Endoscopic ultrasonography-guided gastroenterostomy versus surgical gastrojejunostomy for palliation of malignant gastric outlet obstruction (ENDURO-study)

PROTOCOL TITLE ‘’Endoscopic ultrasonography-guided gastroenterostomy versus surgical gastrojejunostomy for palliation of malignant gastric outlet obstruction (ENDURO-study)’’

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Coordinating investigator	Y.L. van de Pavert, MD, MA, PhD-candidate y.l.vandepavert@umcutrecht.nl
Project leader	Prof. dr. F.P. Vleggaar, MD, PhD f.vleggaar@umcutrecht.nl
Principal investigator(s)	*Universitair Medisch Centrum Utrecht (UMCU)* Prof. dr. F.P. Vleggaar, MD, PhD, gastroenterologist f.vleggaar@umcutrecht.nl
Multicenter research: ***per site (random order)***	*Regionaal Academisch Kankercentrum Utrecht (RAKU)* Prof. dr. F.P. Vleggaar) (UMC Utrecht) Dr. M.P. Schwartz (Meander Medisch Centrum) Dr. R.C. Verdonk (St. Antonius Ziekenhuis Nieuwegein) *Leids Universitair Medisch Centrum (LUMC)* Drs. A. Inderson *Universitair Medisch Centrum Groningen (UMCG)* Dr. H.M. van Dullemen

Martini Ziekenhuis, Groningen
Drs. R. Bijlsma

Amsterdam UMC, locatie VUmc
Dr. R.L.J. van Wanrooij

Erasmus Medisch Centrum, Rotterdam
Prof. dr. M.J. Bruno

Medisch Spectrum Twente (MST), Enschede
Dr. N.G. Venneman

Isala Ziekenhuis, Zwolle
Dr. A.C. Poen

Catharina Ziekenhuis, Eindhoven
Dr. W.L. Curvers

Antoni van Leeuwenhoek ziekenhuis (AVL), Amsterdam
Dr. T.R. de Wijkerslooth

Maastricht UMC+
Drs. R.J.J. de Ridder

Reinier de Graaf
Drs. R. Quispel

Haaglanden Medisch Centrum
Drs. L.E. Perk

	OLVG *Dr. S.D. Kuiken*
Sponsor:	UMC Utrecht
Subsidising party	KWF Kankerbestrijding
Independent expert (s)	*Prof. dr. B.L.A.M. Weusten* *UMC Utrecht* *Heidelberglaan 100, 3584 CX, Utrecht*
Laboratory sites	Not applicable
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
Head of Department: *Prof. dr. F.P. Vleggaar,* *Gastroenterologist*		**2021-01-10**
Principal investigator: *Prof. dr. F.P. Vleggaar,* *Gastroenterologist*		**2021-01-10**

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator's Brochure
IC	Informed Consent
IMDD	Investigational Medical Device Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

LIST OF ADDITIONAL RELEVANT ABBREVIATIONS

EUS-GE	Endoscopic-ultrasonography guided gastroenterostomy
GOO	Gastric outlet obstruction
GOOSS	Gastric Outlet Obstruction Scoring System
LAMS	Lumen Apposing Metal Stent
SEMS	Self-Expendable Metallic Stent
SGJ	Surgical gastrojejunostomy

SUMMARY

Rationale: Malignant gastric outlet obstruction (GOO) is a common problem in patients with advanced primary or metastatic malignancies located at the distal stomach and (peri)pancreatic region. The two standard methods of treating GOO are placement of an enteral self-expendable metallic stent (SEMS) or a surgical gastrojejunostomy (SGJ). In patients with a reasonable prognosis, placement of an enteral SEMS is not feasible since it carries high rates of reobstruction or stent migration after a certain amount of time. Therefore, in these patients, surgical gastrojejunostomy is indicated to bypass this obstruction and palliate obstructive symptoms.
Despite high technical success rates and a durable effect, SGJ is an invasive treatment that is associated with significant short-term morbidity, such as delayed gastric emptying, resulting in an ongoing inability to eat and a prolonged hospital stay. Endoscopic ultrasonography-guided gastroenterostomy (EUS-GE) using a Lumen Apposing Metal Stent (LAMS) is the newest technique in the palliative treatment of malignant GOO. EUS-GE creates a bypass in a minimally invasive manner, with the potential of providing both fast and lasting relief of obstructive symptoms. Despite promising preliminary data, current literature is limited to small and retrospective series. A prospective and comparative study is warranted, to compare short and long term efficacy of EUS-GE with SGJ.
Objective: To evaluate the efficacy of EUS-GE compared with SGJ in patients with malignant GOO.
Study design: Randomized Controlled Trial
Study population: Adult patients with a malignant gastric outlet obstruction due to locally advanced or metastatic, inoperable and unresectable cancer, without curative options.
Intervention: One group will be treated with the standard treatment (SGJ) and the other group will be treated with the investigational treatment (EUS-GE with LAMS [off label use]).
Main study parameters/endpoints: The main study endpoint is the ability to eat, measured with co-primary endpoints: 1) time to ability to tolerate at least soft solids (GOOSS ≥ 2), and 2) persistent or recurrent GOO symptoms requiring reintervention.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden and risks of EUS-GE are expected to be lower than those of the standard treatment (SGJ). Participation in this therapeutic study offers patients with malignant GOO the opportunity to undergo EUS-GE, an investigational and minimally invasive treatment, instead of surgery. No additional visits or physical examinations are required for this study, unless medically indicated. The burden of follow-up within this study is limited and mainly concerns time that is spent to fill in a diary, short quality-of-life questionnaires and receive four short follow-up phone calls. Though the short-term results of

EUS-GE are promising and seem to be beneficial, the long-term patency of EUS-GE has yet to be established and compared with the current standard treatment (SGJ). This can only adequately be achieved by comparing the efficacy of EUS-GE versus SGJ in these patients, in a randomized and prospective study with solid follow-up.

1. INTRODUCTION AND RATIONALE

Malignant gastric outlet obstruction (GOO) occurs in 15-20% of patients with advanced distal stomach, duodenal and (peri)pancreatic malignancies.[1] Mechanical obstruction of the gastric outlet impairs gastric emptying. Accompanying obstructive symptoms such as vomiting, nausea and inability to eat are a burden to patients and can quickly lead to malnutrition and poor performance status.[2] Due to the advanced and often metastatic or unresectable stage, the main goal of treating gastric outlet obstruction is palliation of these symptoms (i.e. relief of obstruction), to improve quality of life and restore ability to eat.

The two standard techniques to treat GOO are endoscopic duodenal stent placement and surgical gastrojejunostomy (SGJ). Both interventions are effective palliative treatments, and both have their advantages and disadvantages.[2,3] Duodenal stent placement is minimally invasive and associated with faster relief of symptoms, improvement of food intake and continuation of systemic therapy. However, it also has a significant risk of late complications such as stent migration and recurrent obstruction, necessitating reinterventions.[2–6] SGJ, on the other hand, is more invasive and associated with surgery-related morbidity such as gastroparesis, requiring a longer hospital stay. But, once this bypass is functional, it provides longer patency over time, with less need for reinterventions.[2–6] Consequently, in patients with expected survival of more than six weeks, SGJ is favoured over duodenal stenting.[2] Nevertheless, although SGJ is effective, its surgical invasiveness and significant morbidity are undesirable in a terminal phase of life.[7] Therefore, an alternative minimally invasive treatment, providing faster recovery as well as durable long-term relief of symptoms, is needed in this patient group.
Endoscopic ultrasonography-guided gastroenterostomy (EUS-GE) using a lumen-apposing metal stent (LAMS) is the newest technique in the palliative treatment of malignant gastric outlet obstruction. A LAMS fully covered stent and with bilateral flanges. With these flanges, the stent is able to hold two lumina together and create a transluminal gastroenteric anastomosis, a bypass for food passage.[8] EUS-GE seems to combine the best features of both currently used treatments. It is minimally invasive with rapid relief of symptoms, comparable to duodenal stenting. Moreover, it has the potential of low reintervention rates and long-lasting patency, similar to SGJ. Several clinical studies have demonstrated feasibility and safety of EUS-GE.[9–16] When compared with SGJ, EUS-GE was suggested to be an effective alternative.[13,14] However, despite promising preliminary data on effectiveness and safety, current literature mostly consists of small series that are retrospective in design, requiring caution when interpreting results. A prospective and comparative trial with solid

follow-up is warranted in order to properly assess effectiveness, durability and safety of EUS-GE.versus.SGJ.

The aim of this study is therefore to investigate short and long-term efficacy of EUS-GE compared with SGJ, in patients with malignant gastric outlet obstruction..

2. OBJECTIVES

The aim of this study is to compare the effectiveness, durability and safety of EUS-GE versus SGJ, in patients with malignant GOO.

Primary Objective: to investigate and compare the effect of EUS-GE and SGJ on patients' short- and long-term ability to eat* (time to ability to tolerate at least soft solids, and reinterventions for persistent or recurrent symptoms of GOO within 6 months of follow-up, respectively).

* The ability to eat will be measured by the Gastric Outlet Obstruction Scoring System (GOOSS) score, as adapted by Adler et al: 0=no oral intake, 1=liquid intake only, 2=soft solids, 3=low residue/full diet.[17]

Secondary Objectives):

Additionally, the following questions will be addressed:

- What is the technical success rate of EUS-GE vs SGJ?
- What is the clinical success rate of EUS-GE vs SGJ?
- What is the rate of gastroenterostomy dysfunction after EUS-GE vs SGJ?
- What is the reintervention rate after EUS-GE vs SGJ?
- What is the time to reintervention in case of persistent or recurrent symptoms after EUS-GE vs SGJ?
- What is the adverse event rate of EUS-GE vs SGJ?
- What is the effect of EUS-GE vs SGJ on quality of life?
- What is the time to start chemotherapy (if applicable) after EUS-GE vs SGJ?
- What is the length of hospital stay of EUS-GE vs SGJ?
- What is de rate of readmissions after EUS-GE vs SGJ?
- What is the patient's weight after EUS-GE vs SGJ?
- What is the overall survival time after EUS-GE vs SGJ?
- What are the costs associated with EUS-GE vs SGJ?

Our objectives are further defined as endpoints in section 8.1 Study parameters/endpoints.

