rate of gastric emptying and close to 90% reported symptomatic improvement after treatment with gastroduodenal stents. The only available previous publication on gastric emptying after treatment with gastroduodenal stents is by Meatani et al [110]. This study used a liquid meal was used to evaluate GE in 14 patients, where 8 patients still had delayed gastric emptying after duodenal stent treatment, but the SEMS effect on gastric emptying could not be evaluated since no emptying test was performed prior to stent treatment. Interestingly, we found a higher proportion of patients with a normal rate of emptying (about 50 %) after treatment, even though we used a solid meal,

which is more challenging for the stomach to grind and empty. Maetanis study population consisted mainly of patients with gastric cancer while we included mainly patients with pancreatic cancer. They used smaller diameter stents (18 mm Ultraflex esophageal stents in 50 % of their patients) while we used a stent with 22 mm diameter in all our patients, which may have contributed to the difference in outcome.

Some patients had no symptomatic effect despite a successfully placed and open stent, and some patients had a symptomatic effect despite little improvement in GE rate. In addition, there was not always a correlation between the endoscopic findings and GE rate. This indicates that other factors are involved in advanced cancer in this location, as neurologic infiltration affecting GE

Another aspect we wanted to explore was if a GE test could be a predictor of expected survival. Jeurninck et al[192] had found that the WHO performance score was the only significant predictor of survival in patients with malignant gastroduodenal obstruction. Van Hooft et al [193], that pain on the EORTC C30 scale and the use of opioid analgetics were significant predictors of survival in the same group of patients. We were not able to detect a relation between survival and gastric emptying, nor were an improved gastric emptying rate related to increased survival. Our conclusion is that if a patient suffers from GOO, should palliative stent treatment should be considered due to its effect on QoL. The gastric emptying test does not add important information that can help in clinical decision making.

Colonic stents as a bridge to surgery

The overall mortality rate after emergency surgery for malignant colonic obstructions is around 20 % [112-114;194-197], and even up to 40 % in patients in ASA class 4[40]. The introduction of SEMS as a BTS in the early 1990 was based on encouraging publications showing that serious treatment complications and creation of stomas could be avoided.

In the present series, we were able to achieve tumour resection with primary anastomosis in 77 % of the patients. Including 4 patients with rectal resections with a low anastomosis on the pelvic floor level, that had a routine protective loop ileostomy in an elective setting. This was achieved with no procedure related mortality, a clinical perforation rate of 5 % and an overall complication rate of 16%. Our results are in line with multiple reviews[10;74;198], observational studies [143;199-202;202-205] and two RCT[206;207]. The premises for SEMS as BTS have been challenged by the findings in two recent RCT's comparing SEMS and emergency surgery [208;209] , an observational study [210] and metaanalyses of the available RTCs [211-215]. A metanalysis Tan et al[211] reported a technical- and clinical success rates of 70 % and 69 % in 234 patients treated with colonic SEMS in an emergency setting. The clinical perforation rate was 7 % and the rate of silent perforations was 14 %. Overall did SEMS intervention lead to a higher rate of primary anastomosis, but there were no difference in mortality or complications between stenting and emergency surgery. A Cochrane review by Sagar 2011[212] concluded that the use of stents in malignant colon obstruction had no advantage over emergency surgery.

What are the explanations for the unexpected inferior results? Firstly, the technical success rates in the two RTCs were unusually low (47% and 70%), which led to very low rates of primary anastomosis when intention to treat analysis was performed. The technical success rate depends on several factors, such as the endoscopist's skills, the grade of stenosis and the location of the obstructing tumour. Van Hooft et al speculate if a higher proportion of complete obstruction (70% - compared to around 50 % in the literature) [143;182], explains the high rate of failed procedures in their series. One has to speculate if the endoscopists possessed the required experience and skills to perform this challenging procedure and if the high rate of complications can be related to the same issue. Secondly, the fairly high mortality rate in the stent group can be influenced by the fact that patients with unsuccessful stent procedures underwent emergency surgery. Thirdly, the exclusion of patients with high surgical risk (ASA 4) might have lowered the mortality in the emergency surgery group, and thereby offset the expected differences between the two groups.

The role of SEMS as BTS is not resolved as we see it. The discussion whether complications to stent placement worsens the oncologic outcome in potentially curable patients has been a long on-going, but studies of long-term outcomes and safety are still sparse and inconclusive [86;204;214] . Data form observational and retrospective studies might be encumbered with selection biases that have led to an overestimation of the positive effect of SEMS, and the evidence from present RCT's is limited by small sample sizes and patients selection. Larger scale studies, preferably RTCs, are required to clarify the safety and oncologic long-term outcome of colonic stents as BTS in obstructing left-sided colorectal cancer. Such trials have proven difficult to conduct, which makes data from prospective observational studies valuable, preferably in the form of treatment registers. Skills in advanced endoscopy are required to use SEMS as BTS successfully in an emergency setting, and thereby achieve the treatment goals which are primary anastomosis and a low rate of complications. Each physician will have to determine if they have the sufficient skills when considering SEMS as BTS in young potentially curable patients.

Conclusions

- A literature review revealed that available reports regarding the clinical outcome of treatment with gastroduodenal stents were insufficient. Relevant information of the clinical outcome was lacking, and few studies had utilized objective parameters to evaluate outcome and no studies had assessed PRO.

- Patients evaluate treatment with SEMS as effective in relieving symptoms related to malignant GI-obstruction. SEMS as palliative principle seems to be effective independently of location. Our conclusion is strengthened by the fact that patients in this study were included and treated at small local centers, not large expert centers.

- The present study demonstrates a significant difference in how the physicians and patients evaluate treatment effects and thereby emphasizes the importance of taking patient reported outcomes into account when evaluating clinical palliative interventions.

- Long-term outcomes demonstrated that palliative treatment with SEMS was safe and that 70 % of the patients did not need any reintervention for obstructive symptoms. Reobstruction was the reason for 80 % of the stent failures, but could usually be solved with a repeated endoscopic procedure. There are significant differences in patency and survival between the four stent locations. The prevalence of serious adverse events for all stent localizations was low.

- Almost 80% of the patients treated with gastroduodenal stents had a significant improvement in the rate of gastric emptying. This indicates that if a patient

suffers from GOO, palliative stent treatment should be considered. The improved rate of emptying does not seem to have effect on survival.

- Treatment with colonic stents as bridge to surgery was safe in patients with left-sided large bowel obstruction; there was no procedure related mortality and few serious complications. Stenting was effective in avoiding the use of a diverting stoma.

