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Delayed gastric emptying in Ivor Lewis Gastro-oesophagectomy

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Delayed Gastric Emptying in Ivor Lewis Gastro-Oesophagectomy

by

Ji Chung Tham

A thesis submitted to the University of Plymouth
in partial fulfilment for the degree of

DOCTOR OF MEDICINE

School of Medicine, Dentistry, and Biomedical Sciences

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- And my daughters Florence and Amelie

Author's Declaration

'At no time during the registration for the degree of Doctor of Medicine has the author been registered for any other University award without prior agreement of the Doctoral College Quality Sub-Committee.

Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment.

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Abstract

Delayed Gastric Emptying in Ivor Lewis Gastro-Oesophagectomy

Ji Chung Tham

Delayed gastric emptying(DGE) affects 17.5% of Ivor Lewis Gastro-oesophagectomy(ILGO) patients in my unit. DGE diagnosis is varied globally due to definition subjectivity. Definition standardisation along with a diagnostic algorithm will assist clinicians in obtaining accurate diagnoses. Additionally, DGE pathophysiology is unknown and understanding it will guide treatment.

10 patients with and without DGE from our ILGO database between 1/12/2011 to 30/06/2017 had their chest X-ray and nasogastric tube(NG) algorithm from our enhance recovery protocol assessed. DGE was considered if net NG output and/or conduit size was >50% with its performance assessed. To assess treatment, those patients were divided into: patients receiving intra-operative pyloric botulinum toxin(BOTOX) injections and those without. Comparative analysis against DGE diagnosis was performed.

To assess pathophysiology and a novel investigation, 65 patients from 01/12/2017 to 31/12/2019 had blood and breath sampled postoperatively with ingestion of a carbon-13 laced meal. DGE patients had repeated test after pyloric dilatation. Analyses of gut hormones(GH): glucagon-like-peptide-1(GLP-1) and peptide tyrosine tyrosine(PYY), were conducted based on DGE status and treatment. Post-operative DGE-related symptoms(PODRS) were assessed using a modified questionnaire.

The algorithm had sensitivity of 100.0%, and specificity of 80.0%. 16.9% of patients with BOTOX compared to 17.8% without, had DGE, p=0.876. For GH, there were no differences in GLP-1 but PYY was raised in non-DGE patients with similar findings in post-dilatation patients. The breath test was found to be inaccurate and the symptomology scores showed no differences between DGE and non-DGE patients.

Hence, the algorithm showed high diagnostic accuracy and can be used to standardise DGE definition. BOTOX did not show efficacy in treating DGE nor was the breath test an effective tool. Only PYY showed a difference in GH profile but the significance is unknown. PODRS appeared similar in all patients suggesting that DGE treatment with pyloric dilatation did not cause detriment.

300 words

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Chapter 1: Introduction – oesophageal cancer in general

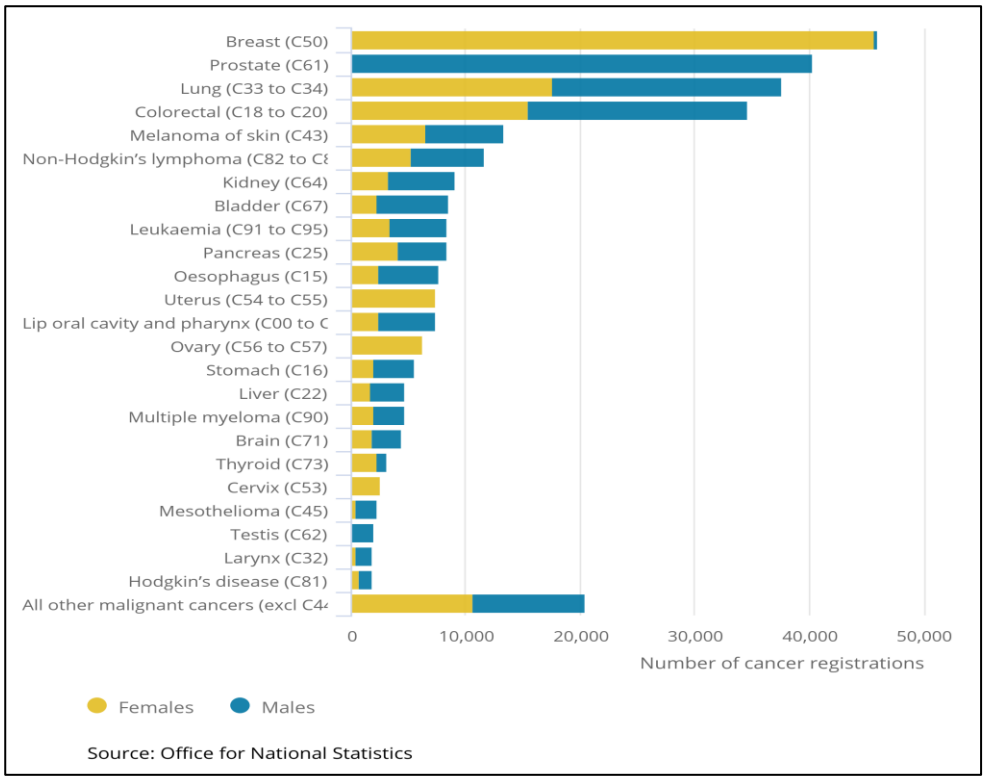
Chapter 1: Introduction

1.1 Background of Oesophageal Cancer

Epidemiology and the importance in reducing complications

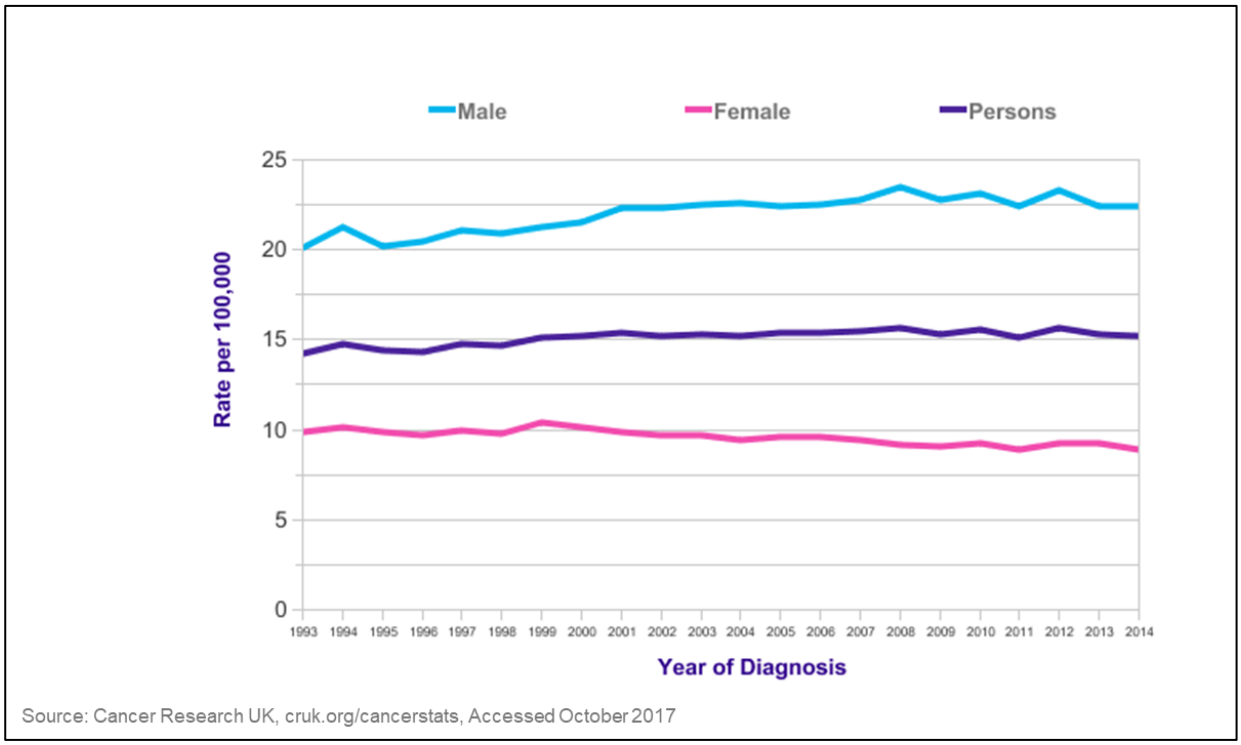
In 2015, oesophageal cancer was the 11th most common cancer in the United Kingdom (UK) and the overall incidence is increasing (1) (shown in Figure 1 and Figure 2).

However, over the last decade, mortality from oesophageal cancer has decreased by 8%, and the mortality rate is projected to fall by 16% in the UK, between 2014 and 2035, to 13 deaths per 100,000 people by 2035 (2). Table 1 showed the overall survival of oesophageal cancer at 1-, 5-, and 10-years. The current treatment for locally advanced oesophageal cancer is dependent on tumour type, site, and the current practice in the treatment unit (3) Chemoradiotherapy suggested by the CROSS trial showed that median overall survival was 48.6 months in the neoadjuvant chemotherapy plus surgery group compared to 24.0 months in the surgery alone group (3). On the other hand, the FLOT regimen which comprises of 4 cycles of neoadjuvant chemotherapy followed by 4 cycles of adjuvant chemotherapy showed a median overall survival of 50 months in patients with gastro-oesophageal junction (GOJ) tumours (4). Current trend of longer survival in patients, earlier detection of oesophageal cancers, and increasing number of oesophageal resections may result in a greater socioeconomic impact if complication rate increases. Therefore, it is important to minimise complications from surgery to improve each patient's quality-adjusted life year (QALY). QALY is a generic measure of disease burden in both quantity and quality of life (QOL) lived which has both a social and an economic impact.



Source of figure:
https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2015

Figure 1: The number of cancer registrations by the 24 major sites, Persons, England 2015



Source of figure: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/incidence#heading-Two

Figure 2: Oesophageal Cancer (C15): 1993-2014 European Age-Standardised Incidence Rates per 100,000 Population, by Sex, UK

		1-Year Survival (%)	5-Year Survival (%)	10-Year Survival (%)
Men	Net Survival	44.2	15.5	11.8
	95% LCL	43.9	13.9	9.2
	95% UCL	44.4	17.1	14.8
Women	Net Survival	38.4	14.6	12.9
	95% LCL	37.8	12.4	9.6
	95% UCL	39.0	17.0	16.8
Adults	Net Survival	41.9	15.1	12.3
	95% LCL	41.6	13.9	10.1
	95% UCL	42.2	16.5	14.6

Five- and Ten-year survival has been predicted for patients diagnosed in 2010-2011 (using an excess hazard statistical model)
95% LCL and 95% UCL are the 95% lower and upper confidence limits
Prepared by Cancer Research UK, Accessed October 2017
Original data sources:
Survival estimates were provided on request by the Cancer Research UK Cancer Survival Group at the London School of Hygiene and Tropical Medicine. http://www.lshtm.ac.uk/eph/ncde/cancersurvival/

Source of figure: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/survival#heading-Zero

Table 1: Oesophageal Cancer (C15): 2010-2011 One-, Five- and Ten-Year Net Survival (%), Adults Aged 15-99, England & Wales

Anatomical locations and types of cancer

Oesophageal cancer is usually classified into 4 main locations: upper third, middle third, lower third, and GOJ. In the west, it most commonly occur in the lower third, followed by the GOJ (5). Biologically, due to embryological origins of the tissue in each location, squamous cell cancers are usually confined to the upper and middle third while adenocarcinoma usually affect the middle third, lower third, and GOJ. Tumours at the GOJ can be subdivided using the revised Siewert classification depending on the location of the lesion relative to the gastric cardia and GOJ (6,7) (Siewert classification was defined in Table 2). According to the latest classification by the American Joint Committee on Cancer (AJCC), Siewert III tumours should be classified as gastric cancers (7). Other rarer causes of oesophageal cancer include lymphoma, melanoma, endocrine tumours, small cell carcinoma, and gastrointestinal stromal tumours (8). The identification of the cell type is important because treatment differs between each cancer type (8).

Siewert Classification	Definition
I	Adenocarcinoma of the distal oesophagus that usually arises from an area of specialised intestinal metaplasia and which may infiltrate the GOJ from above. The epicentre of the tumour should lie within 1-5 cm above the GOJ.
II	True carcinoma of the cardia arising from the cardiac epithelium or short segments of intestinal metaplasia at the GOJ; this entity is also referred to as 'junctional carcinoma'. The epicentre of the tumour lies between 1 cm above the GOJ and 2 cm below the GOJ.
III	Subcardial gastric carcinoma, which infiltrates the GOJ and distal oesophagus from below with the epicentre of the tumour lying 2-5 cm below the GOJ

Table 2: Gastro-oesophageal junction tumours as described by Siewert et al 1998 (6)

1.2 Initial investigations

Investigations are usually performed within a fortnight, following the 2-week wait rule in the UK. Investigations can occur prior to attending an outpatient appointment with an Oesophago-Gastric specialist, which is a referral straight to investigation referral system for an oesophagogastroduodenoscopy (OGD) – OGD that can be initiated by the General Practitioner (GP). Occasionally, oesophageal cancer is found during emergency admissions and those individuals should also undergo the same investigation after management of the acute surgical emergency. Initial investigations for suspected oesophageal cancer include clinical assessment, and luminal assessment.

Oesophagogastroduodenoscopy

OGD is the gold standard diagnostic tool for oesophageal cancer and should be performed with endoscopic biopsies. The British Society of Gastroenterology (BSG) and the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) have suggested that any lesion that appears malignant should have a minimum of 6 biopsies along with photo-documentation (9). Endoscopy reports should follow a standard format including: appearance, dimension, and location of lesion(s) in relation to anatomical landmarks; usually distance from the incisors (8).

1.3 Further investigations, staging, and classification

Once oesophageal cancer is diagnosed, the stage of the disease needs to be determined to ensure the correct management plan is employed. Staging is usually performed using radiological imaging, sonographic imaging, and surgical/procedural assessment.

Computed Tomography

Following confirmation of oesophageal cancer from endoscopic biopsies, computed tomography (CT) is the next investigation for staging. CT of the thorax, abdomen, and pelvis is used for the detection of metastatic disease (5,8). Current accuracy of CT staging is between 86% and 98% for distant metastases (10,11). T staging of oesophageal tumours is poor for differentiating T1 and T2 disease (12) but has an accuracy between 80% and 82% in staging between early (T1/T2) and late (T3/T4) oesophageal cancer (13). Additionally, the accuracy of correctly identifying nodal status is around 63% to 69% (11,14).

Positron Emission Tomography with Computed Tomography

Positron emission tomography (PET) combined with CT is performed to increase the diagnostic yield and accuracy for detecting distant metastases and nodal disease. PET-CT is conducted if initial CT does not show inoperable disease. The test involves the administration of a dose of positron-emitting radionuclide (usually an analogue of glucose such as 18-fludeoxyglucose). Cancer cells preferentially use glucose for metabolism and also do so in a much increased rate compared to normal cells through increased anaerobic glycolysis even in the presence of adequate oxygen – a phenomena coined the Warburg effect (15,16). Current sensitivity, specificity, and accuracy of PET-CT for distant metastases is 88% to 94%, 92% to 93%, and 91% to 92%, respectively (17,18). However, nodal assessment is still lacking with sensitivity, and specificity of 67% to 71%%, and 93% to 97%, respectively (19,20).

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) provides direct sonographic visualisation of the layers infiltrated by the tumour, characteristics of local lymph nodes, and the opportunity for fine needle aspiration of suspicious lymph nodes. From a meta-analysis by Puli et al, the overall sensitivity and specificity of EUS to diagnose T1 disease is 81.6%, and 99.4%, respectively (21). For T4 disease the sensitivity is 92.4%, and 97.4%, respectively (21). N staging sensitivity was 84.7% but with the addition of FNA, there was an improvement to 96.7% (21).

Endobronchial Ultrasound

Suspicious lymph nodes adjacent to the respiratory tree and status of local tumour invasion that are not readily examined by EUS should have endobronchial ultrasound (EBUS) assessment. EBUS allows direct visualisation and tissue sampling of the respiratory tract along with ultrasound guided biopsies of lymph nodes, thus, improving the accuracy of staging stratification (8). Although EBUS is not routinely used as part of the staging process, it can be used as an adjunct to complete ultrasonographic staging if the EUS probe cannot traverse the tumour (22).

Staging Laparoscopy and Video-assisted Thoracoscopic Surgery

Staging laparoscopy should be considered in those with distal and junctional tumours. Low volume liver, lung, peritoneal, and pleural metastases are not reliably assessed with CT, EUS and PET. Pooled sensitivity and specificity of CT versus PET are 52% and 91% versus 71% and 93%, respectively (23). Those figures suggest that false positives are small but false negatives can be substantial. Small volume disease is more reliably detected with direct visualisation, whereby laparoscopy can achieve sensitivity and specificity of 94.1% and 100%, respectively, for peritoneal or superficial liver metastases (24). Additionally, sampling of suspicious lesions during laparoscopy can be undertaken if uncertainty is present. Currently, video-assisted thoracoscopy is not routinely used in the staging process.

Endoscopic Resection

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) can be employed, both, as a staging investigation and/or as treatment. EMR and ESR are suitable as definitive treatment for early stage adenocarcinoma (confined to the mucosa or submucosa without metastases), moderately and well differentiated tumours, and mucosal dysplasia (8). The resection results in 95% 5-year disease free survival and has low morbidity (8). If the resection specimen shows that the resection is inadequate, or tumour extent is deeper than initial findings, then progression to oesophageal resection can be undertaken. If the resection specimen is complete, then the patient is spared from invasive surgery.

Classifications from Staging

From the results of the investigations, patients can be stratified for optimal treatment by staging the disease. The classification used for staging has been agreed by the AJCC, the Japanese Joint Committee (JCC) and the International Union Against Cancer (UICC) since 1986 (25). The classification used is the Tumour, Node and Metastasis Classification for solid cancers (TNM) system and it is based on histology and anatomy of the oesophageal cancer. The stage from the classification reflects prognosis.

T Classification	Description
TX	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
T1	Tumour invades lamina propria, muscularis mucosa, or submucosa.
T1a	Tumour invades lamina propria, or muscularis mucosa.
T1b	Tumour invades submucosa.
T2	Tumour invades muscularis propria.
T3	Tumour invades adventitia.
T4	Tumour invades adjacent structures.
T4a	Resectable tumour invading pleura, pericardium, or diaphragm.
T4b	Unresectable tumour invading other adjacent structures such as aorta, vertebral body, trachea, etc.
N Classification	**Description**
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastases.
N1	Metastases in 1-2 regional lymph nodes.
N2	Metastases in 3-6 regional lymph nodes.
N3	Metastases in ≥ 7 regional lymph nodes.
M Classification	**Description**
M0	No distant metastases.
M1	Distant metastases.

Table 3: TNM staging for oesophageal cancer, adapted from Edge SB, et al. The American Joint Committee on Cancer: the 7th Edition of the AJCC cancer staging manual and the future of TNM

In the TNM classification, T represents the extent of local invasion of the primary tumour, N represents the volume of nodal disease, and M represents the presence of distant metastatic disease. The TNM classification for oesophageal cancer is shown in Table 3. Once the tumour classification is determined, the patient can be staged according to the AJCC cancer staging manual (available at https://cancerstaging.org).

1.4 Curative treatment of oesophageal cancer

Neoadjuvant therapy followed by surgery

Neoadjuvant therapy is usually reserved for patients with locally advanced tumours (staging ≥ T2N0), and without distant metastases. Preoperative radiotherapy alone does not confer any benefit for oesophageal adenocarcinomas (26) but neoadjuvant chemotherapy and chemoradiotherapy do provide improved survival. Occasionally, patients undergoing neoadjuvant therapy do not progress to surgery, either due to, deterioration in health status, patient choice or death. For squamous carcinomas, definitive chemoradiotherapy can be used as a treatment option for more proximal lesions (3,27).

Various surgical techniques are available and are dependent on the tumour site and local practice. Tumours located in the cervical oesophagus or upper oesophagus will require either a 3 stage McKeown gastro-oesophagectomy or a transhiatal gastro-oesophagectomy with neck dissection. The McKeown gastro-oesophagectomy requires 3 operative approaches: abdominal, thoracic, and cervical. The transhiatal approach allows the possibility of simultaneous left neck dissection and abdominal approach while avoiding a thoracotomy.

For tumours located in the middle, lower, or oesophago-gastric junction, the operative procedure is either the thoraco-abdominal approach, or more commonly, the Ivor Lewis gastro-oesophagectomy (ILGO). Since oesophageal cancers are more common in the lower third and the GOJ, the ILGO is the most commonly performed procedure (5,28,29). Recent advances in laparoscopic techniques now allow the possibility of minimally invasive oesophagectomy (MIO), whereby the abdominal phase is performed laparoscopically and the thoracic approach is performed thoracoscopically.

For this thesis, the discussion will focus on the ILGO, including both the total open approach and the open thoracotomy with laparoscopic abdomen (hybrid MIO).

Ivor Lewis Gastro-oesophagectomy

The following description of the Ivor Lewis gastro-oesophagectomy is the technique performed at the Peninsula Oesophago-gastric Centre, University Hospitals Plymouth NHS Trust, in accordance to the Randomised Oesophagectomy: Minimally Invasive or Open trial (ROMIO)(30).

The operation involves a 2-stage gastro-oesophagectomy with a two-field lymphadectomy (abdominal and thoracic). The general overview of the oesophageal and gastric anatomy was shown in Figure 3 and showed the arteries and nerve that will be involved in the procedure. Figure 4 and Figure 5 showed the portion of the oesophagus and stomach that will be resected including the severance of the vagus nerve and the final location of the stomach, which will be in the thoracic cavity.

The ILGO can be performed as either a total open procedure (open thoracotomy with laparotomy) or as a laparoscopic abdominal approach with an open thoracic approach as described below.

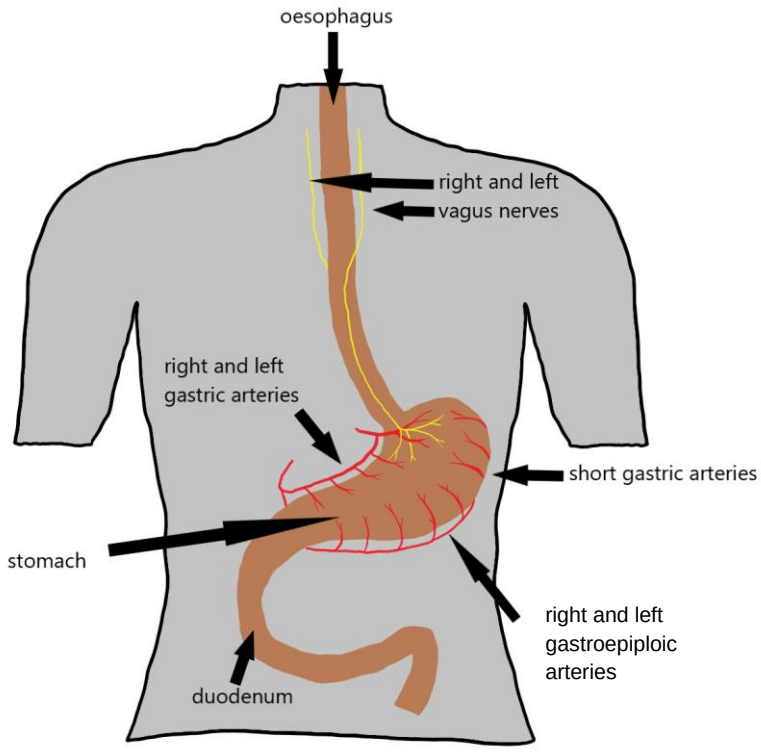


Figure 3: Simplified anatomy of the stomach, and oesophagus with the vagus nerve and gastric arteries

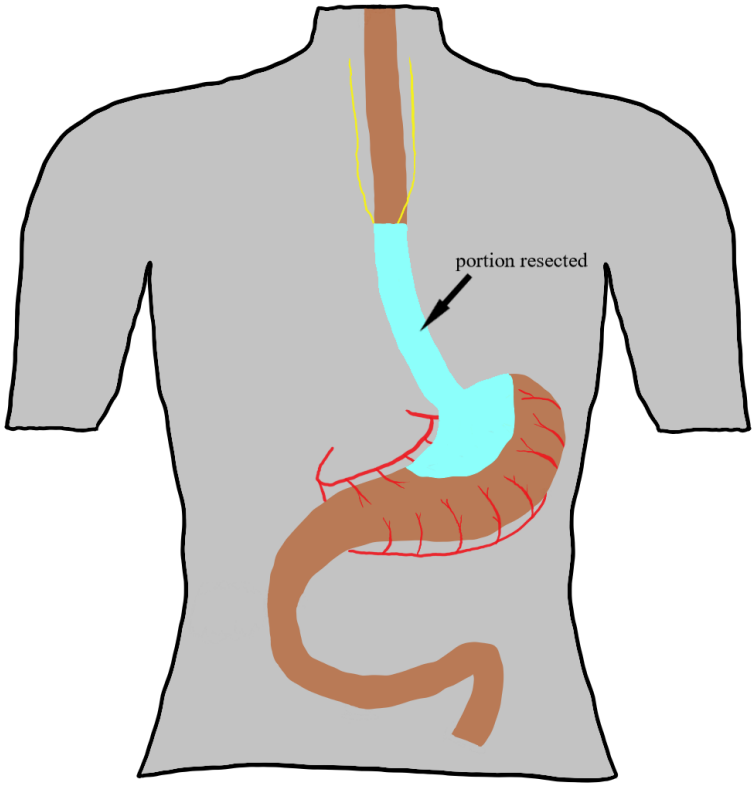


Figure 4: Generalised overview of the portion of the oesophagus and stomach that is resected. Note that the vagus nerve is severed as part of the procedure

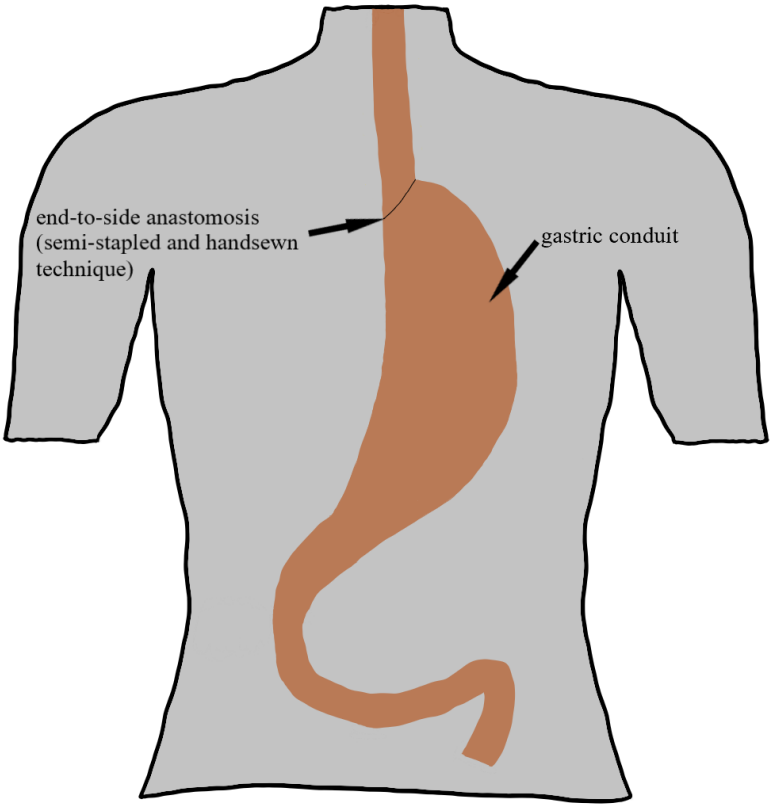


Figure 5: Generalised overview of the location of the stomach at the end of the Ivor Lewis oesophagectomy

Abdominal stage:

The open abdominal stage is the first step in an ILGO. The stomach is mobilised from the lesser and greater omentum with preservation of the right gastro-epiploic and right gastric pedicle. A pyloric drainage procedure may be performed during this stage and includes pyloroplasty, pyloromyotomy or intrapyloric botulinum toxin injection. Lymphadectomies are conducted along the common hepatic artery, right and left gastric artery, peri-coeliac axis, and splenic artery, either *en bloc* or separately. If there is suspicion of tumour involvement of the crura, then removal of crural fibres or a cuff of diaphragm can be performed. The pericardial fat pad is also removed. Feeding jejunostomies are not placed routinely but can be considered if clinically appropriate.

Open thoracotomy stage:

The patient is positioned in the left lateral position with a support for the right arm. The operation table is also "broken" at the level of the patient's waist to produce a slight left flexion. A right thoracotomy is made at the 4^{th} or 5^{th} thoracic space from the border of the erector spinae, to just inferior of the tip of the scapula, and to the anterior clavicular line. Once the pleural cavity is accessed, the right lung is fully deflated, the pulmonary ligament is divided, and the deflated lung retracted anteriorly. The oesophagus is excised in continuity with the overlying mediastinal pleura. The antero-lateral wall of the aorta is the posterior limit of the oesophageal dissection. The specimen excised at this point will include the thoracic duct and peri-oesophageal tissues which contains regional lymph nodes. The superior extent of the oesophageal mobilisation is between the Azygos vein and apex of the chest. Subcarinal and peri-oesophageal lymph nodes can be removed *en bloc* with the oesophageal excision or separately. The thoracic duct is ligated *en bloc* with surrounding fatty tissue followed by delivering the stomach into the thoracic cavity. After excision of the specimen (Figure 4), the anastomosis is performed using a semi-mechanical technique, whereby, the posterior anastomosis is performed with a linear stapler and, anteriorly, with interrupted sutures. The procedure is completed with insertion of 2 chest drains (anterior and posterior to the anastomosis), reinflation of the right lung and closure of the thoracotomy wound.

1.5 Complications of surgery

Complications from an oesophagectomy can be divided into general and specific. General complications include atelectasis, pneumonia, pleural effusion, pneumothoraces, respiratory failure, post-operative haemorrhage, cardiac dysrhythmia, thromboembolic events, and wound infections (31). The risk of pneumonia is relatively high and is at 23%, while post-operative haemorrhage, and wound infections are lower, at a rate of 6% (32).

Specific complications that can occur are related to the radical nature of the surgery such as vagal denervation, extensive dissection and lymphadenectomy, difficult anastomosis, and proximity of various sensitive structures. The consequential complications may include DGE (17.5%), chyle leak (4.7%), anastomotic leak (up to 11.4%), anastomotic stricture (11.2%), recurrent laryngeal nerve injury (14%), conduit necrosis (1.3%), and "Lasting symptoms" after oesophageal resection (31–35). Lasting symptoms are a constellation of symptoms studied by Markar et al in the LASER study, which include 6 symptoms clusters, namely, lethargy, musculoskeletal pain, dumping, lower gastrointestinal, regurgitation or reflux, swallowing, or conduit symptoms (34). Patients with DGE often complain of symptoms related to regurgitation or reflux, along with swallowing issues. Those cluster of symptoms can be further divided into food regurgitation, nausea, vomiting, heartburn, coughing, nocturnal chocking sensation, and dental issues for regurgitation and reflux. Additionally, dysphagia to solids or liquids, and early satiety and/or hiccups describes swallowing or conduit symptoms (34). Those symptoms, which will be classified as Post-operative DGE-related symptoms (PODRS) in this thesis, can occur in 5% to 30% of patients as independent symptoms or in combination, but impact on function and symptomology is yet determined.

This thesis will focus on DGE along with PODRS and further discussion regarding the subject will take place in chapter 2 and chapter 7.

1.6 Conclusion and Summary

Oesophageal cancer is not uncommon and if curative treatment is provided, patient survival appears to be satisfactory and is improving. The investigations, adjuvant treatment, and surgical treatment that patients must endure is extensive. Radiation exposure during the investigative period and, if required, during the treatment process is

substantial. Hence, every attempt should be undertaken to reduce the morbidity that is associated with the treatment of oesophageal cancer.

In order to achieve the above, I chose to investigate the following:

i. The definition and clinical diagnosis of DGE using an algorithm that can be easily used at the bedside,
ii. The pathophysiology of DGE by exploring the gut hormone profile (GHP) of post ILGO patients,
iii. An alternative investigative tool to confirm the diagnosis of DGE that can be carried out by the bedside,
iv. The treatment of DGE using intra-pyloric botulinum toxin injection,
v. And the post-operative symptoms that are associated with DGE in ILGO patients using a modified questionnaire.

The thesis hypothesis was as follows:

i. A clinical algorithm of using bedside parameters such nasogastric tube (NG) net output and simple radiological examination such as the chest X-ray (CXR) can be effective used to diagnose DGE,
ii. Gut hormones (GH) such as peptide tyrosine tyrosine (PYY) and glucagon-like peptide-1 (GLP-1) will be raised and have an exaggerated post-prandial response in DGE patients,
iii. A simple bedside test such as a breath test for following a Carbon-13 laced meal can be used to diagnose DGE,
iv. Botulinum toxin injection to the pylorus will effective treat DGE,
v. DGE patients will have more post-operative symptoms and therefore a worse modified questionnaire score, even after pyloric dilatation as treatment.

Chapter 2: Delayed gastric emptying

Chapter 2: Delayed gastric emptying

2.1 Delayed gastric emptying as a complication of oesophagectomy

As discussed in Chapter 1: Introduction, the ILGO is associated with not insignificant morbidity and mortality. Therefore, as survival and operative rate increases, the importance of reducing complications rises (36). According to the National Oesophago-gastric Cancer Audit (NOGCA) 2016 report, the overall mortality rate was 2.9% for in-hospital, 1.7% for 30-day and 3.2% for 90-day (5). The post-operative complication rate in 2011 to 2013, from the 2015 NOGCA report, was at 33.9%, which included anastomotic leak (11.7%), chyle leak (4.7%), cardiac complications (5.1%), wound infection (1.9%), respiratory complications (14.1%), and re-operation for complications (13.5%) (37). Another common complications is DGE and it can occur between 10% to 50% of patients, making it a significant contributor to morbidity (33,38,39). The vast differences in incidence of DGE between centres may be due to the lack of a definition prior to August 2015 and the relatively subjective nature of the definition proposed by the Esophagectomy Complications Consensus Group (ECCG) in August 2015 (40). The current definition by the European Minimally Invasive Oesophagectomy Think Tank (EMIOTT) was more objective, but further refinement is still required (41). The definitions was shown in Table 5. Therefore, there is a need to further improve the definition and this will be discussed further in Chapter 3: Defining delayed gastric emptying (38). Symptoms of DGE may include early satiety, reflux, nausea, vomiting, aspiration pneumonia, malnutrition, anastomotic leak and prolonged length of stay (LOS) (33,39).