3. STUDY DESIGN

Design: Randomized Controlled Trial (1:1)
Intervention: EUS-GE (investigational treatment) versus SGJ (standard treatment)
Follow-up per patient: 6 months
Duration of the study: 4 years
Setting: National multicenter study

Patients with malignant GOO and adequate WHO performance status, who would normally qualify for SGJ, will be randomly allocated with a 1:1 ratio to undergo either EUS-GE or SGJ. Patients with a poor WHO performance status (WHO 4) will be offered endoscopic duodenal stenting, according to current clinical guidelines.[18]

This study-protocol was developed in collaboration with the Dutch Pancreatic Cancer Group (DPCG). This will provide a large, strong framework for the study.
EUS-GE remains a new and experimental treatment. No prospective, well-designed studies have been performed yet to support this as an established practice. In retrospective literature and in our own experience EUS-GE shows promising results, but this is not sufficiently evidence-based. It is a known pitfall of new interventions, which initially seem very effective, but eventually prove not to be as good as expected. It is therefore crucial to conduct a well-designed trial and obtain solid evidence, before new techniques are implemented in clinical practice.
Therefore, in our opinion it is justifiable and of great importance to perform a randomized controlled trial.

4. STUDY POPULATION

4.1 Population (base)

The population of this study involves adult patients with advanced, incurable malignancy of various aetiologies. All patients presenting with a symptomatic malignant GOO (GOOSS 0-1 with obstructive symptoms) will be screened for eligibility.

4.1 Inclusion criteria

Along with the clinical multidisciplinary meetings, eligibility for the ENDURO-study will be discussed with the ENDURO-review panel (i.e. consisting of at least 3 endoscopists and 3 surgeons), as patients need to qualify for both EUS-GE and SGJ and are required to meet the in- and exclusion criteria.

In order to be eligible for this study, a subject must meet all of the following criteria:

- Adult patients with symptomatic malignant gastric outlet obstruction, presenting with nausea, vomiting and/or inability to eat;
- Gastric Outlet Obstruction Scoring System Score of 0 (no oral intake) or 1 (liquids only);
- Obstruction due to irresectable or metastatic malignancy without curative treatment options;
- Radiologically or endoscopically confirmed gastric outlet obstruction;
- Location of obstruction extending from the pyloric region to the distal duodenum (third part).
- Both treatments (SGJ and EUS-GE) are technically and clinically feasible;
- Written informed consent.

4.2 Exclusion criteria

A potential research participant who meets any of the following criteria will be excluded from participation in this study:

- Radiological or clinical suspicion of other strictures or obstructions along the gastrointestinal tract (distal of the ligament of Treitz), with small intestinal dilation/ileus. *Note*: patients with diffuse dilatation of the intestines should not be excluded;
- Cancer extending into the distal region or corpus of the stomach or around the ligament of Treitz. These types may pose a risk of negatively affecting gastrointestinal motility next to causing gastric outlet obstruction.
- Duodenal tube feeding is not tolerated, despite adequate position of the tube;
- Altered anatomy after previous gastric, periampullary or duodenal surgery;

- Previous SGJ as palliative treatment for the same condition;
- Inability to undergo surgery or upper endoscopy due to severe comorbidities (including large-volume ascites);
- WHO performance score of 4 (in bed 100% of time);
- Uncorrectable coagulopathy, defined by INR > 1.5 or platelets < 50 x 10^9/L;

4.3 Sample size calculation

For the primary endpoint (time to ability to tolerate at least soft solids (GOOSS ≥ 2)), the median time to (re)gain the ability to eat soft solids after laparoscopic SGJ was estimated at 3 days, based on a retrospective study.[19] In this study, the median time for EUS-GE was 1 day. Assuming a reduction of time to oral intake from 3 days to 1 day for EUS-GE, a follow-up of 6 months, a two-sided alpha of 0.05 and an exponential survival, the estimated number of patients needed to obtain 90% power to detect a difference is 21 per arm.

The POWER Procedure
Log-Rank Test for Two Survival Curves

Fixed Scenario Elements	
Method	Lakatos normal approximation
Form of Survival Curve 1	Exponential
Form of Survival Curve 2	Exponential
Follow-up Time	183
Total Time	183
Alpha	0.05
Number of Sides	2
Number of Time Sub-Intervals	12
Group 1 Loss Exponential Hazard	0
Group 2 Loss Exponential Hazard	0

Computed N per Group					
Index	Med Surv Time 1	Med Surv Time 2	Nominal Power	Actual Power	N per Group
1	1	3	0.8	0.815	16
2	1	3	0.9	0.905	21
3	1	2	0.8	0.809	36
4	1	2	0.9	0.905	48
5	2	3	0.8	0.804	99
6	2	3	0.9	0.902	132
7	1	4	0.8	0.818	11
8	1	4	0.9	0.918	15
9	2	4	0.8	0.810	36
10	2	4	0.9	0.906	48

The co-primary endpoint (i.e. persistent or recurrent symptoms of GOO, requiring a reintervention) can be assumed to be about 15% for both treatments based on literature and experience. Based on three retrospective comparative studies of EUS-GE vs. SGJ, the combined rate for technical failure and reinterventions range from 5,4-30,5% (EUS-GE; pooled rate17,4%) and 0-21,4% (SGJ; pooled rate 10,5%).[13,19,20] The reintervention rate for persistent or recurrent gastric outlet obstruction should not be significantly worse in the new intervention (EUS-GE) compared to the current treatment (SGJ). A non-inferiority limit of 35% (Δ 20%) is deemed acceptable, as it may be compensated with other benefits of EUS-GE (less invasive, less complications, less costs). Also, this rate is still not exceeding the

recurrence rate of duodenal stenting.[21] Using a non-inferiority margin of 20% and a one-sided alpha of 0.05, the estimated number of patients needed to show non-inferiority with 80% power is 44 per group.

The POWER Procedure
Farrington-Manning Score Test for Proportion Difference

Fixed Scenario Elements	
Distribution	Asymptotic normal
Method	Normal approximation
Number of Sides	1
Alpha	0.05
Group 1 Proportion	0.15
Group 2 Proportion	0.15

Computed N per Group				
Index	Null Proportion Diff	Nominal Power	Actual Power	N per Group
1	-0.10	0.8	0.801	163
2	-0.10	0.9	0.901	225
3	-0.15	0.8	0.803	75
4	-0.15	0.9	0.902	103
5	-0.20	0.8	0.808	44
6	-0.20	0.9	0.901	59

Based on the above-mentioned calculations a sample size of 44 per group seems adequate to cover both endpoints. In total, and correcting for a 10% drop-out, a sample size of 96 patients is required.

For EUS-GE to be the preferred treatment, the primary endpoint (time to ability to tolerate at least soft solids (GOOSS ≥ 2)) should be superior and the co-primary endpoint (persistent or recurrent symptoms of GOO requiring reintervention) should be non-inferior.

To avoid the 'multiple testing' problem with the need to adjust the alpha level, we will use a hierarchical testing procedure. First the superiority of the new treatment on the time to ability to eat soft solids will be tested and only when this test is statistically significant, the non-inferiority on the recurrent gastric outlet obstruction rate is tested. When both tests are statistically significant the new treatment will be deemed the preferred treatment and can be adopted in treatment guidelines.

5. TREATMENT OF SUBJECTS

This is a therapeutic intervention study. Patients presenting with symptomatic malignant GOO, who fulfil the eligibility criteria and have given written informed consent in this study, will be treated with either EUS-GE (investigational) or SGJ (standard treatment).

5.1 Investigational treatment

Investigational treatment: EUS-GE

The EUS-GE procedure has been standardized and protocolized in detail in an EUS-GE collaborators' meeting, to assure its application in a uniform manner.

EUS-GE preprocedural measures:

- *Fasting*: aim for an as empty as possible stomach, by 12 hours fasting for solid food, 6 hours fasting for liquids.
- *Nasogastric tube*: nasogastric tube placement to allow emptying of the stomach and limit gastric distension is obligatory prior to EUS-GE to reduce risk of aspiration of gastric contents. If indicated, plain abdominal radiography will be performed to verify an adequate position of the nasogastric tube.
- *Jejunal feeding tube:* if already placed for tube feeding, the tube will be left in situ to be used for flushing and filling the post-stenotic duodenal-jejunal loop during the EUS- GE placement.
- *Antibiotics*: One dose of prophylactic intravenous antibiotics, covering intra-abdominal infections will be administered 30 minutes prior to or during EUS-GE. For example, a single dose of Ceftriaxone 2000 mg and Metronidazole 500 mg, or an equivalent in accordance with local protocol based on local resistance patterns.
- *Anticoagulants and antiplatelet drugs:* In case vitamin K antagonists are used, INR needs to be < 1.5. Direct acting oral anticoagulants need to be discontinued 48 hours prior to the procedure. Antiplatelet monotherapy is allowed. In case of dual antiplatelet therapy, one of the two drugs need to be discontinued 5 days prior to the procedure, in accordance with the intervention with high-bleeding risk guideline. Anticoagulants and/or antiplatelet agents are restarted 24 hours post-procedurally.

EUS-GE procedure:

A Standard Operating Procedure (SOP) is used to perform EUS-GE in a standardized manner. A 20 mm LAMS will be used. The procedure is executed with patients under propofol-mediated sedation. Roughly, the EUS-GE procedure will be performed as follows: The direct puncture technique will be used. A gastroscope is introduced proximal to the

stenosis. Residual gastric contents will be removed. A feeding tube or nasobiliary drain is placed distal to the stenosis through the working channel. The endoscope is then removed, followed by the introduction of a linear array EUS endoscope into the stomach. With the EUS-scope, the jejunal or duodenal loop is identified by flushing saline mixed with a small amount of dye (indigo carmine) into the post-stenotic duodenal-jejunal loop. At will, the endoscopist may choose to use additional fluoroscopy to evaluate the correct position of the potential place of puncture before creating the fistula tract.
The loop is punctured directly using an electrocautery-enhanced delivery system. The distal flange of the 20mm LAMS (Hot AXIOS^{TM} Stent, Boston Scientific Corporation) is deployed, followed with traction of the distal flange against the wall of the small intestine. The proximal part of the stent is deployed and pushed out the working channel during gentle retraction of the echo-endoscope. Position and passage of the stent is confirmed by backflow of the indigo colored saline from the small intestine back into the stomach. The stent will be left to expand naturally, without immediate balloon dilation of the stent. The nasogastric tube and/or duodenal feeding tube will (both) be removed.