Clinical implications

This study confirms that palliative treatment with SEMS represents a safe and effective treatment for most patients with malignant GI- and biliary obstruction. It can be expected that around 70 % will have a patent stent until death, and that if reobstructions occurs, can this be could solved with a repeated endoscopic procedure. This study confirms that the treatment can be performed with good results in a decentralized manner, as in Norway.

Patients and physicians can evaluate the severity of symptoms differently. The use of PRO adds important information about treatment outcome in clinical trials, but can also be used everyday clinical practice to identify and priorities the patients' problems before a consultation, and improve the delivery of palliative care.

BTS can be performed safely in the majority of patients with left-sided colonic cancer and effectively prevent stomas, but skills in advanced endoscopy are required to achieve a technical success rate and avoid serious complications. It is unresolved whether SEMS as BTS adversely affects oncologic in patients treated with curative intent. The potential risks emergency surgery and stents have to be weighed against each other for every individual patient.

Future perspectives

Palliative stenting of malignant gastrointestinal obstruction is considered a safe and effective treatment option for most patients, but there are issues that need further investigation and clarification.

Further development of covered SEMS anti- migration properties is important. Increased knowledge about the optimal balance between stents diameter, length, radial- and expansive forces will improve clinical success rates and reduce the rate of complications. There seems to be an association between esophageal SEMS, radiation therapy and increased risk of esophago-tracheal fistulas, but results from clinical trails are divergent. It seems like the timing of the two treatment modalities are important, and this requires further investigation. Prospective randomized trials would be the gold standard to clarify these issues, but it has proven difficult to include the sufficient number of patients to be able to draw conclusions.

The establishment of a national SEMS register could be a possible way to collect data large enough to clarify unanswered questions and develop national treatment guidelines. The Cancer Registry of Norway possesses detailed information about the cancer prevalence in Norway. Combined data from this two registers would provide important information about SEMS prevalence's and differences between health regions

There use of SEMS as BTS in patients with curative colonic cancer has been under reevaluation in recent years. Theoretically SEMS related complications can lead to tumor dissemination and unfavourable oncologic outcome in potentially curable patients. Our opinion is that RCTs are encumbered to many weaknesses to draw final conclusions about the use of SEMS as BTS and further investigations are needed. It is unlikely that RTCs good and large enough to settle these issues it will be conducted and therefore are prospective data from treatment registers important.

Erratum

Paper 3 page 1509: Survival gastroduodenal stents, corrected from 64 (1-113) to 64 (1-413).

Appendices

ULLEVÅL universitetssykehus

Pasientinformasjon og forespørsel om deltagelse i en undersøkelse:

Bruk av stenter ved kreft i mage-tarmkanalen

Hensikt med undersøkelsen

Ved kreft i mage-tarmkanalen vil kreftsvulsten etter hvert kunne lage et passasjehinder som gir forskjellige plager avhengig av hvor svulsten sitter. Du vil få behandling for dette med en selvekspanderende metallstent (SEMS) . Dette er et nettingrør av metall som legges inn ved hjelp av instrumenter som brukes ved endoskopisk undersøkelse. Røret vil legges igjennom svulsten og lage en åpning som vil lindre plagene som skyldes trang passasje.

Innlegging av SEMS er et nytt behandlingsprinsipp som har vist seg å være et godt og trygt alternativ til kirurgi. Komplikasjoner er sjelden, og vanligvis ikke alvorlige. Bruken og effekten av innleggelse av SEMS er imidlertid ikke tilstrekkelig studert. Denne undersøkelsen har derfor som formål å studere bruken og nytten av behandlingen.

For å gjennomføre undersøkelsen ønsker man å registrere opplysninger knyttet til alle innleggelser av SEMS i Osloregionen i løpet av en 2 års periode. Hos en utvalgt gruppe pasienter vil man spesielt kartlegge effekten av behandlingen med tanke på hvordan pasientene selv opplever nytten av denne.

Konsekvenser for deg

Dersom du velger å delta i undersøkelsen betyr dette i første omgang at du vil bli bedt om å svare på noen spørsmål angående plagene dine forut for behandlingen. Ved hjemreise fra sykehuset vil du få med deg et skjema med spørsmål som du skal svare på 2 uker etter behandlingen og som deretter sendes tilbake til oss

i posten. I tillegg vil vi registrere en del data rundt selve behandlingen du får. Disse dataene hentes fra din journal.

Opplysningene vil bli lagret i ett avidentifisert register ved Ullevål universitetssykehus. Et prosjektnummer knytter deg som person til prosjektet gjennom en navneliste. Kun prosjektansvarlig har adgang til navnelisten. Etter at undersøkelsen er avsluttet og resultatene er ferdig analysert vil navnelisten slettes, senest i juni 2011. Alle opplysningene i denne undersøkelsen vil bli behandlet konfidensielt. Personvernet ivaretas i samsvar med betingelser gitt i melding til personvernombudet ved Ullevål sykehus.

Dine rettigheter

Det er helt frivillig å delta i undersøkelsen. Du kan når som helst be om innsyn eller trekke deg fra registeret uten at du må gi noen forklaring. Du har rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Hvis du på et senere tidspunkt velger å trekke deg fra studien, kan du kreve at opplysninger om deg slettes. Ved henvendelse til prosjektansvarlig kan du få nærmere opplysninger om dette.

Denne undersøkelsen er kun en registrering og om du velger å ikke delta i studien vil dette ikke få konsekvenser for den behandlingen du får. Ditt bidrag er imidlertid viktig for at vi skal kunne gi pasienter best mulig behandling.

Regional komité for medisinsk forskningsetikk, Øst-Norge har vurdert prosjektet, og har ingen innvendinger mot at dette gjennomføres.

Prosjektansvarlig/Mer informasjon

Hvis du har spørsmål om studien, kan du kontakte din lege eller prosjektansvarlig:
Dr.Lene Larssen, gastromedisinsk avdeling Ullevål universitetssykehus.Tlf.93041073/22119100, e-post: lene.larssen@ulleval.no eller lene.larssen@medisin.uio.no

EORTC QLQ-C30 (version 3.0.)

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette en ring rundt det tallet som best beskriver din tilstand. Det er ingen "riktige" eller "gale" svar. Alle opplysningene vil bli behandlet konfidensielt.