Clinically, DGE occurs when passage of ingested solid or liquids from the stomach into the small bowel is prolonged. As a result, the gastric conduit may distend causing a rise in intraluminal pressure. The high volume and pressure in a distended conduit can cause nausea, vomiting, regurgitation and, hence, lead to pneumonia. The complication that affects patient QOL and symptomology the most is an anastomotic leak. It is thought that DGE may give rise to anastomotic leaks due to rising pressure from within the gastric conduit inducing ischaemia on the newly formed anastomosis (33). Anastomotic leaks often require a re-operation, placement of chest drain, placement of a feeding jejunostomy and, prolonged hospital stay. The recovery from anastomotic leaks can be protracted, and with improving post-operative survival, the QALY of the

affected individual can be severely diminished. Therefore, detecting and treating DGE early may result in reduced incidence of anastomotic leaks.

2.2 Pathophysiology of delayed gastric emptying

Gastric and pyloric vagal anatomy and function (Figure 6)

The stomach receives the posterior vagus nerve from the right oesophageal vagus nerve and the anterior vagus nerve from the left oesophageal vagus nerve (42). The pylorus obtains its parasympathetic innervation mainly from the nerve of Latarjet, also known as the posterior nerve of the lesser curvature which is a branch of the anterior vagal nerve with little or no supply coming from the posterior vagus nerve (42). Both branches of the vagus nerve are sacrificed during a typical ILGO.

Neurotransmitters associated with pyloric function include acetylcholine, nitric oxide, enkephalins and vasoactive intestinal polypeptide; with cholinergic fibres conveying basal tone that is antagonised by nitrergic fibres (42). The sympathetic function is conveyed from the hepatic plexus and directly from the greater splanchnic nerves, both originating from the fifth to the ninth thoracic spinal segment (42). Sympathetic nerves are not severed in the ILGO. The main bulk of gastric emptying appears to be driven by contractions of the stomach body; proven by the administration of an α_2-adrenergic agonist that increases tonicity of the body, relaxation of the antrum, and increased gastric emptying (43). The initiation of contractions of the body seems to originate from a pacemaker located at mid-body along the greater curve, 5 to 7 cm from the cardia and the impulse propagates to the lesser curve and towards the pylorus (44).

Severance of the anterior and posterior vagus nerve in the ILGO causes disruption in parasympathetic innervation while sympathetic and enterogastric nerve function remains preserved. The presence of unopposed sympathetic stimulation results in reduced gastric motility and increased pyloric tone. This scenario is seen in procedures for gastric ulcer disease with highly selective vagotomy whereby pyloric disruption procedures are required to prevent DGE. Therefore, preserving the vagus nerve should prevent the occurrence of DGE in post-ILGO patients. However, preservation of the vagus nerve for oesophagectomies is extremely difficult and has been describe on highly selected patients with T1 tumours and definite absence of lymph node disease (45). Such vagal sparing oesophagectomies are not normal practice and is not the usual management of oesophageal cancer. Since the vagus nerve has to be sacrificed, pyloric

disruption procedures should prevent DGE but this is not reflected in current literature (38,46), suggesting that DGE incidence may be multifactorial in origin. One such factor may be the loss or reduction in gastric motility due to dysfunction of the gastric pacemaker (47) and would explain the difference in gastric emptying function when compared to gastric ulcer patients, whereby a pyloroplasty with normal gastric motility overcomes the issue of having a hypertonic pylorus.

It is suggested that GHs, such as GLP-1 and PYY play a role in gastric and pyloric function too; of which both hormones appear to enhance postprandial satiety, evident with exaggerated levels after an oesophagectomy (48). Elliott et al also showed that the administration of octreotide dampens the exaggeration of GLP-1 and PYY, reducing the sensation of postprandial satiety allowing patients to increase their oral input (48). Since satiety and gastric emptying are closely related, it can be postulated that GHs may play a role in the regulation of gastric emptying through modulation of the functions of the body, antrum, and pylorus of the stomach.

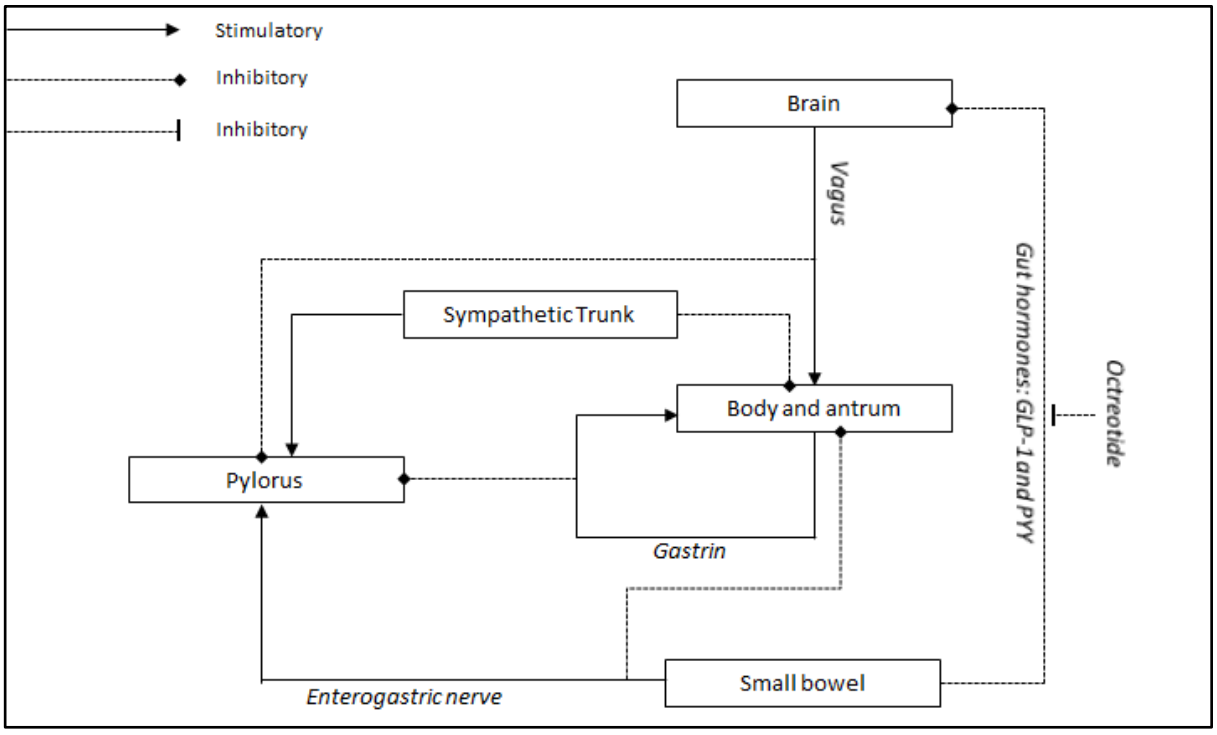


Figure 6: Proposed physiology of gastric emptying

Post-oesophagectomy pyloric and gastric function

In the post-oesophagectomy patient, pyloric pressure does not differ compared to healthy subjects but pyloric compliance is significantly reduced and the reduction in compliance is correlated with a reduction in QOL as shown in the GIQLI

(Gastrointestinal Quality of Life Index) scores by Gourcerol et al (49). However, the sample size in that study was small and there are currently no other identical studies available to verify the results. Larger studies will be required to verify those findings.

Nakabayashi et al showed that in the immediate post oesophagectomy period, gastric body motility is absent but antral and pyloric motility, although diminished, were present (50). A further study on manometry and electrogastrography of post-oesophagectomy patients showed that gastric contractility was absent in subjects with gastrointestinal symptoms but contractility was present in healthy controls and asymptomatic post-oesophagectomy patients (47). The reduced gastric function, if prolonged, contributes to delayed gastric emptying (DGE) and may cause complications such as aspiration pneumonia, and anastomotic leaks. Over time, pyloric function seems to improve spontaneously and may explain the eventual clinical improvement with or without operative pyloric disruption (39,50,51). However, the reasons for electrical dysfunction of the stomach and pyloric function remain unclear and may be the result of vagal transection, inflammation, or other causes such as GH changes.

The results discussed above showed that the exact pathophysiology of post-ILGO DGE remains unclear. Symptoms associated with DGE such as difficulty in swallowing both solids and liquids, early satiety, hiccoughs (34) cluster symptoms related to regurgitation or reflux are manifestations of DGE which could be due to volume or pressure excess but the exact mechanism of action is also unknown (34). More importantly is the impact of those symptoms on the function and the QOL of patients, which will be discussed further in chapter 7.

2.3 Management of delayed gastric emptying

As highlighted previously, anastomotic leaks are a potentially life-threatening problem for patients. Since there is an association between the incidence of developing DGE and having an anastomotic leak (33,46,52), numerous strategies have been developed to tackle DGE. Such strategies may include the use of medical therapy or surgical treatment. Medical therapy that can be used to improve gastric emptying include dopamine agonist, erythromycin and nizatidine (53,54). Currently, there is still a common practice of performing intra-operative pyloric disruption which include finger fracture (55), pyloroplasty, endoscopic balloon dilatation, or botulinum toxin injection (38,39,46,56). However, there is currently no agreed gold standard technique that can be employed to reduce the incidence of early DGE (38,46,51,57). Additionally, surgical

interventions increase operative time, are related to morbidity such as bile reflux, pyloric closure site leak and perforation due to dilatation (36,46,56,58,59). Furthermore, if intra-operative pyloric interventions are performed prophylactically, it will result in exposing all patients to the risk of intervention with only a small proportion receiving benefit. In view of this, the intra-operative pyloric botulinum toxin injection appears to be safe, easier to perform, temporary in its effects, least invasive and requires the least amount of time to perform (36,51,58–63). Current evidence of pre- or intra-operative botulinum toxin and/or balloon dilatation against control or surgical pyloric disruption to prevent DGE can be referenced in Table 4. However, more evidence in the form of a randomised controlled trial (RCT) is required to prove its effectiveness. Further discussion of the effectiveness of intra-operative pyloric botulinum toxin injections were discussed in Chapter 4: Botulinum toxin and delayed gastric emptying and a summary of management options were discussed in chapter 8.

Author and year	**Type of study**	**No. of patients**	**Intervention**	**DGE Rate, %**	***p* value**
Kent et al, 2007	Retrospective case control	15	Botulinum toxin vs control	21.4 vs N/A	0.7
Cerfolio et al, 2009	Retrospective case control	221	Botulinum toxin vs pyloroplasty vs control	59.0 vs 96.0 vs 96.0	0.024
Martin et al, 2009	Case series	45	Botulinum toxin	4.0	-
Swanson et al, 2012	Case series	25	Balloon dilatation	4.0	-
Bagheri et al, 2013	RCT	60	Pyloroplasty vs botulinum toxin	No difference	N/A
Antonoff et al, 2014	Retrospective case control	361	Botulinum toxin with dilatation vs pyloroplasty or pyloromyotomy vs dilatation vs control	* 6.8 vs 2.5 vs 0 vs 15.9	0.003
Eldaif et al, 2014	Retrospective	322	Botulinum toxin vs pyloromyotomy vs pyloroplasty	16.0 vs 5.0 vs 13.0	0.14
Fuchs et al. 2016	Retrospective case control	41	Botulinum toxin vs control	0 vs 30.0	<0.05
Stewart et al, 2017	Retrospective case control	71	Botulinum toxin vs control	8.6 vs 5.6	0.62
Marchese et al, 2018	Multicentre, prospective case control	90	Botulinum toxin vs pyloroplasty vs control	N/A (Botulinum worst; pyloroplasty no better than control)	0.001

RCT: randomised controlled trial, DGE: delayed gastric emptying, N/A: Not available
p value < 0.05 is significant
* study reported results as need for pyloric dilatation rather DGE incidence

Table 4 Summarised review of pre- or intra-operative botulinum toxin and/or balloon dilatation against control or surgical pyloric disruption to prevent delayed gastric emptying

2.4 Summary

Dramatic changes to the physiology and mechanical function of the stomach occur after an ILGO. The mechanisms by which these changes occur are currently not well understood. However, the intra-operative pyloric botulinum toxin injection appears to be safe, has temporary effects, has the least impact on patients, and is quick to perform. Further assessment of the effects of botulinum toxin in the ILGO patient in terms of efficacy and reduction of ILGO complications will strengthen the argument that DGE after an ILGO is mainly a mechanical dysfunction of the stomach. The use of botulinum toxin as a form of prophylactic treatment against DGE can be reviewed in chapter 4.

Chapter 3: Defining delayed gastric emptying

Chapter 3: Defining delayed gastric emptying

3.1 Introduction

In 2015, DGE after an ILGO was defined by the Esophageal Complications Consensus group (ECCG) as any patient with DGE requiring intervention or delaying discharge or requiring maintenance of nasogastric drainage for more than 7 days post-operatively (Table 5) (31). No changes to the definition occurred on their second consensus in 2019 (Table 5). DGE was not an uncommon complication and can occur in up to 17.5% of ILGO patients (33). Some studies have even reported DGE to be as high as 50 - 60% (38,64). As previously discussed, DGE is a serious condition that requires early diagnosis as it is linked to an increased risk of anastomotic leak which can prolong hospital LOS (33).

Standardisation of definitions are important to allow a common understanding of a word or phrase that is used, to allow discussions to be held at the same level of comprehension, and data to be analysed more accurately. Definitions that have been used based on international consensus is shown in. Previously, the lack of a standardised definition for DGE had been shown to result in variation of published DGE incidence (38), prevalence (36) and difficulties in comparing results from different studies (51). The 2015 definition of DGE as described by the ECCG provides a good framework to solve those issues and to help clinicians diagnose DGE but only after the complication has occurred (31). Clinically, a definition developed from an algorithm to diagnose DGE (33,65) may help detect DGE earlier and further refine the current definition. The algorithm may be a useful tool for daily use in managing in-patient post-operative patients. Additionally, early detection and prompt treatment may help reduce the impact of DGE on patient LOS, QOL, symptomology, and other subsequent complications.

After conducting the study described later in this chapter, I found an updated definition for post ILGO DGE authored by Konradsson et al (41). In that publication, the group, EMIOTT, devised a study which ran multiple questionnaire's as part of a modified Delphi process that included interim live discussions to narrow down specific diagnostic and a symptom grading tool for DGE (41). In all, 3 rounds of questionnaires and 2 live discussions occurred with the results of their findings shown in Table 5 (41). The results by Konradsson et al is not too dissimilar from the results in this chapter.

Groups of international specialist	Year	DGE definition
ECCG	2015	Is DGE if requiring intervention or delayed discharge or requiring maintenance of NGT drainage >7 post-operative days
ECCG	2019	No change from 2015
EMIOTT	2020	Either 1. >500ml diurnal NGT output measured on the morning of post-operative day 5 or later (but within 14 days of surgery; Or 2. >100% increase gastric tube width on frontal CXR projection (in comparison to baseline CXR taken on day of surgery) together with the presence of an air-fluid level

ECCG: Esophagectomy Complication Consensus Group, EMIOTT: European Minimally Invasive Oesophagectomy Think Tank, NGT: nasogastric tube, CXR: chest X-ray

Table 5 Definitions for delayed gastric emptying based on international consensus groups

To better define DGE, I proposed that a modified algorithm from Ford et al (65) may be used to help in the clinical diagnosis of DGE. This may allow improved detection of DGE and, possibly reduce the risk of post-operative pneumonia, anastomotic leak, and LOS. The enhanced recovery protocol proposed by Ford et al was designed in 2011 and contained a section aimed at diagnosing DGE (65). The protocol was adapted from the enhance recovery protocol from Virginia Mason Medical Centre, Seattle and altered to meet local needs through discussions with anaesthetist, physiotherapist, surgeons, specialist nurses, and hospital executives. NG output and conduit appearance on CXR were used as surrogate markers for conduit distension and clearance. The study included 196 patients and the protocol resulted in a 3-day reduction in LOS with a reduction in anastomotic leak rate (65). The senior author of that publication proposed a refinement in that algorithm by changing the measurement of only NG output to net difference in NG input against output. The logic behind that proposal was that NG output, and by surrogacy conduit clearance, would be influenced by oral/NG input. Therefore, with a known denominator (input), the ratio of net NG output would a more valid parameter to measure compared to absolute predetermined figures. Hence, in the next sub-section we will discuss the development of the modified algorithm,

3.2 Development of an algorithm to detect delayed gastric emptying

Currently, there are no proven universal bedside tools available to assist clinicians in detecting and diagnosing DGE. Investigative tools such as radio-opaque contrast swallows and scintigraphy can provide definitive diagnosis but lead to an increased radiation exposure in patients that have already had multiple CTs and PET scans.

Additionally, clinical tools such as measuring NG output with oral input, and clinical questioning (such as nausea and presence of vomiting episodes) have not been standardised and varies between different units.

Enhance recovery protocols have been developed for post-ILGO patients in view of reducing complication rates and shortening hospital LOS (65). Utilisation of parameters already used in enhance recovery protocols would not increase the burden on clinicians but will ease their workload by helping detect and diagnose DGE earlier. Two parameters that can be used are the size of the gastric conduit on chest x-rays (CXR) and the volume difference between NG output with oral input. Standardisation of the parameters and methods for measuring gastric conduit size and net output and intake volumes will be vital to avoid any subjectivity. This chapter aims to validate the modification performed on net output and input volumes in my unit's enhance recovery protocol, and show that the use of both parameters increases accuracy of diagnosing DGE.

3.3 Methods

From the Peninsula Oesophago-gastric Centre database of patients with oesophageal cancer undergoing ILGO from January 2012 to December 2016 (a total of 201 patients), random acquisition of 10 patients without DGE and 10 patients with DGE was performed. Random selection was done using a stratified lottery selection system and was described in detail below. Data was extracted retrospectively from a prospectively collected local comprehensive database. All data entered was performed by the consultant responsible for each patient at the time of intervention and morbidity data updated weekly at the joint consultant meeting. All data were from patients undergoing ILGO for curative intent. Demographics of those patients: age and gender were obtained. DGE was defined using the ECCG definition of "delayed conduit emptying requiring intervention or delaying discharge or requiring maintenance of NG drainage >7 days post-operation" (31). Information regarding oral input, NG output and CXR was collected retrospectively. For the estimation of the size of the CXR gastric conduit, the measuring tape integrated tool in the Insight Picture Archiving and Communication System (PACS) from Insignia Medical Systems was utilised and made by both the clinical team and the author. Any differences in size were discussed and an agreement

on estimated size made. The enhance recovery protocol algorithm suggested by Ford et al (65) was used with the following modification (Table 6):

1. For the NG tube output on day 4, consider removal of NG if oral intake was > 1 litre and < 50% net NG output with a gastric conduit size of < 50% of hemithorax on CXR. Those measurements were repeated on days 5 and 6,
2. The gastric conduit on CXR was measured using the maximal horizontal diameter at the mid-point of the following area: from the level of the diaphragm up to the level of the azygos vein/superior border of the right main bronchus, and from the right atrial silhouette to the lateral border of the gastric conduit compared against the thoracic width in that hemithorax at the same level of the conduit measurement.

Using the above algorithm, clinical DGE was considered if the net NG output was > 50% and/or if the gastric conduit size was > 50%. The net NG output measurements were taken daily to ensure patency of the NG tube and clearance or drainage of the conduit. On the third post-operative day, a spigot was inserted and the NG bag removed with the NG aspirated every 4 to 6 hourly. Measurement using the described algorithm above was then used, daily thereafter, to make the decision for the removal of the NG or whether pyloric dilatation should be undertaken. Those measurements would be complimented by CXRs taken on days 1, 3 and 5 post-operatively.

Based on current literature, with a DGE incidence set at 55% (38,64), power of 80%, p = 0.05, the sample size required was at least 9 in each group. Patients were selected at random from the local database. As noted above, random selection was performed using a stratified lottery selection system – patients were divided into DGE and non-DGE groups. Then in each group, numbers were allocated to each patient, numbers written on pieces paper, then folded, mixed in a box, and picked. Sensitivity, specificity, positive predictive value, and negative predictive value of each parameter in the algorithm and the algorithm as a whole were calculated. The distribution of the collected data was tested for normality using the Skewness test and Shapiro-Wilk test. Differences in gender between groups was tested with Fisher's exact test and the differences in age between groups was tested with the t-test. Receiver operating characteristic (ROC) curve analysis was used to determine the suitability of each test and the algorithm to diagnose DGE.

	Day of operation (Day 0)	1st day after operation (Day 1)	2nd day after operation (Day 2)	3rd day after operation (Day3)	4th day after operation (Day 4)	5th day after operation (Day 6)	6th day after operation (Day 6) - discharge
Monitoring	Hourly obs Heart monitor attached Humidified O_2 via mask TED™ stockings in situ	2 – 4 hourly obs Hourly urine output TED™ removed and legs checked	4 – 6 hourly obs			Stop O_2	6 hourly obs
Pain Control	PCA and local anaesthetic infusion IV paracetamol	Diclofenac PR if required and eGFR normal				Stop PCA and local anaesthetic infusion Switch to oral analgesia	
Exercise	Supported to lie upright in bed Sit out in chair Leg movements in bed Breathing exercises using incentive spirometer	Sit out in chair Support patient to mobilise 4 times/day Other exercise as per day 0					
NG Tube	In place			Spigot with 4 – 6 hourly aspiration	Consider removal if: 1. oral intake >1L 2. Oral intake and NG output difference >50% 3. conduit <50% on chest x-ray Else 8 hourly aspiration	As per day 4; else DGE present. Book pyloric dilatation from day 7 onwards	As per day 4 and 5
Chest Drains	In place				Consider removal of 1	Consider removing others	
Urinary Catheter	In place					Consider removal	
Central Line	In place					Consider removal	
IV Fluids	6 hourly litre bags				Consider reducing rate	Consider stopping	
Eating and Drinking	Sips of water ≤ 100 ml/hour – consider supplements (Fortisip Compact Protein)			Free fluids		Pureed food (half portions)	
Wound Care		Change drain dressings and check surgical wound if necessary				Leave surgical wound undressed if dry and healing well	
Investigations	Chest x-ray in recovery	Chest x-ray		Chest x-ray		Chest x-ray	
		FBC, U&E, CRP, Mg^{2+}	FBC, U&E, CRP	FBC, U&E, CRP	FBC, U&E, CRP	FBC, U&E, CRP	FBC, U&E, CRP

TED: Thrombo embolus Deterrent, Obs: observations, PCA: Patient Controlled Analgesia, IV: Intra-venous, PR: Per rectal, eGFR: Estimated Glomerular Filtration rate, NG: Nasogastric tube, DGE: Delayed gastric emptying, FBC: Full blood count, U&E: Urea and electrolytes, CRP: C-reactive protein, Mg^{2+}: Magnesium

Table 6: Enhanced recovery protocol for oesophagectomy patients and algorithm for delayed gastric emptying diagnosis

A p value of < 0.05 was considered statistically significant. International Business Machines Corporation's (IBM©) Statistical Package for the Social Sciences (SPSS) statistics software version 25 was used as the statistical program for data analyses and graph plots (https://www.ibm.com/analytics/spss-statistics-software).

As this was a retrospective data review to evaluate our service and the information did not affect the care of those patients included in the study, no ethical board review was required.

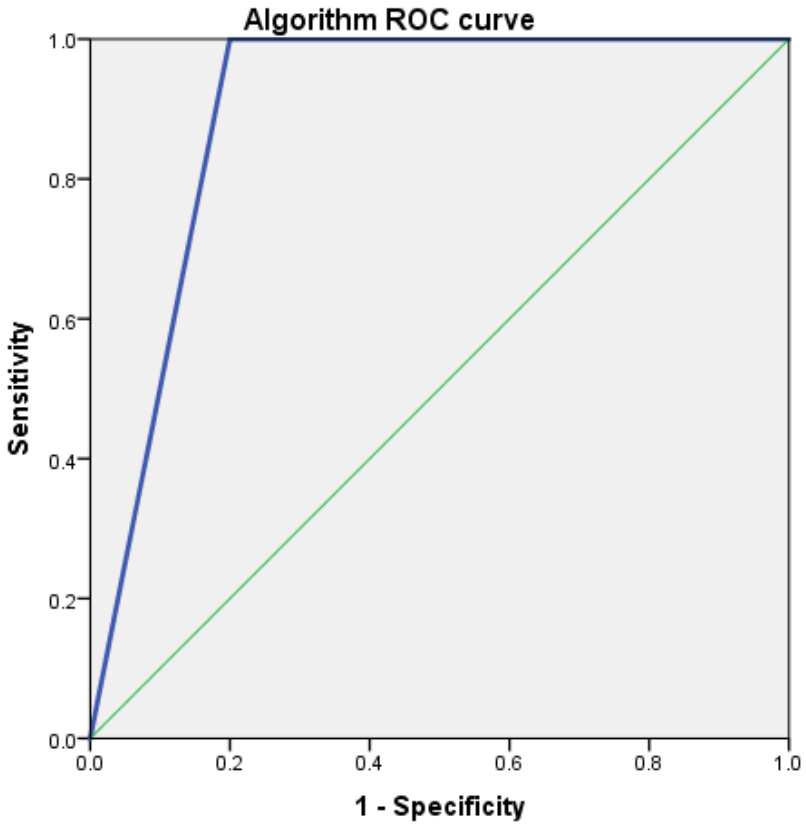
3.4 Results

From a 5-year period, 20 randomly acquire patients which consisted of 10 patients with DGE and 10 patients non-DGE were selected. The distribution of age was parametric (skewness 0.687, $p > 0.05$). There were no differences in age 73.50 ± 2.46 (p = 0.054) or gender ($p = 0.972$) between the 2 groups of patients. No differences in CXR gastric conduit measurements were found between the reviewers.

The sensitivity and specificity of CXR using the set criteria for diagnosing DGE was 90% for both. There were 1 false positive and 1 false negative. The positive and negative predictive value were also 90% for both. ROC curve analysis showed an area under the curve (AUC) of 0.875 ($p = 0.005$) with a cut-off point of gastric conduit size >50% producing the above stated sensitivity and specificity.

For net NG output using the set criteria, the sensitivity and specificity was 90% and 80%, respectively. There were 2 false positives and 1 false negative. The positive and negative predictive value was 81.8% and 88.9%, respectively. ROC curve analysis showed an AUC of 0.830 ($p = 0.013$) with a net NG output cut-off point of ≥ 55% producing a sensitivity of 90% and specificity of 70%.

In combination of both tests, as per the algorithm, the sensitivity and specificity were 100.0% and 80%, respectively. The positive and negative predictive value of the test was 83.3% and 100%, respectively. ROC curve analysis shows that the AUC was 0.900 ($p = 0.002$) (shown in Figure 7).



Note: Green line denotes reference line and blue line denotes ROC curve for the algorithm

Figure 7: Receiver Operator Characteristics curve analysis for the algorithm as a test for delayed gastric emptying

3.5 Discussion

Enhance recovery protocols are now used routinely for patient care after an ILGO. This study showed that adapting the enhance recovery protocol to include an algorithm to diagnose DGE was both a viable and excellent tool (AUC = 0.900) for clinical use. The use of CXR alone had high accuracy yield but including net NG output appeared to improve diagnostic accuracy. As both CXR and net NG output were routinely performed on post-ILGO patients, adapting them for regular use would not further burden the clinician or patient. The algorithm also provided a platform to form a new definition for DGE that can be used to detect DGE earlier compared to current definition for DGE, thus making it more clinically relevant.

Scintigraphy can be used to diagnose DGE accurately in ILGO patients (66) but involves both a high radiation exposure and high cost. Scintigraphy also requires specialist facilities and specialist radiologist to interpret the information. The use of serial CXR reduces radiation dosage and is less costly. CXR can also be interpreted by non-specialist and the x-rays can be taken into the ward using a portable x-ray machine

for imaging. Additionally, using the criteria set for measuring the gastric conduit size, no significant discrepancies between reviewers were found, suggesting ease of use.

Further review of the false positive and false negative results revealed that one of the patients with a false positive result for net NG output had a pyloroplasty performed intraoperatively. That patient had their NG removed despite having >50% output and was discharged within 7 days. Unfortunately, no further follow-up data was available, which may suggest no re-admission. Therefore, issues regarding oral intake, nausea, and vomiting that the patient may have suffered was not known. No other patients in the series had an intraoperative pyloroplasty. The underlying reason for a high NG output after a pyloroplasty was unclear. It is uncertain whether pyloric interventions or procedures can produce physiological changes that can facilitate gastric emptying. Current evidence demonstrated that earlier data from systematic review and meta-analysis showed a significantly reduction in DGE rate following a pyloroplasty or pyloromyotomy (51), but more recent reviews have not found a similar outcome (46,62). The discrepancy in findings raised the question of the actual pathophysiology of DGE.

One of the limitations of this study was the small sample size could lead to selection bias. In order to reduce that risk, randomisation of selection was performed. However, to ensure both groups were similar, stratified randomisation had to be conducted. Stratification in this study brings about the risk of wrong allocation but doing so usually results in a false negative result. A false positive result should not occur in wrong allocation. Hence, selection bias should be low in this study. The risk of performance bias was unlikely in this study due to its retrospective nature but the risk of detection bias was high. Since the study population was small and was retrospective, no blinding could have been done for the study, and most patients would have been known to me and the second reviewer in the clinical setting. Hence, the diagnosis of DGE would already be known. As net NG output was purely a mathematical calculation, the risk would be low but subjectivity can occur when interpreting CXRs. Therefore to reduce the risk of subjectivity, landmarks easily identified on X-rays were used, and this should increase reproducibility of the results too.

3.6 Conclusion

The algorithm adapted from the enhance recovery protocol proposed by Ford et al was a clinically relevant and suitable tool to help diagnose DGE. The combination of serial

CXR and net NG output increased diagnostic accuracy and can be easily applied for daily clinical use. However, further validation will be required by increasing the sample size, be conducted in other centres/units, and be compared against the gold standard for diagnosing DGE (scintigraphy).

3.7 Issues confronted and solutions

Gastric conduit size measurement using the proposed algorithm may still be biased and subjective as the measurements was based on its radiological appearance, which can be difficult to ascertain at times, compared to the size of the hemithorax. Clinically, this method was easy to use and employed readily in the ward setting. The combination of the NG algorithm should reduce false results.

The documentation of the NG input and output can sometimes be illegible. Fortunately, in the charts of those 20 patients, the occasionally illegible writing did not hamper the interpretation of the total sums of the input or output. No solution could be employed to prevent similar issues now due to time constrains but progress towards electronic documentation should stop this problem from occurring in the future.

3.8 Summary

The above study showed that the use of simple clinical parameters such as net NG output and CXR appearance helped to diagnose DGE and refined its definition. The ECCG definition cannot be used to diagnose DGE early and can be subjective. The proposed definition made diagnosing DGE more objective and was more beneficial in expediting patient care. Therefore, the algorithm can be used as an algorithm to diagnose DGE, but larger prospective trial are still needed to be performed to confirm its findings.

Chapter 4: Botulinum toxin and delayed gastric emptying

Chapter 4: Botulinum toxin and delayed gastric emptying

4.1 Introduction

There is current interest in the application of intrapyloric botulinum toxin injection for the management of DGE due to its reversible effect, low risk, ease of administration, and is the least invasive approach compared to other pyloric interventions (38,46,51,58,60–63). Botulinum toxin A is a neurotoxin produced by *Clostridium botulinum* that prevents the release of acetylcholine from neurones at the neuromuscular junction resulting in flaccid paralysis and only results in temporary relaxation of the muscle for up to 3 months. *C. botulinum* is a gram positive, spore-forming, obligate anaerobic bacilli that is motile and can produce a variety of neurotoxins. Botulinum toxin A is the neurotoxin that is relevant for this clinical situation and has been shown to be effective in treating chronic anal fissures (67) and for facial cosmesis. Therefore, the use of botulinum toxin may be plausible for managing DGE after an ILGO since it has been shown to improve gastric emptying in gastroparesis patients (68).

The first published use of pyloric botulinum toxin injections to prevent and treat DGE were by Kent et al in the University of Pittsburgh Medical Centre (69). The study was small, with 14 patients receiving intra-operative pyloric botulinum toxin injections, but none of those suffered from DGE (69). Since then, numerous studies have been conducted to evaluate the effectiveness of intrapyloric botulinum toxin injections to prevent DGE after an ILGO and showed varying results (56,58,60,61,70–72). A summary of the results was shown in Table 7. Of the 8 studies, 2 reported favourable results for botulinum toxin treatment (58,60) with ≥ 30% reduced incidence of DGE in the sample patients. There were 2 other studies that suggested botulinum toxin should be used because it was comparable to pyloric disruption procedures, was safer, easy to perform, and had temporary effects (69,70). One other study showed that although botulinum toxin was not as effective as pyloroplasty, pyloromyotomy, or pyloric dilatation, they still recommended botulinum toxin as it was comparably better than no intervention, no risk of closure site leak, and its effects were temporary (56). On the other hand, Stewart at el showed no benefit for botulinum toxin (72), while Giugliano et al and Eldaif et al showed that botulinum toxin increased complication risks without providing any benefit (61,71). The differences in results may be due to differences in operative techniques, definition for DGE and post-operative care.

However, there was currently a lack of high quality evidence as highlighted by three recent systematic reviews, which discussed the lack of standardisation of diagnosis, management, and the paucity of RCTs to determine the gold standard treatment (38,46,51).

Author, year	Type of study	Number of patients, n	Results for DGE, %
Antonoff et al, 2014 (56)	Cohort; Pyloroplasty (PP) or pyloromyotomy (PM) vs botox vs dilatation vs none	293; PP or PM vs botox vs dilatation vs none: 197 vs 44 vs 8 vs 44	PP or PM vs botox vs dilatation vs none: 2.5 vs 6.8 vs 0 vs 15.9; $p = 0.0003$
Bagheri et al, 2013 (70)	Controlled trial; PP vs botox	60; 30 in each group	PP vs botox: 8.3 vs 5; p = NS
Cerfolio et al, 2009 (60)	Cohort; PP vs PM vs botox vs none	221; PP vs PM vs botox vs none: 28 vs 71 vs 68 vs 54	PP vs PM vs botox vs none: 96 vs 93 vs 59 vs 96; $p = 0.02$
Eldaif et al, 2014 (61)	Cohort; PM vs PP vs botox	322; PM vs PP vs botox: 45 vs 199 vs 78	PM vs PP vs botox: 4.6 vs 12.9 vs 18.8; $p = 0.08$
Fuchs et al, 2016 (58)	Cohort; Botox vs none	41; Botox vs none: 14 vs 27	Botox vs none: 0 vs 30; $p < 0.05$
Giugliano et al, 2014 (71)	Cohort; PP vs botox vs PM vs none	146; PP vs botox vs PM vs none: 59 vs 41 vs 38 vs 8	PP vs botox vs PM vs none: 31.7 vs 25.8 vs 18.4 vs 12.5, $p < 0.05$
Kent et al, 2007 (69)	Cohort; Botox vs PM	22; Botox vs PM:15 vs 7	$p = 0.87$
Stewart et al, 2017 (72)	Cohort; Botox vs none	71; Botox vs none: 35 vs 36	Botox vs none: 8.6 vs 5.6, $p = 0.62$
DGE: delayed gastric emptying; PP: pyloroplasty; PM: pyloromyotomy; botox: intraoperative intrapyloric botulinum toxin injection; NS: no statistical significance			

Table 7: Studies comparing the use of intraoperative intrapyloric botulinum injections (botox) against other management strategies for delayed gastric emptying

Therefore, evaluation of the effectiveness of intraoperative endoscopic botulinum toxin injection to the pylorus in preventing DGE after ILGO, requirement for postoperative endoscopic dilatation, and LOS should be conducted as a feasibility study in view of conducting a future RCT.