In some cases per-procedural complications or technical failure – for example, when misdeployment of the distal flange of the AXIOS stent results in intestinal perforation – warrant immediate or rapid surgical intervention. Hence, participants are required to provide written consent to undergoing SGJ after being allocated to EUS-GE, technical failure ensues and the situation requires surgical intervention/SGJ during the same session.

EUS-GE is technically demanding. To secure patient safety and avoid inclusion of a learning curve in this study, EUS-GE will only be performed by trained advanced endoscopists, with sufficient EUS-GE experience. Preferentially, EUS-GE should be performed by two advanced endoscopists.

Centers will be enrolled as either ‘experienced’ or ‘supervised’ centers.
A center is considered an ‘**EUS-GE experienced center’** if it has performed at least 20 EUS-GE procedures. This number includes endoscopic ultrasound guided transgastric ERCP (EDGE).
Centers not fulfilling this criterium, but with the ambition to perform EUS-GE AND with experience in at least 20 LAMS placements for other indications (gallbladders, pancreatic collections, drainage of the biliary tract), may participate as ‘**supervised center’**.
A center which has performed **less than 10** EUS-GE placements will be directly proctored by an experienced center until this number is reached and the EUS-GE experienced endoscopist is fully confident that the proctored endoscopist is proficient in undertaking the

procedure safely unsupervised. Competence after training will be confirmed at the discretion of the experienced EUS-GE endoscopist, before the proctored endoscopist can perform EUS-GE within the ENDURO-study independently.
In case a supervised center has successfully completed **more than 10 but** less than 20 EUS-GE's, the center is allowed to perform the procedure independently after approval of an EUS-GE experienced endoscopist. A 'supervised center' will become an 'EUS-GE experienced center' after having performed 20 EUS-GE's.
Nevertheless, supervised centers are recommended to perform all of the EUS-GE procedures within the ENDURO-study under supervision, as this will guarantee sufficient training, optimal gain of experience and maximum safety.
Centers without ambition to perform EUS-GE themselves will refer their patients to an 'EUS-GE experienced center'.

EUS-GE post-procedural measures:

- *Nasogastric tube or duodenal feeding tube:* all tubes will be immediately removed after EUS-GE is completed. Tubes left in the gastrointestinal tract after EUS-GE pose a risk of stent dislodgement.
- *Diet*: the day of the intervention a clear liquid diet can be initiated. The next day this will be advanced as tolerated, to an easily digestible/low residue food diet, and if this is accepted well, to solid food. Since patients and/or caregivers tend to feel anxious to restart oral intake, this should be clearly communicated and encouraged. A skilled dietician can be contacted upon request to answer intake related questions.
- *Antibiotics*: No post-procedural antibiotics are administered, unless indicated.
- *Discharge*: when judged clinically possible.

Due to the limited prognosis of the research participants and the expected burden of recurrent endoscopic interventions, the LAMS will be left in place permanently.

Comparator: SGJ (standard treatment)

Pre-procedural:

The center where SGJ is performed will be determined in multidisciplinary consultation and proceed according to the usual healthcare pathways. Patients will be prepared for SGJ in a similar fashion to EUS-GE (see page 18, EUS-GE preprocedural measures)

Procedural:

The SGJ procedure will be executed as follows:

- SGJ is performed laparoscopically;
- The anastomosis is preferably positioned at the most distal side of the stomach, on the posterior side of the stomach. The exact position depends on tumour localization (antrum or antrum/corpus);
- An antecolic side-to-side gastrojejunostomy is created with or without separation of the omentum (without a Roux-Y reconstruction);
- The anastomosis is created with a 60 mm stapler (e.g. Endo GIA^{tm}) and closed with a v-loc 3-0 suture or similar wound closure device;
- The length of the biliary loop (distance between bile duct and gastrojejunostomy) must be at least 50 cm;
- A surgical jejunostomy to allow enteral tube feeding is not routinely constructed.

Since SGJ is regarded a standard procedure, no learning curve is expected. Nevertheless, in order to guarantee maximal procedural safety, SGJ will only be performed in centers with experience in upper gastrointestinal or hepatopancreatobiliary surgery. When necessary, patients will be referred to one of these centers.

<u>Post-procedural:</u>

- *Nasogastric tube:* According to medical protocol, all patients will receive a nasogastric tube after SGJ. The morning after the SGJ procedure, the nasogastric tube will be disconnected from the collection bag but remain *in situ*. After 4 hours gastric residual volume will be determined. When the residual volume is less than 200 ml, the tube will be removed. When the volume exceeds this limit, every 24 hours gastric residual volume will be determined. When the residue is less than 200 ml measured over four hours, the tube will be removed.
  We acknowledge this difference of post-procedural treatment between EUS-GE and SGJ. However, as a nasogastric tube may result in stent dislodgement after EUS-GE and, on the other hand, tube placement is standard of care after SGJ, this discrepancy is accepted.
- *Nasojejunal feeding tube:* A nasojejunal feeding tube will not routinely be placed in patients after SGJ. In case of apparent delayed gastric emptying, a nasojejunal feeding tube will be placed under endoscopic guidance.
- *Diet*: Patients will not commence oral intake unless the gastric residual volume is at an acceptable level (see *nasogastric tube*). However, a clear liquid diet is tolerated immediately after SGJ. When the gastric residual volume is acceptable, patients will start

with a soft solid food diet. This will be advanced in a stepwise manner, eventually – if tolerated – to a full solid diet.
- *Antibiotics*: No post-procedural antibiotics are administered, unless indicated.
- *Discharge*: when judged clinically possible

Excessive gastric residual volume before EUS-GE/SGJ

Despite adequate removal of gastric residual, it may occur that an excessive volume of gastric contents remains prior to EUS-GE or SGJ, preventing the safe administration of sedatives. In this situation, EUS-GE or SGJ will be rescheduled after additional extensive gastric decompression. This situation will not be considered technical failure.

Persistent or recurrent symptoms after EUS-GE/SGJ

In case of persistent symptoms of gastric outlet obstruction (nausea, vomiting > 2 times during 24 hours, inability to tolerate oral intake or liquids at most) after EUS-GE or SGJ, patients will be treated with a *nil per os* regimen, nasogastric tube, and prokinetics (e.g. metoclopramide, domperidone, or erythromycin). If limited or no oral intake at post-procedural day five persists (GOOSS 0-1), a jejunal feeding tube will be placed under endoscopic guidance, after an intestinal ileus is excluded (distended abdomen, absent or high-pitched peristalsis, no passage of flatus or faeces). Endoscopic tube placement enables simultaneous assessment of anastomotic patency, and, in case of stent dysfunction or obstruction of the anastomosis, additional treatment. When feeding over a jejunal tube is not adequately tolerated, parenteral nutrition will be initiated. In some cases, a percutaneous endoscopic/radiologic gastrostomy (with or without jejunal extension) or endoscopic/surgical jejunostomy will be constructed. This decision will be left at the discretion of the treating physician.

In case of recurrent symptoms of gastric outlet obstruction (recurrence of nausea, vomiting > 2 times during 24 hours, inability to tolerate oral intake or liquids at most after initial clinical success) *experienced in hospital,* will be treated identical to patients experiencing persistence of symptoms. This implies a *nil per os* regimen, nasogastric tube, and prokinetics (e.g. metoclopramide, domperidone, or erythromycin). At day five of symptom recurrence, a gastroscopy will be performed to place a nasojejunal feeding tube and to inspect the anastomosis.

In case of recurrent symptoms experienced after discharge from hospital, upper endoscopy will be planned as soon as possible to inspect the anastomosis and, if possible, treat dysfunction.

Upper endoscopy, in addition to above-mentioned circumstances, or radiologic imaging will be performed at indication, e.g. suspected bleeding in case of haematemesis or melena.

Post-procedural care (e.g. management with feeding tubes, antibiotics, introduction of oral intake etc) is standardized and equalized by protocol as far as possible, for both study arms. This is crucial, as differences in post procedural management might influence the outcomes. Existing differences that are inherent in the nature of the procedure will remain (e.g. differences in nasogastric tube regimen).

5.2 Use of co-intervention

Biliary drainage in case of cholestasis
Patients with GOO have increased risk of cholestasis from malignant biliary obstruction during the course of their disease.

If cholestasis occurs, biliary drainage will be performed according to standard of care and the usual healthcare pathways. Biliary interventions will not be performed in the same session as EUS-GE or SGJ.

Data on the presence of cholestasis and its treatment will be registered, to allow separate (sensitivity) analysis, if needed.

5.3 Escape medication (if applicable)

Not applicable. In case of acute pain or infection, symptoms will be treated in accordance with the standard of care. There are no restrictions regarding escape medication (i.e. analgesics or antiemetics). Use of escape medication will be registered.

5.4 Escape intervention

If re-endoscopy is clinically indicated, it is not allowed to perform this through a LAMS that is placed shorter than 6 weeks before. The first 6 weeks after stent placement, the fistula tract might not be stable and the AXIOS stent could dislocate.

If a patient had additional tube feeding prior to EUS-GE/SGJ, this is discontinued after EUS-GE/SGJ, in order to allow a fair chance of accepting oral intake. If necessary, tube feeding may be restarted, only if the patient has proven not to be able to maintain an adequate oral intake, despite EUS-GE/SGJ. At post-procedural day five, patients not tolerating oral intake will receive a jejunal feeding tube.

If deemed necessary, e.g. in case of not tolerating enteral tube feeding due to a paralytic ileus, total parenteral nutrition will be initiated.

As mentioned in section 5.1, (urgent) SGJ may be required after technical failure of EUS-GE. In certain cases, e.g. when intestinal perforation occurs, SGJ during the same session may be warranted. Participants must provide explicit informed consent.