		Ikke i det hele tatt	Litt	Endel	Svært mye
1.	Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	1	2	3	4
2.	Har du vanskeligheter med å gå en lang tur?	1	2	3	4
3.	Har du vanskeligheter med å gå en kort tur utendørs?	1	2	3	4
4.	Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	1	2	3	4
5.	Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	1	2	3	4

I løpet av den siste uka:

		Ikke i det hele tatt	Litt	Endel	Svært mye
6.	Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	1	2	3	4
7.	Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	1	2	3	4
8.	Har du vært tung i pusten?	1	2	3	4
9.	Har du hatt smerter?	1	2	3	4
10.	Har du hatt behov for å hvile?	1	2	3	4
11.	Har du hatt søvnproblemer?	1	2	3	4
12.	Har du følt deg slapp?	1	2	3	4
13.	Har du hatt dårlig matlyst?	1	2	3	4
14.	Har du vært kvalm?	1	2	3	4

Bla om til neste side

I løpet av den siste uka:	**Ikke i det hele tatt**	**Litt**	**Endel**	**Svært mye**
15. Har du kastet opp?	1	2	3	4
16. Har du hatt treg mage?	1	2	3	4
17. Har du hatt løs mage?	1	2	3	4
18. Har du følt deg trett?	1	2	3	4
19. Har smerter påvirket dine daglige aktiviteter?	1	2	3	4
20. Har du hatt problemer med å konsentrere deg, f.eks. med å lese en avis eller se på TV?	1	2	3	4
21. Har du følt deg anspent?	1	2	3	4
22. Har du vært engstelig?	1	2	3	4
23. Har du følt deg irritabel?	1	2	3	4
24. Har du følt deg deprimert?	1	2	3	4
25. Har du hatt problemer med å huske ting?	1	2	3	4
26. Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	1	2	3	4
27. Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	1	2	3	4
28. Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	1	2	3	4

Som svar på de neste spørsmålene sett en ring rundt det tallet fra 1 til 7 som best beskriver din tilstand

29. Hvordan har din helse vært i løpet av den siste uka?

1	2	3	4	5	6	7
Svært dårlig						Helt utmerket

30. Hvordan har livskvaliteten din vært i løpet av den siste uka?

1	2	3	4	5	6	7
Svært dårlig						Helt utmerket

Endel pasienter opplever av og til at de har noen av følgende symptomer eller problemer. Vær vennlig å angi i hvilken grad du har hatt disse symptomene eller problemene i løpet av den siste uka. Sett en ring rundt det tallet som best beskriver din tilstand.

I løpet av den siste uka:	**Ikke I det hele tatt**	**Litt**	**Endel**	**Svært mye**
31. Har du hatt problemer med å innta fast føde?	1	2	3	4
32. Har du hatt problemer med å innta moset eller bløt føde?	1	2	3	4
33. Har du hatt problemer med å innta væske?	1	2	3	4
34. Har du følt ubehag ved spising?	1	2	3	4
35. I hvilken grad har huden din vært gul?	1	2	3	4
36. Har du hatt kløe?	1	2	3	4
37. Har du hatt magesmerter?	1	2	3	4
38. Har du hatt oppblåst mage?	1	2	3	4

Sendes til: Dr.Lene Larssen, gastromed.avd.Ullevål Universitetssykehus

Kirkeveien 144, 0407 Oslo. Ved spørsmål ring: 93041073

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Ref Type: Online Source

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Treatment of malignant gastric outlet obstruction with stents: An evaluation of the reported variables for clinical outcome

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Abstract

Background: Malignant gastric outlet obstruction (GOO) is commonly seen in patients with advanced gastric-, pancreatic-, duodenal, hepatobiliary or metastatic malignancies. Ten to 25% of patients with pancreatic cancer will develop duodenal obstruction during the course of the disease. Duodenal stenting with self-expandable metal stents is an alternative treatment to surgical bypass procedures. Our aim was to review the published literature regarding treatment of malignant GOO with stents to reveal whether the information provided is sufficient to evaluate the clinical effects of this treatment

Methods: A literature search from 2000 – 2007 was conducted in Pub Med, Embase, and Cochrane library, combining the following search terms: duodenal stent, malignant duodenal obstruction, gastric outlet obstruction, SEMS, and gastroenteroanastomosis.

All publications presenting data with ≥ 15 patients and only articles written in English were included and a review focusing on the following parameters were conducted: 1) The use of graded scoring systems evaluating clinical success; 2) Assessment of Quality of life (QoL) before and after treatment; 3) Information on stent-patency; 4) The use of objective criteria to evaluate the stent effect.

Results: 41 original papers in English were found; no RCT's. 16 out of 41 studies used some sort of graded scoring system. No studies had objectively evaluated QoL before or after stent treatment, using standardized QoL-questionnaires, 32/41 studies reported on stent patency and 9/41 performed an oral contrast examination after stent placement. Objective quantitative tests of gastric emptying had not been performed.

Conclusion: Available reports do not provide sufficient relevant information of the clinical outcome of duodenal stenting. In future studies, these relevant issues should be addressed to allow improved evaluation of the effect of stent treatment.

Background

Malignant gastric outlet obstruction (GOO) is commonly seen in patients with advanced gastric-, pancreatic-, duodenal, hepatobiliary or metastatic malignancies. Ten to 25% of patients with pancreatic cancer will develop duodenal obstruction during the course of the disease [1,2].

GOO may result in nausea and vomiting, leading to dehydration and cachexia, which severely reduces the patients' Quality of Life (QoL).

Traditionally, a surgical by-pass procedure, usually a gastrojejunoanastomosis (GEA), has been the palliative treatment offered, but up to 31% of the patients do not experience sufficient symptom relief following GEA [1,3]. Furthermore, GEA has a peri-operative morbidity as high as 35% and a mortality rate of about 2% in later studies [1,4-7].

Duodenal stenting with self-expandable metal stents (SEMS) is an alternative treatment to surgical bypass procedures. In several studies, this treatment has been evaluated as safe and efficient with a technical success rate of 90–100%, a clinical success rate of 67–100%, a rate of severe complications about 7% and non-severe complication rate about 20% [2,6-8,8-47]. Compared with surgery, the patients treated with stents have fewer serious complications and less need for intensive care unit (ICU) [5] Furthermore, the hospital stay is shorter, which is essential in palliative treatment [5,9,20,32,7].

In palliative cancer treatment, improvement of QoL is a primary goal and needs to be addressed when new treatment strategies and procedures are implemented and evaluated. Relief from obstructive symptoms is the most important parameter for evaluating the clinical effect or treatment outcome following duodenal stenting of GOO, but complications, stent patency and need for re-interventions are also parameters influencing QoL. In the available reports, objective criteria of treatment effects are often missing, which make it difficult to compare results and draw conclusions concerning effects of the treatment offered.

To review the published literature regarding treatment of malignant GOO with stents to reveal whether the information provided is sufficient to evaluate the clinical effects of this treatment, and whether QoL has been assessed.