4.2 Development of the intraoperative pyloric botulinum toxin injection

Currently, there are no RCTs to evaluate the efficacy of intraoperative pyloric botulinum toxin injections to prevent DGE in post-ILGO patients. Evidence from the studies mentioned previously (56,58,60,61,69–72) showed heterogenous results. Hence, an initial feasibility study was required prior to conducting a RCT based on current best research practice.

The methods for the intervention was taken from Fuchs et al (58), whereby botulinum toxin was injected endoscopically in all 4 quadrants of the pylorus. Since, a pre-surgical endoscopy was always performed on-table, addition of 4 injections did not significantly increase operative times. However, not all tumours were traversable endoscopically and an intra-abdominal approach to injecting the pylorus was occasionally required. Kent et al described only injecting the anterior aspect of the pylorus but I deemed that this would not provide the same effect that would be achieved endoscopically, therefore, would nullify the similarity of the treatment (69). On the other hand, Cerfolio et al described a 4-quadrant pyloric injections during the laparotomy phased but no clear description about duodenal mobilisation or the exact technique used to administer the injection to the posterior part of the duodenum was found (60). My unit felt that intra-abdominal 4-quadrant pyloric injections were not feasible for ILGOs due to the requirement for a fully mobile duodenum, whereby a Kocher's manoeuvre was performed to dissect free all the peritoneal attachments of the duodenum. This would, not only add extra operative time to the procedure, but also increased the risk of complications. Therefore, a compromise of a 3-quadrant injection was conducted with the same dose and volume of botulinum toxin.

4.2 Methods

This study was performed as a prospective study comparing the use of intrapyloric botulinum toxin injection versus no intervention and was conducted in the Peninsula Oesophago-gastric centre at Derriford Hospital. The data from the control group was extracted retrospectively from a prospectively collected local comprehensive database, and hence, was historical data. Data from the treatment group were collected prospectively from the time point when they were diagnosed, to having the ILGO and up to 90 days post-operatively. All data was entered by the consultant responsible for each patient at the time of intervention and morbidity data updated weekly at the joint consultant meeting. All patients undergoing ILGO for curative intent, using the semi-mechanical anastomosis technique (73) between 1st December 2011 and 30th June 2017 were included. Patients not undergoing enhanced recovery (65), or those who had pyloroplasty were excluded, to ensure that surgical technique and post-operative care were standardised and equivalent in all patients. The reason to exclude patients not undergoing enhanced recovery was to have uniformity of data and to allow matched comparison between patients. All ILGOs were performed either as laparoscopic, or

open abdominal approach with open thoracotomies. Botulinum toxin injection to the pylorus was routinely given from the 2nd of April 2016. Administration was via endoscopy, whenever the tumour was traversable (200 units made up to 10 ml with saline, using a 5 mm sclerotherapy needle in 4 separate quadrants as described by Fuchs et al) (58). In the event that the endoscope was not traversable through a stenosed tumour, botulinum toxin was administered directly into the pylorus, using a spinal needle in both open or laparoscopic approaches in 3 quadrants (74). Patient demographics including age, gender, pre-operative neoadjuvant therapy use, tumour stage, co-morbidity, American Society of Anaesthesiology (ASA) grade, surgical approach, tumour characteristics and site, presence of DGE, DGE management, and LOS were collected.

The patients were divided into two groups as follows:

(1) Intra operative botulinum toxin injection into the pylorus, BOTOX group,
(2) No intra operative botulinum toxin, NONE group.

Primary outcomes for each patient group included the presence of DGE, interventions used to manage DGE, and LOS. ECCG defined DGE as delayed conduit emptying requiring intervention, delaying discharge, or requiring maintenance of nasogastric drainage >7 days postoperatively (31). As this was a very subjective definition, an objective algorithm (**Error! Reference source not found.**) was introduced into our e nhanced recovery protocol (65) to diagnose DGE. Our enhanced recovery encourages all patients to mobilise on day 1, with the allowance of oral clear fluids up to 100ml/hour. The NG tube would be kept on free drainage until day 3, whereby a spigot would be placed, and 4-hourly aspirations would be performed from then on. DGE was then diagnosed if the patient did not meet the 'NG tube' removal criteria on day 5 (Table 6**Error! Reference source not found.**). These criteria were retrospectively applied by review of case notes, fluid balance charts, and CXRs by two independent reviewers to reduce bias and subjectivity. Our standard practice was to commence domperidone in patients with possible DGE on day 4. If pyloric dilatation was required to treat DGE, a 30mm balloon (Rigiflex™) was used as we have previously not noticed any benefit with a 20mm balloon. Secondary outcomes include complication rate, classified using the Accordion score (Table 8) (75).

Sample size was determined using an updated DGE incidence of 37% (36) and an estimated reduction of DGE to 18% post-intervention (71) (effect size of 19%) (36,71), power of 80%, $p = 0.05$ and an enrolment ratio of 2.5:1 (due to feasibility of recruiting adequate numbers for the intervention in a 1-year period). Hence, the required sample size for the BOTOX group was 65 patients, and for the NONE group, at least 155 patients. Group comparison analyses were performed using the Chi squared test (for nominal data with >5 in each 2X2 group), the Fisher's exact test (for nominal data with at least 1 group having <5 in the 2X2 group), and Mann Whitney U test (to compare non-parametric continuous data between the groups). Post hoc Bonferroni correction was used for the statistical comparisons of the groups where applicable. To assess the distribution of the continuous data, a skewness, and Shapiro-Wilk test was used. Non-parametric data was presented as median with range. A p value of < 0.05 was considered statistically significant.

No ethical approval was required for this study because the study was designed as an audit for our current management of post-ILGO DGE, and botulinum toxin was already used as regular practice in various international units.

Accordion Score	Description
1	Mild complications: use of intravenous infusion for simple medication (anti-emetics, antipyretics, analgesia, or electrolytes), urinary catheter, nasogastric tubes, and wound infections.
2	Moderate complications: other medication use such as antibiotics, blood transfusion and total parenteral nutrition'
3	Severe: management with surgical or endoscopic procedures without use of general anaesthetic (GA).
4	Severe: management with surgical or endoscopic procedures requiring GA or patient developed single organ failure.
5	Severe: complications resulting in multiorgan failure.
6	Death.

Table 8: Expanded Accordion classification for complications

4.3 Results

A total of 433 patients underwent an ILGO between 1st December 2011 and 30th June 2017. Overall, 143 did not undergo enhanced recovery, 22 patients did not have semi-

mechanical anastomosis, and 40 had pyloroplasties (all prior to 2nd April 2016). Therefore, 228 patients were included in this study of which 52 patients were female (22.8%), and the median age was 69 (range 39 to 85) years. 65 of those patients were new prospective patients while 163 were historical patients. All demographics and pathology results segregated into each intervention type were shown in Table 9 and all continuous data were non-parametric with $p < 0.05$ for skewness and Shapiro-Wilk test. A total of 124 (54.4%) operations were performed laparoscopically, 11 of which (4.8%) were converted to open procedures, and 104 (45.6%) were open operations (Table 9).

	BOTOX, n (%)	NONE, n (%)	*p*
DEMOGRAPHICS			
Gender:			0.326
Female	13 (20.0)	39 (23.9)	
Male	52 (80.2)	124 (76.1)	
Age, years (range)	69 (42-85)	69 (39-85)	0.956
Pre-operative treatment:			0.003*
Neoadjuvant Chemotherapy	29 (44.6)	93 (57.1)	
Chemoradiotherapy	14 (21.5)	10 (6.1)	
Straight to surgery	22 (33.9)	60 (36.8)	
PATHOLOGY STATUS			
Tumour type:			0.287
Adenocarcinoma	49 (75.5)	135 (82.8)	
Squamous	13 (20.0)	23 (14.1)	
Adenosquamous	1 (1.5)	4 (2.5)	
Other epithelial	1 (1.5)	0 (0)	
High grade dysplasia	1 (1.5)	1 (0.6)	
Pathology status: T			0.488
pT0	9 (13.8)	9 (5.5)	
pTis	0 (0)	2 (1.2)	
pT1a	3 (4.6)	9 (5.5)	
pT1b	8 (12.3)	25 (15.4)	
pT2	7 (10.8)	28 (17.2)	
pT3	34 (52.3)	79 (48.5)	
pT4a	4 (6.2)	10 (6.1)	
pT4b	0 (0)	1 (0.6)	
Pathology status: N			0.055
pN0	33 (50.8)	70 (42.9)	
pN1	7 (10.8)	45 (27.6)	
pN2	15 (23.1)	28 (17.2)	
pN3	10 (15.5)	20 (12.3)	
Pathology status: Margins			0.512
R0	45 (69.2)	123 (75.5)	
R1	20 (30.8)	39 (23.9)	
R2	0 (0)	1 (0.6)	

*Post hoc Bonferroni correction applied with significance set at $p < 0.0167$

Table 9: Patient demographics, treatment and pathology results in each group

Between 05/04/2016 and 30/06/2017, 65 of the 228 (28.5%) patients underwent intraoperative pyloric botulinum toxin injection (performed by all the surgeons whose patients underwent enhanced recovery). Overall, DGE occurred in 40 (17.5%) patients. A total of 11 from 65 (16.9%) in BOTOX, compared to 29 from 163 (17.8%) in NONE, had DGE, $p = 0.876$. Medical management (Accordion score 1 and 2) was required in 14 of 228 (6.1%) cases (prokinetics, intravenous fluids, prolonged NG tube usage): 3 (4.6%) in BOTOX and 11 (6.7%) in NONE. Pyloric dilatation (Accordion score ≥3) was required in 26 of 228 (11.4%): 8 of 65 (12.3%) in the BOTOX and 18 of 163 (11.0%) in NONE. Apart from pre-operative treatment, there were no differences in demographics between each group (Table 9) and requirement for intervention, $p = 0.881$. Overall median LOS was 10 (6.0-75.0) days: 9 (7.0-75.0) in BOTOX and 10 (6.0-70.0) in NONE, $p = 0.516$.

Comparison of DGE versus non-DGE patients showed a median LOS of 14 (7-75) versus 9 (6-57) days ($p < 0.0001$), pneumonia in 30.0% versus 27.7% ($p = 0.478$) and anastomotic leak rate of 10.0% versus 2.1%, $p = 0.014$. Overall leak rate was 3.5%.

The overall incidence of complications was 67.1% (includes all Accordion score ≤ 2 complications). There were 43 of 65 (66.2%) in BOTOX and 110 of 163 (67.5%) in NONE, $p = 0.482$. In-hospital mortality was 1 (0.44%), 30-day mortality was 2 (0.88%), and there were no 30-day readmissions. The 90-day mortality was 5 (2.2%).

Operative technique	**BOTOX, n**	**NONE, n**	***p***
Laparoscopic abdomen	36	77	
Open abdomen	26	78	0.539
Laparoscopic converted to open	3	8	

Table 10: Operative technique volume for BOTOX versus NONE group

4.4 Discussion

The true prevalence of DGE in the early post-operative and late follow-up stage is not known. Our study showed that using our clinical definition, DGE occurs in 17.5% of patients. However, the variation in incidence in the current literature is vast (38). This problem had been highlighted in a meta-analysis on DGE in 2002, in which the authors also showed that the lack of a standard definition for DGE resulted in difficulties with

comparing results from different studies (51). Similar difficulties can be seen with measuring QOL and/or symptomology outcomes concerning DGE. Deldycke et al showed an incidence of 37% for DGE, with difficulties in establishing predictors or prevalence for DGE (36). There was no doubt that heterogeneity of the patient groups due to subjective definition played a role in the variability of DGE rates.

In the past, the obligatory pyloric drainage procedure after a vagotomy for peptic ulcer disease treatment was thought to prevent DGE due to pyloric dysfunction from vagal nerve disruption. Since the vagus nerve was also sacrificed in an ILGO, pyloric drainage had also been commonly performed. In 2002, Urschel et al examined 9 RCTs with a cumulative total of 553 patients and found that pyloric drainage procedures reduced DGE relative risk by 0.18 [95% Confidence Interval (95%CI) of 0.03, 0.97 and $p = 0.046$] (51). However, more recent systematic reviews and meta-analysis comparing various methods of preventing DGE after an ILGO showed no advantage of pyloric drainage in terms of gastric emptying (38,46). Subsequently, Gourcerol et al assessed gastroparetic patients against post oesophagectomy patients with healthy controls, and found that DGE was related to reduced pyloric compliance and not pyloric resting pressure (49). The treatment of choice suggested by the authors was pyloric balloon dilatation. Additionally, a study of 436 patients undergoing oesophagectomy without or with pyloric drainage showed that pyloric drainage actually increased DGE (Pyloric drainage vs no pyloric drainage: 28% vs 18%, $p = 0.01$) and pyloric balloon dilatation was required in each group with a total success rate of 95% (39). However, performing the intra-operative balloon dilatation on all ILGO patients may not be appropriate based on the risk of the procedure and number needed to treat. A better approach would be more precise detection of DGE and only treating those affected. Currently, there is no explanation regarding the difference in effectiveness of balloon dilatation and pyloroplasty.

A more recent technique in managing DGE was the use of pyloric botulinum toxin injection. Fuchs et al showed that intraoperative pyloric botulinum toxin injections for total oesophagectomies may result in a reduced rate of DGE incidence from 30% to 0% (58). Similar dramatic response rates were also found in a study conducted by Cerfolio et al (60). However, similar to other pyloric interventions, results of more recent systematic review and meta-analysis did not support the effectiveness of pyloric botulinum toxin injections (46,56). These findings suggested that pyloric drainage procedures, including botulinum toxin, did not reduce the incidence of DGE, whilst

balloon dilatation postoperative was more effective. Those findings highlighted the need to further elucidate the exact pathophysiology of DGE after an ILGO through other avenues other than mechanical issues of the pylorus such as electrophysiology (47) or GH changes after an ILGO (48,76).

Anastomotic leak after an ILGO is not uncommon with a risk of 3.5% to 26% (77). It had been suggested that leaks may occur more frequently in DGE due to gastric stasis and anastomotic stress (46). Our results showed a significant increase in anastomotic leak in those patients with DGE. Additionally, 3 of 4 DGE patients with anastomotic leaks had their NG tube removed early according to our retrospectively applied algorithm. All other leak patients had their NG in-situ up to the time of anastomotic leak diagnosis. It was possible that leaving the NG in-situ may have prevented the leak.

Limitations of this study included the fact that it was not randomised and used a retrospectively applied criteria for defining DGE. However, the rate of DGE was so similar in the two groups, that a RCT would require a very large sample size. Our two study groups showed similar demographics apart from a significant increase in chemoradiotherapy use in the BOTOX group. This was due to the effect of the "ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study" (CROSS) in 2015 (3). The differences were not deemed significant because there was no known association between neoadjuvant chemoradiotherapy and DGE (39). Secondly, the heterogeneity in technique for administering botulinum toxin would definitely result in different outcomes. Additionally, different methods of administration of the toxin was performed in this study due to the logistical difference required in open versus laparoscopic approach and tumour traversability. In a larger study, sub-analysis of open versus laparoscopic botulinum toxin injections could be performed to clarify this matter. Lastly, the uniformity in terms of the depth of injections could not be standardised. This could have resulted in subtherapeutic placement of the toxin, thereby rendering the procedure ineffective. In practice, this more likely in the laparoscopic approach compared to the open approach as tissue haptics and feedback from a shorter injection needle is more refined in the latter.

4.5 Conclusion

In this study, the results showed that intra-operative pyloric botulinum toxin injections were ineffective in preventing DGE (BOTOX group vs NONE group: 16.9% vs 17.8%,

p = 0.876) or reducing post-operative complications. DGE was relatively common (17.5%), with more than half of affected patients requiring pyloric balloon dilatation, and it caused prolonged LOS (increase from 9 to 14 days). DGE was associated with anastomotic leaks with an increase in risk from 2.1% to 10.0% in DGE patients. Better understanding of DGE will guide assessment, investigation, and management of the condition. Hence, there is a need for a higher quality study in the form of a RCT with blinding.

4.6 Issues confronted and solutions

Although this study showed that intraoperative pyloric botulinum toxin injections were not efficacious in preventing DGE, a larger study in the form for a well conducted RCT may still be worth pursuing. However, as the results of my study did not support the use of botulinum toxin, I feel that further understanding of the causes of DGE was required. Upon reflecting on bariatric surgery patients, it had been highlighted that GHP changes dramatically with concurrent changes in gastrointestinal symptoms (78) and appeared to similarly occur in post-ILGO patients (79). Hence, direct observation of GHP in post-ILGO patients without and with DGE can help determine whether GHP changes post-surgery may be another factor that is involved in gastric function.

The administration of botulinum toxin into the pylorus endoscopically was safe and easy but occasionally, the oesophageal tumour could not be traversed. A solution to this issue was then to proceed with the ILGO and perform the injections either via open or laparoscopic. However, to perform a 4-quadrant injection, the duodenum with the pylorus needed to be mobilised fully. This additionally procedure would increase the risk of ILGO and increase the operative time dramatically. A compromise was to perform the injections at 3 points: 1o'clock, 5 o'clock, and 9 o'clock in a cross-section view of the pylorus. The same dose and volume could be delivered and should provide the same effect. But then, perhaps, the same 3 point injection technique should be employed for either approach for standardisation of technique should further studies be conducted.

4.7 Summary

Intra-operative pyloric botulinum toxin injections did not appear to reduce the risk of post-ILGO DGE. It was therefore likely that the cause of DGE was multifactorial and mechanical dysfunction of the pylorus was not the only underlying cause for its development. Further investigations into the physiological changes to the pylorus and stomach after an ILGO will be vital to improve knowledge on the development of DGE and to sought out other factors involved in DGE. Furthermore, the risk of complications in DGE patients were substantial but current knowledge into the impact of those complications on patients QOL or symptomology are currently lacking and require further assessment.

Chapter 5: Pathophysiology of delayed gastric emptying

Chapter 5: Pathophysiology of delayed gastric emptying

5.1 Introduction

GUT HORMONES AND GASTRIC FUNCTION

In 1975, it was hypothesized that the duodenum acted as the central feedback system of the gastrointestinal tract through its control and secretion of various gastro-active hormones (80). That frame of thought was further enforced when several peptides were discovered in the hypothalamus that were also found in the gut and vice versa (81–83). Those findings highlighted that the gastrointestinal tract is a highly complex organ with multiple channels of feedback mechanisms to maintain its function. One type of cells that is of interest is the L-cells, which is abundant in the ileum and colon. The quantity of those cells and therefore, hormone concentration produced, increases progressive from proximal to distal parts of the gastrointestinal tract (84,85). PYY and GLP-1 are GHs that are released by L-cells upon the presence of bile and nutrient ingestion in the upper gastrointestinal tract (85–89). For GLP-1, the 3-76 sequence in particular is specific for humans and is raised in the post-prandial setting (90). PYY decreases appetite and food intake (91), possibly through central satiety stimulation but it was not known whether it exerts any direct mechanical effects on the gastrointestinal tract (92). Additionally, PYY can exert direct effect on gastric function through reduction of acid output and secretions (92). On the other hand, GLP-1 is an incretin, and its analogues had been found to be an effective treatment for diabetes. Incretins are a group of metabolically active hormones that decreases blood glucose levels. Of more interest is its effects on gastrointestinal motility, notably, increases in GLP-1 levels was linked to prolonged gastric emptying time (93). GLP-1 had also been found to reduce gastric acid secretion too (94,95). Furthermore, a meta-analysis showed GLP-1 resulted in a reduction in food intake and postulated that an increased gastric emptying time may contribute to a patient's increased sense of satiety (96).

LESSONS LEARNED FROM BARIATRIC SURGERY PATIENTS

Surgical treatment used to be the last line of choice for the treatment of obesity, based on the traditional doctrine that least invasive treatments such as non-medical and medical treatment was more favourable in terms of risk and benefits. However, recent literature had shown that surgery may be superior to medical therapy in treating obesity and

diabetes (97–108). Additionally, a study in Finland was conducted to compare bariatric surgical treatment against non-surgical treatments and it was found that non-surgical treatment was 1.5 times higher than the corresponding costs of bariatric surgery during a period of 10 years (109). The cost effectiveness of bariatric surgery was also associated with an improvement in QOL in the postoperative period, which was sustained up to 10 years (109). Hence, there has been a growing move towards proposing surgery as first-line therapy for patients with obesity and type 2 diabetes. More interest was then driving the research community into grasping the underlying basis of the metabolic and physiological changes in patients after bariatric surgery.

Currently there are four options for treating obesity surgically, namely the gastric band (GB), Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion without or with a duodenal switch (BPD/DS), and sleeve gastrectomy (SG). Each surgical procedure produced its effects via a combination of different modalities. Traditionally, the GB was said to be a predominantly restrictive procedure, while the other three procedures had a mixture of effects with the BPD/DS being predominantly malabsorptive, and both the RYGB and SG being a mixture of both restrictive and malabsorptive. The thought of their mechanisms of action are now changing especially the latter three procedures, where the current mechanism of action proposed was very different from the traditional views. The GB, RYGB and SG will be discussed in the following sub-sections.

The gastric band

Originally, it was thought that the size reduction of the stomach by producing a smaller gastric pouch above the band produced the effects of satiety, hence, GB was labelled as a restrictive procedure (110). Dixon et al proposed that simply the presence of food in a smaller pouch may not be the only mechanism of action which resulted in prolonged and earlier satiety experienced by GB patients (110). Experiments by Burton et al revealed that obtaining optimal intraluminal pressure within the GB was the key to achieving the feeling of satiety during eating (111–114). When the pressure within the band is optimal, satiety is achieved, and dysphagia is absent. The proposed mechanism of action was that during the passage of food boluses through the GB, pressure within the mucosa of the band was increased resulting in a stimulus for satiety and not the previously thought of stretching of the gastric pouch above the band causing the stimulation (111–113,115). They further described that during the passage of food boluses between the GB, receptors in the gastric mucosa surrounded by the GB were stimulated, sending ‘satiety’ signals to

the brain via the vagus nerve. We now know that the nerve endings that were stimulated during the passage of food through the band are called the intra-ganglionic laminar endings (IGLEs) (115). No changes in hormone profiles had been detected in patients who have had a GB (115). The absence of GHP changes suggest that the operation help resolve the metabolic syndrome by gradually inducing weight loss through increased satiety.

In terms of ILGO patients, a vagal response would not be achieved through stretching of a smaller gastric conduit as the vagus nerve would be sacrificed. Hence, other mechanisms of action must be present to explain similar gastrointestinal function changes seen in both ILGO and bariatric surgery patients.

The roux-en-y gastric bypass

The traditional knowledge that the RYGB was both a restrictive and malabsorptive procedure is outdated. Available evidence suggested that the procedure is a metabolic operation which results in hormonal and physiological changes. The reduced size of the stomach, in the form of a small pouch, may have a role but it was probably insignificant. Numerous studies have investigated the relationship between pouch size and weight loss but have produced mixed results (116–119). For instance, Nishie et al and O'Connor et al noted no correlation between pouch size and excess weight loss within 1- and 2-year follow-up while, on the contrary, Topart et al noted correlation of a smaller pouch and more excess weight loss but this was only present in the first and not the second year of follow-up (116,118,119). Heneghan et al on the other hand observed that there was a correlation between smaller pouch length, pouch volume and anastomotic diameter with excess weight loss but the only independent factor that was related to more excess weight loss was the anastomotic diameter (117). It is possible that the effect of weight loss due the gastric pouch size was so small that only large population studies was be able to determine its role. Hence, further review of other factors was necessary.

With regards to gastrojejunal stoma size as observed by Heneghan et al, some supported the idea that a small anastomotic stoma size increased weight loss (117,120), while some disagreed (116,121). We know that dysphagia and vomiting occur if the stoma size was too small and it may result in a reoperation (122). Furthermore, rat model studies showed that the main mechanism may lie in sparing the vagus nerve (123), while pouch nor stoma size affected their food intake (124). Hence, the contradicting results suggested that the

role of the pouch and gastrojejunal stoma size may be less important as compared to other mechanisms of action of the bypass procedure.

The reconfiguration of the RYGB which involved excluding the proximal bowel (duodenum and about 20-100 cm of jejunum) from contact with nutrient and reduction of the alimentary limb length had been implicated as the cause of the metabolic changes seen. Perhaps the sequestration of the gastric fundus from nutrients produced a reduced stimulation to neuroendocrine cells which secrete the 'hunger hormone' ghrelin. Ghrelin is a 28 amino acid peptide identified in 1999 as an endogenous peptide which increases appetite and food consumption (125,126). Initially, ghrelin levels seem to fall postoperatively, but at 1 year, levels may even be higher that pre-operative levels (127). The observation that was more significant was the reestablishment of the physiological response of ghrelin to food, where there was a restoration of the postprandial fall in ghrelin levels that was previously absent (127). Conceivably, the preservation of the stomach was important in maintaining a physiological hunger-satiety cycle. Reduction of the length of small bowel available for nutrient absorption may contribute to malabsorption, therefore weight loss. However, it was unlikely for malabsorption to be an issue as the amount of small bowel bypassed only ranged between 100 cm and 150 cm only. With an average small bowel length of 600 cm in humans, the logically assumption was that malabsorption does not occur. This hypothesis had been proven in studies that showed the effects of a longer compared to a shorter alimentary limb made no difference in weight loss after 1 year nor resulted in any detrimental symptoms (128–132). Hence, it can be postulated that the mechanical reconfiguration of the gastrointestinal tract induced profound physiological changes that produced the desired outcome of weight loss.

In the first week after a RYGB procedure, there is an exaggerated PYY and GLP-1 response, and inhibition of those hormones reversed the gastrointestinal symptoms of patients (133). This response was persistent in the long term and was related to gastrointestinal symptoms, and patient eating habits (134,135). Observations of gastrointestinal symptoms and eating habits in ILGO patients prompted investigations into GHP changes that were seen in bariatric surgery patients. Elliott et al found similar GHP changes in a small number of patients and concluded that similar physiological changes seen in bariatric surgery patients did occur in ILGO patients too (76). In addition, suppression of those GHs in ILGO patients reversed patients' appetite behaviour; resulting in increased appetite, food intake, and weight gain (79). Therefore, it was postulated that GHP changes after an ILGO may contribute to the occurrence of DGE.

However, this link is tenuous, as there is no intestinal bypass involved in the ILGO. As the SG procedure is anatomically more similar to ILGO, we explore the physiological changes that occur after that procedure in hope that the findings can be translated into post-ILGO physiological outcomes.

The sleeve gastrectomy

The SG was initially thought to be a restrictive procedure (136). More recent studies had proposed that removal of the fundus may be the keystone for weight loss as ghrelin producing cells resided in the fundus (137,138). The possibility that ghrelin may play a role in weight loss was again raised. Scintigraphy examination post SG revealed that the physiological process that cause weight loss may lie in the increased gastrointestinal transit time due to a smaller gastric volume (139). The same study also revealed that the increased gastrointestinal transit time resulted in earlier satiety and improved metabolic profile (139). Another study noted that ghrelin levels fall significantly in the post-operative period with permanently attenuated levels (127). They also showed that GLP-1 levels were increased alongside the decreased ghrelin levels, which may explain the improvements seen in glycaemic control of patients. Comparisons were made between SG and RYGB in 2 studies that revealed a greater fall in ghrelin levels in the SG group but the RYGB group produced a higher exaggerated increase in GHs PYY and GLP-1 (127,140). Further animal studies performed in the Obesity Research Centre and the Metabolic Disease Institute in the University of Cincinnati showed that both RYGB and SG resulted in increased GLP-1 levels, independently of weight loss (141,142). The latter finding suggested that the GLP-1 level change was intrinsic and directly related to the surgical procedure rather than a result of weight loss.

With regards to ghrelin, Patrikakos et al revealed that two types of ghrelin exist: acyl ghrelin and des-acyl ghrelin; with acyl ghrelin being responsible in stimulating appetite and promoting adipogenesis while the function of the des-acyl ghrelin was not well understood but seem to antagonise the actions of acyl ghrelin (143). Patrikakos et al found that after a SG in Wistar rats, overall ghrelin was decreased with a notable decrease in des-acyl ghrelin levels but no changes occurred with the acyl ghrelin levels (143). Those findings, again, suggest that the role ghrelin play may not be significant.

The conclusion that can be drawn from the observations from those surgical procedures were that the increased transit of food through the gastrointestinal tract altered GH physiology, induced satiety and improved endocrine function. Changes in ghrelin levels

were not contributory to metabolic changes seen. The role of GLP-1 and PYY in SG patients was like RYGB patients but the mechanism of weight loss was due to increased gut transit. The mechanism behind the changes in symptoms and eating behaviour seen in ILGO patients will likely due to an increased post-prandial PYY and GLP-1 from increased gut transit and perhaps, also linked to gastric emptying times.

DELAYED GASTRIC EMPTYING AND GASTRO-OESOPHAGECTOMY

DGE can occur in up to 17.5% of ILGO patients and is associated with an increased risk of complications including an anastomotic leak (33,39). However, the current cause for DGE after an ILGO is not well understood. Optimal investigation and treatment can only be devised once the exact aetiology of DGE is known.

In the past, pyloric drainage procedures were performed in patients having a vagotomy for peptic ulcer disease. It was thought that the pyloric tone would increase post-operatively and may predispose patients to DGE. A similar practice had been observed in ILGO patients because the vagus nerve is also severed as part of the procedure. However, the efficacy of pyloric drainage procedures appeared to be ineffective in preventing DGE (38,46,57). Hence, there was doubt in a single aetiology cause of DGE in ILGO patients.

The pathophysiology of DGE after an ILGO could be multifactorial and may include innervation disruption, external influences from the central nervous system, hormonal, and myogenic changes (144). An area that was not well understood was the association between GHP changes and the development of DGE. It has been established that GHs such as GLP-1 were increased after an oesophagectomy and was associated with gastrointestinal symptoms such as early satiety, gastrointestinal pain or discomfort, altered taste and diarrhoea (76). As previously highlighted, gastric functions such as prolonged gastric emptying time, and reduction in gastric secretion was observed in RYGB patients, and the same was observed in ILGO patients (93–95). Additionally, suppression of GLP-1 and PYY appeared to improve patient appetite and alleviate early satiety in oesophagectomy patients (48). However, there are yet any studies that had scrutinised the association of GHs with gastric emptying in ILGO patients.

We proposed that DGE occurs in patients with an exaggerated GH response. This will allow earlier detection of patients that were at risk of DGE and allow prompt

management including possible targeting with GH analogues. Additionally, we also proposed to use the GH response, if any, as a diagnostic tool to diagnose DGE.

5.2 Development of gut hormone profile analysis

Based on a study by Pournaras et al and Arakawa et al (78,145), GHs such as PYY and GLP-1 were shown to play a role in gastrointestinal function. Analyses of those hormones were conducted in Imperial College London Biochemical laboratories. Hence, establishing contact to analyse samples in that unit was performed with completion of an inter-departmental pathology research feasibility form and inter-departmental materials transfer agreement form. Both PYY and GLP-1 were chosen as GHs that were analysed in post-ILGO patients based on recent studies, which showed similar profile and gastrointestinal function changes seen in bariatric surgery patients (48,76,78,79,145). Another unit that performed such analysis was in Dublin but storage and shipment of samples to a different country across the Irish Channel would have made the cost prohibitive.

To induce stimulation of the gastrointestinal tract to assess GHP changes in patients, a semi-solid to liquid meal that would comply with local oral intake protocol was required for the study. Since, patients were only allowed 100 ml of liquid per hour during the first few days of post-operative recovery, a compromise of 100 ml of ice-cream as the test meal was made.

The collected blood samples required laboratory skills and equipment for processing before storage and transfer. To establish adequate training for processing blood samples prior to transfer to Imperial College London Biochemical laboratories for GHP analyses, the following tasks were undertaken:

1. Laboratory induction for health and safety,
2. Laboratory code of conduct and equipment log usage,
3. Refrigerated centrifuged and -80^{o}C freezer operation training,
4. Pipetting technique training,
5. Health Research Authority, Research Ethics committee, and local Research and Development (R&D) approval was obtained.

5.3 Methods

Data collection

Data was collected prospectively from patients undergoing an ILGO for oesophageal cancer between 01/12/2017 to 31/12/2019 in the Peninsula Oesophago-gastric centre at Derriford Hospital.

Inclusion and exclusion criteria

All physiologically fit adult patients with operable oesophageal cancer were included. Patients were excluded if they were not undergoing enhanced recovery, refused surgery, were found to have unresectable cancer during surgery, or refused to participate in the study. The reason to exclude patients not undergoing enhanced recovery was to have uniformity of data and allowed matched comparison between patients. Patients were also excluded if they developed complications that caused symptoms of DGE due to an obstructive pathology (e.g. paraconduit hernia) during their in-patient stay as mechanical causes of DGE are out of the scope of this thesis.

Demographic data collected

Patient demographics and data such as age, gender, BMI, ASA grade, smoking status, conduit size (width and length), DGE status as outlined in our previous chapter (Chapter 3: Defining delayed gastric emptying) and in Appendix III: Enhanced recovery protocol, GHP, and post-operative intervention were collected. DGE signs and symptoms (DES) such as nausea, vomiting, early satiety, dysphagia, post-prandial abdominal pain, and radiological evidence of a distended gastric conduit were assessed in each patient from discharge.

Definition for DGE

Briefly, as described in chapter 3, DGE was diagnosed using CXRs and NG input/output volume as per the algorithm. If the patient had a gastric conduit that crossed more than half the hemithorax (at the midpoint from the level of the diaphragm up to the level of the azygos vein and cardiac silhouette) and/or produced > 50% of nasogastric aspirate upon consuming more than 1000 ml of oral fluids, then a diagnosis of DGE was given. Those parameters were collected from day 4 to 6 from the enhance recovery protocol. Diagnosis of DGE was made by the researcher and clinical team responsible for the patient.

If a patient returned to hospital after discharge, with nausea, vomiting, early satiety, dysphagia, post-prandial abdominal pain, and CXR evidence of a distended gastric conduit then they were deemed to have DES and late DGE. Patients with late DGE then had further investigation with CT to delineate between a mechanical cause or true DGE as the cause of the issue.