6. INVESTIGATIONAL PRODUCT

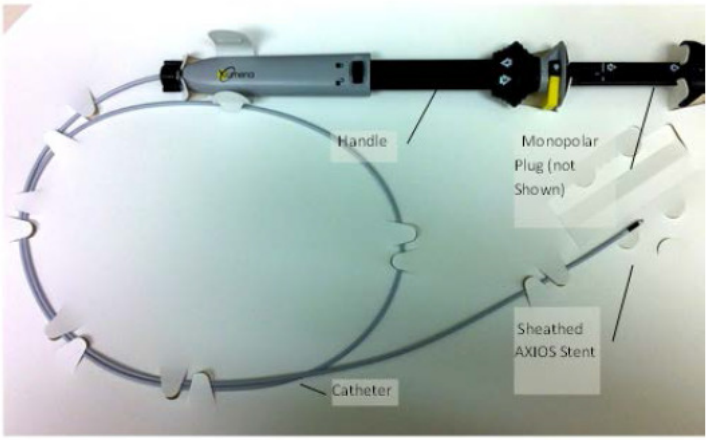
Medical device used to perform EUS-GE:
Lumen-apposing metal stent (LAMS): Hot AXIOS™ Stent, Boston Scientific Corporation.
The 20mm x 10mm stent will be used, the largest luminal diameter stent available at this moment. This device will be used off-label, for an unauthorized indication.
The stent will be placed through the Hot AXIOS™ Electrocautery-Enhanced Delivery System (Boston Scientific corporation)

6.1 Name and description of investigational product(s)

Hot AXIOS™ Stent, Boston Scientific Corporation
''The Hot AXIOS system is used under combined endoscopic and EUS guidance. The Hot AXIOS Stent is a flexible, MR conditional, fully covered self-expanding Lumen-Apposing Metal Stent (LAMS), that is preloaded within the Hot AXIOS Stent and Electrocautery-Enhanced Delivery System. The AXIOS Stent creates a secure, transluminal conduit between the gastrointestinal tract and a neighboring fluid-filled cavity to facilitate drainage or create a bypass around a stricture or blockage. In Europe, the Hot AXIOS Stent is CE approved for facilitating drainage of pancreatic pseudocysts or the biliary tract.''

(http://www.bostonscientific.com/en-EU/products/stents-gastrointestinal/axios-stent-and-electrocautery-enhanced-delivery-system.html)

Since 2015, the Hot AXIOS Stent has also been used to treat malignant GOO, by creating a gastrojejunostomy, in a clinical experimental setting. However, the Hot AXIOS Stent is not officially registered for this indication and it will therefore be an off-label and experimental use in this study. This will be executed according to the Medical Device Regulation and the Central committee on Research Involving Human Subjects (CCMO). Further product details can be found in the Investigational Medical Device Dossier (IMDD).



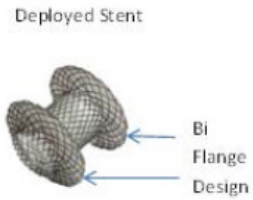


Figure 1: Hot AXIOS Stent and Electrocautery-Enhanced Delivery System

6.2 Summary of findings from non-clinical studies

See Investigator's Brochure, page 7.

6.3 Summary of findings from clinical studies

See Investigator's Brochure, page 8-9.

6.4 Summary of known and potential risks and benefits

Known and potential benefits of EUS-GE

With a successful deployment of the Hot AXIOS stent, an anastomosis between the stomach and the jejunum will be created, bypassing the gastric outlet obstruction. The benefit of EUS-GE is a quick and potentially long-term relief of obstructive symptoms, by means of a minimally invasive treatment. Chen et al report a mean time to oral intake of only 1.32 ± 2.76 days, which is in line with our own experience.[22]

Compared to the SGJ, EUS-GE is a less invasive treatment. It has the advantage of less days of hospitalization and less surgery-related morbidity such as infections or gastroparesis.[14] It is minimally invasive, while having the potential of creating an anastomosis as durable as a surgical bypass. Lastly, in a healthcare system with rising expenses, EUS-GE is a potentially less expensive treatment than SGJ.[15]

Known and potential risks of EUS-GE

Several adverse events have been described in the literature to date, such as post-procedural bleeding, infection, abdominal pain or antibiotics administration requiring hospitalization, surgery because of a suspected perforation, and stent dislocation.[14–16] In literature, reported adverse event rates range from 3.5% to 26.7%.[9,10,12–14,16] Pooled in a meta-analysis of 12 studies, adverse events occurred in 12% (95% CI 9%-17%).[23] Especially

those patients in whom stent misplacement resulted in a perforation of the small intestine are at risk. Worst case, this could lead to peritonitis, sepsis or death. This was reported in three studies.[14–16] Misdeployment of either of the flanges might be managed endoscopically with placement of a second LAMS (stent-in-stent), a bridging fully covered self-expanding metallic stent, or removal of the Hot AXIOS stent and closure of the defect with a clip.[14,16,24] In case of a perforation, a bleeding, or other per-procedural complication that cannot be salvaged endoscopically, conversion to (emergency) surgical treatment may be required.

In addition, recurrent obstruction due to stent dysfunction is a potential risk after EUS-GE. Recurrence of GOO symptoms and the need for unplanned re-intervention occurred in a pooled incidence of 9% of patients (95%CI 6%-13%).[23] Causes of stent dysfunction included food impaction, inflammatory or hyperplastic tissue overgrowth, and stent ingrowth.[9,10,12,13,22] A buried gastric flange of a LAMS has also been reported recently.[25] Stent dysfunction can usually be solved endoscopically, by balloon dilation, stent-in-stent placement or removal of the obstructive agent (e.g. food).

Little is known about long term outcomes, as long-term follow up is scarcely reported in literature and mostly retrospectively collected. One study specifically reported about long-term outcomes after EUS-GE in benign and malignant GOO, with a 196 day follow-up in malignant strictures. In the total cohort, only two adverse events occurred. Reintervention was required in 11.4% in patients with malignant GOO.[12]

As for the reported procedural adverse events, such as stent misplacement, EUS-GE technique has refined over time (e.g. elimination of guidewire assistance, development of a technique to salvage initial failed placements) and more knowledge about the risks and pitfalls of performing EUS-GE became available.[26] Adverse events reported in literature of earlier years may not always reflect contemporary practice but rather individual learning curves and the development of technical and clinical practice over recent years.

Finally, the manufacturer of the Hot AXIOS stent, Boston Scientific, reports the following potential complications when using the Hot AXIOS stent for its indicated purposes:

1. Anesthesia complications
2. Improper AXIOS Stent placement; incomplete deployment; stent migration into the pseudocyst or GI tract; separation of coating material from stent; stent fracture; coating material wear; coating material failure; puncture of coating material
3. Tissue ingrowth or overgrowth leading to difficulty or a failure to remove stent

4. Stent dislodgement
5. Adverse reaction to implant materials and/or delivery system (e.g., abdominal or back pain, nausea, infection, fever, chronic inflammation or foreign body reaction).
6. Minor or excessive bleeding requiring intervention
7. Leakage of pseudocyst or bowel contents causing inflammation or peritonitis
8. Stent occlusion
9. Local infection at the implant site
10. Tissue damage during stent implantation and/or removal
11. Ulceration or erosion of mucosal or organ wall linings
12. Pneumoperitoneum
13. Sepsis (bacterial, endotoxin or fungal)
14. Perforation
15. Surgical intervention (endoscopy, transfusion or surgery)
16. Persistent connection to the pseudocyst after removal (fistula) *(not applicable in this study)*
17. Unintended electrical shock, muscle stimulation or burns
18. Cardiac arrhythmia or arrest
19. Death[27]

A structured risk analysis including all study details will be given in chapter 13 and in the IMDD.

6.5 Description and justification of technique

Since EUS-GE is being performed, advancements in interventional EUS techniques, instruments and devices have been made. Currently, there are several EUS-GE techniques available, such as the direct puncture technique, the balloon-assisted approach, or the EUS-guided double-balloon-occluded gastrojejunostomy bypass (EPASS).[28,29] Since the development of an electrocautery-enhanced delivery system (as applied in the Hot AXIOS Stent), some challenges of puncturing (multiple steps procedure, tenting of the needle tip into the wall without puncturing it, moving the distended small bowel away from the stomach by pushing the guidewire and causing stent misplacement) are overcome, facilitating direct penetration and deployment of the LAMS without the need of separate puncturing and guidewires.[28] The benefit of the free hand technique compared with the over-the wire-technique was shown by Itoi et al., reporting a technical success rate of 100% versus 82%, respectively.[11] In addition, it has been demonstrated that the direct technique can achieve

similar technical and clinical success rates when compared to the balloon assisted technique, while being associated with a significantly shorter procedure time.[22]

Consequently, the direct puncture technique will be applied in our study, using a electrocautery-enhanced delivery system (Hot AXIOS™). The advantage of the direct technique is that it involves a minimum of steps. Reducing the amount of steps implies reducing the extra risk of complications per step. The direct puncture technique does not involve the use of a guidewire which might cause the jejunum to move away from the stomach, resulting in stent misplacement.[11] It also does not involve the use of balloon assistance, as this requires a longer procedure time without enhancing the safety of the EUS-GE procedure.[22]

6.6 Dosages, dosage modifications and method of administration

Not applicable.

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Our main study parameter is the ability to eat. This will be measured with two co-primary endpoints, covering the short- and long-term effects:

1a. Time to oral intake of soft solids is defined as the number of days until a patient is able to tolerate soft solids (GOOSS ≥ 2) without vomiting. Day of intervention is considered day 0.
1b. Persistent or recurrent GOO symptoms requiring reintervention is defined as any new intervention after EUS-GE or SGJ directed at improving or restoring nutritional intake, in case of persistent or recurrent obstructive symptoms of gastric outlet obstruction, such as nausea, vomiting and inability to tolerate oral intake (GOOSS 0-1).
Persistence or recurrence for which a reintervention is necessary may occur in three different instances:

- The procedure may be technically unsuccesful, after which a reintervention at a later instance will be scheduled (failure to achieve technical success, for a definition see below);
- The procedure may be technically successful, but symptoms do not disappear after the procedure (failure to achieve clinical success, for a definition see below), after which a reintervention will be scheduled;
- The procedure may be technically and initially clinically successful, however at a later stage symptoms of gastric outlet obstruction reoccur, after which a reintervention will be scheduled;

Reinterventions may be categorized as follows:

- Endoscopic procedures aimed at evaluating and, if applicable, treating anastomotic dysfunction, such as removing impacted food/tissue overgrowth, insertion of a second LAMS after migration of the first, or procedures aimed at creating an alternative route for food passage, such as placement of an enteral stent or construction of a percutaneous jejunostomy, or placement of a venting endoscopic gastrostomy;
- Surgical procedures aimed at treating dysfunction of the gastroenteric anastomosis or creating alternative ways for food passage, such as creation of a jejunostomy;
- Radiologic procedures to treat symptoms of gastric outlet obstruction, such as construction of a radiologic gastrostomy or jejunostomy;
- Initiation of total parenteral nutrition;

Radiologic procedures solely aimed at diagnosing anastomotic dysfunction are not included in this definition.