Methods

A search for published literature for the time period January 2000 – September 2007 was conducted in Pub Med, Embase, and Cochrane library, combining the following search terms: duodenal stent, malignant duodenal obstruction, gastric outlet obstruction, SEMS, and gastroenteroanastomosis. Reference lists were hand-searched for additional literature. Furthermore, reference lists of review articles and metaanalyses from the relevant time period were used to identify additional literature. Abstracts were not included. Only studies presenting data with ≥ 15 patients and only articles written in English were included in the present review. When studies included identical patients, the most recent study was included.(see additional file 1)

The identified studies were reviewed with regard to the following parameters:

1. The use of a graded scoring systems evaluating clinical success

2. Assessment of QoL before and after treatment

3. Information on stent-patency

Stent patency defined as the time period without need for re-intervention

4. The use of objective criteria to evaluate the stent effect

Results

When applying the search criteria, 41 original papers and four review articles in English were found (See table 1). The number of patients included in the original papers was 15–213. Of the studies using a combined endoscopic/fluoroscopic method for stent placement ten were prospective and 18 retrospective, corresponding numbers for the studies in which only fluoroscopy was applied were 10 and three, respectively. All prospective and retrospective studies are listed in table 2 and 3 respectively. No randomized controlled trials (RTC's) treating ≥ 15 patients with stents were found.

Clinical effect and scoring systems

To evaluate the clinical effects of stent treatment, 16 out of 41 studies used some sort of graded scoring system (see table 4). The level of oral intake before and after stent treatment was divided into four to five levels, which

Table 1: Characteristics of studies included in the review (n = 41)

Characteristics	n (% of total)
Prospective studies	20 (49%)
Retrospective studies	21 (51%)
Stent deployed by fluoroscopic guidance	13 (32%)
Stent deployed by combined endoscopic/fluoroscopic guidance	28 (68%)

Table 2: Prospective studies

Author	Year	Patients (n)
Jung (16)	2000	**19**
Lopera (11)	2001	**16**
Pabon (12)	2001	**29**
J.H. Kim (13)	2001	**29**
Park (14)	2001	**24**
Jung (17)	2002	**39**
Lee(21)	2003	**17**
Tang (22)	2003	**21**
Nassif (23)	2003	**63**
Holt (26)	2004	**28**
Jeong (27)	2004	**25**
Johnsson (5)	2004	**21**
Hayashi (47)	2005	**31**
Yoon (35)	2006	**82**
Espinel (36)	2006	**24**
Song (42)	2007	**20**
Mutignani(43)	2007	**64**
J.H Kim (41)	2007	**213**
Lowe(44)	2007	**87**
Maetani (45)	2007	**37**

allows some comparison of the results. The scoring systems used are adapted from studies on dysphagia in esophageal cancer. One of the most frequently used is **G**astric **O**utlet **O**bstruction **S**coring **S**ystem (GOOSS) presented by Adler in 2002 [2] (0 = no/inadequate oral intake, 1 = liquids/thickened liquids, 2 = semisolids/low residue diet, 3 = unmodified diet). This system assigns a point score based on the level of oral intake. Song et al

Table 3: Retrospective studies

Author	*Year*	*Patients (n)*
Yim (9)	2001	**29**
Razzaq (10)	2001	**23**
Aviv (18)	2002	**15**
Maetani (15)	2002	**23**
Adler (2)	2002	**36**
M. Kaw (19)	2003	**18**
Mittal (6)	2003	**16**
Stawawy (20)	2003	**24**
G.H. Kim (24)	2004	**49**
Lindsay (25)	2004	**40**
Telford (29)	2004	**176**
Mosler (30)	2005	**36**
Bessoud (32)	2005	**72**
Del Piano (31)	2005	**24**
Maetani (7)	2005	**22**
Maire (33)	2006	**24**
Kazi (34)	2006	**23**
Kiely (37)	2007	**30**
T.O. Kim (40)	2007	**53**
J. van Hooft (38)	2007	**62**
Jeurnink (8)	2007	**53**

Table 4: Evaluation criteria applied in the reviewed studies (n = 41)

Evaluation criteria	n (% of total)
Quality of Life assessment	0
Objective criteria for stent function	9 (22%)
Clinical effect by graded scoring	15 (37%)
Stent patency	33 (80%)

[48] introduced another similar scoring system (0 = able to eat normal diet, 1 = able to tolerate fragmented solid food without vomiting, 2 = able to tolerate soft food without vomiting, 3 = able to tolerate only liquid diet without vomiting, 4 = not able to tolerate any oral intake without vomiting, 5 = vomiting even without oral intake), mostly used in radiological literature, in which vomiting as an important symptom of obstruction is included. The GOOSS score was applied by 6/41 studies, 1/41 applied the Song score and 8/41 used similar graded scores. Furthermore, in 2007 Lowe et al introduced a Gut function score (0 = profuse vomiting or gut not functioning, 1 = nausea and occasional vomiting, 2 = nausea only, 3 = normal gut function). This function score is used in addition to GOOSS and grades the level of nausea and vomiting. At present, the Gut Function Score has only been applied in the study, in which it was originally presented [44].

QoL in the evaluation of clinical success

No studies had objectively evaluated QoL before or after stent treatment, using standardized QoL-forms (see table 4). Seven of 41 studies used the Karnofsky performance scale before and after stent treatment (A physical performance scale from 100-0, where a scoring of 100 is normal function and 0 is dead).

Stent patency

Concerning stent patency, 32/41 studies reported on this variable (see table 4), either by reporting the exact number of stent failures and time to failure after stent deployment or by calculating the patency. The rate of re-obstruction was reported in 36/41 studies, the migration rate in 34/41 studies.

Objective criteria for stent function

An oral contrast examination was performed after stent placement in 9/41 studies (see table 4). Objective quantitative tests of gastric emptying before and after treatment were not performed in any of the evaluated studies.

Discussion

The present review demonstrates that a graded scoring system for symptom assessment was used in 40% of the evaluated papers. No studies provided information on QoL, although 17% of the studies used the Karnofsky scale.

Information on stent patency was given in 80% of the studies and 22% had performed oral contrast examination following stent placement to objectify the stent effect. No studies quantified the effect of stent placement on rate of gastric emptying.

The main complaints of patients suffering from malignant duodenal obstruction are often nausea, severe vomiting, bloating and abdominal pain. It is questionable whether the applied scoring systems in the papers reviewed provide adequate and sufficient information about relief from these symptoms after stent placement. Improvement of symptoms estimated by a dysphagia score provides limited information concerning the effect of duodenal stenting, and should thus be used in combination with a scoring system providing information about the more characteristic symptoms of GOO. The Gut Function Score may be a step in the right direction [44], but this scoring system needs further evaluation and validation.

