Nasobiliary Drain Assisted EUS-guided Gastroenterostomies in Unresectable Malignant Gastric Outlet Obstruction

1. Background

Importance of gastric outlet obstruction in malignant disease

Gastric outlet obstruction (GOO) counts among the most severe adverse events presenting in malignant tumors located in the gastrodoudenal junction. It usually presents with abdominal pain, nausea, vomiting and weight loss. Gastric cancer is its most frequent cause; it presents in 20-30% of stage IV gastric neoplasias (1). Restarting oral intake is a foremost priority in these patients. Due to their usually poor performance score and short life expectancy, the ideal procedure should be minimally invasive, present a low adverse event rate and have a low risk of recurrence.

Management options and adverse events

Traditional management consists in a gastroduodenal derivative surgery. Unfortunately, long hospital admissions, and relevant short term morbitidy were serious issues regarding this procedure, although it presents the lowest recurrence rates among proposed procedures (2).

The development of endoscopic stents have allowed endoscopic stent placement to be considered the currently first line treatment in these patients, reaching a clinical success in 90% of patients in selected centers (3). Nevertheless, endoscopic stent placements presents some relevant drawbacks. First of all, the clinical success rates in less selected centers is probably lower. Secondly, adverse events during follow-up are relatively frequent, especially recurrent GOO due to tumoral ingrowth or, less frequently, to stent migration. Recurrent GOO might present in up to 30% of patients (3). The high recurrence rate is specially relevant, as some recent studies report median survivals in advanced gastric cancer of 13 months (4) Thus, we should not only aim at restoring bowel transit, but to keep it functioning until the patient's death.

Novel endoscopic alternatives

The first endoscopic approach to achieve a functional gastrojejunostomy was through natural orifice transluminal endoscopic surgery (NOTES), where the peritoneal cavity is reached throught the stomach. Once in the peritoneal cavity, a jejunal loop is clasped with a grasper an retrieved into the gastric cavity, suturing both hollow estructures (5). Although prospective prospective, proof of concept animal studies have shown its feasibility (6,7) and successful procedures in humans have been performed (8), it is a very demanding procedure even in highly skilled endoscopists. Endoscopic ultrasound guided gastroenterostomy (EUS-GE) is currently the preferred method to achieve an endoscopic gastric bypass in malignant GOO. An echoendoscope is used to identify the target bowel loop from the gastric cavity. To ease the identification of the target, different fluid solutions are injected into the bowel to distend it. Various methods have been proposed to reach this distention. In the endoscopy units taking part in the present study, the nasobiliary drain assisted EUS-GE is used, where a nasobiliary drain is advanced through the malignant stricture into the distal duodenum or the jejunum, and, once in place, liquids are pumped into the target bowel loop. Once the target bowel loop is identified, a lumen apposing metal stent (LAMS) is placed across both organs. After demonstrating its feasibility in animal studies (9,10), , it has been extensively used in patients (11).

Available results of EUS-GE

Self-expandable metal stents SEMS) achieve technical success in 97% of patients, with 87% achieving technical success, while a relevant proportion of patients present recurrent GOO, which presents approximately 3 months after deployment (12). A recent multicenter retrospective study comparing SEMS and EUS-GE observed similar proportions of technical and clinical success rates, while EUS-GE presented

lower rates of recurrent GOO and reintervention (13). Due to the low number of centers performing this procedure, the nasobiliary drain assisted EUS-GE has not yet been standardized, with significant differences among operators.

2. Objectives

Primary aim

- To describe different variants in the nasobiliary drain assissted EUS-GE technique, offering a detailed step by step description of the procedure performance by different endoscopists

Secondary aims

- To describe the proportions of technical and clinical success.
- To describe the adverse encountered, their severity according to ASGE standards and their management.
- To describe the time elapsed between the procedure and the initial oral intake.
- To describe the evolution of the oral intake during the first month after the procedure
- To assess the impact of the operators experience on procedure times, adverse events and technical issues.
- To assess the impact of the procedure on the quality of life of the participating patients.

4. Design

Prospective, multicenter case-series

5. Methods

Study population

All consecutive patients over 18 years of age submitted to any of the participanting center's endoscopy units to receive a nasobiliary drain assisted EUS-GE for unresectable malignant GOO are eligible to participate in this study.

Inclusion and exclusion criteria

Inclusion criteria:

- Unresectable malignant gastric outlet obstruction
- Scheduled placement of a nasobiliary drain assisted EUS-GE
- Age >18 years.