8.1.2 Secondary study parameters/endpoints

Our secondary endpoints are defined as follows:

2. Technical success is defined as successful creation of a gastroenterostomy by means of the allocated technique (EUS-GE or SGJ). Successful (stent-in-stent) placement of a second Hot AXIOS stent during the same procedure after the initial attempt failed is also considered technically successful. If additional techniques, modalities or different type of stents (e.g. self-expandable metallic stents) were required, it will be regarded as technical failure.

3. Clinical success is defined as relief of symptoms and toleration of soft solids (GOOSS ≥2) without vomiting.

4. Gastroenterostomy dysfunction is defined as recurrence of obstructive symptoms (GOOSS 0-1) due to recurrence of GOO at the gastroenterostomy site after initial clinical success, confirmed endoscopically or radiographically.

5. Reintervention is defined as any radiologic, endoscopic or surgical intervention for an adverse event, persistent obstructive symptoms or recurrent obstructive symptoms, that is needed after EUS-GE or SGJ. This includes creating an alternative route to improve or restore adequate nutritional intake – either through placing a nasal feeding tube, construction of a gastrostomy or jejunostomy, or through initiating parenteral nutrition.

6. Time to reintervention for persistence or recurrence of symptoms is defined as the time in days between EUS-GE/SGJ and reintervention for recurrence of symptoms of GOO (nausea, vomiting, inability to tolerate oral intake).

7. Adverse events are specified according to the ASGE lexicon for endoscopic adverse events. An adverse event is defined as “an event that prevents completion of the planned procedure and/or results in admission to hospital, prolongation of existing hospital stay, another procedure (needing sedation/anesthesia), or subsequent medical consultation.”[30] Late adverse events are considered events occurring beyond thirty days after the study procedure. Severity of adverse events is graded according to the Clavien-Dindo Complication Score (severe is defined as ≥ 3B).[31,32]

Common or expected AEs are the following: abdominal pain, bleeding, perforation, anastomotic leakage, peritonitis.[23,33] For more detailed information, see 9.2 AEs, SAEs and SUSARs

8. Quality of life will be measured by 2 cancer specific questionnaires (core-questionnaire EORTC QLQC30 supplemented with a disease-specific module EORTC QLQ-STO22 focusing on gastric complaints) to measure health related quality of life of cancer patients. In addition, the EQ-5D-3L questionnaire is used to calculate quality-adjusted life years (QALYs)

9. Time to start chemotherapy is defined as the number of days after EUS-GE/SGJ until chemotherapy is started (if applicable).
10. Length of hospital stay is defined as days of hospitalization between EUS-GE/SGJ and hospital discharge. If patients are transferred back to a referring hospital, the final date of discharge from their referring hospital will be registered.
11. Readmission: number and duration of hospital readmissions within 30 days after EUS-GE/SGJ.
12. Weight is defined as patients' weight in kilograms. Comparison is made between weight at baseline and weight one month after EUS-GE/SGJ.
13. Survival is defined by the number of days after EUS-GE/SGJ until death. The cause of death will be registered.
14. Costs are defined as the intramural costs that were involved with EUS-GE/SGJ, collected from the electronic hospital records and linked to the Dutch unit costs. Primary outcome measures from our economic evaluation are Quality Adjusted Life Years (QALY) and Incremental Cost Effectiveness Ratios (ICERs).

The review panel involved in this study (also judging eligibility of patients) will perform outcome assessment of our primary endpoints and of adverse events, as these are potentially subject to interpretation. These outcomes will be evaluated by all panel-members independently, blinded for the intervention that has been performed, and consensus meetings will be held to discuss discrepancies.

8.1.3 Other study parameters

Patient characteristics at baseline and follow up:

- Age;
- Sex;
- Nature of obstructive symptoms before treatment (nausea, vomiting, pain, bloating, weight loss etc);
- Duration of obstructive symptoms before treatment in days;
- Ability of food intake (GOOSS score) before treatment;
- Type of malignancy causing GOO;
- Site of obstruction;
- Mean WHO score / ECOG score;
- BMI and weight (loss) (in kg);
- ASA-classification;
- Comorbidities;

- Indication for palliative treatment (unresectable locally advanced, (distant) metastases, poor medical condition, comorbidities);
- Peritoneal carcinomatosis present radiologically
- Ascites present radiologically: none, slight, substantial;
- Serum albumin (within the last month before EUS-GE/SGJ);
- Previous oncologic treatment (chemotherapy lines, duodenal stenting, surgery, dilation);
- Treatment plan after EUS-GE/SGJ (palliative chemotherapy, best supportive care);
- Biliary drainage before or after EUS-GE/SGJ;
- Presence (previously or currently) and treatment of cholestasis due to malignant biliary obstruction;
- Use of antiplatelet agents and anticoagulants;
- In case of reintervention for gastroenterostomy dysfunction due to persistent or recurrent GOO:
  - patency duration in days:
  - cause of stent dysfunction (e.g. food impaction, tissue ingrowth, stent collaps, dislocation);
  - type of reintervention (surgical, endoscopic, radiological);
- Procedural characteristics:
  - Type of intervention performed (EUS-GE/SGJ);
  - Procedural time;
  - Perprocedural complications;
  - Date of intervention;
- Number of EUS-GEs performed by endoscopist at the moment of intervention;
- Supervised or experienced center;
- Duration of the procedure;
- Procedural adverse events;
- Aberrant course of the procedure (e.g. conversion laparoscopic to open SGJ).

8.2 Randomisation, blinding and treatment allocation

Patients will be randomly allocated with a 1:1 ratio to one of the study arms (EUS-GE or SGJ). Blinding is not feasible, as it concerns one endoscopic and one surgical treatment.

Randomisation will be done by block randomisation, using random block size, stratified by center (> 10 and ≤ 10 EUS-GE's at the initiation of the study) and WHO performance status (0-1 & 2-3), through using Castor EDC.

8.3 Study procedures

Patient selection and inclusion

Selection and inclusion of participants will proceed as follows: patients will present at their treating physician (gastroenterologist, oncologist or surgeon) with malignant gastric outlet obstruction, to discuss treatment options. This will be at the in- or outpatient department. Patients with a reasonable life expectancy, defined in terms of an adequate WHO performance status, who would normally qualify for SGJ, will be screened for eligibility. Patients with a poor WHO performance status (WHO 4) will be considered for duodenal stenting in accordance with the guidelines, and will not be part of this study. Eligibility for the ENDURO-study will be discussed by treating physicians in clinical multidisciplinary meetings and the ENDURO-review panel (i.e. consisting of at least 3 endoscopists and 3 surgeons), as patients need to qualify for both EUS-GE and SGJ and are required to meet the eligibility criteria. Patients eligible for EUS-GE who fulfil the inclusion criteria and give written informed consent for participation in the ENDURO-study, will be included.

If patients are eligible, the treating physician will explain the study and provide the patient information folder (PIF). After the patient had the opportunity to ask additional questions and has had sufficient time to decide about participation, written informed consent for the ENDURO-study will be obtained.

If agreed to participate, baseline characteristics will be registered locally, on electronic Case Report Forms (eCRFs) in Castor Electronic Data Capture, a validated and GDPR compliant data management program. Patients will be randomized and SGJ/EUS-GE will then be performed as a standardized procedure, according to protocol.

Screening- and exclusion registration

All patients screened, as well as reasons for exclusion or non-participation will be recorded in an exclusion log. Consent will be asked to register their data and for an observational follow-up. If patients eligible for the PACAP or POCOP cohorts are encountered, who are not yet registered there, they will be invited for these observational cohorts.

Performance of the procedures (EUS-GE or SGJ)

See chapter 5, page 17-19.

Follow-up

After the procedure took place and the patient is discharged, follow-up will be coordinated by the coordinating investigator from the UMC Utrecht.

Follow-up: Diary of symptoms

In order to measure our co-primary endpoints (time to oral intake of soft solids; persistent or recurrent obstruction) adequately, obstructive symptoms and intake will be registered on a daily basis during the first month after the procedure (EUS/SGJ), as patient reported outcomes.

Four items will be scored as multiple choice questions: 1. Diet tolerability 2. nausea, 3. vomiting, 4. pain. The validated gastric outlet obstruction scoring system (GOOSS) will be used to score diet tolerability (GOOSS 0 = no intake, GOOSS 1 = liquids only, GOOSS 2 = soft solids, GOOSS 3 = low residue/full diet). This score is designed to provide an objective grade to a patients' ability to eat before and after gastric outlet obstruction procedures such as SGJ or EUS-GE.[17] The GOOSS score will be thoroughly explained and categorized, using examples.

A diary will be used to register these 4 questions daily, in order to capture the moment of improvement of food intake (primary outcome, time to oral intake of soft solids) and relief of symptoms, which is expected within the first month. After the first month, this will be done once a week. In addition to the 4 multiple choice questions, a patient will be asked to weigh him/herself and to specify intake at four prespecified time points during follow up (at week 2 and 4 and month 3 and 6). so that the research team, with support of an independent dietician, can verify and objectify the reported GOOSS-score with the actual reported intake at the end of the study. Depending on the preference of the patient, this diary will be filled in online through Castor, or by means of a paper diary.

Follow-up: Quality of life

We will investigate quality of life, a highly important endpoint for this study and in any palliative treatment. To measure quality of life, two validated questionnaires will be used: The EORTC QLQ-C30 core questionnaire (30 multiple choice questions) is an important tool for assessing the generic aspects of quality of life of cancer patients in clinical trials. This core-questionnaire is rather general and will therefore be supplemented with the disease-specific EORTC-QLQ-STO22 module (22 multiple choice questions), to focus on quality of life related to obstructive symptoms. The disease-specific questionnaire cannot be used without a core-questionnaire. In addition, the short EQ-5D-3L questionnaire will be used to properly calculate quality-adjusted life years (QALYs) and measure cost effectiveness.