In the present review, no studies were identified using standardized forms to assess QoL before and after stent treatment. One randomized study used SF-36 to evaluate the QoL in 10 patients treated with duodenal stents [49], which is a validated and frequently used QoL questionnaire. This study was, however, too small for inclusion in this review. In 16% of the studies, the Karnofsky scale was used, but this scale captures only one aspect of QoL (physical function) and is today considered inadequate for evaluation of QoL [51]. Also for surgical treatment of GOO, data on the effect of QoL is limited [3]. There have been developed and validated several complex and advanced questionnaires for specific symptoms and specific diseases for the assessment of QoL [51]. EORTC C30 and the organ specific modules are now widely used for the evaluation of palliative cancer treatment. By applying these validated tools, the information about the QoL of patients is improved, and a possible discrepancy between the QoL of the patient estimated by the physician and the patient might be revealed. Studies regarding QoL in palliative cancer treatment have shown that physicians tend to overestimate improvement in QoL of the patients [52,53].

Stent-patency related to survival is an important parameter, because the need for re-interventions and re-hospitalizations most likely will reduce the patients QoL. Re-obstruction of the stent by tumor in- and overgrowth is known to occur in 15–20% of the patients [28] and is probably the most important factor influencing stent patency.

The main effect of stent treatment in GOO is re-establishing the passage of food from the stomach to the duodenum. Evaluation of the stent effect can hence be provided by measuring the rate of gastric empting before and after stent placement. None of the reviewed studies included information on this issue. In a recent study by Maetani et al, delayed gastric emptying of a liquid meal after stent placement was demonstrated. The patients resumed oral intake after stenting and those with a severe delay of emptying had a reduced survival time [54]. Rate of gastric emptying was, however, only recorded after stenting, and the quantitative effect of stenting was thus not revealed. More detailed data on the effect of stenting on rate of gastric emptying is thus required, and can be used to improve the knowledge on the relation between GOO and obstructive symptoms. This is an important issue, since the relation between gastrointestinal symptoms and gastric emptying might be rather weak [55]. Furthermore, knowledge concerning the effect of SEMS on gastric emptying could possibly help identifying subgroups of patients, in which stenting is particularly beneficial. Gastric emptying is a complex process involving grinding and emptying of the meal, and it is not likely that the re-establishment of passage is followed by a more rapid rate of gastric emptying in all subjects treated.

Conclusion

Only 40% of the studies reviewed used a graded scoring system to evaluate the clinical effect of their treatment. Furthermore, most studies using a graded scoring system applied a point score adapted from dysphagia in esophageal cancer and did thereby not address the symptoms more specific for GOO. The presence of obstructive symptoms (severe vomiting, nausea and bloating) is probably severely reducing the patients QoL. In palliative cancer care, improvement of QoL is a main treatment goal, and data on this issue are missing in all the evaluated papers. Objective evaluation of gastric/duodenal function after stenting is limited and no studies have performed quantitative tests of gastric emptying. The present review thus indicates that the available reports do not provide sufficient relevant information of the clinical outcome of duodenal stenting. In future studies, these relevant issues should be addressed to allow improved evaluation of the effect of stent treatment.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LL performed the systematic search and drafted the manuscript in cooperation with AWM and TH. All three authors have read and approved the final manuscript.

Additional material

Additional file 1
supplementary file including all details concerning the search.
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ORIGINAL ARTICLES

Patient-reported outcomes in palliative gastrointestinal stenting: a Norwegian multicenter study

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Abstract
Background The clinical effect of stent treatment has been evaluated by mainly physicians; only a limited number of prospective studies have used patient-reported outcomes for this purpose. The aim of this work was to study the clinical effect of self-expanding metal stents in treatment of malignant gastrointestinal obstructions, as evaluated by patient-reported outcomes, and compare the rating of the treatment effect by patients and physicians.
Methods Between November 2006 and April 2008, 273 patients treated with SEMS for malignant GI and biliary obstructions were recruited from nine Norwegian hospitals. Patients and physicians assessed symptoms independently at the time of treatment and after 2 weeks using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire supplemented with specific questions related to obstruction.
Results A total of 162 patients (99 males; median age = 72 years) completed both assessments and were included in the study. A significant improvement in the mean global health score was observed after 2 weeks (from 9 to 18 on a 0–100 scale, $P < 0.03$) for all stent locations.

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Both patients and physicians reported a significant reduction in all obstruction-related symptoms (>20 on the 0–100 scale, $P < 0.006$) after SEMS treatment. The physicians reported a larger mean improvement in symptoms than did the patients, mainly because they reported more severe symptoms before treatment.

Conclusion SEMS treatment is effective in relieving symptoms of malignant GI and biliary obstruction, as reported by patients and physicians. The physicians, however, reported a larger reduction in obstructive symptoms than did the patients. A prospective assessment of patient-reported outcomes is important in evaluating SEMS treatment.

Keywords Stents · Palliative care · Gastrointestinal cancer · Biliary tract neoplasm · Outcome assessment · Quality of life

Palliative treatment with self-expanding metal stents (SEMS) is regarded as a safe and highly effective procedure for relief of symptoms caused by malignant obstructions of the gastrointestinal (GI) tract [1–8]. Most studies concerning treatment with SEMS, whether randomized, comparative, or merely descriptive, focus on technical success (e.g., correct deployment of the stent), clinical success (restored passage), procedure-related complications, and cost-effectiveness. Typically, the clinical outcomes of SEMS treatment have been evaluated by the physician [9]; only a few prospective studies reported repeated symptom assessments by the patient [10–16]. Since patients' and physicians' ratings of treatment effects do not always correspond well, palliative treatment efforts such as SEMS for malignant GI obstructions should be evaluated by individual outcome measures reported by the patients as well as by the physicians [17–22].

The main objective of this multicenter study was to use patient-reported outcomes to evaluate the treatment effects of SEMS on quality of life (QoL) and symptoms related to malignant GI and biliary obstruction. An additional aim of the study was to compare patient- and physician-reported evaluations of the treatment's effects.

Materials and methods

Nine Norwegian hospitals performing SEMS treatment for GI obstructions participated in the present study. The inclusion period was from November 2006 to April 2008. Patients were eligible for consecutive inclusion according to the following criteria: (1) symptoms related to malignant GI obstruction, (2) indication for treatment with all types of metal stents established, (3) fluency in oral and written Norwegian, and (4) cognitive capability to complete the questionnaires. Patients who received their colonic stent as a "bridge to surgery" (i.e., to relieve the acute obstruction prior to elective surgery) and underwent bowel resection within 2 weeks after stent placement were not asked to complete the questionnaire after 2 weeks and were thus not included in the analyses. The study was approved by the Regional Committee for Medical Research Ethics in Southern Norway and the Data Protection Supervisor at Oslo University Hospital, Ullevål. All patients received oral and written information about the study. Written informed consent was obtained from all participants.