Patient sampling, gut hormone analysis and intervention

The GHPs were conducted on all recruited patients between day 4 to 6 post-operatively. The patients were fasted 6 hours prior to the test and for the entire period of the test. An ice cream meal of 100 ml with 193 calories was given after an initial baseline blood test was taken using BD™ venepuncture kit and into an EDTA tube from BD Vacutainer®. Repeated blood sampling was conducted every 30 minutes up to 2 hours. Each blood sample was immediately taken to the centrifuge and spun at 1500 rpm for 10 minutes at 4 ^{o}C. Centrifuge used was the CENHBR from Munro Scientific™. Then the serum was extracted and stored at -80 ^{o}C.

The serum samples were analysed using radioimmunoassay for both PYY and GLP-1 in Imperial College London. The radioimmunoassay used for both GHs were developed as an in-house kit in Imperial College Biochemistry laboratories with an error range of < 9% and < 15% for within assay and inter-assay variation, respectively, for PYY, and less than 10% for GLP-1 (90). All patients with DGE were treated with anti-emetics, prokinetics and endoscopic pyloric balloon dilatation (30mm Rigiflex™ balloon). This intervention was usually performed from day 7 onwards. Patients with DGE and had a dilatation will undergo the GHP test again as described above.

Patient groups and statistical analyses

Patients were initially categorised into 2 groups for analyses: non-DGE versus DGE group and non-dilated versus dilated group. The non-DGE sub-group were patients designated as not having DGE according to the algorithm (Appendix III: Enhanced recovery protocol) (33) while the DGE sub-group were patients with DGE. The non-dilated sub-group were patients that did not receive pyloric dilatation during their in-patient stay while the dilated sub-group received dilatation. For the DGE sub-group, 2 further groups were designated based on their pyloric dilatation intervention timing: pre-dilatation and post-dilatation. Pre-dilatation patients were the DGE group, while post-dilatation patients were the same group of patients, but after pyloric dilatation. IBM's© SPSS statistics software version 25 was used as the statistical program for data

analyses (https://www.ibm.com/analytics/spss-statistics-software). Graphs were drawn using Graphpad Prism version 9 (https://www.graphpad.com). Sample size was determined using an updated DGE incidence of 17.5% (33) and an estimated reduction of DGE to 0% in the post-intervention period (71) (effect size of 17.5%), power of 80%, $p = 0.05$ and an enrolment ratio of 3:1 (due to feasibility of recruiting adequate numbers for the intervention in a 2-year period). The calculated sample size required for the study was 80 patients, with 60 in the non-DGE group and 20 in the DGE group. To assess the distribution of the continuous data, a skewness and Shapiro-Wilk test was used. Comparisons of characteristics between each group were performed using the Chi square test for nominal data, the Mann-Whitney U test for continuous data and the Wilcoxon signed-rank test for paired continuous data. Then, the AUC of the GHP of all patients was calculated using the trapezoid rule and compared using the Mann Whitney U test for independent samples and the Wilcoxon signed rank test for paired samples. Additionally, the GHP results of all patients, excluding post-dilatation results, were compared with the need for pyloric dilatation using the ROC curve to assess the AUC for DGE predictive capability. If the AUC revealed a significant result of more than 90% then the GHP was deemed an excellent test for predicting the need for pyloric dilatation (146). If the AUC was between 70% to 90%, then the GHP was deemed a satisfactory test (146). If the ROC curve showed that the GHP was a viable test, then the sensitivity and specificity would be calculated. All non-parametric data were presented as median, range, and/or 95%CI. A p value of < 0.05 was deemed statistically significant.

Ethical approval

The London Bromley Research Ethics Committee approved the study (REC 17/LO/1759), which was conducted in accordance with the principles of the Declaration of Helsinki with written informed consent provided by all patients.

5.4 Results

There were 65 patients included during the 24-month period of the study. Further recruitment was halted as the time limit for the study was reached. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram in Figure 8 showed the phases of patient recruitment and progress throughout the study.

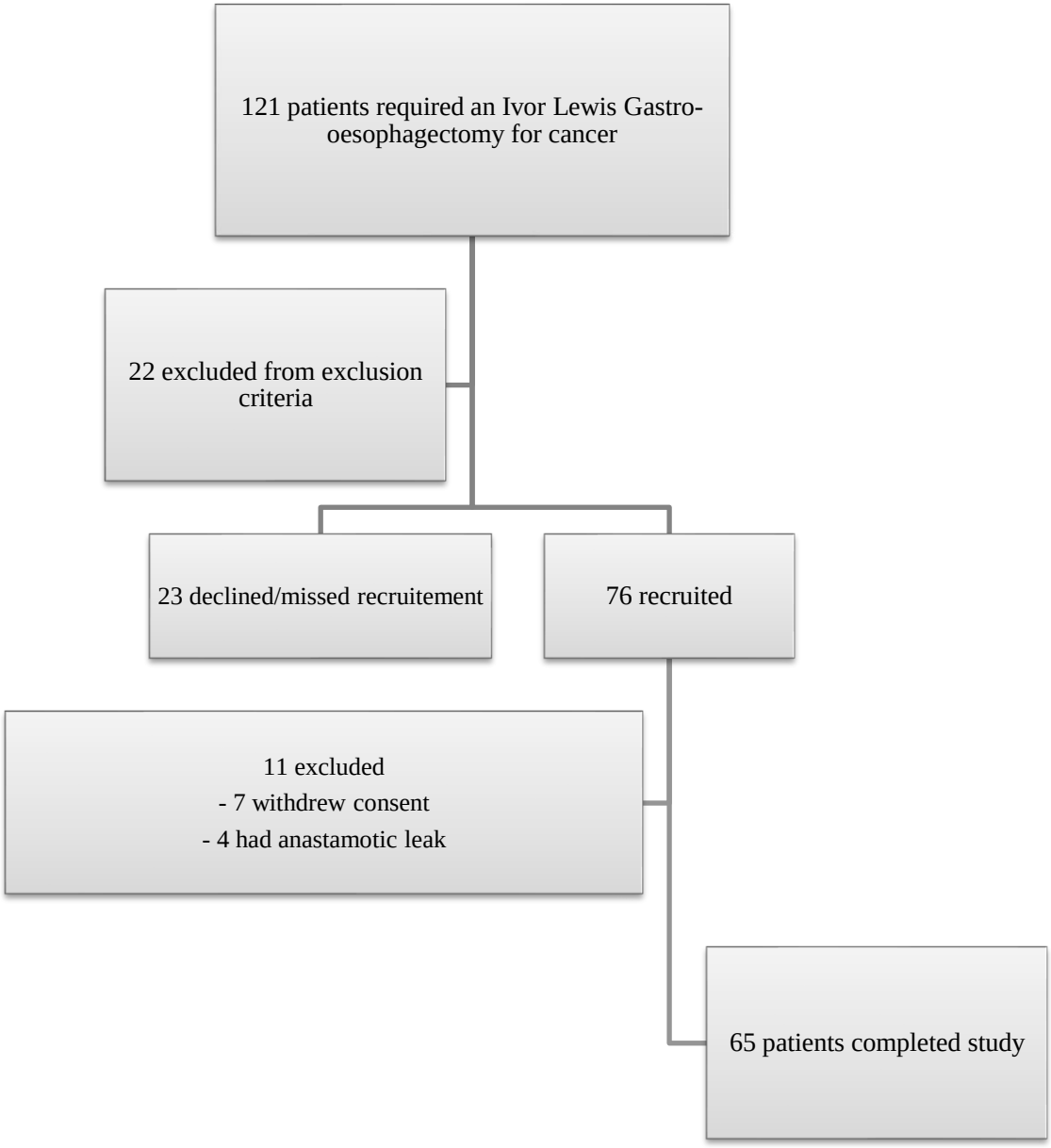


Figure 8: Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the patient recruitment and progress

Non-DGE versus DGE group

The flow chart of the patient progress was shown in Figure 9, while the patient demographics and characteristics were shown in Table 11. All continuous data for patient demographics and characteristics were non-parametric in distribution. Therefore, non-parametric analyses were used; the Mann Whitney U test was used for independent samples and the Wilcoxon signed rank test was used for paired samples. Overall, 24 (36.9%) patients had DGE, while 41 (63.1%) patients did not. A total of 16 (24.6%) female patients and 49 (75.4%) male patients with median age of 70 (43 to 86)

years old completed the study. Their overall median BMI were 26.0 kg/m^2 (19.0 to 36.7). There were no differences in demographics between the 2 groups Table 11.

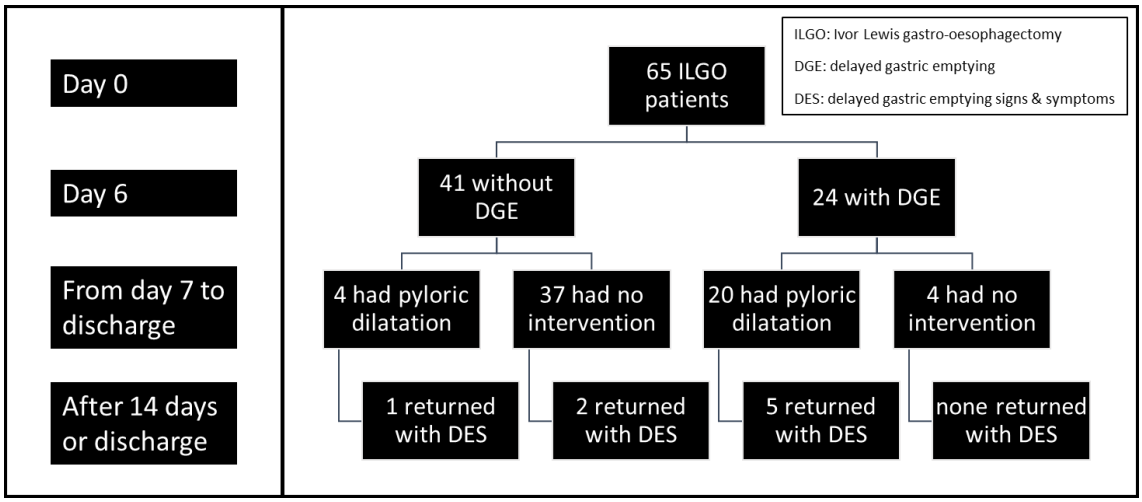


Figure 9: Flow chart of patient progress and diagnosis using the study's algorithm

	Non-DGE patients, n = 41	**DGE patients, n = 24**	***p* value**
Age	73.10 (44-86)	70.23 (50-81)	0.314
Gender:			0.065
Female	6	10	
Male	35	14	
BMI	26.80 (17.60-36.70)	25.40 (19.00-33.00)	0.610
ASA grade:			0.255
2	27	19	
3	14	5	
Smoking:			0.732
No	12	9	
Ex-smoker	26	14	
Yes	3	1	
Conduit width	5 (4-15)	5 (4 -20)	0.747
Conduit length	15 (4 – 24)	15 (4 – 23)	0.404

p value < 0.05 was deemed statistically significant, DGE: Delayed gastric emptying, BMI: Body mass index, ASA: American Society of Anaesthesiology

Table 11: Characteristics of patients with and without delayed gastric emptying as defined by the algorithm

In the group without DGE, 4 out of 42 patients received pyloric dilatation. Of those 4 patients, 3 patients received pyloric dilatation on the grounds of symptoms of nausea and/or vomiting and with dislodgement or removal of NG tube too early in the

algorithm, and hence, clinical judgement was used by the clinical team for decision making. The remaining 1 patient had dilatation due to borderline CXR, and symptoms of severe nausea. For patients diagnosed with DGE, 4 did not receive dilatation due to lack of symptoms, and whilst awaiting dilatation, the algorithm parameters improved after day 6. The sensitivity and specificity of the algorithm to predict the need for pyloric dilatation was 83.3% and 90.2%, respectively. The positive predictive value (PPV) was 83.3%, and the negative predictive value (NPV) was 90.2%.

All patients with DES were re-admitted after 6 weeks. Overall, there were 8 DES patients of which 4 (50%) had an anatomical issue (3 paraconduit hernia and 1 'folded' conduit) and 4 had true DGE. Of the 4 patients with anatomical issues, 3 had DGE whilst an in-patient and had previously undergone pyloric dilatation. Additionally, of the 4 with true DGE, 3 had pyloric dilatation whilst an in-patient.

Figure 10 showed the GHP of both non-DGE and DGE groups. There were no differences in AUC for PYY for the test duration between the 2 groups ($p = 0.078$) [95%CI for non-DGE (1572.20, 3005.10) and DGE (912.97, 1706. 77)] (Figure 11A). For PYY serum levels, there were differences between the groups at 60 minutes [non-DGE: 12.79 ρmol/L, (95%CI 12.81, 37.85 ρmol/L)] and [DGE: 7.76 ρmol/L, (95%CI 6.85, 15.28 ρmol/L)] ($p = 0.024$) (Figure 10A).

For GLP-1, no differences in AUC for the test period were found ($p = 0.072$) [95%CI for non-DGE (2919.69, 4527.21 ρmol/L), and for DGE (2367.02, 3030.48 ρmol/L)] (Figure 11B). Additionally, there were no differences in GLP-1 levels between non-DGE and DGE patients for each sampling time point (Figure 10B).

As the AUC assessment showed no significant results for either PYY or GLP-1, ROC analysis was not performed.

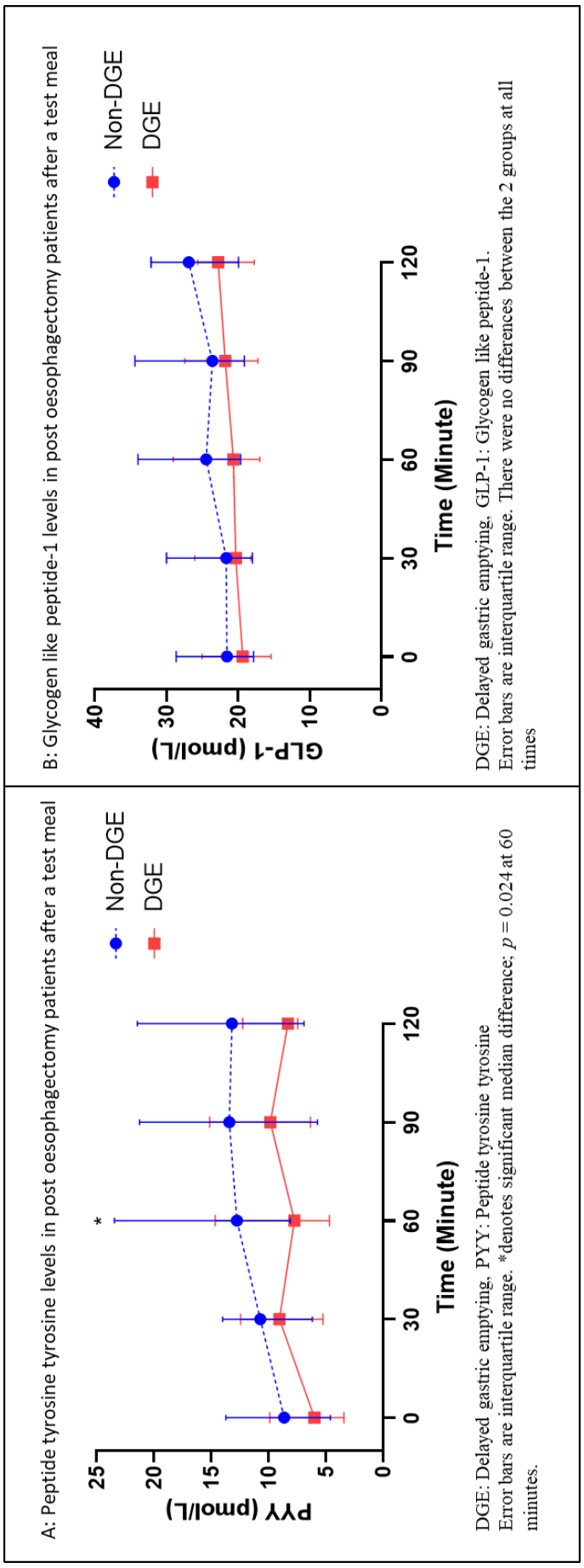
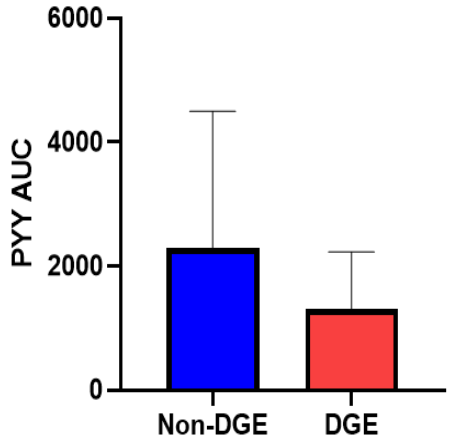


Figure 10: Gut hormone profiles in patients without and with delayed gastric emptying according to the algorithm

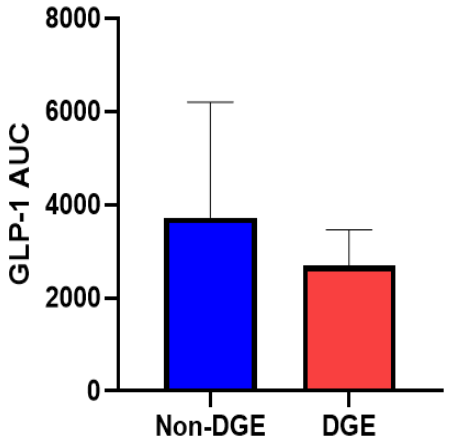
Figure 11: Gut hormone profiles represented as area under the curve in patients without and with delayed gastric emptying according to the algorithm

A: Total peptide tyrosine tyrosine levels represented as area under curve during the 2-hour test period of patients with and without delayed gastric emptying



DGE: Delayed gastric emptying, PYY: Peptide tyrosine tyrosine, AUC: area under the curve
There were no differences between the 2 groups ($p = 0.078$)

B: Total glycogen like peptide-1 levels represented as area under curve during the 2-hour test period of patients with and without delayed gastric emptying



DGE: Delayed gastric emptying, GLP-1: Glycogen like peptide-1, AUC: area under the curve
There were no differences between the 2 groups ($p = 0.072$)

Dilated versus non-dilated group

The flow chart of the progress in this group was shown in Figure 12. Patient characteristics, DGE incidence, and conduit size in each group were shown in Table 12. From the 65 patients, there were 24 (36.9%) patients that received pyloric dilatation and 41 (63.1%) patients without. Their median age was 70 (43 to 86) years old, with 16 female patients (24.6%) and 49 male patients (75.4%). Overall median BMI of 26 (19.00 to 36.70).

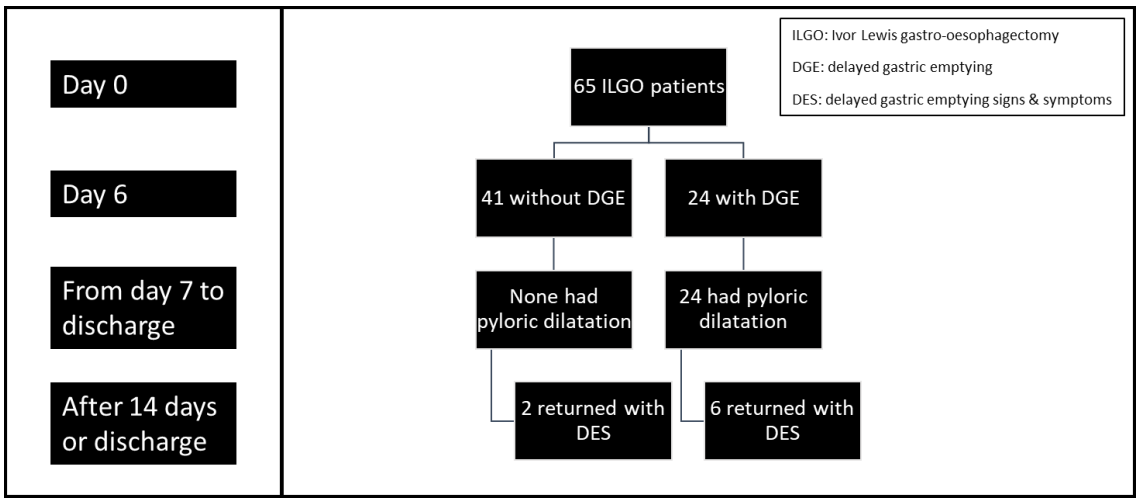


Figure 12: Flow chart of patient progress and diagnosis based on pyloric intervention

	Non-dilated patients, n = 41	Dilated patients, n = 24	*p* value
Age	73.10 (44-86)	70.23 (50-81)	0.187
Gender:			0.015
Female	6	10	
Male	35	14	
BMI	26.00 (19.00-36.70)	26.00 (19.00-31.50)	0.663
ASA grade:			0.088
2	26	20	
3	15	4	
Smoking:			0.732
No	12	9	
Ex-smoker	26	14	
Yes	3	1	
Conduit width	5 (4-20)	5 (4 -15)	0.563
Conduit length	15 (4 – 23)	14 (5 – 24)	0.082

p value < 0.05 is deemed statistically significant, BMI: Body mass index, ASA: American Society of Anaesthesiology

Table 12: Characteristics of non-dilated and dilated patients

All continuous data for patient demographics and characteristics were non-parametric in distribution. Therefore, non-parametric analyses were used; the Mann Whitney U test was used for independent samples and the Wilcoxon signed rank test was used for paired samples. Characteristics of the patient demographics in each group were shown in Table 12. Apart from gender, there were no differences between the groups. Proportionally, there appeared to be more male patients without dilatation compared to female patients (71.4% versus 37.5, $p = 0.015$) (Table 12).

The GHP of both groups at day 4 to 6 were shown in Figure 13. There were differences between the 2 patient groups for median PYY level at baseline [non-dilated: 9.50 ρmol/L (95%CI: 5.00,14.75 ρmol/L); dilated: 6.00 ρmol/L, (95%CI: 3.00, 8.50)] ($p = 0.030$) and for peak median PYY level which was at 60 minutes [non-dilated: 14.00 ρmol/L (95%CI: 8.00, 24.75 ρmol/L); dilated: 7.00 ρmol/L, (95%CI: 4.00 – 14.00 ρmol/L)] ($p = 0.003$). Along with a higher median baseline level for PYY in non-dilated patients, there was also a more exaggerated response to a meal (Figure 13A). The AUC of PYY for the 2-hour period between the 2 groups was higher in non-dilated patients ($p = 0.021$) and was shown in Figure 14A.

For comparative analysis of GLP-1, no differences between non-dilated and dilated patients were found at any time point (Figure 13B). Both median baseline level [non-dilated: 21.00 ρmol/L, (95%CI: 17.00, 28.00 ρmol/L); dilated: 21.50 ρmol/L, (95%CI: 16.50, 26.00 ρmol/L)] ($p = 0.674$) and median peak GLP-1 level which was at 120 minutes [non-dilated: 24.00 ρmol/L, (95%CI: 18.00, 31.50 ρmol/L); dilated: 24.00 ρmol/L, (95%CI: 20.00, 28.50 ρmol/L)] ($p = 0.827$) remained similar. The AUC of GLP-1 for the 2-hour period between the 2 groups was not significant ($p = 0.499$) and was shown in Figure 14B.

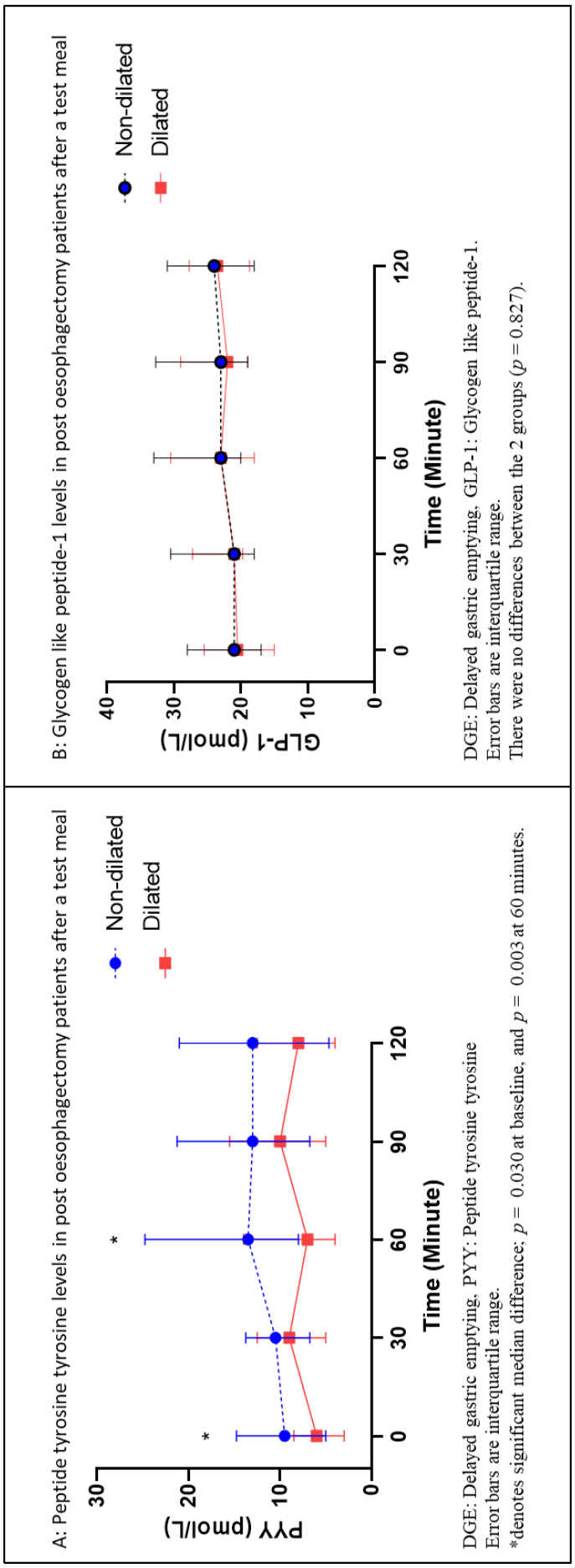
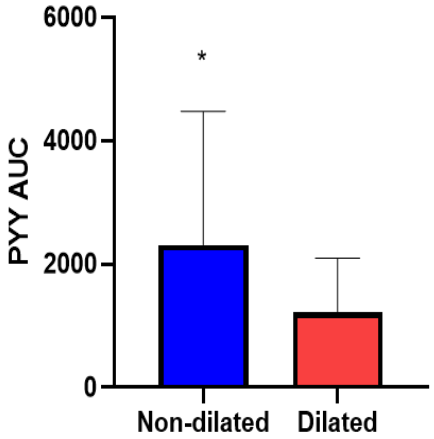


Figure 13: Gut hormone profiles in non-dilated and dilated patients

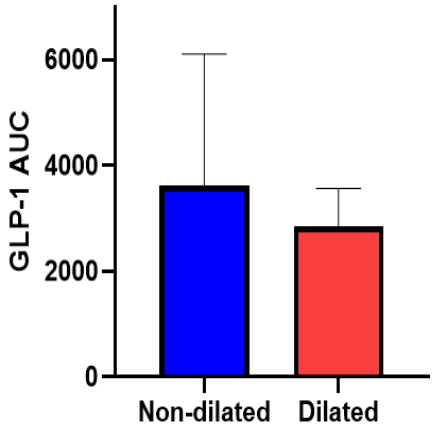
Figure 14: Gut hormone profiles represented as area under curve during the 2-hour test period in non-dilated and dilated patients

A: Total peptide tyrosine tyrosine levels represented as area under curve during the 2-hour test period of non-dilated and dilated patients



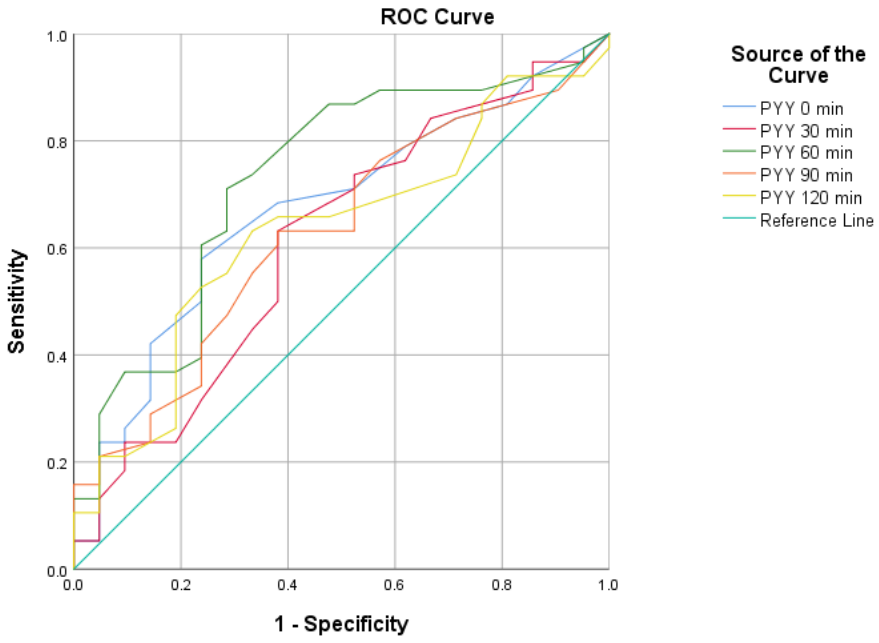
PYY: Peptide tyrosine tyrosine, AUC: area under the curve
There were differences between the 2 groups ($p = 0.021$), significance denoted with *.

B: Total glycogen like peptide-1 levels represented as area under curve during the 2-hour test period of non-dilated and dilated patients



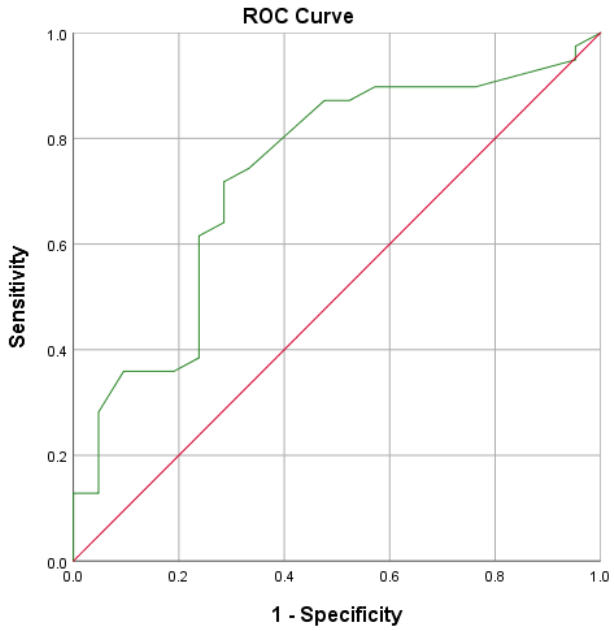
GLP-1: Glycogen like peptide-1, AUC: area under the curve
There were no differences between the 2 groups ($p = 0.499$)

The results of the reliability of PYY as a test for dilated patients was shown in Figure 15Figure 15Figure 15. The refence line, again, has an AUC of 50%. That ROC curve graph showed that for time periods at baseline, 30-minute, 90-minute, and 120-minute, PYY did not reliably predict the need for dilatation in post-oesophagectomy patients. However, PYY levels at 60 minutes did indicate a significant result with an AUC = 73.0% (*p = 0.003*) (Figure 16); all other times have an AUC of < 70% (61.2% to 67.2%, $p > 0.05$). Apart from the 60-minute period, these results likely highlighted the lack of correlation between PYY levels and the occurrence of DGE for the test period. Table 13 showed the individual coordinates of the ROC curve for PYY levels at 60 minutes. For the best balance between optimal sensitivity and specificity, a PYY level of > 9.50 ρmol/L at 60 minutes after a test meal was chosen from that table. At that PYY level, the sensitivity and specificity of indicating DGE is 71.8% and 71.4%, respectively.



PYY: Peptide tyrosine tyrosine

Figure 15: Receiver operating characteristic analysis for peptide YY



Green line: receiver operating characteristics of peptide YY levels at 60 minutes, red line: reference line

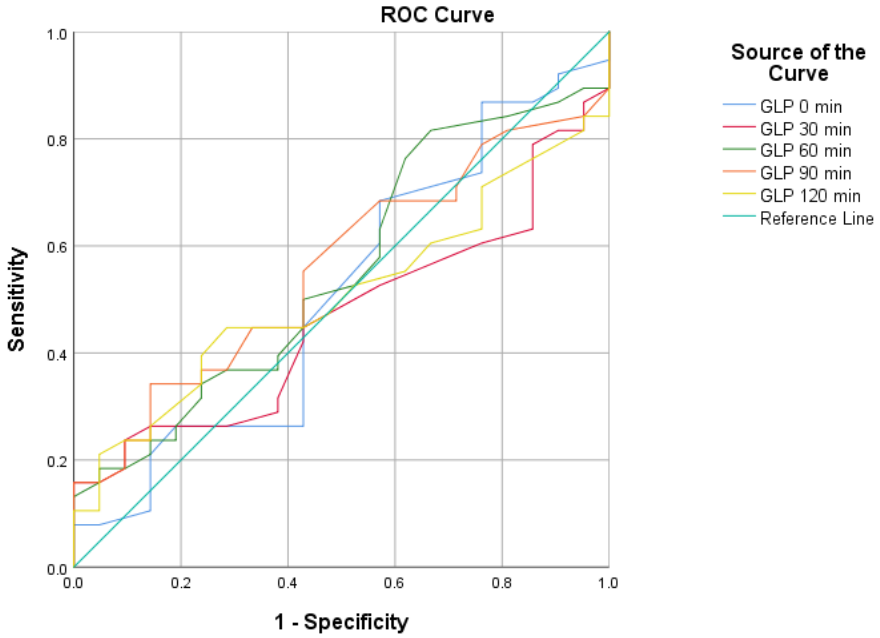
Figure 16: Receiver operating characteristic analysis of peptide YY levels at 60 minutes

For GLP-1, its reliability to predict the need for pyloric dilatation was depicted in Figure 17. The reference line for the ROC curve had an AUC of 50%. Having a ROC curve that follows the 50% line signifies that the chances of obtaining a positive or negative result would be 50/50. The ROC curve graph showed that result for all time periods; GLP-1 had an AUC of between 46.4% and 55.9% which signified that GLP-1 did not reliably predict pyloric dilatation requirement in the post-oesophagectomy patients. This also likely implied the lack of relationship between GLP-1 levels and the occurrence of DGE. Hence, further analysis in terms of a coordinate curve and best balance estimation for the sensitivity or specificity of GLP-1 for predicting pyloric dilatation were not made as accuracy of the test will be low and will not be significant. Additionally, the estimation of a significant hormone level of GLP-1 to indicate DGE was not performed as well.