Validity is based on the combination of both questionnaires. Both questionnaires will be conducted before treatment (baseline), after 2 weeks, 1, 3 and 6 months, in order to evaluate short- and long-term effects of EUS-GE and SGJ. These time points have been chosen in anticipation of the possibility of a short lifespan for these patients with advanced

malignancies. Again, depending on the preference of the patient, the questionnaires will be filled in online through Castor or on paper. It will take ± 15 minutes to complete the questionnaires.

Follow-up: Telephone contact

The coordinating investigator will call the patient at 2 weeks, 1 month, 3 and 6 months, to ask if the patient has encountered any problems or particularities. This will allow us to stay informed about the occurrence of adverse events or recurrence of obstructive complaints. Usually, at least one telephonic consultation with the treating physician after EUS-GE or SGJ will also be performed as part of regular care.

Rationale for the frequency of follow-up

To minimize follow-up burden for patients, we have considered not registering regularly but asking patients to contact us in case of deterioration or recurrence of obstructive symptoms. However, to evaluate as accurately as possible and to prevent recall bias, we decided to follow up closely and actively request this information from patients, initially on a daily basis, later on once a week. Our primary endpoint is a matter of days, so daily registration is crucial. Additionally, patients will be asked to contact us in case of recurrent obstructive symptoms.

By contacting patients after 2 weeks, 1, 3 and 6 months, we can keep an eye on the occurrence of adverse events. Patients confirmed the usefulness and importance of a close follow-up when it concerns their own health status regarding the study objectives. This approach was supported in the local patient-participation meeting in the UMCU (‘Klankbordgroep’ 13 December 2018). To verify if this is indeed the case, the experienced burden of the (frequency of) follow-up will be checked during the telephonic appointments during follow-up.

Figure 2: Schedule of follow-up **TIJD**

	Week					**Maand**				
ACTIVITEIT	Baseline	1	2	3	4	2	3	4	5	6
Dagboek klachten en intake (4 vragen)	x	Dagelijks (1x/dag)				Wekelijks (1x/week)				
Dagboek eetlijst + gewicht	x		x		x		x			x
Kwaliteit van leven vragenlijsten (EORTC + EQ-5D-3L)	x		x		x		x			x

Telefonisch contact				x		x		x		x

EUS-GE/SGJ

Data collection

Data will be extracted by authorized research group personnel, through electronic Case Report Forms (eCRFs). This will be stored in Castor Electronic Data Capture, a validated and GDPR compliant data management program. The eCRF will be supplemented and checked by the study coordinator and the PIs. Castor EDC has an audit-trail, so changes and documentation within the eCRFs will be tracked. This feature can also be used for monitoring. Every local investigator will receive a Castor account. Local investigators do not have access to study records of patients from other centers. Questionnaires will also be distributed via Castor, unless patients prefer to receive them on paper. Questionnaires on paper will be returned to the study coordinator and then transferred to Castor. Collected data will be coded and pseudonymized. Every included patient will be given a unique study number. In a separate list, this unique study number will be linked to the included patient, to be able to retrieve the source data when needed. This list will be stored in a separate and secured file.

Baseline: After informed consent has been obtained, the local investigator will inform the study coordinator or research nurse about the new study participant. A new study record will be created and the local investigator will register the baseline and patient characteristics in Castor. Baseline questionnaires on quality of life, intake and symptoms will also be registered by the patient (through the diary), either on paper or via Castor, depending on the preference of the patient.
Procedural: EUS-GE or SGJ will be performed. The predefined and requested procedural details will be registered in the patient file by the treating physician who performed the treatment. The local investigator or research nurse will transfer this data to Castor. This can also be done by the study coordinator at a later moment.
Post-procedural: Symptoms will be patient-reported after the procedure was performed and continued after discharge from the hospital (diary and quality of life questionnaires – online or paper). A telephone consult will be performed by the study coordinator after 2 weeks, 1, 3 and 6 months to evaluate recurrence of obstructive symptoms or adverse events. Post-procedural data will be collected by the study coordinator, assisted by the research nurse.

Data-validation will be performed, with multiple checks on completeness and consistency of the data. The audit trail will be saved. New or derivate variables based on the collected data (for example hospitalization period based on hospital admission and discharge data) may be

created. Castor EDC and the local UMC Utrecht network provide safe storage of digital data and automatic back-ups.

Data management

A data management plan will be drafted in collaboration with the local research office, before the start of this study. Data management will be performed by the study coordinator, assisted by a research nurse and the local internal data manager of the division Internal Medicine and Dermatology. There will be no external trial management agency involved. Staff involved will be BROK-qualified. Only the research group personnel and the monitor will have access to the source data and to the database, as will be agreed upon in the informed consent form. All informed consent forms will be filled out by the study coordinator or the authorized local treating gastroenterologist/surgeon (i.e. the local investigator). They will be stored locally, in a secured place.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

8.5 Replacement of individual subjects after withdrawal

Individual subjects will not be replaced after withdrawal. The drop-out in this study is expected to be low, because follow-up is regarded little burdensome. Also, we expect patients to endorse the importance of this study and its follow-up. Still, depending on the clinical condition, it could be possible that patients in a palliative setting drop-out (withdrawal during follow-up). These patients will not be replaced. Therefore, to secure a sufficient number of inclusions, an extra 10% will be added to our sample size to compensate potential drop-out (see sample size calculation).

8.6 Follow-up of subjects withdrawn from treatment

If patients in the EUS-GE arm require an SGJ due to compelling medical reasons (see ‘5.1 Investigational treatment’), they will cross-over to the SGJ arm. These cases will be registered and analysed within both the intention-to-treat protocol and per-protocol analysis.

If patients withdraw from follow-up, after EUS-GE/SGJ has already been performed, follow-up will proceed according to the local standard of care, by their regular physician. Patients will be specifically asked if they also wish to withdraw their informed consent for registration of their clinical course, future treatment and outcomes, as this data could be extracted and used from their medical records.

8.7 Premature termination of the study

No interim-analysis is planned. Safety data on (S)AEs will be tracked by the ENDURO-review panel. We do not expect that the study will be terminated prematurely due to ethically unacceptable events. As mentioned in the study design, this study will only allow endoscopists with sufficient experience to perform EUS-GE independently. This will not only prevent that the study is biased by a learning curve, but will also prevent unacceptably high complication rates in the EUS-GE arm.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

EUS-GE/SGJ related AEs are:

- Intra-procedural bleeding, instrumental event (perforation, penetration, impaction, malplacement) OR
- Post-procedural bleeding, infection, drug reaction, pain, anastomotic leakage OR
- Cardiovascular, pulmonary, thromboembolic events during or within 30 days after intervention
- Any other event *with a probable or definite causal relation with EUS-GE/SGJ* as judged by the treating physician and/or expert panel

These AEs are defined according to the American Society of Gastrointestinal Endosopy (ASGE) lexicon for endoscopic adverse events.[30] These AEs will be reported in listings once a year. The AEs will be judged by its relation to the procedure (unlikely, possible, probable, definite) and its severity.

Other relevant adverse events are defined as follows:

- Anastomotic leakage: Adapted from the Esophagectomy Complications Consensus Group: Complete defect of anastomosis or staple line independent of presentation or method of identification. Type I: local defect which does not require intervention/does not result in abnormal post-operative course; type II: local defect which does require an additional (but not surgical) intervention; type III: requiring surgical intervention.[34]

- Peritonitis: clinically and radiographically confirmed inflammation of the peritoneum, secondary to EUS-GE/SGJ.
- Severe inflammatory response syndrome (SIRS): Two or more of: temperature > 38 ºC or < 36 ºC; heart rate > 90/min; respiratory rate > 20/min or $PaCO_2$ > 32 mm Hg (4.3 kPa); White blood cell count > 12 000/mm`^{3} or < 4000/mm^3 or > 10% immature bands.[35]
- Sepsis: SIRS reaction caused by an infection.[35]
- Delayed gastric emptying: In line with the International Study Group of Pancreatic Surgery definition. Delayed gastric emptying may only be considered when a patent anastomosis is confirmed and/or small bowel obstruction is excluded endoscopically or radiographically. Grade A: requiring nasogastric tube 4-7 days after EUS-GE/SGJ or reinsertion after day 3, and inability to tolerate solid oral intake 7 days after EUS-GE/SGJ; Grade B: requiring nasogastric tube 8-14 days after EUS-GE/SGJ or reinsertion after day 7, and inability to tolerate solid oral intake 14 days after EUS-GE/SGJ; Grade C: requiring nasogastric tube >14 days after EUS-GE/SGJ or reinsertion after day 14, and inability to tolerate solid oral intake 21 days after EUS-GE/SGJ.[36]
- Hemorrhage: defined as bleeding requiring intervention and/or transfusion.
- Ileus: Adapted from the Esophagectomy Complications Consensus Group: small bowel dysfunction intervening with normal enteral feeding.[34]

These adverse events may have one of the following consequences, in agreement with the classification proposed by Clavien & Dindo:[31,32]

1) Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions (excluding therapeutic regimens such as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy).
2) Pharmacological treatment with drugs other than antiemetics, antipyretics, analgetics, diuretics, electrolytes. Blood transfusions and total parenteral nutrition are also included
3) A. Surgical, endoscopic or radiological intervention not under general anesthesia

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or

- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

Because of the palliative setting of the study population, clinical deterioration and death are inevitable events. For that reason, reporting of SAEs through the web portal *ToetsingOnline* to the METC will be limited to the SAEs that are defined as 3B or higher according to the Clavien-Dindo Classification and which are probably or definitely related to EUS-GE/SGJ.[31,32] These SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor was informed about the serious adverse event.

<u>EUS-GE/SGJ related SAE's are:</u>

Any of the in paragraph 9.2.1 mentioned adverse events, resulting in:

1) An intervention under general anaesthesia;
2) Life threatening complications requiring IC/ICU management;
3) Single organ or multiorgan dysfunction;
4) Death of a patient.