Stent procedure

All stents were deployed endoscopically under fluoroscopic guidance. Both covered and uncovered stents were used for esophageal and biliary stent treatment, while uncovered stents were used in other locations.

Assessment of patient-reported outcomes

The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire, EORTC QLQ-C30, version 3.0 [23], was used to assess patient-reported outcomes, supplemented with selected questions from other relevant EORTC organ- and disease-specific modules (http://www.eortc.be/). The EORTC QLQ-C30 is a cancer-specific 30-item self-reporting questionnaire consisting of both multi-item scales and single-item measures. These include five functional scales (i.e., physical, role, cognitive, emotional, and social), three symptom scales (i.e., fatigue, nausea/vomiting, and pain), and six single items (i.e., dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems), as well as two questions where the patients assessed their overall health and QoL on a scale from 1 to 7. Combining these two scores resulted in a global health score.

EORTC recommends that organ-specific modules be used in addition to the core questionnaire to capture diagnosis- or treatment-specific problems. For the purpose of the present study, a selection of questions was made from the relevant organ-specific modules to reduce the respondent's burden and to focus on specific problems pertaining to the different diagnostic or stent groups. Questions to be answered by the patients receiving esophageal, biliary, and colonic stents were selected from the stomach module EORTC QLQ-STO22 [24], the pancreatic module EORTC QLQ-PAN26 [25], and the colorectal module EORTC QLQ-CR38 [26], respectively (Table 2). Patients who received gastroduodenal stents did not answer any

additional questions as their main obstruction-related symptoms, nausea and vomiting, were specifically addressed by the core questionnaire.

Higher scores on the symptom scales and single items from the core questionnaires and the organ-specific modules indicated more severe symptoms, while higher scores on the functional scales indicate better functioning. All items were to be answered on an ordinal scale ranging from 1 ("Not at all") to 4 ("Very much"), except for the two modified visual analog scales assessing global health and QoL; they ranged from 1 to 7. The time frame was the past 7 days. Scale and item scores were transformed into a continuous scale from 0 to 100, as described in the EORTC Scoring Manual [27]. A mean score difference of 5–10 is usually regarded as a small but clinically noticeable change for the patients, a change between 10–20 as moderate, and >20 as a large clinical change [28, 29].

Administration of questionnaires

All assessments were performed twice, at inclusion (−2 to +1 day before/after the procedure) and 2 weeks after treatment. The questionnaire was administered to the study participants upon admission by the treating physician or a study nurse. The same questionnaire was given to the patients when leaving the hospital. The patients were instructed to complete the second questionnaire 2 weeks after stent treatment and return it by mail. The 2-week time span between assessments was chosen to reach the maximum effect of the stent treatment and reduce the impact of disease progression. To reduce the influence of recall bias, the patients had to complete the initial questionnaire no later than the day after the procedure and the second questionnaire no later than 3 weeks after treatment. The physicians assessed the same organ-specific symptoms at inclusion and the second assessment at hospital discharge or 2 weeks after stent treatment if the patient was still hospitalized. The same physician was responsible for the before and after assessment of symptoms.

Statistical analysis

Power calculations were based on a mean change of 10 with a standard deviation (SD) of 15 of global health, with 90% power and a 5% level of significance, which yielded a sample size of 26 patients in each of the treatment groups for the four stent locations. Wilcoxon signed-rank test with 5% significance level was used when evaluating changes of symptoms before and after treatment. Statistical analyses were performed using SPSS 16.0 (SPSS, Inc., Chicago, IL).

Results

Patient characteristics

A total of 273 patients were eligible for inclusion in the study, varying from 2 to 105 patients at the nine participating centers. Two hundred thirty-eight (87%) patients completed the questionnaire prior to the stent procedure, and 162 (68%) of these completed both questionnaires. Twenty-seven patients did not return the second form for unknown reasons (Fig. 1). Ninety-nine males and 63 females with a median age of 72 years were included. Clinical and demographic characteristics are given in Table 1. The most frequent diagnoses were cancer of the colon and pancreas. Of the 18 patients with gastric cancer who received stents, eight had obstructions located in the cardia ventriculi and were treated with esophageal stents. Ten patients had gastric outlet obstruction and were treated with duodenal stents.

Patient-reported outcomes

Patients reported a clinically and statistically significant reduction in all obstruction-related symptoms in all four stent locations, with a mean reduction of at least 20 ($P < 0.02$). Furthermore, a clinically and statistically significant improvement in global health function ($P < 0.03$) was observed in all treatment groups. Additionally, various other symptoms improved significantly: nausea/vomiting (colon and biliary), appetite loss (biliary and gastroduodenal), pain (gastroduodenal and colonic), and constipation (colonic) (Tables 2, 3, 4, and 5). The total numbers of patients experiencing symptomatic improvement ≥ 20, improvement < 20, or worsening are reported in Table 6.

The scorings from patients who completed the pre-treatment questionnaire before treatment were similar to those from patients who completed it the day after treatment. Sixty-four patients (40%) completed the first assessment the day after stent insertion because of emergency stent treatment or pronounced symptoms before treatment. The rate of missing items was low, 0.9 and 1.0% in the two assessments, respectively. For the multi-items scales, missing values were assigned according to a standard scoring procedure (EORTCs scoring manual, [27]) by replacing missing items with the scale mean values, provided that half or more of the scale items were completed.

Comparison of symptoms evaluated by patients and physicians

When comparing the patients' and physicians' scores, a significant difference in the answers of six of seven