Coordinates of the Curve		
Test Result Variable(s): PYY 60 min		
Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
.0000	1.000	1.000
1.5000	.974	.952
2.5000	.949	.952
4.0000	.897	.762
5.5000	.897	.571
6.5000	.872	.524
7.5000	.872	.476
8.5000	.744	.333
9.5000	**.718**	**.286**
10.5000	.641	.286
11.5000	.615	.238
12.5000	.590	.238
13.5000	.513	.238
14.5000	.436	.238
15.5000	.410	.238
16.5000	.385	.238
17.5000	.359	.190
19.5000	.359	.143
21.5000	.359	.095
22.5000	.282	.048
23.5000	.256	.048
25.5000	.231	.048
29.0000	.179	.048
33.5000	.154	.048
36.5000	.128	.048
44.0000	.128	.000
55.5000	.103	.000
78.0000	.077	.000
97.0000	.051	.000
150.5000	.026	.000
204.0000	.000	.000
The test result variable(s): PYY 60 min has at least one tie between the positive actual state group and the negative actual state group.		

a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.
Chosen PYY level with sensitivity and 1-specificity is indicated in bold.

Table 13: Coordinate points of the receiver operating characteristics for PYY at 60 minute



GLP-1: Glycogen like peptide-1

Figure 17: Receiver operating characteristic analysis for glycogen like peptide-1

Pre- and post-dilatation group

Finally, a sub-group analysis for patients that underwent pyloric dilatation was performed using paired analysis. The GHP at pre- and post-dilatation stages showed a trend for a peaked response to a meal test in the post-dilatation group as opposed to a graduated response in the pre-dilatation group (Figure 18). Paired analysis of the PYY levels were different for all time periods (Baseline $p = 0.001$, 30-minute $p = 0.001$, 60-minute $p = 0.002$, 90-minute $p = 0.000$, and 120-minute $p = 0.001$) (Figure 18A). Based on that figure, a significant exaggerated response to a test meal was found in the post-dilatation, which was absent in the pre-dilatation group. For the pre-dilatation group of DGE patients, median peaked PYY level was 10 ρmol/L (2.00 to 36.00 ρmol/L) at 90 minutes. For the post-dilatation group, median peak level was 34.00 ρmol/L (1.00 – 165.00 ρmol/L) and it occurred at 30 minutes. The AUC of PYY for the 2-hour period between the 2 paired groups was significant ($p = 0.000$) and was shown in Figure 19A.

However, no differences in GLP-1 levels were found for all time periods (Figure 18B). For the pre-dilatation group, median peak GLP-1 level of 23.50 ρmol/L (15.00 – 43.00 ρmol/L) occurred at 120 minutes, while median peak level for the post-dilatation group of 29.00 ρmol/L (10.00 – 98.00 ρmol/L) occurred at 60 minutes. The AUC of GLP-1 for the 2-hour period between the 2 paired groups was not significant ($p = 0.193$) and was shown in Figure 19B.

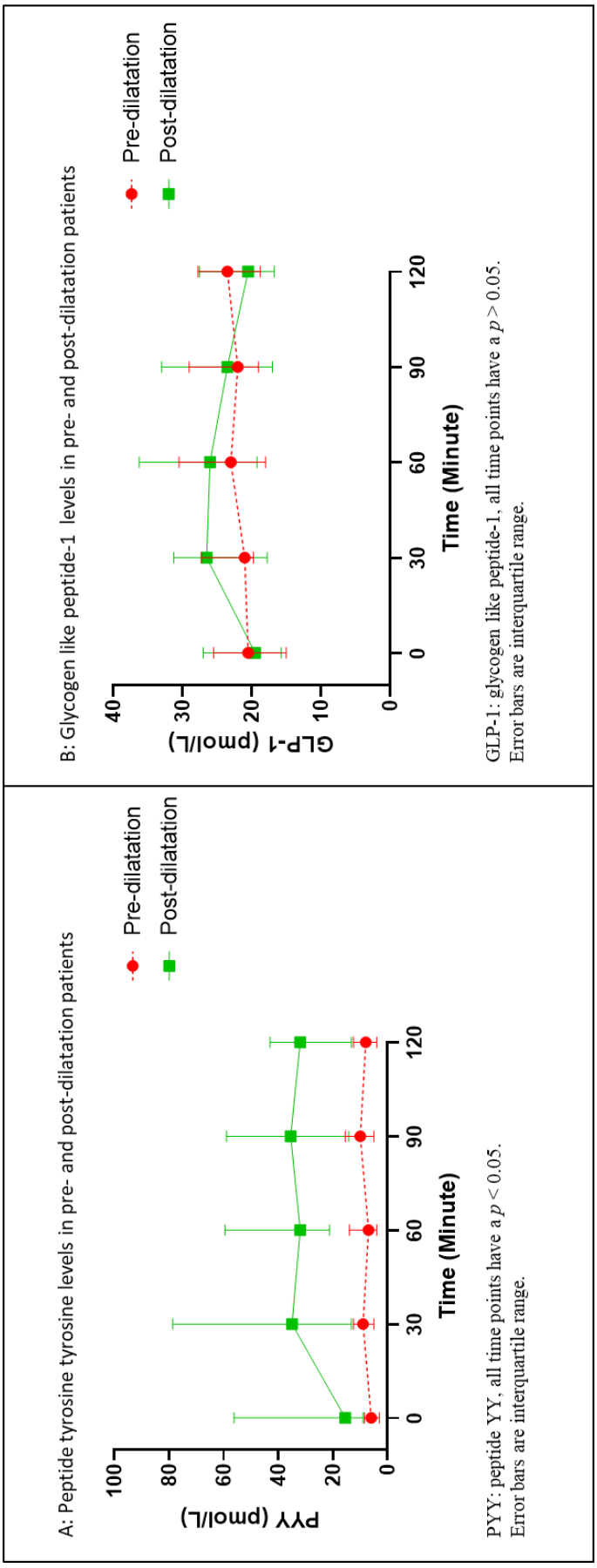
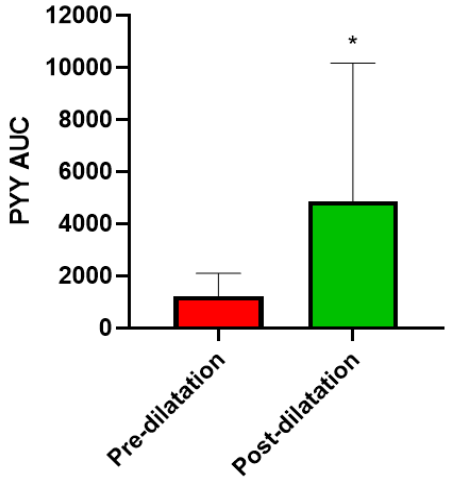


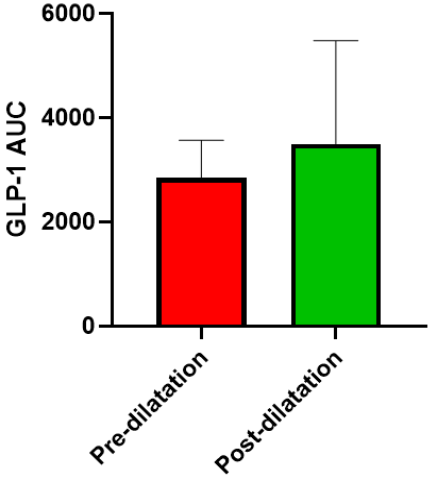
Figure 18: Pre-dilatation and post-dilatation gut hormone profiles in Ivor Lewis gastro-oesophagectomy patients

A: Total peptide tyrosine tyrosine levels represented as area under the curve during the 2-hour test period in pre- and post-dilatation patients



DGE: Delayed gastric emptying, PYY: peptide tyrosine tyrosine, AUC: area under the curve
There were no differences between the 2 groups ($p = 0.000$)

B: Total glycogen like peptide-1 levels represented as an area under the curve during the 2-hour test period in pre- and post-dilatation patients



DGE: Delayed gastric emptying, GLP-1: Glycogen like peptide-1, AUC: area under the curve
There were no differences between the 2 groups ($p = 0.193$)

Figure 19: Total gut hormones profile levels represented as area under curve during the 2-hour test period of Ivor Lewis gastro-oesophagectomy patients before and after pyloric dilatation

5.5 Discussion

The demographics of the patients in this study group appeared similar to our previous study (Chapter 4: Botulinum toxin and delayed gastric emptying) (33) in terms of age, BMI and gender. Therefore the patient sample in this study was representative of our patient population and also appeared to be reflective of the UK ILGO population (28,29). The analysis of serum GHs in ILGO patients revealed novel information about PYY levels in patients that required and received pyloric dilatation. Analysis showed that differences in PYY levels were significant in both non-dilated versus dilated, and pre-dilatation versus post-dilatation patients. Additionally, AUC analysis from this study also showed that the differences in PYY levels between non-dilated and dilated patients were also significant. The post-dilatation PYY levels showed an exaggeration of hormone levels post-test meal compared to pre-dilatation hormone levels. The expected result would be raised day 4 to 6 PYY levels in the dilated group because elevated PYY results in a reduction in the rate of gastric emptying (147). Additionally, the post-dilatation PYY levels showed an exaggerated response in hormone levels post-test meal compared to pre-dilatation hormone levels. These findings suggest that attenuated PYY levels was a result of reduction in the rate of flow of nutrients to the small bowel. However, if the PYY profile was simply due to the restoration of food presence into the small bowel, then GLP-1 profile should respond similarly too. Additionally, baseline PYY levels were significantly raised post-dilatation, even in the absence of food stimuli. The implications of the differences in baseline levels and PYY profile with a different response seen in GLP-1 remained unclear. Further research is required to understand the relationship between pyloric disruption with a balloon and PYY hormone levels in ILGO patients.

The analysis of GHs in ILGO patients revealed no post-prandial differences in GLP-1 levels for patients without and with DGE nor were there any differences in pre-dilatation and post-dilatation GLP-1 levels. Current literature suggest that GLP-1 may help regulate gut function in the post-ILGO setting (79,148). A review conducted by Baggio et al explored the physiological effects of GLP-1 on gastric emptying in healthy individuals and they showed that an exaggerated GLP-1 prolonged gastric emptying time (93). However, a more recent cohort study by Murphy et al showed that gastric emptying times in ILGO patients did not appear to be associated with an exaggerated

post-prandial post-operative GLP-1 level (149). The review by Baggio et al were mainly on patients with diabetes while the study by Murphy et al were specifically on ILGO patients. Therefore, it may be possible that the modulation of gastric emptying by GLP-1 was altered after an ILGO, but our study was underpowered to show those changes.

The exaggerated response in GLP-1 levels was not noted in our pre-dilatation patient group. However, upon dilatation, the peaked response, although not significant, showed a trend that was more comparable to ILGO patients who all had intra-operative pyloroplasty (149). It is still unclear regarding the significance of the blunted response and the return of the peaked response in explaining the physiology of gastric emptying. Therefore, at present, it can be assumed that GLP-1 was neither associated nor causal of DGE in ILGO patients.

Any clinical prediction tool can be affected by challenges in daily ward care, objectivity of radiological assessment, and inaccuracies in charting. Regardless of those issues, the proposed algorithm appeared to have an acceptable level of accuracy in predicting the need for pyloric dilatation. Additionally, only 1 patient who did not meet any of the DGE criteria in the algorithm whilst an in-patient returned with true DGE (non-DGE vs DGE group). The symptom of severe nausea appeared to have swayed the decision for dilatation in a handful of patients. Therefore, we propose the use of the algorithm as a guide to predicting DGE, and final diagnosis should be made using serial examinations and clinical suspicion. Additionally, we propose that further studies, such as radionuclide scans or isotope breath test, be conducted to validate the algorithm against a diagnosis of DGE.

ROC analysis and AUC results of GLP-1 revealed that testing of that GH was not suitable for identifying or predicting DGE. Furthermore, those results suggested that GLP-1 was not involved with gastric function in terms of gastric emptying and was similarly found in a study by Murphy et al (149). On the other hand, ROC analysis and AUC results of PYY revealed that testing of that GH (sensitivity and specificity of >70%) was potentially useful to identify or predict DGE or the need for pyloric dilatation (146). Those results suggested that PYY does play a role in modulating gastric emptying. Based on bariatric surgery patients (145,150), test meals produced an increase in both GLP-1 and PYY in the post-prandial period. In our patient sample, a test meal appeared to produce an independent elevation in PYY in non-DGE patients,

non-dilated patients, and in post-dilatation DGE patients but not significantly in GLP-1. The reason and significance of an obtunded GLP-1 response to a test meal in non-DGE and post-dilatation ILGO patients remained unclear.

With regards to limitations of this study, one possible influence of the results may be attributable to an inadequate sample size resulting in a non-significant finding in the GLP-1 profile as described above. Although a sample size calculation was performed, it was based on the effectiveness of pyloric intervention and not the effective change in GLP-1 levels. However, the patient sample from this study was substantially higher than other studies (76,148,149) that assessed GHP in oesophagectomy patients. Nevertheless, I would suggest that further studies be conducted with larger sample size or the synthesis of a meta-analysis to comprehensively assess the function of GLP-1. Another limitation was this study only showed an association of PYY response in DGE, but no conclusion of causation or mechanism can be deduced. Again, further research into the mechanism of DGE is required to show causality. Both differences in GHP could also be due to heterogeneity in the samples. Since the samples were taken on either day 4, 5 or 6, GHP levels may be different, and significant due to the minute changes that were scrutinised for. Heterogeneity could have also occurred from neoadjuvant therapy, or the lack of. Finally, multiple regression analyses were not performed on the results, limiting the ability of this study to reveal other confounders.

5.6 Conclusion

This study showed that patients who develop DGE or required dilatation was associated with an obtunded post-prandial PYY response in the post-operative period. However, the PYY response appeared to improve post-dilatation. Unexpectedly, GLP-1 levels remained obtunded in those patients and remain so after pyloric intervention. Currently, the significance of this finding is unclear. Further comprehension of the mechanism of action of GHs on gastric function is required to complete the knowledge regarding DGE.

5.7 Issues confronted and solutions

Any research study that is complex and technically challenging is always fraught with obstacles. Firstly, the collection, transfer, and analyses of GH for research was very costly and required adequate funding. Fortunately, laboratory training that was

available on-site for laboratory skills and logistics was well structured and was protocol driven. For financial support, several applications for funding were made and success was achieved with one. The Plymouth Hospitals Charitable Funds generously approved a grant of £20 000 to cover the cost of the study. For funding of my salary, I took up a research fellowship post with the Peninsula Oesophago-gastric Centre in Derriford Hospital, Plymouth.

Secondly, the test meal of ice cream required the use of a conventional household freezer and storage space for the freezer. Unfortunately, the grant did not cover the cost of a freezer nor was there any storage space. However, it was then identified that the local canteen, and the on-site "League of Friends" shop supplied the required ice cream. Direct purchase could be performed on-site instead, on a daily basis. As the ice cream was made and supplied by a local farm, no issues of being out of stock occurred.

Thirdly, the local laboratories stipulated that a backup -80^{o}C freezer needed to be acquired in case of storage deficiencies locally. A meeting was held with the Derriford Research Facility, which is a biomedical and clinical research centre affiliated with the University of Plymouth. Approval for use of their -80^{o}C freezer was achieved and the study was approved for recruitment thereafter. Throughout the study period, the reserve freezer was not required.

Fourthly, GH processing and analyses were extremely costly. Cost savings were made through selecting the most local and cost-effective laboratory, which was in Imperial College London, UK instead of University College Dublin, Ireland. The use of aprotinin (Trasylol, Nordic Group Pharmaceutical) as a Kallikrein inhibitor to slow the breakdown of GHs in the collected blood sample was also not performed. Aprotinin use was required if there was a delay of more than 5 minutes, or if the centrifuge used was not cooled to less than 5^{o}C. As all blood samples were spun immediately at 4^{o}C, aprotinin use was deemed unnecessary as all centrifuges were within a 1-minute walk from the patients - chilled centrifuges were located in the main biochemistry laboratory on level 7, and Lind Research Unit on level 5. The cost of purchasing aprotinin was also prohibitive due to limited production after it was barred by the United States Food and Drug Administration (FDA) in 2007.

The fifth issue was the GH response results were not as predicted. The obtunded GLP-1 levels in all the patient groups remained perplexing and, therefore, still require more research to explain those findings. Hence, I recommend that further research into the

relationship of PYY and DGE in ILGO patients is still needed to fully comprehend the underlying pathophysiology.

Finally, in the early stages on the doctorate, knowledge gaps in statistics and IT skills were identified and acquisition of skills in those areas were required to successful interpret the analysis of the GHP results. Hence, efforts in obtaining online learning and attendance at University of Plymouth workshops were made to update skills and knowledge in statistics and SPSS®. However, the SPSS® statistical program did not have all the graph making tools that was appropriate, so another statistics program was searched for. A suitable program that made the required graphs and was user friendly was needed. Graphpad™ Prism® appeared to fulfil those criteria. However, there were no workshops to learn the program at the University, so learning was based on online learning and help from colleagues.

5.8 Summary

The association between GHP changes and gastrointestinal surgery were observed in bariatric surgery patients. Weight loss in the post-ILGO patient prompted investigations into the link between GHP changes and gastrointestinal function in the post-operative period. PYY post-prandial response seen in healthy individuals and in bariatric patients appeared to be lost in ILGO patients with DGE or those that required pyloric dilatation and was restored after pyloric dilatation. A similar response was not seen in GLP-1 in ILGO patients. Despite the positive findings for PYY, the relationship can only be stated as an association, but not causation. Further research is required to understand the underlying pathophysiology of DGE in ILGO.

Chapter 6: Investigating delayed gastric emptying

Chapter 6: Investigating delayed gastric emptying

6.1 Introduction to Carbon-13 Octanoic acid breath test

Current conventional tools of investigations for DGE include barium swallows and gastric scintigraphy (52,74). Barium swallow requires a patient to consume a meal of barium compound in 'porridge' form which is followed by a series of fluoroscopic image captures. On the other hand, scintigraphy requires a patient to consume a radioisotope meal which is radioactive. The substance used is usually a compound of Technetium-99 mixed in an easily consumable meal (commonly scrambled eggs) and the patient is then placed in a gamma ray detector. Both investigative tools result in an increased exposure of ionising radiation (much higher radiation exposure in scintigraphy than barium studies) in patients that would have had multiple radiological investigations, and possibly neoadjuvant radiotherapy. Hence, there is a need for a test for DGE that avoids the need for further doses of ionising radiation, can be repeated multiple times without side effects, and can be easily conducted.

The Carbon-13 urea breath test was first proposed by Graham et al as an alternative test for detecting *Helicobacter pylori* infections in order to avoid invasive and radiological test (151). Since then, numerous breath tests have been developed to test for various conditions such as lactose intolerance, liver and pancreatic function, and gastric emptying time. Octanoic acid is a naturally occurring eight-carbon saturated fatty acid, also known as caprylic acid. Carbon-13 Octanoic acid is octanoic acid labelled with an isotope of carbon-13 which can occur in extremely small amounts in the environment. The Carbon-13 Octanoic acid breath test (^{13}COABT) is the utilisation of a carbon-13 octanoic acid doped meal to assess gastrointestinal function (66). Upon consumption, the octanoic acid is only absorbed in the small intestine and then metabolised in the liver (66,152). In a healthy subject, half gastric emptying time occurs within 80 minutes and is prolonged in patients with DGE (66). The ^{13}COABT had been validated against scintigraphy to assess DGE (66) and was utilised by Gourcerol et al to assess gastric emptying times of patient with gastroparesis and oesophagectomy against healthy patients in terms of QOL (49). The study by Gourcerol et al also described repeating the test in patients with low pyloric compliance after pyloric dilatation and showed an improvement in gastric emptying times. However, the sample size of the study was small, and a larger scale study is required to validate those results.

6.2 Methods

Data collection

Data from recruited patients with oesophageal cancer undergoing ILGO was collected prospectively from 05/12/2017 to 31/12/2019 in the Peninsula Oesophago-gastric centre at Derriford Hospital and were the same patient groups as the study in chapter 5.

Inclusion and exclusion criteria

All physiologically fit adult patients with operable oesophageal cancer were included. Patients were excluded if they refused surgery, are found to have unresectable cancer during surgery, or refused to participate in the study. Patients were also excluded if they developed complications that caused symptoms of DGE (e.g., paraconduit hernia) during their in-patient stay.

Demographic data collected

Patient demographics and data such as age, gender, BMI, ASA grade, smoking status, conduit size (width and length), DGE status as outlined in my previous chapter (Chapter 3: Defining delayed gastric emptying: Defining delayed gastric emptying), ^{13}COABT results, and post-operative interventions were collected. DGE signs and symptoms (DES) such as nausea, vomiting, early satiety, dysphagia, post-prandial abdominal pain, and radiological evidence of a distended gastric conduit was assessed in each patient from discharge.

Definition for DGE

Briefly, as described in chapter 3, DGE was diagnosed using CXRs and NG input/output volume as per our modified algorithm (Appendix III: Enhanced recovery protocol). If the patient had a gastric conduit that crossed more than half the hemithorax (at the midpoint from the level of the diaphragm up to the level of the azygos vein and cardiac silhouette) and/or produced more than 50% of nasogastric aspirate upon consuming more than 1000 ml of oral fluids, then a diagnosis of DGE was given. Those parameters were collected from day 4 to 6. Diagnosis of DGE was made by the researcher and clinical team responsible for the patient.

Development of the Carbon-13 Octanoic acid breath test

To conduct the ^{13}COABT, various resources and equipment were required, such as the Carbon-13 octanoic acid compound, breath test vials, and laboratory for analysis. Other considerations required were methods to collect each patient's breath and methods to mix the octanoic acid into the test meal. Seahorse Laboratories Limited were the only UK licenced supplier, hence, a purchase of 15 ml (based on estimated volume calculated based on number of patients and test times) of Carbon-13 octanoic acid was made. Ice-cream was chosen as the test meal because of the lack of kitchen facilities, the liquid diet requirement of the post-operative patient, and similar nutritional constituents with scrambled egg. The nutritional constituent of ice-cream is equivalent in terms of fats and calories to scrambled eggs (12 g versus ~12.9 g of fat, and 193 kilocalories (kcal) versus ~176 kcal, respectively. As ice-cream was soft and octanoic acid a liquid, direct pipetting and mixing with a spoon included in the ice cream carton was the method for labelling the meal. The ice-cream used was from a local manufacturer (Langage Farm™). For the collection of the samples, 4.5 ml Exetainer® vials were chosen based on discussions with a local expert in the University of Plymouth (Dr Marc Davies). The vials included straws for exhalation. For analysis of the samples, discussions were made with Iso-analytical Limited and University of Plymouth to obtain the most competitive fee for processing each sample. Even though the University of Plymouth was more competitive, a contract was signed with Iso-analytical Limited due to infrastructure and laboratory equipment issues at the Stable Isotope Laboratory, University of Plymouth. Research approval was covered by the research application for the GH study and funding covered by the Plymouth Hospitals Charitable Funds.

Patient sampling, breath test collection and intervention

The ^{13}COABT was conducted on all recruited patients between day 4 to 6 post-operatively. The patients were fasted 6 hours prior to the test and for the entire period of the breath test. An ice cream meal of 100 ml with 193 calories mixed with 100 microlitres of Carbon-13 Octanoic acid was given after an initial capture of breath, using a straw, into a 12ml Exetainer® vial from Labco Limited. To standardise the breath capture, 5 expirations and inspirations were performed prior to a full expiration of 3 seconds into the vial. A total of 8 post-meal breaths were taken at 30-minute intervals for 4 hours. Breath samples were stored inverted and at room temperature. The samples were in storage for 2 years. The breath tests were then sent off to Iso-Analytical Limited to be analysed using a gas spectrometer. All patients with DGE

were treated with anti-emetics, prokinetics and endoscopic pyloric balloon dilatation (30mm Rigiflex™ balloon from Boston Scientific™). Patients with DGE and had a dilatation underwent the breath test again as described above. This intervention was usually performed from day 7 onwards. Any patient with a post-operative complication that required a reoperation other than a pyloric balloon dilatation had their post-operative days 'reset' to day 0 for the algorithm on that operative day.

Breath test analysis

The mathematical equations and advanced arithmetic model used for ^{13}COABT was based on the work by Ghoos et al (66). The in-depth description of the equations and models were outside the scope of this doctorate. The equations and modelling of the breath test samples from the study patients were obtained from Iso-Analytical Limited and Professor Thomas Preston in the form of a macro-enabled Excel spreadsheet with the formulas pre-programmed into the file. The macro was then used to calculate the half emptying time of the gastric conduit ($t_{½}$ and t_{max}). The paragraphs below described the equations and arithmetic model used in brief and can be used as a reference.

The excretion of carbon dioxide (CO_2) with carbon-13 (C13) isotopes cannot be measured directly. The measurement must be estimated from the %excretion of C13 against carbon-12 (C12) CO_2 (%C13), to account for background C13 in the test meal. The excretion rate of CO_2 can be influenced by the body surface area of the patient, whereby an estimated production of 300 mmol of CO_2 occur per square meter of body surface area per hour. Hence, the height and weight measurement of each patient was collected. The results produced was %C13 excreted per time and formed a non-linear curve that needed to be adjusted to the Siegel fit by minimising the sum of squared errors (66,153).

The % cumulative C13 excretion can then be produced using the following formula:

$$y = m(1-e^{-kt})^{\beta}$$

whereby y was the % of cumulative C13 excretion in breath at time t, m was the total cumulative C13 that will be recovered when t was infinite, k was the gastric emptying rate and β was the y-axis intercept extrapolation at the terminal point of the curve. Both k and β can be derived from the Siegel fit curve. Maximum C13 excretion, t_{max}, can be

calculated as the natural logarithm, Ln, of $^{\beta}/_{k}$. The AUC of the graph can be used to compare %C13 excretion between individual patients more accurately.

The half-emptying time of C13 from the test meal can then be estimated using the following non-linear regression analysis formula:

$$t_{½} = (-1/k) \text{ X } \ln (1\text{-}2\text{-}1/\beta)$$

whereby $t_{½}$ was the half emptying rate, k was the gastric emptying rate calculate from the Siegel fit and β was the y-axis intercept.

Patient groups and statistical analyses

Patients were categorised into 2 initial groups, like in Section 5.3 Methods, for analyses of non-DGE versus DGE group and non-dilated versus dilated group. The non-DGE sub-group were patients without DGE according to the algorithm (Appendix III: Enhanced recovery protocol) (33) while the DGE sub-group were patients with DGE. The non-dilated sub-group were patients that did not receive pyloric dilatation during their in-patient stay while the dilated sub-group received dilatation. For the DGE sub-group, 2 further groups were designated based on their pyloric dilatation intervention timing: pre-dilatation and post-dilatation.

IBM's© SPSS Statistics software version 25 was used as the statistics analysis program and for production of graphs (https://www.ibm.com/analytics/spss-statistics-software). Graphs were drawn using Graphpad Prism version 9 (https://www.graphpad.com). Sample size was determined using an updated DGE incidence of 17.5% (33) and an estimated reduction of DGE to 0% post-intervention (71) (effect size of 17.5%), power of 80%, $p = 0.05$ and an enrolment ratio of 3:1 (due to feasibility of recruiting adequate numbers for the intervention in a 2-year period). The calculated sample size required for the study was 80 patients, with 20 in the DGE group and 60 in the non-DGE group. To assess the distribution of the continuous data, a skewness and Shapiro-Wilk test was used. Comparisons of characteristics between each group were performed using the Chi square test for nominal data, and the Mann-Whitney U test for continuous data.

The AUC of the ^{13}COABT of all patients were calculated using the trapezoid rule and compared using the Mann Whitney U test for independent samples. The AUC represented the total C13 excreted during the 2-hour test period. The AUC results of all patients, excluding post-dilatation results, were compared with the diagnosis of DGE

using Receiver Operating Characteristics (ROC) curve to assess the AUC for DGE predictive capability. If the AUC revealed a significant result of more than 90%, then the ^{13}COABT was deemed an excellent test for predicting the need for pyloric dilatation (146). If the AUC was between 70% to 90%, then the ^{13}COABT was deemed a satisfactory test (146). If the ROC curve shows that the ^{13}COABT was a viable test, then the statistical accuracy of the test was calculated.

The half emptying time ($t_{½}$) and time to maximum C13 excretion (t_{max}) were calculated using the method described by Ghoos et al (66) and results compared using Mann Whitney U test for independence. Both $t_{½}$ and t_{max} results of all patients, excluding post-dilatation results, were compared with the diagnosis of DGE using ROC curve to assess the AUC for DGE predictive capability. If the AUC revealed a significant result of more than 90%, then the ^{13}COABT was deemed an excellent test for predicting the need for pyloric dilatation (146). If the AUC was between 70% to 90%, then the ^{13}COABT was deemed a satisfactory test (146). If the ROC curve showed that the ^{13}COABT was a viable test, then the statistical accuracy of the test was calculated.

Similarly, the AUC, $t_{½}$ and t_{max} of pre- and post-dilatation patients were compared using the Wilcoxon signed rank test for paired samples.

All non-parametric data were presented as median, range, and/or 95%CI. A *p* value of < 0.05 was deemed statistically significant.

Ethical approval

The London Bromley Research Ethics Committee approved the study (REC 17/LO/1759), which was conducted in accordance with the principles of the Declaration of Helsinki with written informed consent provided by all patients.

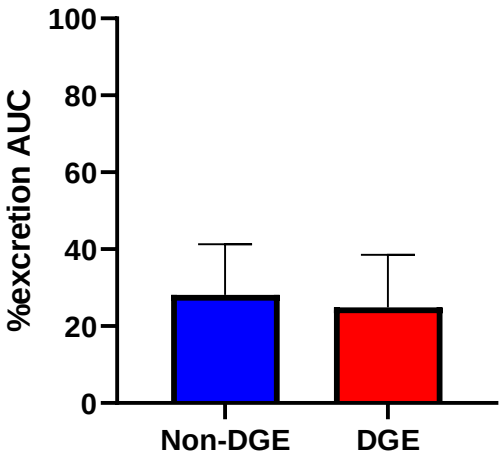
6.3 Results

Non-DGE versus DGE

There were 65 patients included in the study for this group during the 24 months period with recruitment and progress of patients shown in **Error! Reference source not found.** and Figure 9. The distribution of the data was non-parametric. Table 11 shows the patient characteristics, and operative data in each group. There were no differences between each group. There were also no complaints regarding the taste or adverse reaction from the use of the carbon-13 octanoic acid in the meals. No patients were lost

to follow-up and all patients with DES occurred after 6 weeks. Patients with DES were described in Section 5.4 Results.

There were no differences in AUC of excreted %C13 during the 4-hour test period in the 2 groups (p = 0.343) [95%CI for non-DGE: (22.63, 33.55 %) and for DGE: (18.07, 31.65 %)] (Figure 20).



AUC: area under the curve, DGE: delayed gastric emptying

Figure 20: Percentage carbon-13 excretion represented as area under the curve for patient without and with delayed gastric emptying

ROC analysis of AUC was not conducted as no significant results were found. The sensitivity, specificity, positive predictive value, and negative predictive value results were also not calculated.

There were no differences between the groups for both $t_{½}$ and t_{max}. The $t_{½}$ was 3.48 hours [95%CI (3.01, 3.73)], and 3.46 hours [95%CI (3.16, 5.07)] in non-DGE, and DGE patients, respectively (p = 0.410) Figure 21. The t_{max} was 1.83 hours [95%CI (1.55, 2.16)], and 2.12 hours [95%CI (1.77, 3.07)] in non-DGE, and DGE patients, respectively (p = 0.307).

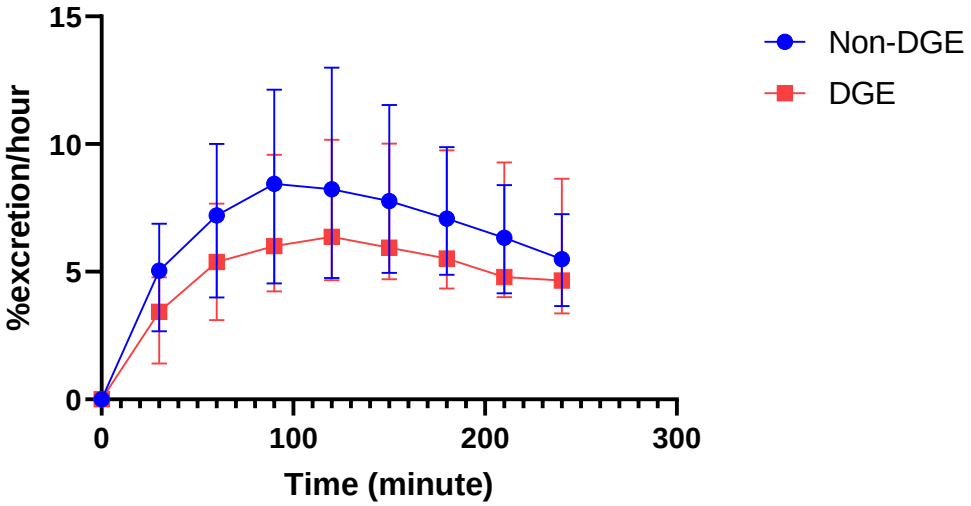


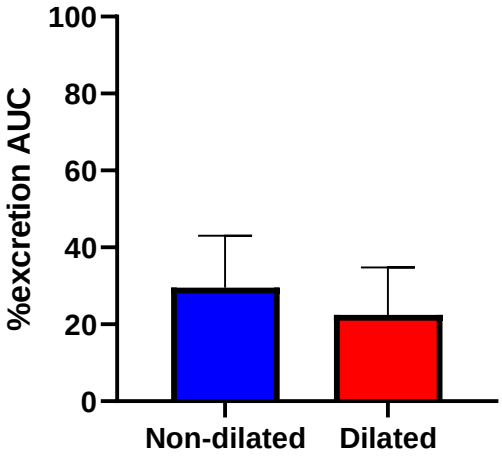
Figure 21: Percentage excretion per hour of Carbon-13 in patients without and with delayed gastric emptying

Similarly, ROC analysis of both $t_{½}$ and t_{max} were not conducted nor were the sensitivity, specificity, positive predictive value, negative predictive value results calculated.

Non-dilated versus dilated

There were 65 patients included in the study for this group during the 24-month period, with recruitment and progress of patients shown in **Error! Reference source not found.** and Figure 9. The distribution of the data was non-parametric. Table 11 shows the patient characteristics, and operative data in each group. There were no differences between each group. There were also no complaints regarding the taste or adverse reaction from the use of the carbon-13 octanoic acid in the meals. There were no lost to follow-up and all patients with DES occurred after 6 weeks. Patients with DES were described in 5.4 Results.

There were no differences in AUC of excreted %C13 during the 4-hour test period in the 2 groups (p = 0.057) [95%CI for non-DGE: (24.10, 34.99 %) and for DGE: (16.13, 28.78 %)] (Figure 22).