These grades of severity are in line with the classification proposed by Clavien & Dindo.[31,32]

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge of SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. Local investigators will report SAE's to the project leader in the UMC Utrecht as soon as possible after having taken knowledge of an SAE. All other SAEs will be reported within a period of maximum 15 days after the sponsor was first informed about the serious adverse events.

All participating clinicians will be made aware of the necessity to report (serious) adverse events to the responsible local investigator. Local investigators will report SAEs to the project leader in the UMC Utrecht as soon as possible after having taken knowledge of an SAE, but at least within the above-mentioned time. The local coordinating investigator will have the responsibility to report the SAEs to the project leader, the project leader will then have the responsibility to report through the web portal *ToetsingOnline* within above-mentioned time period.

Besides the METC, the sponsor will also report the SAE to the manufacturer (Boston Scientific) and to the Central Committee on Research Involving Human Subjects (CCMO), conform the EU Medical Devices Vigilance System (MEDDEV) 2.7.3. The participating centers will also be informed. The influence of the SAE on the continuation of the study will be evaluated by the principal investigators in consultation with the ENDURO-review panel.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported until the end of study within the Netherlands, as defined in the protocol.

9.5 Safety Committee

The ENDURO review panel, consisting of three gastroenterologists and three surgeons will guard the safety of this study by reviewing the data on SAEs that have occurred. Any event which is considered Clavien-Dindo 3B or higher will be reviewed by the panel to evaluate its relation with the procedure (EUS-GE/SGJ). After notifying the involved the competent authority, the review panel will consider the establishment of a data safety monitoring board (DSMB) in close cooperation with the METC. Due to the expected comparable or lower rate of (S)AEs of EUS-GE compared to SGJ, no DSMB will be installed at initiation of the study.

10. STATISTICAL ANALYSIS

Descriptive statistics will be used for patient demographics and for various outcomes. For continuous variables, means with standard deviations (SD) will be computed for normally distributed variables, and medians with interquartile ranges (IQR) for variables with a skewed distribution. Categorical variables will be reported as absolute and relative frequencies.

Intention-to-treat and per-protocol analyses will be performed.

A p-value below 0.05 will be considered statistically significant and no correction for multiple testing will be performed.

10.1 Primary study parameter(s)

For the primary endpoint (time to ability to tolerate at least soft solids (GOOSS ≥ 2), Kaplan Meier (KM) survival curves will be constructed and differences between groups tested using the log-rank test.

To control for the stratification factor(s) used in the randomization (centers having performed ≤ 10 and > 10 EUS-GE/SGJ at initiation of the study and WHO performance status 0-1 and 1-2) a cox-proportional hazards model analysis will be performed as primary analysis. The Hazard Ratio for treatment will be calculated with 95% confidence interval and test for statistical significance (at an alpha level of 0.05).

In these analyses patients will be censored at the end of follow-up (6 months) or death.

What must be mentioned is death could act as a competing event in relation to the primary endpoint of time to ability to tolerate soft solids. Nevertheless, due to the inclusion criterion of WHO/ECOG performance score < 4 we expect to include patients with a reasonable prognosis of several months. Moreover, we expect that (almost) all patients will have reached the primary endpoint after 1-3 days, rendering death as a competing event very unlikely. Lastly, it is expected that time to ability to eat soft solids does not share an underlying prognostic factor (‘frailty’) with the competing event of death. Therefore, choosing conventional cause specific hazard analysis is considered reasonable.[38]

For the sake of accuracy, however, we will perform secondary competing event, cause specific hazard based win-noninferiority analyses and we will describe separate cumulative cause specific hazard and incidence functions for both the primary endpoint and the competing event.[38]

For the co-primary endpoint ‘<u>persistent or recurrent GOO symptoms requiring reintervention</u>’ a logistic regression analysis will be performed corrected for the stratification factor(s) used at randomization (center and WHO performance status). A risk difference with a 90% confidence interval will be constructed and the upper limit of this confidence interval (i.e. one sided test with alpha of 0.05) will be compared against the ‘non-inferiority limit’. When this

upper limit does not cross the non-inferiority limit, the new treatment will be considered non-inferior regarding the co-primary endpoint.

We will employ a hierarchical testing strategy meaning that the co-primary endpoint will only be formally tested when the primary endpoint showed a statistically significant difference. If thereafter the experimental treatment also shows to be non-inferior with regards to the co-primary endpoint, results will be regarded as statistically significantly favouring the experimental treatment.

10.2 Secondary study parameter(s)

For binary, secondary outcomes (technical and clinical success, occurrence of any (S)AE) logistic regression analyses will be performed using the same covariates as for the analysis of the primary endpoints. For secondary, time-to-event endpoints (overall survival, time to start of chemotherapy) a cox proportional hazards model analysis will be used the same way as for the primary endpoint. Continuous secondary endpoints will be analysed using linear regression analysis, again using the same covariates.

Quality of life analyses

Quality of life data will be analysed according to the EORTC QLQ-C30 and STO22 Scoring Manual. Longitudinal analysis of covariance will be performed by estimating a linear mixed model with fixed effects for baseline values, time and interaction between time and group variable. Differences in quality of life will be determined using the Chi-square test.

Cost-effectiveness analyses

Economic consequences of EUS-GE will be estimated from a societal perspective and related to patient outcome in terms of quality-adjusted life years (QALYs). We aim to perform both a retrospective cost analysis and a prospective cost-utility analysis.

Retrospective cost analysis

In our retrospective analysis we aim to gain insight in cost patterns and assess all costs incurred by patients who have already undergone SGJ or EUS-GE in the different hospitals in the last 2 years. Health care consumption will be collected from the electronic hospital records in detail and linked to Dutch unit costs to create detailed overviews of total costs for both retrospective groups. This retrospective analysis will be used to further develop and provide input for the prospective cost-effectiveness model.

Prospective cost utility analysis

In our prospective study we aim to collect all health care consumption in the clinical trial in both groups in every participating hospital. In addition, data on quality of life will be collected for both groups over time. Both cost and outcomes will be linked in a decision analytic model. Primary outcome measures are Quality Adjusted Life Years (QALY) and Incremental Cost Effectiveness Ratios (ICERs). Extensive (probabilistic and deterministic) sensitivity analyses will be performed. The analyses will be performed according to the Dutch guidelines for economic evaluations in healthcare.

QALYs will be calculated with support of the EQ-5D-3L. This short, validated questionnaire assesses quality of life on the basis of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. We decided to use two quality of life questionnaires in this study since the EORTC queries are disease-specific and therefore less applicable to QALY calculations. Participants will fill out the EQ-5D-3L questionnaire four times after the intervention, in conjunction with the EORTC questionnaires.

The cost-effectiveness analyses will be performed by/under supervision of Geert Frederix, health economist from the Julius Center for Health Sciences from the UMCU.

Scripts from statistical analysis software will be saved in the secured research folder.

10.3 Other study parameters

Not applicable

10.4 Interim analysis (if applicable)

No interim analysis will be performed

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO), the Medical Device Regulation (MDR), the General Data Protection Regulation (GDPR) and other guidelines, regulations and Acts.

11.2 Recruitment and consent

Patients presenting with malignant GOO in one of the participating centers will be screened and invited for this trial during consultation by the treating physician. Further information about the trial will be provided by the local or coordinating investigator, the treating physician, or the research nurse. Informed consent will be discussed by either a (research) nurse or investigator. The patient information folder will be provided. Patients will be given the time they need to consider their decision and ask questions. Signed informed consent will be obtained in the center where the patient is treated, by the local investigator or research nurse. All eligible patients are required to provide signed informed consent prior to participation. Patients who are ineligible or refuse to participate in the ENDURO-study will be treated according to current clinical practice and will be asked consent for data registration and observational follow-up.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

11.4 Benefits and risks assessment, group relatedness

As for the benefit, participation in this therapeutic study offers patients with malignant GOO the opportunity to undergo EUS-GE instead of surgery. EUS-GE is less invasive, with potential faster relief of symptoms and shorter hospital admission. No additional visits or physical examinations are required for this study, unless medically indicated. The burden of follow-up within this study is limited and mainly concerns time that is spent to fill in the diary, quality of life questionnaires and receive four short follow-up phone calls. We aimed to minimize this as much as possible, and balance the effort required by the patient to answer the questionnaires with the goal of quality of life analysis for this study.
The burden and risks of EUS-GE are expected to be lower than those of the standard treatment (SGJ). EUS-GE is less invasive and requires shorter hospitalization.

Though the short-term results of EUS-GE are promising, the long-term patency of EUS-GE has yet to be established and compared with the current standard treatment (SGJ). This can only adequately be achieved by comparing the efficacy, durability and safety of EUS-GE versus SGJ in these patients, in a randomized and prospective study with solid follow-up.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

None

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

A data management plan has been drafted in collaboration with the datamanager affiliated with the department. This plan is attached as a separate file. Detailed information can be found in this document.

Data will be extracted by authorized research group personnel and entered by local investigators into electronic Case Report Forms (eCRFs) (http://castoredc.com/nl/). This will be stored in Castor Electronic Data Capture, a validated and GDPR compliant data management program. With Castor, GCP-compliant data collection and data management is available for audit trail, electronic signing, reason for change, monitoring module, direct validation of data entered, authorization per form, user and institute, Adverse Event (AE) reports, and field comments. Local investigators will only have access to eCRFs of their own patients. The PI's, coordinating investigator and data manager will have access to all data.

The eCRF will be developed and checked by the study coordinator and the PIs, assisted by the division datamanager. Castor EDC has an audit-trail, implying that changes and documentation within the eCRFs will be tracked. This can also be used for monitoring. Every local investigator will receive a Castor-account. Local investigators do not have access to study records of patients from other centers. Questionnaires and diaries will also be distributed via Castor, unless patients prefer to receive them on paper. Questionnaires or diaries on paper will be returned to the study coordinator and then transferred to Castor. The paper questionnaires will be archived.
Collected data will be coded and pseudonymized. Every included patient will be given a unique study number. In a separate list, this unique study number will be linked to the included patient, to be able to retrieve the source data when needed. This list will be stored in a separate and secured file (O-drive) on the local network of the sponsor. This drive can only be accessed by the principal investigator, local investigator and research data manager.