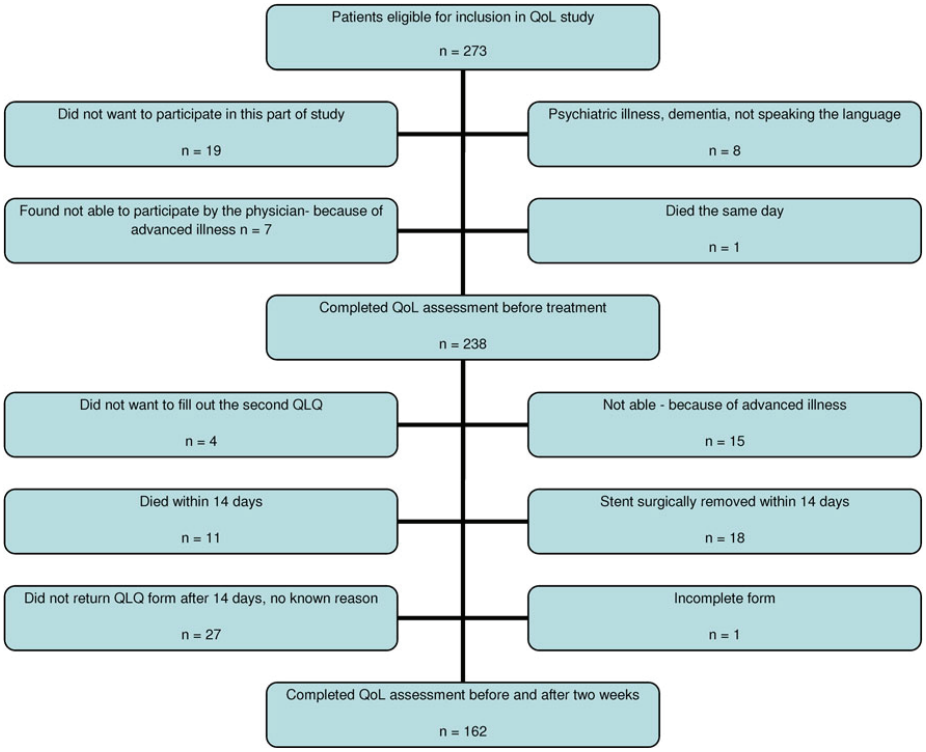

Fig. 1 Flowchart showing the selection of the 162 patients included in this study

questions before treatment was found, whereby the physicians indicated symptoms as more pronounced than the patients ($P < 0.02$). However, when comparing the post-treatment evaluation, the scores tended to be similar (a statistically significant difference was found for two questions, see Table 7). When evaluating the clinical effect as an improvement in obstructive symptoms, the physicians reported a larger mean reduction in obstructive symptoms and, thus, a better treatment effect as compared to the patients.

The median hospital stay was 4 days (range = 0–64). Therefore, physicians completed their second symptom assessment <7 days after the first registration in (131/162) 81% of the cases. The patients completed their second assessment of symptoms after 2 weeks (assessing symptoms between days 7 and 14).

Short-term outcome/complications

During the first week, 12 of 162 patients (7%) experienced complications: three nonfunctional stents, two stent migrations, two bleeding episodes, two episodes of cholangitis, one tracheal-esophageal fistula, one stent obstruction by food impaction, and one stent obstruction by tumor overgrowth. There was no procedure-related mortality.

Discussion

This study is one of very few that evaluates the symptomatic effect of palliative GI stenting based on patient-reported outcomes. Furthermore, to our knowledge it is the first to compare patients' and physicians' assessments of the symptomatic effect of SEMS treatment. The present study demonstrates that the majority of patients found treatment with SEMS effective in relieving obstructive symptoms in all GI tract locations. Additionally, patients reported a significant clinical improvement in global health after 2 weeks for all four stent locations. The physicians tended to evaluate pretreatment symptoms as more severe than did the patients. The postprocedure scorings were more similar.

This study shows that treatment with SEMS is effective in relieving symptoms related to malignant GI obstruction.

Table 1 Clinical and demographic characteristics of 162 patients treated by self-expanding metal stents for malignant gastrointestinal obstruction

Age [median (range)]	72 (33–93)
Gender M/F	99/63
Survival [median (range)] (days)	111 (15–535)
Diagnoses	
Colon cancer	49 (30%)
Pancreatic cancer	41 (25%)
Gastric cancer	18 (11%)
Esophageal cancer	28 (17%)
Bile duct cancer	9 (6%)
Other malignancies[a]	17 (11%)
Other palliative treatment	
Chemotherapy (during day 0–14)	18 (11%)
Radiotherapy (during day 0–14)	7 (4%)
Stent locations	
Esophageal	41 (25%)
Gastroduodenal	33 (20%)
Biliary	40 (25%)
Colon	48 (30%)

[a] Breast cancer, $n = 1$, lymphoma, $n = 1$; lung cancer, $n = 3$; prostate cancer, $n = 2$; hepatocellular carcinoma, $n = 1$; gallbladder cancer, $n = 1$; thyroid cancer, $n = 1$; papillary cancer, $n = 1$; ovarian cancer, $n = 3$; duodenal cancer, $n = 1$; malignant melanoma, $n = 2$

Our conclusion is strengthened by the fact that patients in this study were treated at small local centers, not large expert centers. SEMS as palliative principle seems to be effective independent of location. With regard to the symptomatic effect on esophageal and gastric outlet obstructions, our findings are in accordance with previous studies.

Table 3 EORTC C30[a] results from 33 patients treated with gastroduodenal stents

	Before	After	Difference	*P* value
Global health function[b]	22.0 (19.3)	38.4 (26.4)	16.4 (24.8)	<0.001
Symptom scales[b]				
Pain	57.6 (28.6)	39.9 (36.3)	17.7 (36.3)	0.014
Nausea/vomiting	63.1 (31.1)	30.3 (27.5)	32.8 (38.7)	<0.001
Single items[b]				
Appetite loss[c]	81.8 (25.1)	65.7 (37.7)	16.2 (34.5)	0.013

All values are mean (SD)

[a] A selection of the EORTC QLQ-C30 most relevant scorings was made; no significant change was found in the excluded scores

[b] Scale from 0 to 100; high scores represent more severe symptoms

[c] Scale from 0 to 100; high scores represent higher level of overall functioning

Additionally, were we able to find significantly improved general well-being and better QoL, which most previous studies had not been able to document [10, 12]. A study of colon obstruction using patient-reported outcomes ended early and was therefore not able to make a conclusion [30].

That physicians' and patients' perceptions of symptoms differ is in line with previous studies in palliative medicine that compared physicians and patients, although underestimation of patients' symptoms by physicians is more common [17–21]. We do not know the reasons for the discrepancies in scoring found in our study; but one plausible explanation may reflect the enthusiasm of the physicians performing these procedures and their needs to justify the indication. The study was not designed to clarify this question.