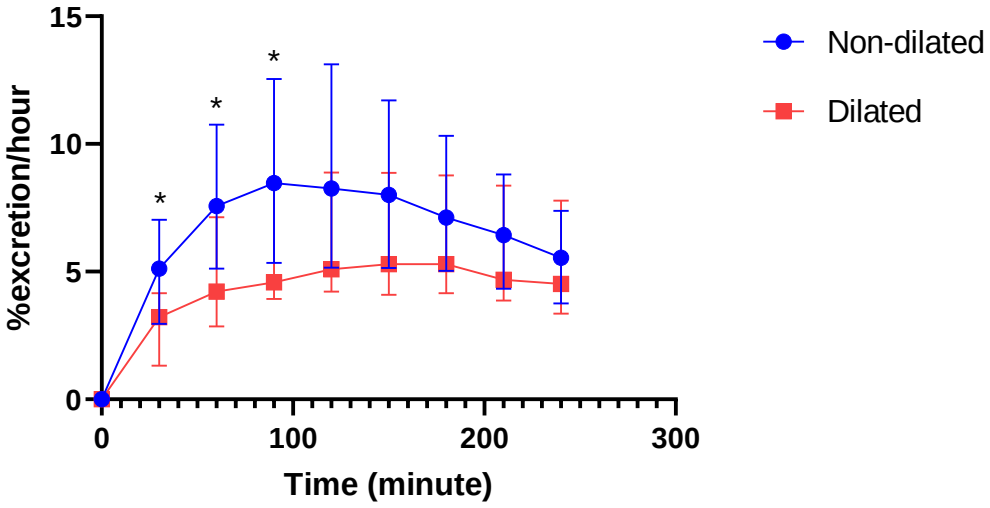


AUC: area under the curve

Figure 22: Percentage carbon-13 excretion represented as area under the curve in non-dilated and dilated patients

ROC analysis of AUC was not conducted as no significant results were found. The sensitivity, specificity, positive predictive value, and negative predictive value results were also not calculated.

There were differences between the groups for both $t_{½}$ and t_{max}. The $t_{½}$ was 3.04 hours [95%CI (2.91, 3.52)], and 3.54 hours [95%CI (3.41, 5.39)] in non-dilated, and dilated patients, respectively (p = 0.034) (Figure 23). Additionally, at time points 30, 60 and 90-minutes, there were difference between the 2 groups with p = 0.04, 0.015, and 0.034, respectively. The t_{max} was 1.68 hours [95%CI (1.45, 2.04)], and 2.15 hours [95%CI (1.98, 3.24)] in non-dilated, and dilated patients, respectively (p = 0.011).



*denotes statistically significant result

Figure 23: Percentage dose per hour excretion of Carbon-13 in non-dilated and dilated patients

The results of the reliability of $t_{½}$ of the ^{13}COABT to predict for the need for dilatation was shown in Figure 24. The ROC curve graph showed that the AUC had an area of 57.4% and $p = 0.410$. The results of the $t_{½}$ of the ^{13}COABT had not shown to be an accurate test to predict the need for dilatation as it had an AUC of less than 70%.

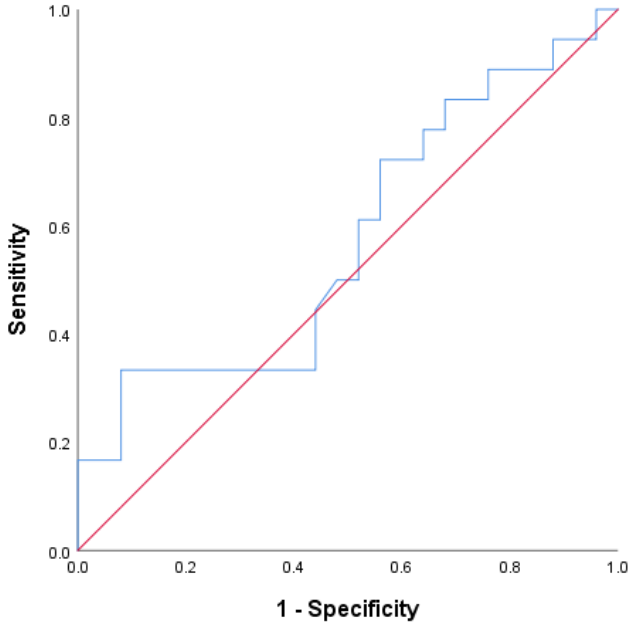


Figure 24: Receiver operator curve for the half emptying time of the Carbon-13 octanoic acid breath test in dilated and non-dilated patients

The sensitivity, specificity, positive predictive value, negative predictive value results were not analysed as the *p* value of the ROC curve was not significant.

The ROC analysis of t_{max} was shown in Figure 25 and the AUC had an area of 59.2% with a $p = 0.307$. The results obtained from the t_{max} of the ^{13}COABT showed that it was also not an accurate test to predict the need for dilatation.

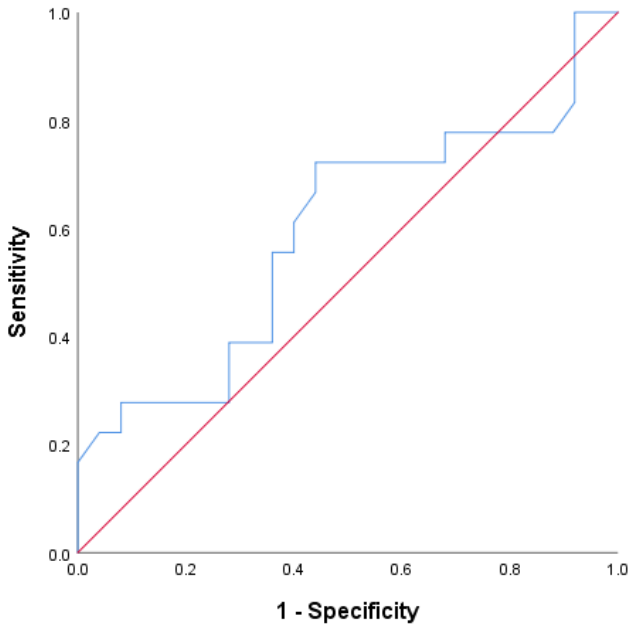


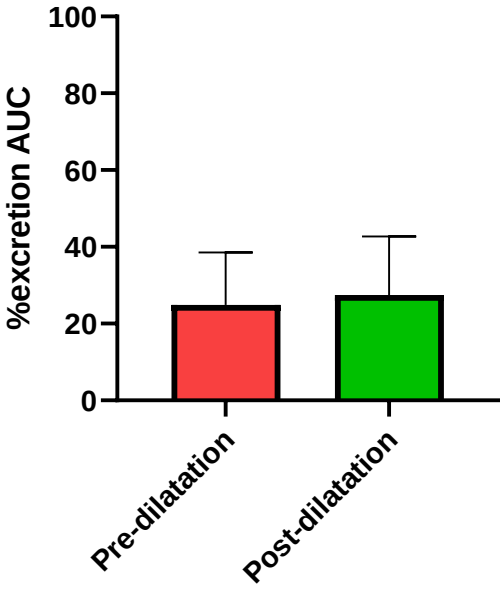
Figure 25: Receiver operator curve for the time to max percentage excretion of the Carbon-13 octanoic acid breath test in non-dilated and dilated patients

Similarly, further analyses for the sensitivity, specificity, positive predictive value, negative predictive value results were not performed as the *p* value of the ROC curve was not significant.

Pre-dilatation versus post-dilatation

There were 24 patients that underwent pyloric dilatation in this study for this sub-group. Those patients underwent further analysis and showed no differences in AUC of excreted C13 during the 4-hour test period. The pre-dilatation median AUC was 20.62 % [95%CI (18.07, 31.65)] while the post-dilatation median AUC was 22.00 [95%CI (18.27, 36.68) with a *p* = 0.646. AUC: Area under the curve

Figure 26 showed the cumulative percentage excretion of %C13 over the 4-hour test period. ROC analysis of AUC was not conducted as no significant results were found. Therefore, the sensitivity, specificity, positive predictive value, and negative predictive value results were also not assessed.



AUC: Area under the curve

Figure 26: Percentage carbon-13 excretion represented as area under the curve in pre- and post-dilatation patients

The %C13 excretion curve was shown in Figure 27. For $T_{½}$ and T_{max}, there were also no differences in the results, p = 0.093, and 0.203, respectively. The median $T_{½}$ was 3.53 hours [95%CI (3.06, 5.60)] for pre-dilatation patients, and 3.11 hours [95%CI (2.35, 4.23) for post-dilatation patients. For median T_{max}, pre-dilatation patients were at 2.26 hours [95%CI (1.88, 3.45)], while post-dilatation patients were at 1.71 hours [95%CI (1.22, 2.56)].

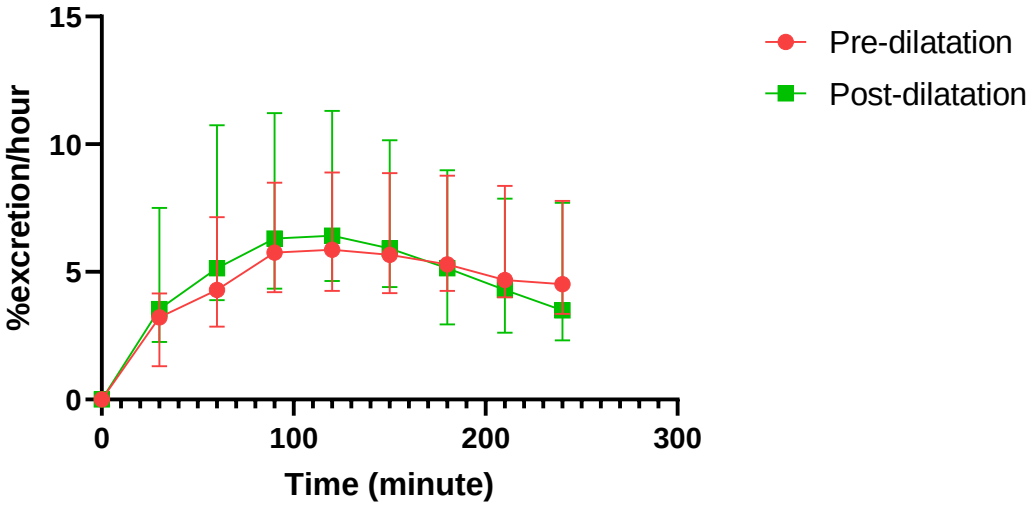


Figure 27: Percentage dose per hour excretion of Carbon-13 in pre- and post-dilatation patients

6.4 Discussion

The results of ^{13}COABT in this study showed that it was not reliable in diagnosing DGE or predicting the need for pyloric dilatation. There were no differences in results between the initial groups and in the paired pre-dilatation and post-dilatation patients in the ROC analyses. The AUC of the percentage excretion over 4 hours should differ between the groups; the total amount of C13 excreted within the test period should be lower in patients with DGE, in those requiring dilatation, and in the pre-dilatation group. However, those findings were not shown. The $t_{½}$ showed delayed emptying in all groups as all their median results were > 80 minutes (66). The only significant findings were differences in the $t_{½}$ and t_{max} in the non-dilated versus dilated group which were clearly shown at time points 30-minute, 60-minutes, and 90 minutes of their excretion curve. However, ROC analysis showed that the test was not adequately reliable and a cut-off %C13 cannot be made.

Those stated outcomes appear different to the reported outcomes by Ghoos et al and Gourcerol et al (49,66). Both publications suggest that patients with DGE should have an increased gastric emptying time with a delayed t_{max}, and lower total %C13 excretion per time, that should improve with pyloric intervention. Various factors could have caused the differing results.

Firstly, the test meal used in this study was a semi-solid meal and was at 0^{o}C. This was not an assessed or validated method of administering the carbon-13 octanoic acid. The test meals used in the study by Ghoos et al (66) were solid meals of recently cooked scrambled egg doped with carbon-13 octanoic acid. The differences in the physical state and temperature of the test meal could have altered the absorption rate of the octanoic acid but currently, there are no studies that used octanoic acid in an ice-cream meal. The octanoic acid appeared to solidify but was easily dispersed into the ice-cream. Perhaps an alternative meal in the form of a yogurt drink may have been a better test meal choice that would have prevented the fatty acid from freezing.

Secondly, the metabolism of octanoic acid in the liver may be altered after major surgery. However, currently, there are no studies on octanoic acid metabolism in the immediately post-operative state. There was a study by Gourcerol et al that studied gastric emptying in 53 patients (5 were post-oesophagectomy) (49). The study showed longer $t_{½}$ times in both pre- and post-dilatation patients compared to this study but with no statistical difference; the mean $t_{½}$ of pre-dilatation patients were 287 minutes (4.78 hours) and the post-dilatation patients were 224 minutes (3.73 hours) (p = 0.15) (49). It

was difficult to make a direct comparison of the emptying times as the oesophagectomy patient group in their study was small (<10%), and it was not clearly stated in the article regarding the post-operative day of the oesophagectomy patients that the test was conducted. Perhaps one method of overcoming this limitation would be to increase the breath test collection points and lengthen the collection time with a larger sample of patients. Further studies regarding octanoic acid metabolism in the post-operative setting is required to clarify this issue.

Thirdly, the initial analysis of the breath samples was supposed to be performed at the Isotope Mass Spectrometry laboratory, University of Plymouth. Therefore, the 4.5 ml Exetainer® vials, which were smaller, were purchased and used for breath sample collection to accommodate for the mass spectrometer. Advise was given to store the vials inverted and in room temperature. The smaller vials may have resulted in lower capture of C13 CO_2. Prolonged storage due to technical issues of the equipment at the University of Plymouth, and the temporary cessation of business at Iso-Analytics may have also led to increased C13 leakage from the vials.

Lastly, with the combination of low concentrations of C13 CO_2 in each vial, and the lack of information regarding the consistency of the leak rate between each vial, the results obtained may contain inaccuracies, or errors. Hence, results that were too scattered were censored or excluded from the analysis. The data censorship or exclusion was discussed with Dr Steven Brookes from Iso-Analytical Limited and agreed that the data scattering from outliers (very low concentration values) were most probably from C13 leakage or breath collection error which may be due to the limitations described above. Therefore, excluding whole datasets which consistently contain very low concentration levels and censoring the occasional data points from patients with occasional low concentration levels for analysis was justified.

The ^{13}COABT may still be a useful test in oesophagectomy patients but the technique requires further refinement. The use of a different breath collection system such as the 12ml Exetainer® vial could be used instead. Breath collection through a t-tube and plastic bag system may increase the C13 CO_2 capture rate. The use of a bedside C13 measuring device such as the Kibion® Dynamic from Seahorse Laboratories will prevent storage issues but is expensive and will require adequate funding. The breath test should also be correlated and validated with scintigraphy in patients that had undergone oesophagectomy recently. Further studies utilising the above strategies should be pursued as breath testing is still cheaper and safer compared to scintigraphy.

6.5 Conclusion

Currently, the ^{13}COABT conducted in this study showed no evidence that it be recommended for use to diagnose DGE or predict the need for pyloric intervention. Refinement of the ^{13}COABT by overcoming the limitations discussed above is required and further studies is needed to assess the test further. The ideal method of conducting the breath test would be using either an alternative carbon-13 fatty acid that has been validated, or an alternative means of delivering carbon-13. Additionally, increasing the breath collection time points and length of time of collection would provide more dataset to better assess the data variability and data inconsistencies. Lastly, on-the-spot breath analysis would prevent the issues with collection vials and leak during storage.

6.6 Issues confronted and solutions

Firstly, in the first week of the post-operative period, our patient group was only allowed a semi-solid meal. Hence, a semi-solid meal with similar nutritional content with scrambled egg had to be found. Ice cream from Langage farm appeared to meet those criteria. Mixing of octanoic acid was then trialled and, although appeared to solidify on contact, mixed well into the ice-cream meal. A slight sour aftertaste was occasionally noticed but did not cause any issues with the patients.

Secondly, consistency in breath capture was prevented by flow obstruction caused by the straight cut ends of the straw. On a few occasions the end of the straw abutted the end of the vial and reduced the exhalation rate of breath into the vials. The result was reduced volume of breath captured and, therefore, may affect the standardisation of breath taken. A taper cut to each straw solved the issue and no further reductions in exhalation rate of breath occurred.

Thirdly, during the study, half the remaining vial of octanoic acid was unfortunately misplaced and lost. Due to the cost of the test substance, a report was filed with the local R&D department. As the loss was below the £5 000 threshold, no further action was required, and the cost was covered by the research department. A further vial was purchased, then labelled with contact details and location to return the vial.

Fourthly, as part of analysing the breath samples, the laboratory at the University of Plymouth had to setup a mass spectrometer to run the test. The available mass

spectrometer was functional but was liable to produce results with a high-level of inaccuracy at not infrequent times. However, the laboratory had already placed plans to purchase an up-to-date mass spectrometer as part of their modernisation plans. For the installation of the new mass spectrometer, a temperature stable and well-ventilated room was required. As part of the assessment of the room, asbestos was found in the ceilings and prolonged the installation process substantially. It was then finally determined that the modernisation process had to be put on hold due to the Coronavirus 2019 outbreak. Hence, renegotiations were conducted with Iso-Analytical to analyse the samples.

The fifth issue was the statistical analysis of the samples was complex and required communication with previous researchers in this field for guidance. There was also a requirement to learn statistical program and training to use the statistical program that can conduct the calculations. It was then realised that the mathematical and modelling problems were out with the scope of the doctorate and my capabilities. Fortunately, help was found with the new sample analysis laboratory, Iso-Analytical. Although they were costlier than the University of Plymouth, they also provided assistance in data analysis and contact with Professor Thomas Preston in the University of Glasgow for the data modelling and macro files.

Finally, as faced in Chapter 5: Pathophysiology of delayed gastric emptying, it was identified early that there were several knowledge gaps in statistics and IT skills in statistical analysis. Hence, online learning and University of Plymouth workshops were used to update skills and knowledge in statistics and SPSS®. Additionally, the SPSS® statistical program did not have all the graph making tools that was appropriate, so another statistics program was searched for. Graphpad™ Prism® appeared to be user-friendly and produced the graphs that was needed. Online learning was used to familiarise its functions.

6.7 Summary

The technique used for breath sampling in this study cannot yet be recommended for analysis of C13 in ILGO patients. Further refinement of the test meal, breath collection, and storage is required to produce a higher quality and more consistent results. The issues and solutions discussed in this chapter should be used as a guide for the

refinement. The ^{13}COABT may still be a valid test for DGE once honed. As compared to the gold standard, gastric scintigraphy, ^{13}COABT has a lower cost, is radiation-free and can be performed at ease at the bedside. The 4-hour test time appeared to be the optimal time to be used for further studies. However, in order for the ^{13}COABT to be a practical clinical test, a one-off test will be much better accepted. An optimal one-off test time post-test meal and level of exhaled carbon-13 needs to be determined. Such testing methods have been achieved previously with the Carbon-13 Urea breath test.

Chapter 7: Symptomology after surgery and delayed gastric emptying

Chapter 7: Symptomology after Surgery

7.1 Introduction

From the perspective of patients, the improvement of their function and freedom of burden of complications can sometimes be more important than operative outcomes. Numerous QOL questionnaires had been devised for gastrointestinal surgery and specifically oesophageal cancer surgery (36,154,155). The questionnaires assessed patients through symptom probing questions such as presence of nausea, vomiting, early satiety, deterioration in eating habits, negative self-image about eating, dyspepsia, and pain. Numerous QOL questionnaires are available but the European Organisation for Research and Treatment of Cancer (EORTC) appeared to have developed validated system-specific forms. The EORTC developed the first QOL questionnaire for use in international clinical trials in oncology in 1993 (156). The EORTC QLQ-C30 (QOL life question - core questions) comprised of 30 core questions that covered 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, nausea, and vomiting), and a global health with QOL scale (156). The EORTC QLQ-OES18 (oesophageal module 18) was then developed and validated for use in oesophageal cancer in 2003 as an update for the EORTC QLQ-OES24 (oesophageal module 24) that was developed in 1996 (157). However, such questionnaires are usually comprised of multiple questions and may not be performed quickly as a snapshot of patient's symptoms. More specifically, there was no focused assessment of DGE in patients after an ILGO in terms of symptomology. The following study focused on obtaining a quick snapshot of the impact of DGE on patients' symptoms.

7.2 Methods

Data collection

Data from recruited patients with oesophageal cancer undergoing ILGO was collected prospectively from 05/12/2017 to 31/11/2019 in the Peninsula Oesophago-gastric centre at Derriford Hospital.

Inclusion and exclusion criteria

Patients were included if they were physiologically fit adult patients with operable oesophageal cancer. Exclusion criteria included patient refused surgery, unresectable cancer during surgery, or refused to participate in the study. Patients were also

excluded if they developed complications that caused symptoms of DGE (paraconduit hernia) during their in-patient stay. DGE was defined using the criteria set out in Chapter 3: Defining delayed gastric emptying.

Demographic data collected

Data collected include age, gender, BMI, ASA grade, smoking status, conduit size (width and length), DGE status as outlined in Chapter 3: Defining delayed gastric emptying, post-operative intervention, and questionnaires for symptoms.

Development of the modified symptomology questionnaire

The development of a short questionnaire that was quick and easy to complete was the main objective. Current available questionnaires were thought to be repetitive for patients as many would have been enrolled in trials which employed their use. EORTC QOL questionnaire for oesophageal cancer also known as the EORTC QLQ OES-18 (157) is a validated tool for assessing oesophageal cancer patients. Selection of specific questions which were related to poor or DGE was performed by the me and 8 questions were selected. Compared to the EORTC questionnaire which contains 4 parameters to select for each question, a 5^{th} parameter was added to increase the discriminating power of the questions. The additional parameter was added by splitting the 'Quite a bit' parameter in to 'Quite a bit and not troublesome' and 'Quite a bit and troublesome'. Besides the specific requirement to interrogate for symptoms of DGE, the modified question was used instead of the EORTC questionnaire was because of concurrent R&D conflict with another on-going study – the ROMIO trial.

It was noted that in the immediate post-operative setting, numerous factors such as medication, immediate complications (ileus, anastomotic leak, pneumonia), and being in an in-patient environment may bias the questionnaire response. Hence, the questionnaire was only planned to be presented at week-4 and month-4, including a baseline prior to surgery. Any patient with DGE would have been detected while as an in-patient and treatment provided. Hence, the questionnaire devised aimed to assess the differences in function of patients without and with DGE in the longer term.

Symptomology data collected

Patients were presented with a questionnaire for symptoms to assess symptomology (shown in Appendix V) pre-operatively, at week 4 post-operatively and at 4 months post-operatively. The questions probed into gastrointestinal symptoms and

psychological aspects of eating. Each question had 5 parameters with 1 point allocated for 'Not at all' and, in incremental progression, up to 5 points for 'Very much'. Hence, patients was able to score a minimum of 8 points and a maximum of 40 points.

Patient groups and statistical analyses

Initially, patients were categorised into 2 groups: non-DGE versus DGE, and non-dilated versus dilated as described in Chapter 5: Pathophysiology of delayed gastric emptying and Chapter 6: Investigating delayed gastric emptying. Patients without DGE according to the algorithm (Appendix III: Enhanced recovery protocol) (33) were designated as non-DGE, while patients with DGE according to the algorithm were designated as DGE. Patients that did not receive pyloric dilatation during their in-patient stay were designated as non-dilated while the dilated sub-group received dilatation. For the dilated sub-group, 2 further sub-analysis groups were allocated to them based on their pyloric dilatation intervention timing: pre-dilatation and post-dilatation. A final sub-analysis was performed for patients without late delayed gastric emptying symptoms (DES) and with DES.

Statistical analysis was performed using the IBM's© SPSS Statistics software version 25 (https://www.ibm.com/analytics/spss-statistics-software). For the production of graphs, Graphpad Prism version 9 was used instead (https://www.graphpad.com). Sample size was determined using an updated DGE incidence of 17.5% (33) and an estimated reduction of DGE to 0% post-intervention (71) (effect size of 17.5%), power of 80%, $p = 0.05$ and an enrolment ratio of 3:1 (due to feasibility of recruiting adequate numbers for the intervention in a 2-year period). The calculated sample size required for the study was 80 patients, with 60 in the non-DGE group and 20 in the DGE group. A skewness and Shapiro-Wilk test were used to assess the distribution of the continuous data. Univariate analyses (Chi square test and Mann-Whitney U test) were performed between each group to compare their characteristics. The Kruskall-Wallis test was used to analyse differences between symptomology scores of the 2 groups in each phase: pre-operative, and post-operatively at 4 weeks and at 4 months. Additionally, the Friedman test was used to analyse the 3 time-points (pre-operative, 4-weeks, and 4-months) as paired samples within each individual group. All parametric data were presented as median, range and/or 95%CI. A p value of < 0.05 was deemed statistically significant.

Ethical approval

The London Bromley Research Ethics Committee approved the study (REC 17/LO/1759), which was conducted in accordance with the principles of the Declaration of Helsinki with written informed consent provided by all patients.

7.3 Results

Non-DGE versus DGE

There was a total of 65 patients included for analysis and the recruitment date ranged from 05/12/2017 to 25/11/2019. The recruitment and progress of patients was shown in the CONSORT flow diagram in **Error! Reference source not found.** and Figure 9. T here were no differences in patient characteristics as shown in Table 11. Total pre-operative symptomology scores of all patients were varied with a median score of 10 (8-33). Median of the week-4 scores was 11 (8-33) while the month-4 median score was 10 (8-33). Table 15: Table 15 Table 14 showed the scores, ranges, and statistical result for in-group analysis in the 2 groups. Comparison of the symptomology scores of patients between the groups at pre-operation, week-4 and month-4 showed no statistical significance between the results.

	Median symptomology score	**Range**		**Median symptomology score**	**Range**	***p***
Non-DGE patients			**DGE patients**			
Pre-operative	11	8-33	Pre-operative	9.5	8-25	0.420
Week-4	11	8-33	Week-4	10	8-24	0.133
Month-4	10	8-33	Month-4	9	8-23	0.535

DGE: Delayed gastric emptying

Table 14: Symptomology score in patients without and with delayed gastric emptying prior to surgery, and at 1 month and 4 months after surgery

The pre-operative symptomology scores did not influence the subsequent post-operative symptomology scores, but a majority of patients had a trend towards improvement over time as depicted in Figure 28 and Figure 29. Friedman test analyses revealed that within

the non-DGE groups, symptomology scores differed between the 3 groups (p = 0.027). The differences occurred between the symptomology scores at 4 weeks [95%CI: (12.30,

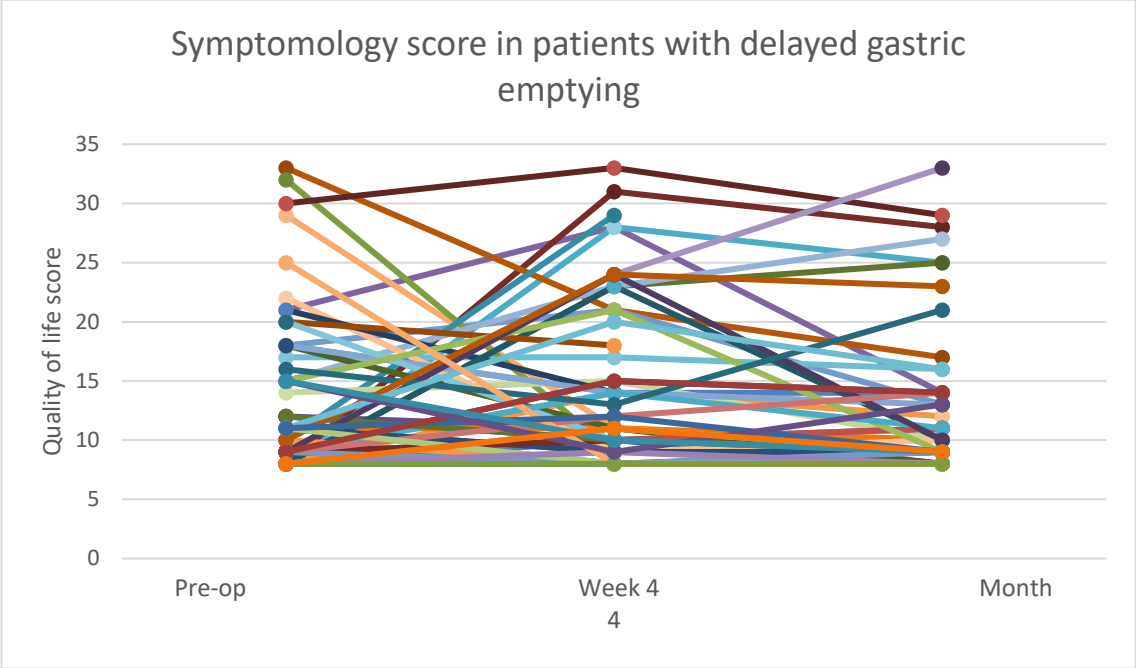


Figure 28: Symptomology scores in patients without delayed gastric emptying at 3 measured time points

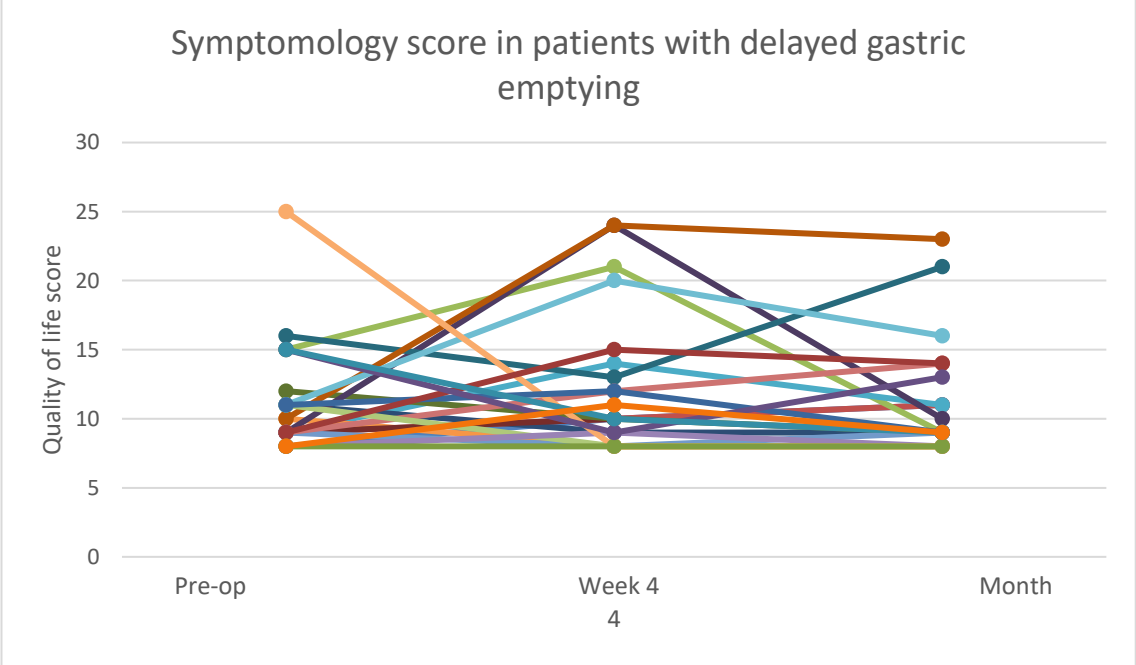


Figure 29: Symptomology scores in patients with delayed gastric emptying at 3 measured time points

17.16)], and at 4 months [95%CI: (10.79, 15.49)], (p = 0.005) but not with the pre-operative scores. However, in the DGE group, no differences in symptomology scores occurred over time (p = 0.540).

Out of the 24 patients with DGE, 5 were diagnosed with symptoms attributable to late DES (Figure 9). All 5 had in-patient pyloric dilatation. Of those 5 patients, 3 had mechanical issues (2 paraconduit hernias and 1 "folded" conduit). Confirmation of the mechanical issue was made using CT. The 2 patients with DES with true DGE received pyloric dilatation; both received the intervention after 6 post-operative weeks.

Sub-analysis of individual scores for each question did not show any significant differences in the 3 time periods. The most common symptom afflicting both patient groups in the week 4 period was filling full up too quickly and symptoms of acid indigestion or heartburn. Generally, these symptoms improved by the month 4 period. There was a total of 4 patients that had worsening scores of > 2 from the week 4 to month 4 period. The underlying reasons for worsening symptoms were tumour recurrence, a diagnosis of late DES, or just received adjuvant chemotherapy.

There were 2 patients with missing data for the week 4 questionnaire and 6 patients with missing data in the month 4 questionnaire. The reasons for the missing data include 1 death prior to week 4, 1 patient moving away to a different region without contact details and 4 deaths prior to month 4.

Non-dilated versus dilated

A total of 65 patients were included in the analysis from 05/12/2017 to 25/11/2019 with recruitment and progress of patients shown in the CONSORT flow diagram in **Error! R eference source not found.** and Figure 12. There were no differences in patient characteristics as shown in Table 12. Total pre-operative symptomology scores between patients were varied with a median score of 10 (8-33). Median of the week-4 scores was 11 (8-33) while the month-4 median score was 10 (8-33). Table 15: Table 15 showed the scores, ranges, and statistical result for in-group analysis in the 2 groups. Comparison of the symptomology scores of patients between the groups at pre-operation, week-4 and month-4 showed no statistical significance between the results.

The pre-operative symptomology scores did not influence the subsequent symptomology scores, but a majority of patients had a trend towards improvement over time as depicted in Figure 30 and Figure 31. Friedman test analyses revealed that within the dilated group, no differences in symptomology scores occurred over the 3 time periods ($p = 0.450$). However, in the non-dilated group, symptomology scores differed between the 3 groups ($p = 0.025$). The significant difference occurred between the

symptomology scores for week 4 [95%CI: (11.98, 16.56)] and month 4 [95%CI: (10.89, 15.60)], (p = 0.005).