Exclusion criteria:

- Previous gastroduodenal surgery
- Previous endoscopic or surgical treatment for gastric outlet obstruction
- Simultaneous malignant biliary obstruction requiring endoscopic treatment
- Unable to understand the questionnaires
- Distal bowel obstruction
- Ascites grade 2 or superior
- Uncorrectable coagulation disorders (INR>1,5) or severe thrombocytopenia (<50000 platelets/mm3).

Definitions of the outcomes employed to assess primary and secondary variables

1. Technical success: Dichotomous variable. Defined as a correct placement of the LAMS, with one flange inside the gastric cavity and the other one in the small bowel. It should be confirmed endoscopically or fluoroscopically

2. Clinical success: Dichotomous variable. Defined as a GOOSS ≥2. It will be assessed at days +7 and +30.
3.
4. Recurrent GOO: Dichotomous variable. In patients achieving clinical success in day +7, recurrent GOO is defined as the development of nausea and vomiting and/or a GOOSS<2.
5. Persistent GOO: Dichotomous variable. Continuing nausea, vomiting, and inability to tolerate PO intake up to or occurring within 2 weeks after the procedure.
6. Major complications: life-threatening or severe complications requiring treatment and/or hospitalization (The adverse event severity will be graded according to the ASGE lexicon).
    a. Early major complications: complications occurring within 7 days after the intervention.
    b. Late major complications: complications occurring 7 days or later after the intervention.
7. Minor complications: not life-threatening or moderate or severe complications that do not require hospital admission.
8. Reintervention: Dichotomous variable. Any procedure (endoscopic, radiologic or surgical aiming at treating a recurrent GOO, persistent GOO or any procedure related adverse evento.
9. Gastric outlet obstruction score system: Presents the following categories 0 (*nil per os*), 1(liquids), 2(soft diet), 3 (full diet or low residue diet).
10. Target bowel loop diameter (mm): Diameter measured with the EUS of the dilated bowel loop. It should be measured just before placing the stent.

11. Total volume infused (ml) : Volume of saline, methilene blue solution or radiopaque contrast solution instiled to dilate the target bowel loop (each one will be individually measured).
12. Balloon dilation: Dichotomous variable. At discretion of the endoscopist, after deploying the stent, it might be dilated with a controlled radial expansion balloon dilator.

Intervention

At inclusion

Informed consent will be obtained. A clinical interview and a physical examination will be performed. The European Organization for Research and Treatment of Cancer QoL Questionnaire Core 30 (EORTC-QLQ-C30), which includes 30 items covering a global health status scale, five functional scales and ten symptom scales will be assessed in a telephone interview.

Endoscopic procedure

All procedures will be performed under sedation. An assistant endoscopist or research nurse will retrieve all data regarding the procedure. Firstly, un upper digestive endoscopy is performed with a conventional gastroscope. A guidewire is passed through the malignant lesion causing the gastric outlet obstruction. Once the guidewire is located in the distal duodenum/proximal jejunum, a nasobiliary drain (Nasal Biliary Drainage Sets, Cook medical, Indiana) is advanced over the guidewire until its distal end is placed in the distal duodenum/jejunum. At this point the gastroscope is substituted by a therapeutic echoendoscope. With the echoendoscope in place, the target bowel loop is filled with saline combined with methilene blue and radiopaque contrast. The echoendoscope is used to identify the target bowel loop. AFter

identifying the target, a lumen apposing metal stent (Axios, Boston Scientific, Massachusetts) is deployed across the gastric and bowel using its electrocautery enhanced deployment device.

Post procedure

Oral liquid intake can be restarted 4h after the procedure in patients presenting no signs or symptoms suggesting any adverse event. Pacients with an adequate tolerance might be discharged.

Follow-up

Clinical telephone interviews by an experienced research nurse will be held via telephone calls 1 day, 7 days and 30 days after the procedure. Oral intake and adverse events will be assessed every visit. Thirty days after the procedure a second evaluation of the EORTC-QLQ-C30 will be performed.

Sample size

Although EUS-GE is a rather infrequent procedure, we aim at including at least 5-10 procedures/endoscopist, in order to present each operator's *modus operandi.* Thus, recruitment will be active until a minimum of 5 procedures/endoscopist is reached or until a total sample size of 50 patients is reached, with at least 4 endoscopists including >5 procedures). To assess the secondary endpoint of the quality of life, previously published papers assessing QoL in patients with unresectable malignant GOO using the EORTC-QLQ-C30 reported mean global health status scores of 36.6 (SD: 20.1) and 45 (SD: 20.3) before treatmen. To detect at least a 14-points change

with a 5% alfa risk and an 80% power, 33 subjects were estimated to be needed. Assuming a 20% of losses, 40 patients were required.