Table 2 Scores from EORTC C30[a] and selected obstruction-related questions from EORTC OES 18 given by 41 patients treated with esophageal stents

	Before	After	Difference	*P* value
Global health function[b]	30.0 (18.0)	39.1 (26.1)	9.2 (26.4)	0.03
Symptom scales[a,c]				
Nausea/vomiting	37.8 (31.0)	33.7 (31.7)	4.1 (39.6)	0.49
Pain	43.5 (29.6)	51.2 (31.5)	−7.7 (34.6)	0.20
Single items[c]				
Appetite loss	69.1 (38.3)	61.8 (39.1)	7.3 (41.8)	0.31
Organ-specific questions from EORTC OES 18[c]				
Have you had problems eating solid food?	86.8 (26.3)	51.0 (40.1)	36.0 (51.6)	<0.001
Have you had problems eating liquidized or soft food?	63.1 (35.3)	30.0 (37.3)	32.4 (52.3)	0.001
Have you had problems drinking liquids?	38.6 (36.8)	16.7 (26.5)	22.0 (41.2)	0.002

All values are mean (SD)

[a] A selection of the EORTC QLQ-C30 most relevant scorings was made; no significant change was found in the excluded scores

[b] Scale from 0 to 100; high scores represent higher level of functioning

[c] Scale from 0 to 100; high scores represent more severe symptoms

Table 4 Scores from EORTC C30[a] and selected obstruction-related questions from EORTC PAN26 from 40 patients treated with biliary stents

	Before	After	Difference	*P* value
Global health function[b]	30.4 (25.9)	48.3 (28.0)	17.9 (34.3)	0.003
Symptom scales[c]				
Pain	48.3 (36.2)	28.8 (25.0)	19.6 (31.8)	0.001
Nausea/vomiting	35.0 (30.8)	21.3 (23.3)	13.8 (28.7)	0.005
Single items[c]				
Appetite loss	61.7 (41.0)	45.8 (41.8)	15.8 (32.0)	0.007
Organ-specific questions from EORTC PAN 26[c]				
Have you been itching?	46.6 (39.1)	23.3 (32.2)	23.3 (51.3)	0.01

All values are mean (SD)

[a] A selection of the EORTC QLQ-C30 most relevant scorings was made; no significant change was found in the excluded scores

[b] Scale from 0 to 100; high scores represent higher level of overall functioning

[c] Scale from 0 to 100; high scores represent more severe

The physicians completed the second questionnaire earlier than the patients (earlier than day 7 for 81% of the patients). The study protocol did not include a scheduled follow-up after stent treatment. The patients were often severely ill, with long travelling distance to hospital, and an extra hospital visit to allow the physician to perform a symptom assessment was hence not included in the follow-up. As the hospital stay related to the stent procedure usually was of short duration, the physicians' scoring often had to be performed at discharge from hospital. However, it is likely that the questionnaire's 1-week time format reduced the influence of the discrepancy of when the physicians and patients did the second assessment.

Although there were significant improvements for the group in total, there was interindividual variation and some patients did not experience improvement in their obstructive symptoms. A review of the medical charts revealed that absence of symptomatic improvement often could be explained by dysfunctional stents, migrations, infections, pain, or intercurrent diseases during the first 2 weeks. This represented a limited number of patients and separate subanalyses were not performed. Furthermore, ongoing treatment with other modalities (e.g., chemotherapy) can potentially influence symptom scoring negatively. We found no significant difference in the scorings of the 25 patients who received chemo- and/or radiation therapy during the assessment period.

Table 5 Scores from EORTC C30[a] and selected questions from EORTC CR38 from 46 patients treated with colon stents

	Before	After	Difference	*P* value
Global health function[b]	38.0 (24.8)	48.7 (23.7)	10.7 (24.5)	0.009
Symptom scales[a, c]				
Pain	49.3 (33.9)	28.4 (30.0)	20.9 (39.0)	0.001
Nausea /vomiting	29.4 (34.1)	13.8 (21.5)	15.6 (33.6)	0.003
Single items[c]				
Appetite loss	45.4 (40.8)	31.9 (35.4)	13.5 (45.4)	0.04
Constipation	53.9 (43.7)	24.8 (32.2)	29.1 (46.0)	<0.001
Diarrhea	37.6 (37.2)	45.4 (33.6)	−7.8 (45.7)	0.26
Organ-specific questions from EORTC CR38[c]				
Have you had abdominal pain?	53.6 (38.2)	32.6 (28.5)	21.0 (37.4)	<0.001
Have you felt bloated?	67.4 (36.2)	27.5 (30.0)	40.0 (44.8)	<0.001

All values are mean (SD)

[a] A selection of the EORTC QLQ-C30 most relevant scorings was made; no significant change was found in the excluded scores

[b] Scale from 0 to 100; high scores represent higher level of overall functioning

[c] Scale from 0 to 100; high scores represent more severe symptoms

Table 6 Patient-reported symptomatic effect of stent treatment

	Number of patients with clinical effect on ≥1 symptoms	Number of patients with no effect or worsening of symptoms
Esophageal stent	34 (81%)	8 (19%)
Gastroduodenal stent	16 (48%)	17 (52%)
Biliary stent	20 (50%)	20 (50%)
Colonic stent	33 (69%)	15 (31%)

Table 7 Comparison of scoring by patients and physicians before and after stent treatment

Stent location	Symptom score before stent treatment			Symptom score after stent treatment			Change in symptom score		
	Patient	Physician	*P* value diff.	Patient	Physician	*P* value diff.	Patient diff. before/after	Physician diff. before/after	*P* value diff.
Esophagus									
Have you had problems eating solid food?	87	93	0.13	51	58	0.44	37	34	0.78
Have you had problems eating liquidized or soft food?	63	82	0.002	30	33	0.49	33	49	0.22
Have you had problems drinking liquids?	39	64	0.001	17	14	0.63	25	50	0.001
Stomach/duodenum									
Have you vomited?	63	83	0.002	30	19	0.24	32	65	0.007
Biliary tree									
Have you been itching?	47	60	0.015	23	26	0.38	24	34	0.24
Colon									
Have you had abdominal pain?	54	70	<0.001	33	12	<0.001	21	58	<0.001
Have you felt bloated?	67	78	0.002	28	15	0.03	40	64	0.007

All values are mean. Scale from 0 to 100; high scores represent more severe symptoms

Our study did not identify subgroups of patients that regularly did not benefit from SEMS treatment and, therefore, should have received alternative palliative treatment. This might be due to the relatively low number of patients included.

Seventy-six patients completed only the first questionnaire. However, as shown in Fig. 1, only 27 patients failed to complete the second questionnaire for unknown reasons. It is possible that these patients did not experience the expected effect of the stent treatment and that this lack of data could represent a selection bias. However, we know that these 27 patients did not differ in age, pretreatment global health, or survival from the 162 repliers. Three of these 27 patients experienced dysfunctional stents and needed reinterventions during the first 2 weeks, which might have influenced their opinion of stent function. Three patients experienced cholangitis and/or pancreatitis immediately after biliary stenting but had functional stents. For the remaining 21 of the 27 patients, there was not sufficient information in their medical records to explain why they did not return their second questionnaire.

Conclusion

SEMS treatment is effective in relieving symptoms of malignant GI and biliary obstruction, according to assessment by both patients and physicians. This study demonstrates a significant difference in how the physicians and patients evaluate treatment effects and thereby the importance of taking patient-reported outcomes into account when evaluating clinical palliative interventions. Future studies evaluating SEMS treatment should include prospective assessment of patient-reported outcomes to increase our knowledge about the efficacy of this treatment.

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