	Median symptomology score	**Range**		**Median symptomology score**	**Range**	***p***
Non-dilated patients			**Dilated patients**			
Pre-operative	11	8-33	Pre-operative	9.5	8-25	0.318
Week-4	11	8-33	Week-4	10	8-29	0.503
Month-4	10	8-33	Month-4	9	8-23	0.519

$p < 0.05$ was denoted as statistically significant

DGE: Delayed gastric emptying

Table 15: Symptomology score in patients without and with pyloric dilatation prior to surgery, and at 1 month and 4 months after surgery

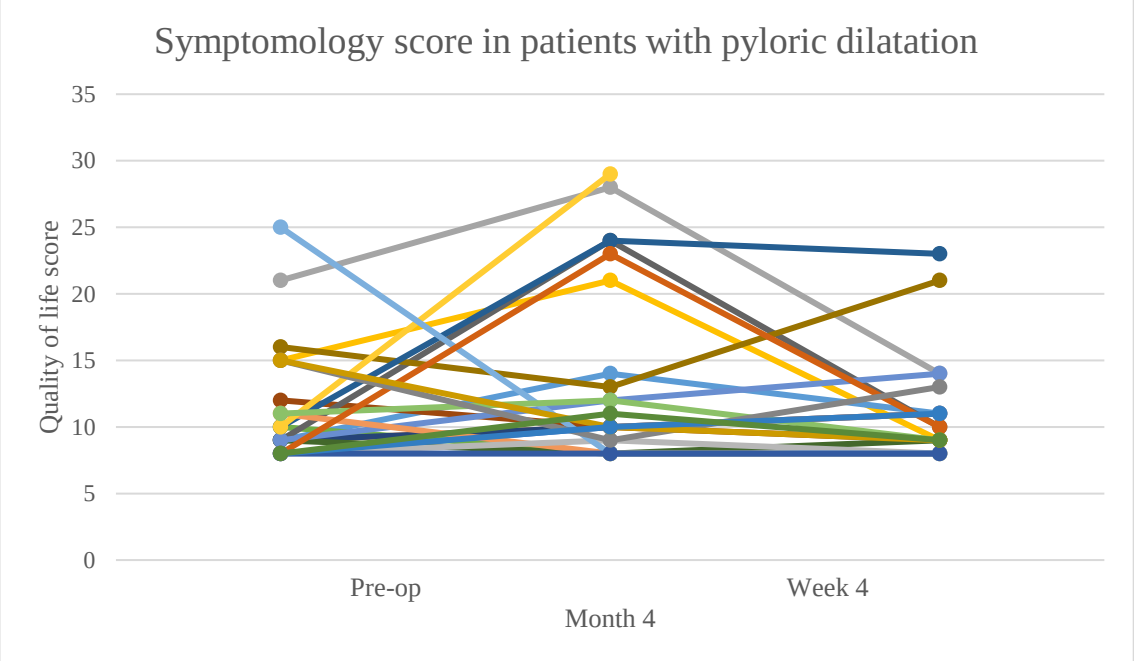


Figure 30: Symptomology scores in patients with pyloric dilatation at 3 measured time points

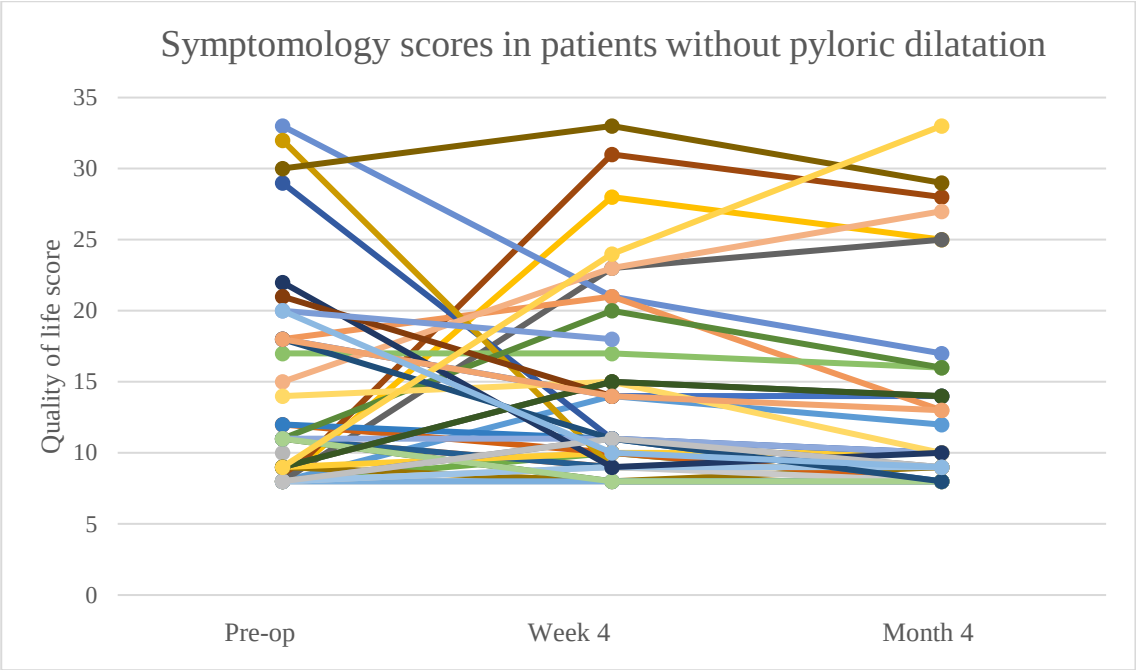


Figure 31: Symptomology scores in patients without pyloric dilatation at 3 measured time points

Out of the 24 patients with DGE, 6 were diagnosed with late DES and 3 received pyloric dilatation after discharged as they were true DGE. All 6 had oral input and oral output that were consistent for DGE. The other 3 patients that were not true DGE, had anatomical issues (paraconduit hernia or "folded" conduit). Confirmation of the anatomical issues were made using CT.

Sub-analysis of individual scores for each question was the same as described in the previous group and so was missing data.

Sub-analysis of patients with late DES

There were no differences in pre-operative, week-4, and month-4 in patients without and with late DES, p = 0.708, 0.670, and 0.58, respectively. For pre-operative symptomology scores, the 95%CI for without DES was (10.96, 14.58), and with DES was (7.55, 19.7). At 4 weeks, the 95%CI for patients without DES and with DES was (11.89, 15.48), and (7.85, 22.15), respectively. Lastly, for month-4 scores, the 95%CI for patient without DES and with DES was (10.25, 13.48), and (9.43, 22.57), respectively.

7.4 Discussion

The results of the study showed that post-operative symptoms between patients without DGE versus with DGE, and non-dilated versus dilated at 4 weeks and at 4 months were similar. Patients without DGE or did not receive pyloric dilatation appeared to have symptomology scores that improved over time compared to more static scores in the other group. In those that had significant worsening of their scores, the causes were due to the presence of significant pathology (primary dilated conduit, tumour recurrence, or anatomical abnormalities) or had recent adjuvant chemotherapy.

Currently, in 3 of the patients with late DGE, there was no indication of DGE based on the in-patient DGE algorithm. These findings suggest that the algorithm was unable to predict late DGE. The current international consensus defined late DGE as the presence of 2 or more of the predefined symptoms (early satiety/fullness, vomiting, nausea, regurgitation or inability to meet caloric need by oral intake) that occurred after 14 days (41). The definition was based on a Delphi consensus and criteria generated from the EORTC QOL questionnaire that was similarly based on the modified questionnaire in this study (157). Konradsson et al suggested that the pathophysiology behind DGE (both early and late) was multi-factorial including factors like anatomical and physiological changes, surgical technique and conduit fabrication, and post-operative care (158). The paucity and lack of high-level evidence-based research in late DGE and its pathophysiology highlights that more robust studies are needed to help understand the condition further.

The symptomology score among pre-operative patients were extremely heterogenous and did not help predict risk of DGE. Results of our study did not show that more extensive co-morbidity predicted poorer scores, and this was contradictory to findings by Djärv et al (155). The heterogeneity of pre-operative scores can be explained by the varied presentation of the patients and tumour behaviour. The most common symptom gathered from the questionnaire in the post-operative setting was early satiety and reflux-type symptoms. The degree of early satiety may be a poor marker of severity due to subjectivity. Pre-operative education of patients about the post-operative changes (159) in the stomach size, size of meal intake and frequency may differ and, hence, may alter their perception of satiety in the post-operative setting. Hence, if patients were not pre-educated, then even if DGE was not present, it was possible that early satiety may be perceived as a prominent problem. Additionally, it was known that in some studies, GH and physiological changes in post-ILGO patients did occur in a similar trend to

post-bariatric surgery patients whereby the post-operative changes in GHs produced early satiety (48,76,79). Due to the multifactorial and multi-symptom nature of DGE, the use of early satiety as a lone factor will not be adequate to diagnose DGE. Reflux-type symptoms such as heartburn, and regurgitation were more frequent in the post-operative period due to the absence of a lower oesophageal sphincter and the resting position of the stomach which is in the chest. These symptoms can be affected by pre-operative education whereby strategies such as advice to prop oneself up in bed at night, limiting the amount of food intake, and the abstinence of food late in the evening, if taught in advance, can limit the occurrence of these symptoms.

It cannot be ascertained from the study that pyloric dilatation significantly improved the symptomology of patients with DGE or required dilatation. Currently, there are no studies that compared symptomology scores pertaining to ILGO and DGE in patients without and with pyloric dilatation in the literature. Although it may seem obvious that the symptomology score should drastically improve after dilatation, those findings were not found in this study. We recommend further research into this area using a larger patient population and more elaborate questionnaire. This study did not measure pre-dilatation scores and was designed in such a way because symptomology score in the early stages of the pre-operative phase will likely be coloured by other factors such as infections, electrolyte imbalances, opiate use, and the unique differences in individual post-operative physiological responses. A more robust methodology will be required to investigate this topic. The ideal study would not only assess symptomology at more time points in the discharged setting but also during the in-patient stay. Symptom assessment before and after dilatation should also be conducted.

The limitations of the study as discussed above, include the fact that the symptomology questionnaire was not infallible. The results could be affected by pre-operative education, patient personality and bias, differences caused by changes in post-operative gut physiology, and differences in surgical technique amongst surgeons. Current definition of DGE, both early and late, is still subjective and is not based on strong evidence. A more robust definition can only be gained by conducting research to build a definition that can be used clinically. Such a definition will not only be more precise and relevant to daily practice but also useful to identify patients with DGE correctly. Secondly, the limited time points reduced the ability of the study to assess symptomology more thoroughly at different stages of the post-operative recovery setting. The limited time points was set by the local R&D department, as advised by the

ethics committee, as a result of concurrent studies being run which was the ROMIO study. Lastly, free text or comments about patient symptoms could have been added to the questionnaire. This would have allowed better patient expression of their post-operative issues and would have allowed qualitative analyses.

7.5 Conclusion

The symptomology of patients with DGE or required dilatation appeared to be similar in the 4-week post-operative period compared to the 4-month period in this study. It was unclear regarding the underlying reason for the lack of improvement in symptomology scores in those patients. Additionally, on a whole, symptomology score in all patients were similar, suggesting that pyloric intervention did not cause patient detriment. Further assessment of symptomology of patients with late onset DGE and in-patient DGE would be vital to understand the impact of DGE on patient's lives.

7.6 Issues confronted and solutions

During the application process for research approval, it was proposed by the HRA and R&D department regarding the validity of the questionnaire as a QOL assessment tool due to the modifications made from its original form. The modified questionnaire was used to establish a baseline function of patients pre-operatively and then their progression over time; in essence, to assess patient symptomology. To further elaborate, the main purpose of the modified questionnaire was not to fully assess each patient's quality of life but whether the affliction and treatment required for DGE would affect a patient in terms of gastrointestinal symptoms and psychological aspects of eating. Additionally, the questionnaire was shortened for ease of daily clinical use. In order to discern each symptom more effectively (as a result of a truncated version), the level of each symptoms was expanded to 5 levels instead of 4.

Lost to follow-up occurred in less than 10% of patients at 4 months. Lost to follow-up was low because every effort was taken to obtain a response. Follow-up was performed using the following methods: during out-patient appointments, telephone follow-up, and mail. Hence, lost to follow-up only occurred in if the patient was deceased or became uncontactable.

The questionnaire was designed to have ease of use and practical clinically. Other methods to increase the information yield would be to allow for free text. Qualitative analysis could then be performed using 'word frequency' and/or 'word cloud' to assess for most commonly used comments which may highlight other issues faced by patients.

7.7 Summary

This study showed that measuring symptomology scores did not distinguish between the patient groups. However, it was noted that in-patient function whilst experiencing DGE was not assessed, such assessment in an unwell post-operative patient would be fraught with many obstacles. More refined methodology will need to be devised prior to conducting such studies.

During the study, several patients with late onset DGE was observed and symptomology questionnaire assessment of those patients in larger scale will be required to obtain statistically sound results. It is also likely that late onset DGE may have a different pathophysiology and treatment modality.

Chapter 8: Thesis summary

Chapter 8: Thesis Summary

8.1 Proposed pathophysiology of DGE and its management

The cause of DGE after an ILGO is multifactorial. The procedure causes gastric conduit denervation through severing the vagus nerve, reduction of gastric capacity through excision of a large portion of the stomach, and GH physiological changes due to anatomical reconstruction. The reconstruction to restore the continuity of the gastrointestinal tract may also result in mechanical issues if anatomical disparities occur (160,161).

Mechanical issues that resulted in DGE appeared to be rare in our study. None were diagnosed whilst an in-patient, while 4 were diagnosed after discharge. The mechanical issue is due to folding of the conduit due to length discrepancy with the thoracic cavity or direct external compression of the pylorus or duodenum (160,161). Management usually required surgical intervention to amend the length difference or to relieve the external compression. Management with prokinetic agents, or endoscopic intervention did not result in success in those cases. Hence, those patients should be classified differently from patients with true DGE and should be classified as gastric outlet obstruction (GOO) instead.

It is known that the stomach has a pacemaker that regulates gastric contractility and pyloric relaxation, with its function altered by vagal denervation (43,44,158). However, no large studies using gastric electrical stimulation have been conducted so far in ILGO (162). An electrophysiological study by Izbeki et al showed that mechanical contraction is related to electrical activity in the stomach which is affected by the ILGO, but function and symptoms tend to improve over time – up to 30 months for full resolution of symptoms (47). These findings may explain the lack of effect from peri-operative pyloric intervention in preventing DGE (33,46) and the presence of late DGE in some patients. Gastric pacemakers have been found to be effective in patients with gastroparesis, whereby 54% had symptom improvement (163). However, since the pathophysiology of the 2 conditions are different, the effectiveness of a gastric pacemaker may be doubtful in ILGO patients. Pyloric intervention after 1 week post-operatively appeared to be an effective treatment in our patient group and should be the treatment of choice currently. In patients or surgeons adverse to balloon dilatation in the post-operative setting, endoscopic botulinum toxin injection to the pylorus which have been shown to provide safe and satisfactory symptom relieve may be used as an

alternative (164). Further refinement of the balloon dilatation and botulinum toxin injection technique needs to occur alongside larger multi-centre RCTs.

The effects of GH changes after an ILGO are still not well understood. Published data is still sparse and studied in only small sample sizes (148,149). The post prandial GH response in ILGO patients in our study appeared obtunded and similar to pre-operative data from Elliott et al and Murphy et al (148,149). The exaggerated response that occurred from day 10 was not seen in our patient group. It was possible that the GHP sampling between days 4 to 6 may had been too early to pick up an exaggerated response and would support the notion of gastric ileus in the early post-operative setting. Additionally, the variable timing in blood sampling and the limited sampling may have contributed to the difference. An exaggerated PYY response was seen in patients without DGE, did not require dilatation, and post-dilatation but such findings were absent in GLP-1. Further studies are required to acquire an explanation for those results. The PYY response in post-dilatation patients compared to pre-dilatation patients could be due to the restoration of flow of nutrient into the small bowel – that idea would support the notion of a mechanical issue with gastric emptying in patients with DGE or require dilatation.

The post ILGO stomach is smaller. Like the SG patient, the stomach has a reduction in volume and has a tube-like reconstruction. However, SG patients do not experience DGE. In fact, the SG had been postulated as an operation to treat DGE in gastroparesis patients (165). In the SG, the gastric emptying time is quicker (139) and has been postulated to be due to an increased in intraluminal pressure (136). The anatomical difference between the conduit of an ILGO and the sleeve of a SG is the greater curve is used for conduit reconstruction in the ILGO whilst the sleeve in the SG is fabricated using the lesser curve. Additionally, the vagus nerve is severed in the ILGO while the nerve is spared in the SG. Hence, those findings suggest that DGE in the ILGO is likely due a neurological dysfunction of the stomach.

Pyloric interventions in the form of pyloroplasty, pyloromyotomy, pyloric botulinum toxin injection, and balloon dilatation should solve the functional issue as seen in the historical vagotomy patients. However, as highlighted previously, numerous studies had shown different results for each intervention (33,38,39,46,51,55,56,60). However, the techniques for each procedure may differ and no standardisation of method had been used which can explained the heterogeneity. To prevent DGE, there should be a

consideration for prophylactic pyloric intervention. If a pyloric intervention is performed on all ILGO patients, not only is a standardised technique required but it needs to be repeatable, easy to perform, and low in risk. Pyloric balloon dilatation had been shown to be reduce DGE incidence by two thirds (166). Current research into the effectiveness of pyloric dilatation is incomplete. There are no systemic reviews and meta-analysis assessing pre- or intra-operative balloon dilatation as a preventative measure for DGE. Only 2 studies so far have studied the effects of pre-operative pyloric dilatation and have shown up to a 3 fold reduction in DGE incidence post-operatively (167,168). The described DGE rate was between 4% and 18.3%. The pre-operative pyloric dilatation was performed using a small balloon – 16mm or 20mm balloon. Additionally the results by Hadzijusufovic et al showed that in the post-operative setting, dilatation using a 30mm Rigiflex™ balloon was more effective compared to the smaller 20mm balloon (168). Further studies should be conducted to assess using either a 30mm balloon in the pre-operative or intra-operative setting.

The benefit of a safe, easily reproducible, and quick pyloric intervention with a low complication rate that is performed intra-operatively will significantly reduce the incidence of DGE and post-operative interventions without adverse effects to patients. This should, in turn, improve the QOL and/or symptomology of ILGO patients in the long term.

8.2 Investigative algorithm and test for delayed gastric emptying

The previous definition for DGE by the ECCG appeared too subjective and was not clinically useful in diagnosing DGE early (31). Current definition for DGE by the EMIOTT was a dramatic improvement and allowed a more objective diagnosis of DGE to be made early in the post-operative setting but some improvements was still required (41). The proposed NG output did not consider oral intake nor was the volume output a proportional difference which can lead to high number of false positives. The CXR parameter was still too subjective and a more precise description of landmarks for measurements should have been considered. The algorithm used in this thesis (33) addressed those issues but validation with a gold standard test such as scintigraphy for DGE is still required.

Based on the study from this thesis, GH profiling to diagnose DGE cannot be recommended as it was found to be too unreliable, costly, and there are limited

laboratories that can analyse the samples. The value of GHP in ILGO remains unknown and further research is required. Perhaps GHs have no role in DGE and their function remains as a negative feedback mechanism for food volume consumption with glucose level regulation via their incretin effect (78,149,169,170). Further studies should include a larger sample size, more bloods collection time points and for a longer time period.

Gastric scintigraphy is still the gold standard for the diagnosis of DGE (66). However, it is still too expensive with limited availability, and is complex to conduct. A cheap, reliable, and easy to use test that is readily available is yet to be found. Inspirations taken from *Helicobacter pylori* breath test (151) and other tests such as the hydrogen and methane breath test for bacterial overgrowth, unfortunately, have not yet come to fruition. Breath tests are easy, considerably cheaper, and can be conducted at the patient's bedside. Additionally, the breath test also does not increase the risk of further radiation exposure to patients. In spite of the findings from the study in this thesis, the ^{13}COABT can still be refined further to achieve those criteria. Areas to improve can be divided into the C13 compound used and the test meal used, the breath test capturing system, and the analysis. Different C13 compounds are available (171) but the test meal itself has to be semi-solid. Adequate mixing of Octanoic acid has never been studied nor are the other C13 isotopes. Further studies into C13 isotope interactions with a semi-solid cold test meal such as ice cream are required. There are numerous methods for breath test capture such as straight into a glass vial or using a t-tube with plastic bag system. Both methods still require the storage of the breath test in a glass vial for a certain duration. A straight to analysis method is available, such as from Seahorse laboratories© the Kibion® Dynamic, will eliminate the need for storage and would provide immediate results. However, current methods for analysing gastric emptying time remain cumbersome and requires testing to be conducted over a 4-hour period. Refinement of the mathematical calculations and generating a cut-off C13 concentration at a specific time-point will ease testing and workload.

The benefit of easier and earlier recognition of DGE that can be performed at the patients beside will allow more prompt management. This should reduce the risk of anastomotic leak, aspiration pneumonia, and, thus, prevent further deterioration of patients' QOL and/or symptomology.

8.3 The impact of delayed gastric emptying on oesophagectomy patients

The morbidity and mortality associated with having an oesophagectomy is significant (36,37). The 3-year survival after curative oesophagectomy, according to the NOGCA in 2020, was around 57.4% (172). With up to 50% of DGE incidence in oesophagectomy patients (38), addressing the impact of DGE on QOL, especially symptomology, becomes a crucial issue. Currently most QOL questionnaires are lengthy and can be cumbersome to complete (156,157). However, those questionnaires tend to be more objective and provide a more thorough assessment of the patient. The modified questionnaire developed for this study aimed specifically at assessing symptoms relating to DGE. Abbreviating the questionnaire was to allow a quicker assessment, be specific to symptoms, and could have been easily performed by the bedside. Further research should now be conducted to validate the modified symptomology questionnaire against the established questionnaires.

Pyloric dilatation as a treatment for DGE did not result in a deterioration of symptomology scores. This implies that pyloric dilatation prevents a deterioration in symptomology scores if a patient develops DGE. However, the sample size or design of our study was not designed to assess the issue. A larger retrospective cohort study assessing the symptoms of patients that developed DGE but did not receive pyloric dilatation should address the issue. This should then be followed by a RCT of intra-operative pyloric dilatation versus none to address the effects of DGE on symptomology in the ILGO patient.

The effects of DGE on symptomology is likely significant but no clear predictors had been identified (36). In our study, there was a preponderance for female patients requiring pyloric intervention in the non-dilated versus dilated group. Large synthesis of studies will be required to identify risk factors for DGE. Perhaps then a scoring system can be devised to stratify the risk and then employ more targeted intra-operative pyloric intervention to patients with a high stratified risk. Such strategy will prevent the need to perform a blanket prophylactic procedure on all patients, and thereby reducing the associated risk, and morbidity.

8.4 Conclusion

The proposed mechanism for DGE after an ILGO would be mechanical stasis of the stomach and continued studies into the disruption of the pylorus as a form of treatment should be pursued. A more robust study into intra-operative pyloric dilatation should be

conducted. A possible study would be to conducted a RCT comparing no intervention versus intra-pyloric botulinum toxin injection versus prophylactic balloon dilatation. The ^{13}COABT cannot yet be recommended as an investigative test for DGE after an ILGO and further refinements of the test is required. I propose the use of a bedside measuring device. The modified symptomology questionnaire showed that pyloric dilatation did not cause patient detriment and validation of the questionnaire is required.

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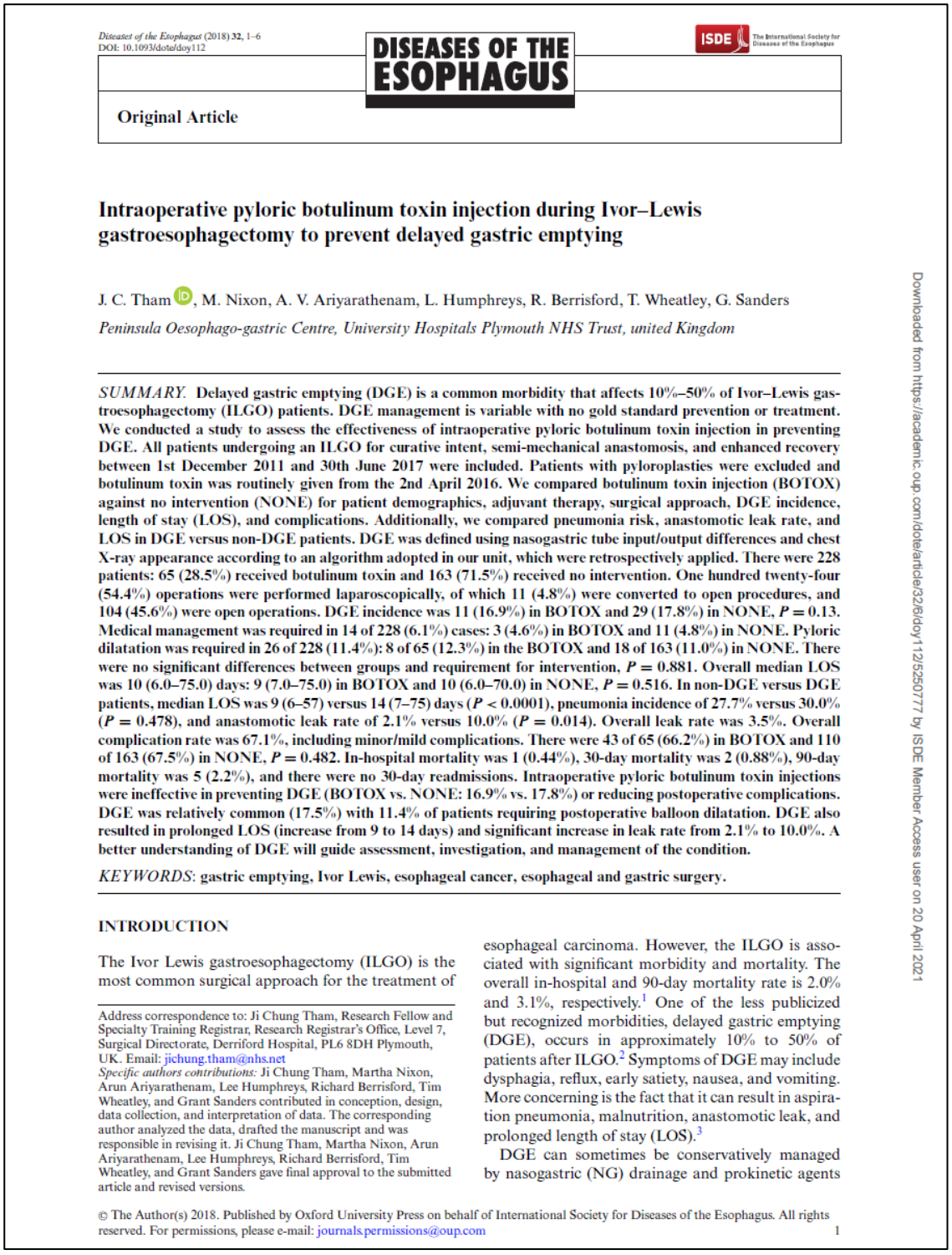
Publications

1. Intraoperative pyloric botulinum toxin injection during Ivor-Lewis gastro-oesophagectomy to prevent delayed gastric emptying



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Original Article

Intraoperative pyloric botulinum toxin injection during Ivor–Lewis gastroesophagectomy to prevent delayed gastric emptying

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SUMMARY. **Delayed gastric emptying (DGE) is a common morbidity that affects 10%–50% of Ivor–Lewis gastroesophagectomy (ILGO) patients. DGE management is variable with no gold standard prevention or treatment. We conducted a study to assess the effectiveness of intraoperative pyloric botulinum toxin injection in preventing DGE. All patients undergoing an ILGO for curative intent, semi-mechanical anastomosis, and enhanced recovery between 1st December 2011 and 30th June 2017 were included. Patients with pyloroplasties were excluded and botulinum toxin was routinely given from the 2nd April 2016. We compared botulinum toxin injection (BOTOX) against no intervention (NONE) for patient demographics, adjuvant therapy, surgical approach, DGE incidence, length of stay (LOS), and complications. Additionally, we compared pneumonia risk, anastomotic leak rate, and LOS in DGE versus non-DGE patients. DGE was defined using nasogastric tube input/output differences and chest X-ray appearance according to an algorithm adopted in our unit, which were retrospectively applied. There were 228 patients: 65 (28.5%) received botulinum toxin and 163 (71.5%) received no intervention. One hundred twenty-four (54.4%) operations were performed laparoscopically, of which 11 (4.8%) were converted to open procedures, and 104 (45.6%) were open operations. DGE incidence was 11 (16.9%) in BOTOX and 29 (17.8%) in NONE, $P = 0.13$. Medical management was required in 14 of 228 (6.1%) cases: 3 (4.6%) in BOTOX and 11 (4.8%) in NONE. Pyloric dilatation was required in 26 of 228 (11.4%): 8 of 65 (12.3%) in the BOTOX and 18 of 163 (11.0%) in NONE. There were no significant differences between groups and requirement for intervention, $P = 0.881$. Overall median LOS was 10 (6.0–75.0) days: 9 (7.0–75.0) in BOTOX and 10 (6.0–70.0) in NONE, $P = 0.516$. In non-DGE versus DGE patients, median LOS was 9 (6–57) versus 14 (7–75) days ($P < 0.0001$), pneumonia incidence of 27.7% versus 30.0% ($P = 0.478$), and anastomotic leak rate of 2.1% versus 10.0% ($P = 0.014$). Overall leak rate was 3.5%. Overall complication rate was 67.1%, including minor/mild complications. There were 43 of 65 (66.2%) in BOTOX and 110 of 163 (67.5%) in NONE, $P = 0.482$. In-hospital mortality was 1 (0.44%), 30-day mortality was 2 (0.88%), 90-day mortality was 5 (2.2%), and there were no 30-day readmissions. Intraoperative pyloric botulinum toxin injections were ineffective in preventing DGE (BOTOX vs. NONE: 16.9% vs. 17.8%) or reducing postoperative complications. DGE was relatively common (17.5%) with 11.4% of patients requiring postoperative balloon dilatation. DGE also resulted in prolonged LOS (increase from 9 to 14 days) and significant increase in leak rate from 2.1% to 10.0%. A better understanding of DGE will guide assessment, investigation, and management of the condition.**

KEYWORDS: **gastric emptying, Ivor Lewis, esophageal cancer, esophageal and gastric surgery.**

INTRODUCTION

The Ivor Lewis gastroesophagectomy (ILGO) is the most common surgical approach for the treatment of esophageal carcinoma. However, the ILGO is associated with significant morbidity and mortality. The overall in-hospital and 90-day mortality rate is 2.0% and 3.1%, respectively.[1] One of the less publicized but recognized morbidities, delayed gastric emptying (DGE), occurs in approximately 10% to 50% of patients after ILGO.[2] Symptoms of DGE may include dysphagia, reflux, early satiety, nausea, and vomiting. More concerning is the fact that it can result in aspiration pneumonia, malnutrition, anastomotic leak, and prolonged length of stay (LOS).[3]

DGE can sometimes be conservatively managed by nasogastric (NG) drainage and prokinetic agents

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such as Domperidone or Erythromycin. However, the evidence base for those interventions is poor. They are also often unsuccessful, and patients may require surgical or endoscopic intervention to disrupt the pylorus to relieve symptoms. Pyloric drainage procedures performed at the time of surgery include pyloromyotomy, pyloroplasty, or balloon dilatation. However, such interventions increase operative time, are related to morbidity such as bile reflux, pyloric closure site leak, and perforation due to dilatation.[4–8] Furthermore, prophylactic pyloric interventions will result in treating all patients, subjecting them all to the risk of the procedure, even in those that may not have a problem with DGE.

Recently, intrapyloric botulinum toxin injection has gained favor in DGE management due to its reversible effect, low risk, ease of administration, and it is the least invasive approach compared to the other methods.[6–13] However, there is lack of high quality evidence as highlighted by three recent systematic reviews, which discuss the lack of standardization of diagnosis, management, and the paucity of randomized controlled trials to determine the gold standard treatment.[2,4,9]

We sought to evaluate the effectiveness of intraoperative endoscopic botulinum toxin injection to the pylorus in preventing DGE after ILGO.

MATERIALS AND METHODS

This study was performed as a feasibility study for a randomized controlled trial comparing the use of intrapyloric botulinum toxin injection versus no intervention and was conducted in a single high-volume tertiary esophagogastric center. The data was extracted retrospectively from a prospectively collected local comprehensive database. All data were entered by the consultant responsible for each patient at the time of intervention and morbidity data updated weekly at the joint consultant meeting. All patients undergoing ILGO for curative intent, using the semi-mechanical anastomosis technique[14] between 1st December 2011 and 30th June 2017 were included. Patients not undergoing enhanced recovery,[15] or those who had pyloroplasty were excluded, to ensure that surgical technique and postoperative care were standardized and equivalent in all patients. All ILGOs were performed either as laparoscopic, or open abdominal approach with open thoracotomies. Botulinum toxin injection to the pylorus was routinely given from the 2nd of April 2016. Administration was via endoscopy, whenever the tumor was traversable (200 units made up to 10 mL with saline, using a 5-mm sclerotherapy needle in 4 separate quadrants as described by Fuchs *et al*).[7] In the event that the endoscope could not traverse a stenosed tumor, botulinum toxin was administered directly into the pylorus, using a spinal needle in both open and laparoscopic approaches in 3 quadrants.[16] Patient demographics including age, gender, preoperative neoadjuvant therapy use, tumor stage, comorbidity, ASA grade, surgical approach, tumor characteristics and site, presence of DGE, DGE management, and LOS were collected.

The patients were divided into two groups as follows:

(1) Intraoperative botulinum toxin injection into the pylorus, BOTOX group
(2) No intra operative botulinum toxin, NONE group

Primary outcomes for each patient group included the presence of DGE, interventions used to manage DGE, and LOS. The Esophagectomy Complications Consensus Group (ECCG) defined DGE as delayed conduit emptying requiring intervention, delaying discharge, or requiring maintenance of nasogastric drainage >7 days postoperatively.[17] As this is a very subjective definition, an objective algorithm (Table 1) was introduced into our enhanced recovery protocol[15] to diagnose DGE. Our enhanced recovery encourages all patients to mobilize on day 1, with the allowance of oral clear fluids up to 100 mL/hour. The NG tube is kept on free drainage until day 3, whereby a spigot is placed and 4-hourly aspirations are performed from then on. DGE was then diagnosed if the patient did not meet the 'NG tube' removal criteria on day 5 (Table 1). These criteria were retrospectively applied by review of case notes, fluid balance charts, and chest X-rays by two independent reviewers. Our standard practice was to commence domperidone in patients with possible DGE on day 4. If pyloric dilatation was required to treat delayed gastric emptying, a 30 mm balloon (Rigiflex) was used as we have previously not noticed any benefit with a 20-mm balloon. Secondary outcomes include complication rate, classified using the Accordion score (Table 2).[18]

Group comparison analyses were performed using the Chi squared test, the Fisher's exact test, and the Mann–Whitney U test. Nonparametric data are presented as median with range. A p value of <0.05 was considered statistically significant.

