Endoscopic stent placement throughout the gastrointestinal tract
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CHAPTER 11

Summary, discussion and future perspectives
SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES

In this thesis we focussed our research on stent placement throughout the GI tract. In search for ideal stents for treatment of malignant oesophageal stenosis and gastric outlet obstruction we evaluated new stent designs in prospective cohort studies. Smaller research projects mainly aimed to investigate safety and feasibility of new treatment modalities for relatively new indications in the upper GI tract. Finally retrospective cohort and comparative studies aimed to provide insight into the benefits and pitfalls of colonic stent placement as treatment for acute malignant colonic obstruction.

PART I OESOPHAGEAL STENT PLACEMENT

Chapter 2 described a multi-centre prospective cohort study investigating a new fully covered self-expanding-metal-stent (SEMS) with anti-migration flaps in 40 patients with dysphagia due to malignant oesophageal stenosis. Stent placement was technically successful in 39 patients (98%). A total of 30 patients were followed until death, 4 patients until stent removal, and 6 patients were still alive after a follow-up period of ≥6 months (range 181–365 days). The median dysphagia-free time after stent placement was 220 days (95% CI 94–345 days). Nine patients (23%) experienced recurrent dysphagia because of stent migration (n = 6; 15%), tissue overgrowth (n = 2; 5%), or fracture of the stent (n = 1; 3%). There were 39 adverse events (severe n=16, mild to moderate=23) in 33 patients, particularly consisting out of retrosternal pain and nausea and vomiting.

Discussion and future perspective:
The main goal of palliative treatment in patients with inoperable malignant oesophageal obstruction is to provide rapid and persistent relief of dysphagia. Although rapid relief of symptoms is achieved in almost all studies that have reported on results of stent placement, the occurrence of recurrent dysphagia is problematic at a rate of ~30%–40%.1-3 This is also underlined by the results of a randomised trial comparing placement of a partially covered stent with brachytherapy.4 On the long-term brachytherapy provided a better relieve of dysphagia, which could be attributed to a recurrent dysphagia rate of 40% in the stent group mainly caused by tumour ingrowth and stent migration.

The 23% rate of recurrent dysphagia in our study was relatively low. Still, stent migration was the main cause of recurrent dysphagia with a rate of 15%. This rate is comparable to the rate for fully covered SEMS that have bilateral flared ends as their only anti-migration feature, suggesting that the flaps of the Hanaro Flap stent are of only limited value for migration prevention. However, it is important to note that migration was only partial in 5/6 patients in our study and could be treated with endoscopic repositioning, which is relatively easy to perform and associated with lower costs than placement of a new stent. Nonetheless, placement of the Hanaro flap stent was associated with a high adverse event rate as compared to rates reported in other studies.1,2,5 However it is impossible to establish whether these (severe) adverse events could be attributed to the stent design,
Summary, discussion and future perspectives

the patient characteristics, the strict follow-up or grading of adverse events in our study. Only a randomised study comparing different stent designs would provide definitive answers. However, this would require very large sample sizes as differences in outcomes of currently used stents are expected to be small. Therefore, we feel that the current practice of testing new stent designs in prospective cohort studies with well-defined outcome measures and strict follow-up is the most logical strategy. If such a study suggests that a stent design is associated with a substantially lower recurrent dysphagia rate and acceptable adverse event rates, this should be compared with the currently most frequently used stent designs in a randomised study. In case a new stent proves to be significantly better than current stent designs, this should again be compared with brachytherapy in a randomised trial.

Instead of altering stent design, stent fixation has been proposed in order to prevent migration. However, small studies with heterogeneous study populations investigating various endoscopic fixation techniques, including endoclips, over-the-scope clips and endoscopic suture devices did not demonstrate a clear decrease in migration rates.6-11

Finally, several groups have investigated cytotoxic drug-eluting SEMS as well as radioactive SEMS. These are very interesting treatment options as these additions might prevent tissue in- or overgrowth. Drug-eluting SEMS have thus far only been studied in animal benign stricture models showing promising results regarding drug delivery and a decrease in tissue hyperplasia.12-14 The next step would be to evaluate safety and efficacy of these stents in clinical trials. Research of radioactive SEMS is already in a further stadium and a recently published Chinese randomised trial compared an uncovered SEMS loaded with 125I seeds with a conventional uncovered SEMS.15 This well-conducted study demonstrated no differences in dysphagia recurrence and adverse event rates, however patients who received the radioactive SEMS survived significantly longer with significantly better dysphagia scores. Further research is needed to confirm these benefits.