Adverse events monitoring

Adverse events (AE) are defined as any event preventing from completing the procedure, causing or lengthening a hospital admission or conditioning further interventions or unscheduled hospital or out-patient clinic visits. According to the time of diagnosis, they are classified as intraprocedure (diagnosed in the endoscopy unit during or immediately after the procedure), postprocedure (diagnosed in the 7 days following the procedure) or delayed (diagnosed beyond the first 7 days after the procedure). Causal relationship will be categorized into definitive (clearly related), probable (probably related), possible (might be related) or unlikely (there are other more likely causes). Severity will be assessed acording to the ASGE recommendations

	Severity			
Consequence	Mild	Moderate	Severe	Fatal
Stop (or not even starting) a procedure	**x**			
Post-procedure out-patient visit	**x**			
Unplanned respiratory support during the procedure		**x**		
Unplanned hospital admission for 3 nights or less	**x**			
Unplanned hospital admission for 4-10 nights		**x**		
Unplanned hospital admission for 11 or more nights			**x**	
Intensive Care Unit admission for 1 night		**x**		
Intensive Care Unit admission for 2 or more nights			**x**	
Blood transfusion		**x**		
Endoscopic procedure		**x**		
Radiologic procedure		**x**		

	Severity			
Consequence	Mild	Moderate	Severe	Fatal
Surgical procedure			**x**	
Permanent disability			**x**	
Death				**x**

The principal investigator at each center is responsible of communicating all adverse events (all severe or fatal adverse events, regardless of the causal relationship and at least possible for moderate or mild events) to the principal investigator.

Data retrieval

Data were collected and managed using the SEED Research Electronic Data Capture tool (REDCap), a secure, web-based application created to support data capture for research studies providing semiautomatic data quality control (9). Patient-related and procedural data were included by the local investigators at stent deployment. Patients will be identified with a unique code. The database is password protected. Only the investigators have access to the database.

Local follow-up was performed according to each center's protocols. Regardless of the local follow-up, all patients underwent a centralized follow-up via telephone calls by an experienced research nurse, at inclusion, 1, 7 and 30 days after stent deployment. The EORTC-QLQ-C30 questionnaires were administered at the inclusion and at the 30 days telephone visits. Only in case the patient was admitted at the principal investigator center and preferred a personal interview, were the questionnaires administered in a face-to-face interview. Oral intake was evaluated 1, 7 and 30 days after the procedure.

6. Statistical analysis

Categorical variables were reported as percentages. Normally distributed continuous variables were reported as the mean with the standard deviation values. Non-normally distributed continuous variables were reported as the median and interquartile range. The EORTC QLQ-C30 descriptive analysis was performed with a specifically programmed Stata command (10). Variables regarding the procedure step by step analysis will only undergo a descriptive analysisDifferences between the different outcomes of the EORTC-QLQ-C30 will be assessed using linear mixed models with fixed effects for baseline values, and interaction with oncological treatment. The statistical analysis will be performed using the Stata package (StataCorp. 2013, College Station, Texas).

7. Ethics

Benefit risk assessment

Patients taking part in the study will not gain any personal benefit. We consider taking part in the study does not increase the risks associated to the procedure. The study is purely observational; data retrieval will not be performed by the operator. Thus, we consider the procedure in participating patients should defer from those EUS-GE performed in other patients . Follow-up will be performed via telephone calls, so the patient will not have to travel to take part. The procedure associated risk are well documented in the published literature, with an adverse event risk of 5% The main risk is a hollow viscus perforation, followed by GI bleeding, and sedation associated procedures (aspiration pneumonia).

The study product, AXIOS ™ (Boston Scientific) 20x10mm and 15x10mm lumen apposing metal stents, was originally designed to create internal drains for pancreatic fluid collections. Currently they are used in various other indications. Their deployment creating EUS-GE in patients presenting malignant unresectable GOO is increasing, both in Europe and in the United States, with various published case series.

8. Timeframe

First year

Recruitment of patients. Follow-up

Second year

Recruitment of patients. Follow-up (Recruitment will be active until the predetermined sample size of a minimum of 5 procedures/endoscopist is reached or until a total sample size of 50 patients is reached, with at least 4 endoscopists including >5 procedures).

Third year

Data análisis. Presentation in scientific meetings. Manuscript redaction.

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