Both Castor EDC and the local UMCU network provide safe storage of digital data and automatic back-ups.

All data will be archived for at least 15 years on the local UMCU network, in accordance with the UMCU policy that is in effect at the time of archiving.

12.2 Monitoring and Quality Assurance

The conduct of this study and of this investigational treatment carries little additional risks compared to the standard procedure (SGJ). Therefore, monitoring based on a low risk classification will be applied. Central internal monitoring of the UMCU will be performed. Trained monitors will provide the necessary service of monitoring this study according to the Netherlands Federation of University Medical Centers (NFU)-guidelines.

For details, please see the monitoring plan.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC at the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

This study will be registered in a publicly-available prospective clinical trial registry before the first patient is included. The results of this study will be submitted for publication by the coordinating investigators to a peer-reviewed scientific journal. All co-investigators will review the manuscript before submission. The principal investigator will have a final decisive call on the order of authors. In addition to the coordinating and principal investigators, an authorship for a surgeon and a gastroenterologist will be available for each participating center in which more than 3 patients are included. In case of 8 or more inclusions at a single center, two surgeons and two gastroenterologists will be offered authorship. The first and last author will be from the institution of the principal investigator.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

For details, see ‘Chapter 6 Investigational product’, in particular ‘section 6.4 Summary of known and potential risks and benefits’. Also see the Investigator’s Brochure.

a. Level of knowledge about mechanism of action

To create an EUS-GE, a Lumen-Apposing Metal Stent (LAMS) is used. This stent is endoscopically placed. It perforates the stomach and the small intestine and connects these two lumina. As the stent deploys, it creates an anastomosis between the stomach and the small intestine, bypassing the obstruction. This is the mechanical mechanism of action.

The Hot AXIOS Stent is a LAMS that is registered for several indications, such as transgastric drainage of pancreatic fluid collections or gallbladders. The manufacturer (Boston Scientific) declares that the products identified above are in conformity with all

relevant provisions of the Council Directive 93/42/EEC of 14 June 1993 concerning Medical Devices. However, creating an EUS-GE is a new application of the Hot AXIOS stent, for which it is not registered yet. The features of the Hot AXIOS Stent are deemed to be very suitable for this indication. In addition, when used to perform EUS-GE, the Hot AXIOS Stent is applied in the same anatomical region as for its indicated use.

b. Previous exposure of human beings to the test product(s) and/or products with a similar biological mechanism

Previous exposure with LAMS for different indications:

The test product (Hot AXIOS Stent) is indicated (CE registered) to facilitate transgastric or transduodenal endoscopic drainage of the gallbladder, symptomatic pancreatic pseudocysts or walled-off necrosis that is adherent to the gastric or bowel wall. In EUS-GE, a transgastric anastomosis will be created between the stomach and the small intestine.

Previous exposure of human beings with LAMS for EUS-GE:

Using the test product for EUS-GE was successfully introduced in porcine studies, showing high technical and clinical success rates.[39,40] This led to the first clinical studies on EUS-GE by means of a LAMS in human patients in 2015.[8,11,41] Since then, several studies have reported promising results.[9,10,12–16,22] Data on EUS-GE for the management of GOO were summarized and meta-analyzed very recently.[23,33]

For further details and literature, see Investigator's Brochure, page 8-9.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Yes, EUS-GE with a LAMS was first successfully studied in porcine studies. Ex-vivo use is not applicable.[39,40]

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Not applicable

e. Analysis of potential effect

Within its registered use, the stent is intended for implantation up to 60 days. For these indications, LAMS placement serves as a temporary solution for a soluble medical condition. In our study, the LAMS is used as a permanent anastomosis in palliative patients, and will not be removed. Furthermore, in literature on EUS-GE, stents are left in situ permanently. To date, this has not led to substantial adverse events. Over time, in particular stent dysfunction

of the LAMS has been reported to occur. Causes of stent dysfunction included food impaction, inflammatory tissue overgrowth, and stent ingrowth.[9,10,12,13,22] A buried gastric flange of a LAMS has also been reported recently.[25] Stent obstruction is similar to what we know about duodenum stents, but it occurs less frequently in EUS-GE, and can often be solved endoscopically. A recent meta-analysis reported that recurrence of symptoms or unplanned reintervention was needed in 9% of patients (95%CI 6%-13%) and adverse events were reported in 12% of patients (95%CI 8%-16%).[23]

As for the nature and seriousness of potential adverse effects, this mainly concerns the technical aspect of the procedure. Every procedure has its risk, and since EUS-GE remains a technically challenging endoscopic procedure, the greatest risk exists during the procedure. When causing a perforation per procedurally, this could lead to peritonitis, sepsis or even death. Especially in patients who are already severely debilitated, a complication as such could be fatal. However, this would be the same case for current standard treatments of malignant GOO (i.e. duodenal stenting or SGJ). The additional risk of EUS-GE compared to SGJ is minimal. It lies in the novelty of the technique and largely depends on the experience and competence of the endoscopist. Therefore, endoscopists performing EUS-GE within this study are required to have performed at least 20 EUS-GE to be an 'EUS-GE expertise center', or have performed at least 10 procedures (together with an experienced EUS-GE endoscopist before starting to perform this procedure). This will not only prevent that our study is biased by a learning curve, but it will also prevent unacceptably high complication rates due to lack of experience.

f. Pharmacokinetic considerations

Not applicable.

g. Study population

The study population consists of patients suffering from advanced and incurable cancer. Patients often are in a catabolic state when presenting with malignant GOO. Treatment is palliative. Patients with a poor performance status (WHO 4) will be excluded. Nevertheless, eligible patients are in the terminal stage of life. The aim of this treatment is to relief patients' obstructive symptoms, improve the ability to eat and to improve quality of terminal life.

h. Interaction with other products

Not applicable.

i. Predictability of effect

- *Technical effect*: the technical effect mainly depends on the technical success of the procedure and the Hot AXIOS stent placement. To date (October 2020), 29/31 (93.5%) of the EUS-GE performed in the UMCU were technically successful.
- *Clinical effect*: seems to depend on the condition of the individual patient. In case of extensive disease, e.g. with peritoneal carcinomatosis, gastrointestinal motility disorders, possibly unrecognized obstruction further along the gastrointestinal tract, or simply progressive cancerous disease, the gastric outlet obstruction may be solved, but intake and symptoms may still not improve.
- Also, if intake and symptoms initially do improve, this does not guarantee intake until the end of life. Even with a functional stent, cancer patients are likely to lose weight and deteriorate, as a consequence of progressive disease. The precise underlying cause might be difficult to predict or distinguish.

j. Can effects be managed?

EUS-GE remains a technically challenging endoscopic procedure and should only be performed by experienced advanced endoscopists, with experience in EUS & LAMS placement.

A perforation due to misplacement or maldeployment could be treated conservatively by closure of the defect with a clip and treatment with antibiotics, or it could be salvaged by a second attempt or bridging with a new stent.[26,42] If this is not possible or desirable, conversion to surgery may be necessary, immediately or at a later instance. Surgeons in the participating centers will be (made) aware of this. Once the Hot AXIOS stent is successfully placed, there might be a risk of recurrent obstruction of the stent, either by tissue ingrowth or by food impaction. This can usually be solved endoscopically.

Post-procedural adverse events (e.g. infection) can be treated according to standard medical care. When recurrent GOO symptoms occur, the functionality of the stent will be checked radiographically and/or endoscopically. Obstruction of the stent can usually be managed endoscopically by removal of the food bezoar or dilation of the stent.

13.2 Synthesis

Uncertainties about EUS-GE:

- Long-term patency of EUS-GE is unknown.
  This is the primary endpoint of this study.
- Potential long-term adverse events related to the LAMS could appear.
  This is one of the objectives of the study
- Adequate performance of interventional endoscopists performing EUS-GE

This will be ensured by requiring participating centers to have performed at least 20 EUS-GE, or at least 10 procedures (together with an experienced EUS-GE experienced endoscopist)

Overall risk:

Technical failure or stent misplacement:

- Range reported in literature 7% - 36% (potentially including learning curves)[9–11,13–15,22];
- Meta-analysis (12 studies, 285 patients): pooled technical failure of 8% (95% confidence interval: 5%-12%)[23];
- UMC Utrecht: 0 stent misplacements (after 30 procedures);

To reduce this risk of stent misplacement due to insufficient experience, endoscopists are required to have performed at least 20 EUS-GE or at least 10 (together with an experienced EUS-GE endoscopist). However, stent misplacement can still occur. In this case, the endoscopist will try to salvage this or convert to a surgical treatment. The surgeons are informed about this.

Stent misplacement might result in perforation, which could lead to peritonitis, sepsis and death. This will be treated as appriopriate

Adverse events:

- Range reported in literature: 3.5% to 26.7%[9,10,12–16,22];
- Meta-analysis (12 studies, 285 patients): 12% (95%CI 9%-17%)[23];

Adverse events included: stent misplacement, infection, peritonitis, bleeding, abdominal pain, gastric leak needing surgical intervention, LAMS dislocation requiring surgical intervention, gastrocolonic fistula due to delayed LAMS migration, sepsis, death.

Recurrence of GOO symptoms and the need for unplanned re-intervention:

- Meta-analysis (12 studies, 285 patients): 9% (95% CI 6%-13%)[23];

The above-mentioned adverse events are inherent in EUS-GE, not exceeding the numbers of the standard treatment (major complications of SGJ: 12.5%; re-intervention rate 11.2%), and deemed acceptable for this type of intervention.[21]

All adverse events will be treated as appropriate. Regular telephonic consultations are scheduled to determine and register adverse events.

Unknown risks

The effect of leaving the stent in the body permanently is unknown. However, to date, there are no reasons to assume this would be problematic or insoluble.

There might be unknown long-term risks that we do not know about yet. This is inevitable, since this procedure is new, and prospective long-term literature is not available. We will investigate these risks in this study. In addition, the ENDURO-review panel will evaluate every SAE possibly related to the procedure, to guard the safety of the participants.

The remaining risks are considered acceptable to the participants in this study, as they well not exceed the risks of the standard treatment (SGJ). In addition, the potential benefits of EUS-GE (less invasive, faster relief of complaints, and shorter hospitalization) might outweigh the risks.

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