Chapter 3 involved a two-center feasibility study on biodegradable stent placement as bridge to surgery in patients undergoing neoadjuvant chemoradiotherapy treatment for advanced oesophageal cancer. This treatment modality was without any serious adverse events and significantly reduced dysphagia complaints without stent migration in the 10 included patients. Unfortunately these positive results were offset by the fact that 9 patients experienced weight loss at the end of follow-up and 7 patients required an additional nutritional intervention because of malnutrition. Furthermore retrosternal pain developed in 6 patients and persisted for more than 10 days in 4 of these patients.

Discussion and future perspective: An increasing number of patients with locally advanced oesophageal cancer undergo treatment with neoadjuvant chemoradiotherapy prior to surgery. Neoadjuvant chemoradiotherapy however could increase symptoms of dysphagia and potentially further jeopardize nutritional status.16 Current treatment consists mainly out of nutritional suppletion via naso-enteral tube feeding, laparoscopic
jejunostomy or total parenteral nutrition and do not provide dysphagia relieve. Therefore stent placement as bridge to surgery is a promising new treatment option. The 0% migration rate found in our study is a positive aspect of the biodegradable stent in the light of migration rates ranging from 31-60% reported in comparable studies using fSEMS or fSEPS.\textsuperscript{17-20} In addition, endoscopic stent removal prior to surgery was not necessary in any of the cases. Despite these apparent benefits the clinical value of the biodegradable stent in its current form has to be questioned in view of retrosternal pain, weight loss and need for additional nutritional intervention. Especially retrosternal pain is a worrisome feature as it cannot be excluded that several patients reduced eating because of this. One could speculate that the relatively high axial force and low flexibility of the current biodegradable stent\textsuperscript{21} in combination with tissue reaction to stent disintegration and radiotherapy induce prolonged pain. Therefore adaptations to biodegradable stent design and probably material used, resulting in lower axial force and higher flexibility, may decrease stent-related pain in this setting. If such a biodegradable stent becomes available and proves superior to other stent designs it should be tested in a randomized trial with a control group receiving standard treatment (i.e. nutritional suppletion when indicated). The outcomes of such a trial should include operative morbidity and mortality, tumour-free resection rate, quality-of-life, weight changes and the number of endoscopic re-interventions.

Chapter 4 represented a multicentre retrospective cohort study in 34 patients with upper GI leaks who were treated with temporary placement of a specific large diameter fully covered SEMS. Technical success rate was 97% (33/34). Clinical success, defined as sufficient leak closure after stent removal without the need for surgical intervention or placement of another type of stent, was 44% (15/34) after 1 stent and 50% (17/34) after an additional stent. There were no stent-related severe adverse events or stent-related mortality. Still, there were 14 (41%) stent migrations (complete n=8, partial n=6) and eventually 4 patients underwent a form of surgery as re-intervention for stent-failure. Moreover 11 patients (32%) died in-hospital because of persisting intrathoracic sepsis (n=10) or pre-existent bowel ischemia (n=1).

**Discussion and future perspective:**

Temporary placement of a stent is a very attractive treatment modality for upper GI leaks. However currently used fully covered SEMS and SEPS have a strong tendency to migrate, while partially covered SEMS are often difficult to remove as a result of tissue ingrowth through the uncovered stent parts.\textsuperscript{10, 22-29} Therefore the primary goal of using a large diameter fully covered stent is preventing these complications. Unfortunately our study could not confirm the presumed benefit of less migration, although stent removal was without any adverse events in all cases.

Endoscopic stent fixation techniques have also been proposed in this clinical setting.\textsuperscript{6-11} However, like in malignant stenosis these do not seem to provide a beneficial effect on migration rates. Another alternative could be to use a partially covered biodegradable stent as tissue ingrowth through the open stent part would anchor the stent, while stent removal would be unnecessary. Though such a stent is not yet available. Furthermore
some recently published small case series reported on endoscopically placed transluminal vacuum therapy.\textsuperscript{30-32} This treatment involves placement of a sponge into the anastomotic defect cavity with suction provided by a transnasal catheter. Results of this technique are promising but need to be confirmed by larger studies.

Besides improving material and techniques it is equally important to establish guidelines dictating which patient groups and which type of upper GI leak should be primarily treated with either conservative measures, temporary stent placement, vacuum therapy or surgery. Experts have proposed several criteria for treatment selection. They suggest surgery for leaks located intra-abdominal or in the proximal cervical oesophagus with a length of >6cm or covering >70% of the circumference and stent placement for smaller leaks located intra-thoracic or in the distal cervical oesophagus.\textsuperscript{33, 34} Nevertheless, grade A evidence is lacking and would only be provided by the results of a randomised trial comparing the different treatment options in well-defined study populations. However, the limited number of patients, the clinical complexity and the promising results of stent placement would make it very difficult to complete such a study.

**PART II DUODENAL STENT PLACEMENT**

Chapter 5 provided an overview of the relevant literature published between October 2003 and May 2011 on duodenal stent placement for malignant gastric outlet obstruction (GOO). Pooled analysis demonstrated mean overall technical and clinical success rates of 97% and 87% respectively. There is no evidence that the type of procedure (i.e. combined endoscopic or sec fluoroscopic), tumour and stenosis characteristics or stent design has an influence on clinical success. Limited data suggest that sec fluoroscopic placement in more distally located stenosis is associated with lower technical success rates, while other variables do not seem to hamper technical success. The most frequently encountered complications are tissue ingrowth for uncovered SEMS and stent migration for covered SEMS. Randomised and comparative studies showed that these negative features of the two stent designs compensate each other resulting in similar stent patency times. Procedure- or stent-related mortality has not been reported and in general the rates of severe complications are low: perforation 0-4%, bleeding 0-4%.

Studies that assessed quality of life (QoL) all demonstrated stable or improved results after stent placement. Moreover the literature suggests that stent placement is superior over surgical bypass in terms of rapid improvement of food intake, shorter hospitalization and lower medical costs. On the contrary, there is a higher recurrence rate of obstruction after stent placement due to tissue ingrowth or stent migration subsequently causing declines in food intake on the long-term and a significantly higher number of re-interventions.

These findings in the literature formed the basis for performing the prospective cohort studies described in Chapter 6 and 7. The goal of these studies was to test safety and efficacy of new SEMS designs in the hope to find an ideal SEMS that prevents both tissue ingrowth as well as migration.
In Chapter 6 we evaluated a new uncovered SEMS in a cohort of 46 patients with incurable malignant GOO whom were included in 2 academic centres. This SEMS exhibits proximal and distal flares as anti-migration feature and a small mesh design to prevent tissue ingrowth. The technical and clinical success rates were 89% and 72% respectively. The GOO scoring system score and QoL scores improved significantly when scores before stenting were compared with scores after stent placement. Median survival was 87 days and stent patency was observed in 66.7% of patients for up to 395 days, accounting for death as a competing risk. Stent dysfunction occurred in 14 patients (30%) (stent ingrowth 9; stent migration 2; extrinsic compression on the stent 2; food impaction 1). Other procedure-related complications included cholangitis (n=1), guidewire perforation (n=1), pancreatitis (n=1) and pain (n=1).

In Chapter 7 we aimed to perform a similar prospective cohort study with a new partially covered big-cup SEMS. The proximal uncovered big cup of this SEMS fits the pyloric area as anti-migration feature, while a fully silicone membrane covered intra-duodenal part was intended to prevent tissue ingrowth. Unfortunately, the study was terminated prematurely due to 3 proximal stent migrations in 6 patients. Migrations occurred at 2, 4 and 29 days respectively and necessitated endoscopic removal and placement of another SEMS. The remaining 3 patients had a patent SEMS at the end of their follow-up of 60, 69 and 228 days respectively.

**Discussion and future perspective:**
Malignant GOO is a troublesome complication of multiple types of cancer in the upper GI tract. It causes nausea, vomiting and often reduces the patient’s ability to eat a normal diet. Median survival in these patients is only around 3 months and therefore palliative treatment should ideally meet 3 criteria: minimally invasive, quick relieve of symptoms, no re-interventions. As confirmed by the studies in this thesis endoscopic stent placement fulfils the first 2 criteria in the majority of patients. However, the largest randomised trial to date as well as a recently published retrospective comparison demonstrated that stent placement was associated with a significantly higher number of re-interventions for re-obstruction as compared to traditional gastrojejunostomy. Unfortunately our studies also did not identify a new stent that withstands both tissue ingrowth as well as stent migration.

A Korean group evaluated a ‘dual SEMS’ consisting of an outer partially covered SEMS and an inner uncovered SEMS in 213 patients. This study demonstrated relatively better results with an overall stent dysfunction rate of 20%. However, the placement technique is complicated and impossible to perform ‘through-the-scope’ due to the abundant material of this stent design. Other recently published pilot studies evaluated the use of endoscopic clips for fixation of the proximal part of SEMS. These studies demonstrated promising results regarding migration prevention, although these results need to be confirmed in larger studies. Furthermore, in one of these studies increasing tumour burden still led to tumour overgrowth and stent compression in 20% of patients. Therefore, the concept
of drug-eluting or radioactive SEMS as described in the part regarding oesophageal stent placement also seems attractive in malignant GOO although this has not yet been investigated. Moreover, endoscopic creation of a gastrojejunal anastomosis by using magnetic compression has been invented with the purpose to combine the safety of stent placement with the long-term efficacy of a surgical bypass. Two feasibility studies demonstrated that creation of the gastrojejunal anastomosis was safe. However, subsequent stent placement to warrant patency of the anastomosis was associated with a high migration rate in both studies and a fatal stent-related perforation in one study. Therefore further research on this interesting concept should focus on the creation of an anastomosis which does not need a stent to keep it patent.

From an evidence-based perspective we can still only advise duodenal stent placement as routine treatment in patients who are no surgical candidate or with a life expectancy of less than 2 months, because fit patients with a better prognosis will likely benefit more from surgical bypass on the long-term. Studies on prognostication in patients with malignant GOO might therefore be helpful in guiding treatment choice. In case a promising new endoscopic treatment emerges after prospective evaluation, this ideally should be compared with laparoscopic gastrojejunostomy in a randomised trial. However experience has shown that patient accrual is very difficult for such a study as a large number of patients will opt for stent placement directly because of the less invasive character.

PART III COLONIC STENT PLACEMENT

Chapter 8 was a single-centre retrospective analysis of outcomes in 48 patients who underwent colonic stent placement as definitive palliation for acute malignant colonic obstruction. Patients were identified from a prospectively collected cohort form a general teaching hospital were endoscopic stent placement is standard of care for treatment of acute malignant colonic obstruction. The technical and short-term clinical success rates were 91% and 85% respectively. SEMS-related mortality occurred in 13% of patients and was caused by SEMS-related perforation in all cases. The SEMS-related morbidity rate was 38%. Endoscopic re-intervention was performed 14 times and 13 patients eventually underwent surgical treatment during follow-up. The stoma-formation rate was 15%. Long-term clinical success was 48% and the estimated stent patency rate was 69% at 1 month, 54% at 6 months and 50% at 12 months. Median overall survival was 4.5 months with follow-up until death in 45/48 patients.

In Chapter 9 we used the same prospectively collected cohort, but now we focussed on 59 patients who received a SEMS as bridge to elective surgery for acute malignant colonic obstruction in a curative setting. The outcomes were retrospectively compared with those of 51 patients who were acutely operated in a comparable hospital where emergency surgery is standard of care for the treatment of acute malignant colonic obstruction. The successful primary anastomosis rate was significantly higher in SEMS patients with
left-sided obstruction (30/43 versus 10/34, p=0.001) while stoma formation was lower versus emergency surgery (11/43 versus 23/34, p<0.001). These differences were not apparent in patients with right-sided obstruction. Stoma rates at the end of follow-up were comparable between treatment approaches (left-sided: 11/43 versus 9/34, p=0.322; right-sided: 1/16 versus 1/17, p=1.000). There were also no significant differences for morbidity and mortality. Moreover, recurrence or survival did not appear to be influenced by SEMS placement, although numbers were small and differences in baseline tumour stage necessitated subgroup analysis.

To gain further insight into oncological outcomes we performed a long-term follow-up of patients with acute malignant colonic obstruction from the nationwide Dutch Stent-In II randomised trial\(^{44}\) in Chapter 10. In total, 32 patients were included in the emergency surgery group and 26 patients in the SEMS as bridge to elective surgery group. Locoregional or distant disease recurrence developed in 9 out of 32 patients in the emergency surgery group and in 13 out of 26 patients in the SEMS group. In the SEMS subgroup of patients with perforation, 5 out of 6 developed a recurrence, which was higher compared to emergency surgery (9/32) or unperforated SEMS patients (9/20). No significant differences were found regarding disease-free, disease-specific and overall survival.

Discussion and future perspective:

Palliative management of acute malignant colonic obstruction is indicated in patients with extensive metastasised disease or in patients who are considered inoperable due to poor clinical condition. Two recently published meta-analyses, including randomised and nonrandomised comparative studies, have compared SEMS placement with traditional emergency surgery in a palliative setting.\(^{45,46}\) SEMS placement was significantly associated with shorter hospitalization (10 vs. 19 days) and a lower intensive care admission rate (0.8% vs. 18.0%), while permitting a shorter time to initiation of chemotherapy (16 vs. 33 days). Moreover stoma formation was significantly lower after palliative SEMS placement (13% vs. 54%), which is in line with the stoma-rate of 15% in our study. Still only the larger meta-analysis showed a lower 30-day mortality rate for SEMS (4% vs. 11%), while no significant difference in overall morbidity between the stent group (34%) and the surgery group (38%) was found.\(^{46}\) Short-term complications did occur more often in the palliative surgery group, while late complications were more frequent in the SEMS group. SEMS-related complications mainly included colonic perforation (10%), stent migration (9%) and re-obstruction (18%). Our overall morbidity rate and 30-day mortality rate were higher compared to these data and especially the perforation rate of 17% was a striking finding. We feel that our study offers a realistic assessment of palliative SEMS placement because all consecutive patients with acute malignant colonic obstruction underwent an attempt of SEMS placement and data were analysed intention-to-treat, while the comparative studies included in the meta-analyses might have suffered from substantial selection bias as there was often no strict protocol defining treatment policies. Because of the relatively small study population we could not identify risk factors for SEMS-related morbidity and mortality in our study. Other studies have identified several risk
factors, including anti-angiogenic chemotherapy (e.g. Bevacuzimab), little endoscopist experience, pre and post SEMS placement stricture dilation, SEMS design and left-sided obstruction. In our opinion, when choosing palliative treatment one should take these risk factors into account as well as the patients clinical condition and prognosis. In addition new colonic SEMS designs, for example partially covered, might prevent (late onset) complications as tissue ingrowth and stent migration in a palliative setting.

In curable patients who present with an acute malignant colonic obstruction the rationale behind ‘bridge-to-surgery’ stent placement is conversion to an elective setting with surgery being performed by a dedicated colorectal surgical team. It was thought that this strategy would reduce morbidity, mortality and stoma-rates as compared to traditional emergency surgery. The most recently published meta-analysis of all 7 RCT’s on this subject indeed found significantly lower overall morbidity, a significantly higher successful primary anastomosis rate and a significantly lower permanent stoma-rate after SEMS placement but no difference in mortality. These RCT’s only included patients with left-sided colonic obstruction. Our study described in Chapter 9 also included patients with right-sided obstruction and our data suggest that bridge-to-surgery SEMS placement has no benefits over emergency surgery in terms of morbidity, mortality and stoma-rates. Although numbers were small, we therefore feel that right-sided SEMS placement should be reserved for the palliative setting. In patients with left-sided obstruction we found a significantly higher successful primary anastomosis and lower stoma-formation rate after SEMS placement, but no effect on morbidity and permanent stoma-rates. These findings regarding left-sided obstruction largely correspond with the results of the Dutch randomised Stent-In 2 study. Moreover, in line with the aforementioned meta-analysis and the Stent-In 2 trial we also found no significant difference in mortality.

Furthermore several recently published studies have indicated that bridge-to-surgery SEMS placement is associated with a negative effect on disease recurrence and oncological outcomes. Our study in Chapter 10 also found a higher recurrence rate after SEMS placement as compared to emergency surgery. However we found that disease recurrence predominantly occurred in the subgroup of patients with SEMS-related perforation.

All in all, for patients with left-sided acute malignant colonic obstruction bridge-to-surgery SEMS placement clearly seems to increase successful primary anastomosis rates and decrease stoma-formation rates. These benefits should be balanced against the possibly negative effect of SEMS placement on disease recurrence and oncological outcomes, especially when considering that SEMS placement does not seem to decrease mortality rates and there are conflicting results regarding morbidity and permanent stoma-rates. Patient selection therefore seems of utmost importance. Multiple studies have identified 2 risk factors associated with morbidity and mortality following emergency surgery in colorectal cancer: increasing age and an American Society of Anesthesiology (ASA) score ≥ III. Therefore, bridge-to-surgery SEMS placement may be considered an acceptable alternative treatment option in patients older than 70 years and/or with an ASA score ≥ III. In case SEMS placement is not technically feasible in this subgroup of patients
a transverse colostomy could serve as a bridge-to-surgery. Younger patients with an ASA-score of < III would probably benefit most from acute resection. In the near future, this treatment strategy will be investigated in a prospective nationwide clinical decision guideline validation study in the Netherlands.
REFERENCE LIST