RESULTS

Out of 433 patients underwent an ILGO between 1st December 2011 and 30th June 2017. One hundred forty-three did not undergo enhanced recovery, 22 patients did not have semi-mechanical anastomosis, and 40 had pyloroplasties (all prior 2nd April 2016). Therefore, 228 patients were included in this study of which 52 patients were female (22.8%) and the median age was 69 (range: 39–85) years. All demographics and pathology results segregated

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Table 1 Enhanced recovery protocol for oesophagectomy patients and algorithm for delayed gastric emptying diagnosis

	Day of operation (Day 0)	First day after operation (Day 1)	Second day after operation (Day 2)	Third day after operation (Day 3)	Fourth day after operation (Day 4)	Fifth day after operation (Day 6)	Sixth day after operation (Day 6-discharge)
Monitoring	Hourly obs, Heart monitor attached, Humidifed O_2 via mask, TED stockings in situ	2-4 hourly obs, Hourly urine output, TED removed and legs checked	4–6 hourly obs			Stop O_2	6 hourly obs
Pain control	PCA and local anaesthetic infusion IV paracetamol	Diclofenac PR if required and eGFR normal				Stop PCA and local anaesthetic infusion, switch to oral analgesia	
Exercise	Supported to lie upright in bed; Sit out in chair; Leg movements in bed; Breathing exercises using incentive spirometer	Sit out in chair. Support patient to mobilise 4 times/day. Other exercise as per day 0					
NG tube	In place			Spigot with 4-6 hourly aspiration	Consider removal if: 1. oral intake > 1 L 2. Oral intake and NG output difference > 50% 3. conduit < 50% on chest X-ray Else 8 hourly aspiration	As per day 4; else DGE present. Book pyloric dilatation from day 7 onwards	As per day 4 and 5
Chest drains	In place				Consider removal of 1	Consider removing others	
Urinary catheter	In place					Consider removal	
Central line	In place					Consider removal	
IV fluids	6 hourly liter bags				Consider reducing rate	Consider stopping	
Eating and drinking	Sips of water ≤ 100 mL/hour—consider supplements (Fortips compact protein)			Free fluids		Pureed food (half portions)	
Wound care		Change drain dressings and check surgical wound if necessary				Leave surgical wound undressed if dry and healing well	
Investigations	Chest X-ray in recovery	Chest X-ray FBC, U&E, CRP, Mg^{2+}	FBC, U&E, CRP	Chest X-ray FBC, U&E, CRP	FBC, U&E, CRP	Chest X-ray FBC, U&E, CRP	FBC, U&E, CRP

NG, nasogastric.

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Table 2 Expanded accordion classification for complications

Accordion score	Description
1	Mild complications: use of intravenous infusion for simple medication (anti-emetics, antipyretics, analgesia, or electrolytes), urinary catheter, nasogastric tubes and wound infections
2	Moderate complications: other medication use such as antibiotics, blood transfusion and total parenteral nutrition
3	Severe: management with surgical or endoscopic procedures without use of GA
4	Severe: management with surgical or endoscopic procedures requiring GA or patient developed single organ failure
5	Severe: complications resulting in multiorgan failure
6	Death

GA, general anaesthetic.

Table 3 Patient demographics, treatment and pathology results in each group

	BOTOX, *n*	NONE, *n*	*p*
Demographics			
Gender			0.326
Female	13	39	
Male	52	124	
Age, years (range)	69 (42–85)	69 (39–85)	0.956
Preoperative treatment			0.003
Neoadjuvant Chemotherapy	29	93	
Chemoradiotherapy	14	10	
Straight to surgery	22	60	
Pathology status			
Tumour type			0.287
Adenocarcinoma	49	135	
Squamous	13	23	
Adenosquamous	1	4	
Other epithelial	1	0	
High grade dysplasia	1	1	
Pathology status T			0.488
pT0	9	9	
pTis	0	2	
pT1a	3	9	
pT1b	8	25	
pT2	7	28	
pT3	34	79	
pT4a	4	10	
pT4b	0	1	
Pathology status: N			0.055
pN0	33	70	
pN1	7	45	
pN2	15	28	
pN3	10	20	
Pathology status Margins			0.512
R0	45	123	
R1[†]	20	39	
R2	0	1	

Note: All patients had M0 status.
[†]Circumferential margin positive: 50 (84.7%); distal and circumferential margin positive: 4 (6.8%); distal margin positive: 3 (5.1%); proximal margin positive: 2 (3.4%).

into each intervention type are shown in Table 3. One hundred twenty-four (54.4%) operations were performed laparoscopically, 11 of which (4.8%) were converted to open procedures, and 104 (45.6%) were open operations (Table 4).

Table 4 Operative technique volume for BOTOX versus NONE groups

Operative technique	BOTOX, *n*	NONE, *n*	*p*
Laparoscopic abdomen	36	77	0.539
Open abdomen	26	78	
Laparoscopic converted to open	3	8	

Between 5th April 2016 and 30th June 2017, 65 of the 228 (28.5%) patients underwent intraoperative pyloric botulinum toxin injection (performed by all the surgeons whose patients underwent enhanced recovery). Overall, DGE occurred in 40 (17.5%) patients. A total of 11 of 65 (16.9%) in BOTOX compared to 29 of 163 (17.8%) in NONE had DGE, $P = 0.876$. Medical management (Accordion score 1 and 2) was required in 14 of 228 (6.1%) cases (prokinetics, intravenous fluids, and prolonged nasogastric tube usage): 3 (4.6%) in BOTOX and 11 (6.7%) in NONE. Pyloric dilatation (Accordion score ≥ 3) was required in 26 of 228 (11.4%): 8 of 65 (12.3%) in the BOTOX and 18 of 163 (11.0%) in NONE. There was no significant difference between groups and requirement for intervention, $P = 0.881$. Overall median LOS was 10 (6.0–75.0) days: 9 (7.0–75.0) in BOTOX and 10 (6.0–70.0) in NONE, $P = 0.516$.

Comparison of DGE versus non-DGE patients showed a median LOS of 14 (7–75) versus 9 (6–57) days ($P < 0.0001$), pneumonia in 30.0% versus 27.7% ($P = 0.478$) and anastomotic leak rate of 10.0% versus 2.1%, $P = 0.014$. Overall leak rate was 3.5%.

The overall incidence of complications was 67.1% (includes all Accordion score ≤ 2 complications). There were 43 of 65 (66.2%) in BOTOX and 110 of 163 (67.5%) in NONE, $P = 0.482$. In-hospital mortality was 1 (0.44%), 30-day mortality was 2 (0.88%) and there were no 30-day readmissions. The 90-day mortality was 5 (2.2%).

DISCUSSION

The true prevalence of DGE in the early postoperative and the late follow-up stage is not known. Our study showed that using our clinical definition, DGE occurs in 17.5% of patients. However, the variation in incidence in the current literature is vast.[2] This problem has been highlighted in a meta-analysis on DGE in 2002, in which the authors also showed that the lack of a standard definition for DGE results in difficulty in comparing results from different studies.[9] Similar difficulties can be seen with measuring quality of life outcomes concerning DGE. Deldycke *et al.* showed an incidence of 37% for DGE, with difficulties in establishing predictors or prevalence for DGE.[6] There is no doubt that the heterogeneity of the patient groups due to subjective definition plays a role in the variability of DGE rates.

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In the past, the obligatory pyloric drainage procedure after a vagotomy for peptic ulcer disease treatment is thought to prevent DGE due to pyloric dysfunction from vagal nerve disruption. Since the vagus nerve is also sacrificed in an ILGO, pyloric drainage has also commonly been performed. In 2002, Urschel *et al*. examined nine randomized controlled trials with a cumulative total of 553 patients and found that pyloric drainage procedures reduced DGE relative risk by 0.18 (95% CI of 0.03, 0.97, and $P = 0.046$).[9] However, more recent systematic reviews and meta-analysis comparing various methods of preventing delayed gastric emptying after an ILGO showed no advantage of pyloric drainage in terms of gastric emptying.[2,4] Subsequently, Gourcerol *et al*. assessed gastroparetic patients against postesophagectomy patients and healthy controls and found that DGE is related to reduced pyloric compliance and not pyloric resting pressure.[19] The treatment of choice suggested by the authors was pyloric balloon dilatation. Additionally, a study of 436 patients undergoing esophagectomy with or without pyloric drainage showed that pyloric drainage actually increases DGE (Pyloric drainage vs. no pyloric drainage: 28% vs. 18%, $P = 0.01$) and pyloric balloon dilatation was required in each group with a total success rate of 95%.[3] However, performing the intraoperative balloon dilatation on all ILGO patients may not be appropriate based on the risk of the procedure and number needed to treat. A better approach would be more precise detection of DGE and only treating those affected.

A more recent technique in managing DGE is the use of pyloric botulinum toxin injection. Fuchs *et al*. showed that intraoperative pyloric botulinum toxin injections for total oesophagectomies may reduce DGE from a 30% incidence rate to 0%.[7] Similar dramatic response rates were also found in a study conducted by Cerfolio *et al*.[10] However, similar to other pyloric interventions, results of more recent systematic review and meta-analysis do not support the effectiveness of pyloric botulinum toxin injections.[4,5] These findings suggest that pyloric drainage procedures, including botulinum toxin, do not reduce the incidence of DGE, while balloon dilatation postoperative is more effective. Those findings highlight the need to further elucidate the exact pathophysiology of DGE after an ILGO through other avenues other than mechanical issues of the pylorus such as electrophysiology[20] or gut hormone changes after an ILGO.[21,22]

Anastomotic leak after an ILGO is not uncommon with a risk of 3.5% to 26%.[23] It has been suggested that leaks may occur more frequently in DGE due to gastric stasis and anastomotic stress.[4] Our results show a significant increase in anastomotic leak in those patients with DGE. Additionally, 3 of 4 DGE patients with anastomotic leaks had their NG tube removed early according to our retrospectively applied algorithm. All other leak patients had their NG in-situ up to the time of anastomotic leak diagnosis. It is possible that leaving the NG in-situ may have prevented the leak.

Limitations of the study include the fact that it was not randomized and used retrospectively applied criteria for defining DGE. However, the rate of DGE was so similar in the two groups, that a randomized controlled trial would require a very large sample size. Our two study groups show similar demographics apart from a significant increase in chemoradiotherapy. This is due to the effect of the 'ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study' (CROSS) in 2015.[24] The differences are not deemed significant because there is no known association between neoadjuvant chemoradiotherapy and DGE.[3]

CONCLUSION

In this study, the results show that intraoperative pyloric botulinum toxin injections are ineffective in preventing DGE (BOTOX vs. NONE: 16.9% vs. 17.8%, $P = 0.876$) or reducing postoperative complications. DGE is relatively common (17.5%), with more than half of affected patients requiring pyloric balloon dilatation, and it results in prolonged LOS (increase from 9 to 14 days). DGE is associated with anastomotic leak with an increase is risk from 2.1% to 10.0% in DGE patients. Better understanding of DGE will guide assessment, investigation, and management of the condition.

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2. Gut hormone profile after an Ivor Lewis gastro-oesophagectomy and its relationship to delayed gastric emptying

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Original Article

Gut hormones profile after an Ivor Lewis gastro-esophagectomy and its relationship to delayed gastric emptying

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SUMMARY. **Delayed gastric emptying (DGE) is common after an Ivor Lewis gastro-esophagectomy (ILGO). The risk of a dilated conduit is the much-feared anastomotic leak. Therefore, prompt management of DGE is required. However, the pathophysiology of DGE is unclear. We proposed that post-ILGO patients with/without DGE have different gut hormone profiles (GHP). Consecutive patients undergoing an ILGO from 1 December 2017 to 31 November 2019 were recruited. Blood sampling was conducted on either day 4, 5, or 6 with baseline sample taken prior to a 193-kcal meal and after every 30 minutes for 2 hours. If patients received pyloric dilatation, a repeat profile was performed post-dilatation and were designated as had DGE. Analyses were conducted on the following groups: patient without dilatation (non-dilated) versus dilatation (dilated); and pre-dilatation versus post-dilatation. Gut hormone profiles analyzed were glucagon-like peptide-1 (GLP-1) and peptide tyrosine tyrosine (PYY) using radioimmunoassay. Of 65 patients, 24 (36.9%) had dilatation and 41 (63.1%) did not. For the non-dilated and dilated groups, there were no differences in day 4, 5, or 6 GLP-1 ($P = 0.499$) (95% confidence interval for non-dilated [2822.64, 4416.40] and dilated [2519.91, 3162.32]). However, PYY levels were raised in the non-dilated group ($P = 0.021$) (95% confidence interval for non-dilated [1620.38, 3005.75] and dilated [821.53, 1606.18]). Additionally, after pyloric dilatation, paired analysis showed no differences in GLP-1, but PYY levels were different at all time points and had an exaggerated post-prandial response. We conclude that DGE is associated with an obtunded PYY response. However, the exact nature of the association is not yet established.**

KEY WORDS: **gastric emptying, Ivor Lewis gastro-esophagectomy, esophageal and gastric surgery, esophageal cancer.**

INTRODUCTION

The incidence of delayed gastric emptying (DGE) is between 10 and 50%[1–3] after an Ivor Lewis gastro-esophagectomy (ILGO). Patients with post-operative DGE appear to have an increased risk of an anastomotic leak.[4] Therefore, understanding the pathophysiology of DGE after an ILGO is important.

Currently, some surgeons advocate a pyloric drainage procedure, mechanically or chemically, to prevent DGE.[5–8] The fundamental rationale for pyloric intervention was that the vagotomized stomach would have an increased pyloric tone post-operatively, and hence, predisposing patients to DGE. However, there is inconsistency in the efficacy of pyloric drainage procedures in preventing DGE,[1–4,9] placing doubt in the etiology of DGE.

The pathophysiology of DGE after an ILGO is complex and likely to be multifactorial. Potential mechanisms may include denervation, external influences from the central nervous system, and hormonal and myogenic changes.[10] An area that is not well understood is the association between gut hormone profile (GHP) changes and the development of DGE. It has been established that gut hormones, such as glucagon-like peptide-1 (GLP-1) and peptide tyrosine

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tyrosine (PYY), are increased after an ILGO and are associated with gastrointestinal symptoms, such as early satiety, gastrointestinal pain or discomfort, altered taste, and diarrhea.[11,12] Briefly, GLP-1 is an incretin that is secreted by cells in the intestine, which, in normal physiology, also increases gastric emptying time, promotes satiety, and results in weight loss.[13–15] PYY reduces gastric secretion and is also secreted in the intestine with the concentration of the hormone increasing toward the distal intestine.[16–18] It was then concluded in a recent study that GLP-1 was not associated with any changes to conduit emptying or intestinal transit times.[19] However, all patients in that study had undergone a pyloroplasty peri-operatively. Hence, further characterization of GHP in patients without pyloroplasty is required.

We proposed that the gut hormone response is different in patients who require pyloric dilatation compared to those that do not. The results will allow better understanding of DGE pathophysiology.

METHODS

Consecutive patients undergoing an ILGO for esophageal cancer between 1 December 2017 and 31 November 2019 were recruited at a single high-volume tertiary esophago-gastric center. All patients with operable esophageal cancer who were physiologically fit for surgery were included. Patients were excluded if they refused surgery, were found to have unresectable cancer during surgery, or refused to participate in the study. Patients were also excluded if they developed complications that may cause symptoms of DGE (paraconduit hernia) during their in-patient stay. Patient demographics and data included were age, gender, body mass index (BMI), American Society of Anaesthesiology (ASA) grade, smoking status, diabetes status, conduit size (width and length), and DGE status. DGE was diagnosed using an algorithm based on chest X-rays and/or NG input/output volumes—measured from day 4 onward, after initiating the patient onto free fluids and with the spigotted NG aspirated every 4 hours.[3] From the day of the operation, patients were allowed up to 100 mL of water per hour and free fluids from day 3 with the aim for pureed foods at day 5.[3] The patients with DGE were designated as 'dilated' and those with no DGE were designated as 'non-dilated'. The designation was chosen based on the requirement for balloon dilatation. For patients treated with pyloric dilatation, further analyses as paired groups: 'pre-dilatation' and 'post-dilatation' based on their intervention timing were conducted. All patients were followed-up for 6 weeks to review for DGE signs and symptoms (DES). DES included nausea, vomiting, early satiety, dysphagia, post-prandial abdominal pain, and radiological evidence of a distended gastric conduit.

All recruited patients had GHPs measured between day 4 and 6 post-operatively at 08:00 h. They were fasted 6 hours prior to and for the entire period of the test. A 100-mL semisolid ice-cream test meal with 193 kcal was given after an initial baseline blood sample test taken in an ethylenediaminetetraacetic acid tube. The ice cream used was from a locally source company and had 17 g carbohydrate, 12 g fat, and 3 g protein. Repeated sampling was conducted for every 30 minutes up to 2 hours. Each sample was immediately spun at 1500 rpm for 10 minutes at 4°C. Plasma was extracted and stored at −80°C.

Radioimmunoassay was used in the analysis for both total GLP-1 and PYY.[14,16] Both GLP-1 and PYY analyses were prepared using chloramine T method and were measured using antibodies raised in gut hormone-immunized rabbits.[14,16] Endoscopic pyloric balloon (30-mm Rigiflex™ balloon from Boston Scientific®) was used for pyloric dilatation of patients deemed to have DGE. This intervention was only performed from day 7 onward. All patients treated with pyloric dilatation underwent the GHP test again, as described above, on the following day with the same fasting and testing regimen.[3]

Statistical analyses were performed using IBM®'s SPSS® Statistics software version 25 (https://www.ibm.com/analytics/spss-statistics-software). Graphs were drawn using GraphPad Prism™ version 9 (https://www.graphpad.com). Sample size was determined using a DGE incidence of 17.5%[3] and an estimated reduction of DGE to 0% post-intervention,[20] power of 80%, $P = 0.05$, and an enrolment ratio of 3:1 (due to feasibility of recruiting adequate numbers for the intervention in a 2-year period). Hence, the required sample size for the DGE group was 20 patients.

Statistical analysis of nominal data was performed using the χ^2 square test and Fisher's exact test. All continuous data were non-parametrically distributed. Therefore, univariate analysis between groups and time points were analyzed using the Mann–Whitney U test and the Wilcoxon signed-rank test. The trapezoid rule was used to calculate the area under the curve (AUC) for GHP. All data were presented as median, range, and/or 95% confidence interval (95% CI). A P-value of <0.05 was deemed to be statistically significant.

The London Bromley Research Ethics Committee approved the study (REC 17/LO/1759), which was conducted in accordance with the principles of the Declaration of Helsinki with written informed consent provided by all patients.

RESULTS

A total of 65 patients were eligible and were included during the 24-month recruitment period. The Consolidated Standards of Reporting Trials flow diagram,

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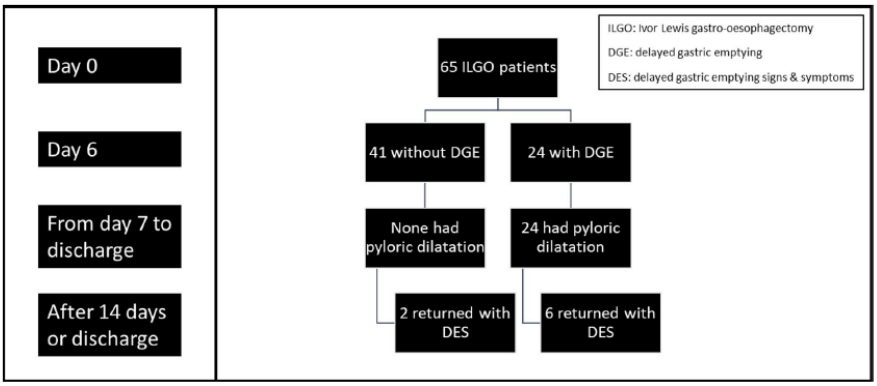

Fig. 1 Flow chart of patient progress through the study.

Table 1 Characteristics of 'non-dilated' and 'dilated' patients

	Non-dilated patients, $n = 41$	Dilated patients, $n = 24$	P-value
Age	73.10 (44–86)	70.23 (50–81)	0.187
Gender			0.015
Female	6	10	
Male	35	14	
BMI	26.00 (19.00–36.70)	26.00 (19.00–31.50)	0.663
ASA grade			0.088
2	26	20	
3	15	4	
Smoking			0.732
No	12	9	
Ex-smoker	26	14	
Yes	3	1	
Diabetes			0.7331
No	36	19	
Yes	6	4	
Conduit width	5 (4–20)	5 (4–15)	0.563
Conduit length	15 (4–23)	14 (5–24)	0.082

P-value < 0.05 was deemed as statistically significant. Parametric data were described as median (range).

as shown in the supplemental data, it described the patient recruitment phases and progress for the study. Figure 1 shows the flow chart for patient progress through the study.

Patient demographics and characteristics are shown in Table 1. There were no differences between the two groups apart from gender. Overall, 24 (36.9%) patients had dilatation and 41 (63.1%) patients did not have dilatation. There were 16 (24.6%) female patients and 49 (75.4%) male patients. The median age of all patients was 70 (43–86) years. The overall median BMI was 26.0 kg/m^2 (19.0–36.7).

Analyses of GHP in patients were grouped as dilated and non-dilated, as shown in Figure 2. For PYY, the AUC for the test period was increased in non-dilated patients ($P = 0.021$) (95% CI for non-dilated [1620.38, 3005.75] relative to dilated [821.53, 1606.18]) (Fig. 3A). For PYY plasma levels, there were differences between the two groups at baseline (non-dilated: 9.50 ρmol/L [95% CI: 5.00, 14.75 ρmol/L]; dilated: 6.00 ρmol/L, [3.00, 8.50 ρmol/L]) ($P = 0.030$); and also, at 60 minutes (non-dilated: 13.50 ρmol/L 8.00, 24.75 ρmol/L; dilated: 7.00 ρmol/L, 4.00, 14.00 ρmol/L) ($P = 0.003$) (Fig. 2A). There were no differences in AUC for GLP-1 for the test duration between the two groups ($P = 0.499$) (95% CI for non-dilated [2822.64, 4416.40 ρmol/L] relative to dilated [2519.91, 3162.32 ρmol/L]) (Fig. 3B). Additionally, there were no differences in the GLP-1 plasma levels between DGE and non-DGE patients for each sampling time point.

For paired analysis of patients who had undergone pyloric dilatation, the differences between the AUC of PYY for the 2-hour period between the groups was significant ($P = 0.000$), as shown in Figure 4A, whereby the post-dilatation group had higher levels. Paired analyses of the PYY levels were different for all time periods (Baseline $P = 0.001$, 30-minute $P = 0.001$,

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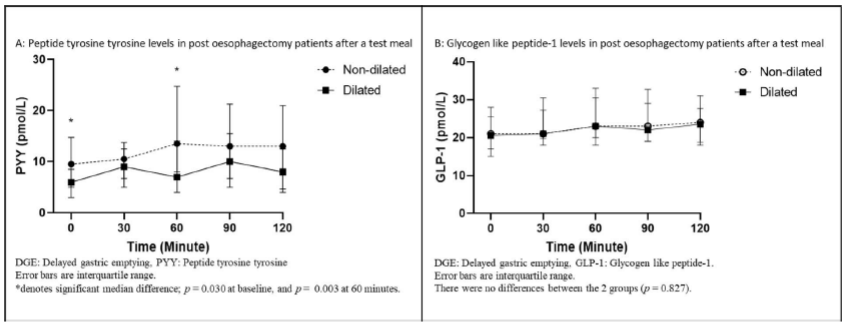

Fig. 2 GHP in 'dilated' and 'non-dilated' groups before and after a test meal.

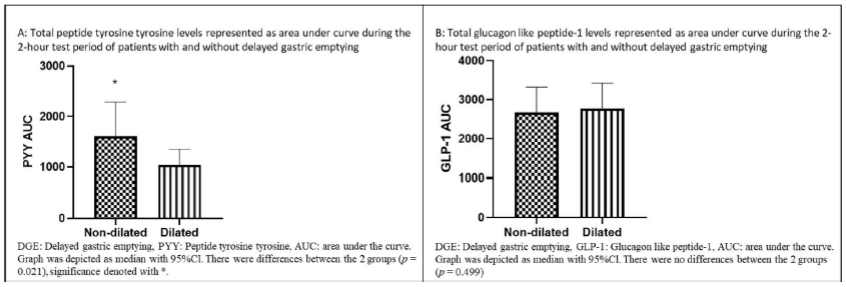

Fig. 3 AUC of GHP in 'dilated' and 'non-dilated' groups before and after a test meal.

60-minute $P = 0.002$, 90-minute $P = 0.000$, and 120-minute $P = 0.001$), as shown in Figure 5A, with the post-dilatation group having had higher levels. An exaggerated peaked response to a test meal can be seen in the post-dilatation group and that response was absent in the pre-dilatation group. Median peaked PYY level was 10 ρmol/L (2.00–36.00 ρmol/L) at 90 minutes for the pre-dilatation group. For the post-dilatation group, median peak level was 34.00 ρmol/L (1.00–165.00 ρmol/L) and it occurred at 30 minutes.

The AUC of GLP-1 showed no differences for the test period (Fig. 4B). The AUC during the test period for GLP-1 was not significant ($P = 0.193$), as shown in Figure 5B. Median peak GLP-1 level occurred at 120 minutes in pre-dilatation patients and was 23.50 ρmol/L (15.00–43.00 ρmol/L), while the median peak level for the post-dilatation group of 29.00 ρmol/L (10.00–98.00 ρmol/L) occurred at 60 minutes.

Overall, all readmissions of patients with DES occurred after 6 weeks. There were eight DES patients. Out of those patients, four (50%) had an anatomical cause (three paraconduit hernia and one 'folded' conduit) and four had true DGE. Of the four with anatomical issues, three had DGE as an in-patient and had previously undergone pyloric dilatation. Additionally, of the other four with true DGE, three previously had pyloric dilatation as an in-patient.

From a different perspective and referring to Figure 1, it can be noted that 30% (6/20) who had in-patient pyloric dilatation returned with DES. There were three patients with anatomical issues, while the other three had true DGE in that DES group of patients. For the two DES patients who did not have an in-patient dilatation, one had an anatomical cause while the other had true DGE (Fig. 1). The anatomical cause for that one patient in that non-dilated DES group was a folded conduit at 3 months (Fig. 1).

DISCUSSION

The results of this study revealed novel information about PYY levels in esophagectomy patients. After an ILGO, the GHP of patients who received pyloric dilatation were different to those that did not have any pyloric intervention, particularly PYY levels. Raised PYY levels in patients with an unaltered gastrointestinal tract occurs secondary to the presence of unim-

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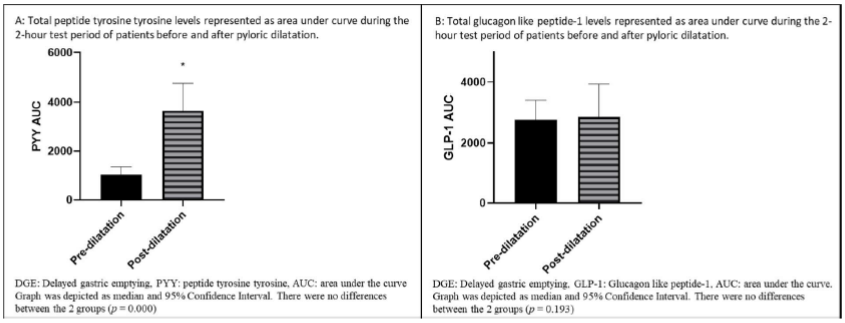

Fig. 4 GHP represented as AUC during the 2-hour test period of patients before and after dilatation.

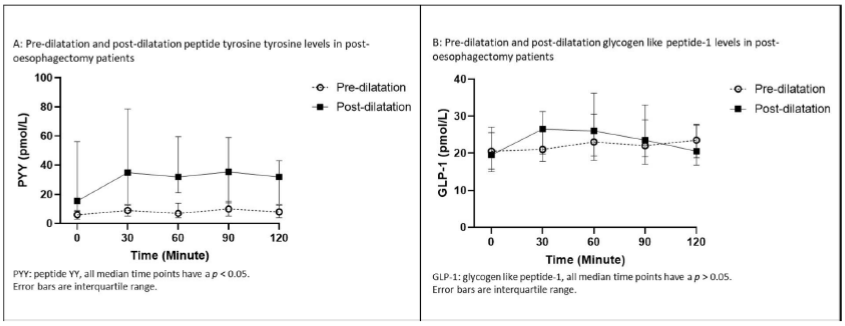

Fig. 5 GHP in 'pre-dilatation' and 'post-dilatation' groups before and after a test meal.

paired movement of nutrients into the small bowel.[16] Therefore, the initial conjecture would be to assume that the changes to PYY levels in DGE patients were due to the reduced movement of chyme into the small bowel. Results from this study appeared to show that interventions on the pylorus after an ILGO altered the GHP of patients. For patients who received pyloric dilatation, PYY levels were dampened before dilatation but appeared to be restored after balloon dilatation of the pylorus. Analysis from this study also showed that the differences in PYY levels between non-dilated and dilated patient were also prevalent on AUC analysis. These findings further substantiate the fact that the reduction in the rate of flow of nutrients into the small bowel resulted in attenuated PYY levels. However, if the PYY profile was simply due to the restoration of food presence into the small bowel, then GLP-1 profile should have responded similarly too. Additionally, baseline PYY levels were significantly raised post-dilatation even in the absence of food stimuli. The implications of the differences in baseline levels and GHP profile remain unclear.

The analysis of GHP in ILGO patients revealed no post-prandial changes in GLP-1 levels. The subgroup AUC analysis of GLP-1 patients showed a slight increase post-dilatation, but the results were not significant. Those GLP-1 findings were different compared to findings by Elliott *et al*.[12] However, compared to the patient group by Elliott *et al*., none of our patients received a pyloroplasty during their ILGO, there was different meal stimulus, and GHP time point measurements were different. Those factors could be the possible explanation for the difference in GHP results. Another possible explanation for the GLP-1 result in this study can be attributable to the fact that changes in GLP-1 levels are smaller compared to PYY and thus, a larger sample size may be required. Other possible reasons for differences in GHP results may be due to sampling variations and/or difference in radioimmunoassay used.

Current literature suggests that GLP-1 may help regulate gut function in the post-ILGO setting,[21,22] but the exaggerated post-prandial post-operative GLP-1 level was not associated with the changes in

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gastric emptying times in ILGO patients, as proposed by Murphy *et al*.[19] Those findings contradict a review on the physiological effects of GLP-1 on gastric emptying in healthy individuals by Baggio *et al*.[13] Therefore, it remains uncertain whether modulation of gastric function can be attributed to altered GLP-1 levels after an ILGO. With current evidence for GHP, it can be postulated that DGE after an ILGO may be purely a mechanical issue, and manipulation of gut hormones will not resolve the issue. Additionally, a standardized method of pyloric intervention for DGE in ILGO is required and should be the focus of future research.

With regard to patients who returned with DES, they can be classed as having late DGE. The diagnostic criteria and symptom grading has been determined by a Delphi consensus,[23] but the underlying cause is still poorly understood and studied. Of the patients who returned with DES in this study, 50% had an anatomical issue to explain their symptoms, and surgical intervention could be employed to fix the mechanical problem. However, the exact cause of late DGE in the other half of patients had not been determined. Therefore, it is uncertain regarding the long-term outcomes of surgical interventions, such as pyloric interventions, for these group of patients.

One of the limitations of this study was the possibility of an inadequate sample size resulting in a non-significant finding in the GLP-1 profile as described above. However, the patient sample from this study was substantially higher than other studies that assessed GHP in esophagectomy patients.[11,12,19,21] Second, no preoperative GHP baseline test was performed. We did not design this study to include preoperative testing as it was not pragmatically and logistically possible to perform testing in our cohort of patients, as our unit covered a large geographical area. Therefore, preoperative tests for a large number of patients were impractical. Additionally, we decided that an additional preoperative test would have added additional/unnecessary burden and stress to those patients. Another limitation was this study only showed an association of PYY response in DGE, but no conclusion of causation or mechanism can be deduced. Again, further research into the mechanism of DGE is required to show causality. Additionally, we cannot yet explain the underlying reason for a preponderance for dilatation in female patients. Finally, for the analysis of the pre- and post-dilatation groups, there was no control group tested at the same time as the post-dilatation group. Therefore, the possibility of an exaggerated gut hormone response due to a longer fasting time (continual fasting for pyloric dilatation and then fasting for GHP test the following day) in the post-dilatation group could have occurred. However, such phenomenon should not be isolated to PYY only and should also be seen with GLP-1 too.

CONCLUSION

This study shows that patients who develop DGE have an associated obtunded post-prandial PYY response in the post-operative period. The PYY response appeared to be restored after pyloric dilatation. Unexpectedly, GLP-1 levels remained unchanged after pyloric disruption. Further comprehension of the mechanism of action of gut hormones on gastric function is required to complete the knowledge regarding DGE.

SUPPLEMENTARY DATA

Supplementary data mentioned in the text are available to subscribers in *DOTESO* online.

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APPENDICES

Appendix I: Patient Information Sheet

PIS, Version 1.4, 8th November 2017

Plymouth Hospitals NHS
NHS Trust

Plymouth Oesophago-Gastric Cancer Centre
Derriford Hospital
Derriford Road
Plymouth PL6 8DH
Tel: 01752432070
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Information Sheet for Patient Research Participants (version 1.4,8th November 2017)
IRAS ID: 228439

You are being provided with a copy of this Information Sheet to understand the research study conducted by the Plymouth Oesophago-Gastric Cancer Centre as part of a Doctor in Medicine postgraduate research project with the University of Plymouth. You should receive this information sheet more than 7 days prior to your surgery and 4 days prior to your pre-operative assessment.

Should you decide to participate, you will be given a signed copy of your consent form.

Title: Delayed gastric emptying after Ivor Lewis gastro-oesophagectomy.

Chief Investigator: Mr Ji Chung Tham
Co-Investigators: Mr Grant Sanders, Mr Tim Wheatley, Dr Stephen Lewis

Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If you do decide to take part, please let us know beforehand if you have been involved in any other study during the last year. You are free to withdraw at any time without explanation. Thank you for reading this information sheet.

What is the purpose of the study?
The Ivor Lewis gastro-oesophagectomy is a complex operation that is performed to treat cancer of the oesophagus (food pipe) whereby most of the oesophagus and upper stomach are removed and the remaining stomach is brought into the chest and joined to the remaining oesophagus. In order to reduce the burden of complications of the procedure, research has been conducted in search of methods to improve the procedure and post-operative outcome. Delayed gastric emptying (how quickly food empties out of your stomach into your small bowel) is a common problem after this operation (20% of patients). The situation can lead to a feeling of being full up, loss of appetite and nausea. Rarely in severe cases, patients may vomit or aspirate food causing a chest infection or develop a leak from the operative joint. It also prolongs hospital stay by an average of 5 days. Treatment currently is uncertain, as is scale of problem (how common it is) and there is no standard definition for delayed gastric

emptying (there is no agreed standard way to describe slow emptying of food from the stomach into the small bowel by experts).

In order to investigate the problem, the study will involve 3 additional tests which are a breath test, additional test performed on your blood samples and completion of an abbreviated quality of life questionnaire (8 multiple choice questions).

The additional test on your blood samples is to measure your gut hormones and the breath test is to measure your gastric emptying time (the time taken for food to empty from your stomach into your small bowel). Where possible, blood sampling will be taken from a dedicated line or at the same time as your other routine postoperative blood tests. Both test will be performed with ingesting a test meal containing Carbon-13 (a non-radioactive version of Carbon). The questionnaire is to assess your quality of life, in terms of delayed gastric emptying, at different points after the operation.

Why have I been chosen?

We are looking for patients who have been offered the Ivor Lewis gastro-oesophagectomy at the Plymouth Oesophago-Gastric Cancer Centre and have understood the information on this leaflet.

You SHOULD NOT take part in this study if:

1. You do not want to undertake any of the 3 additional tests described above.
2. You do not understand the information on this leaflet and the reason for the tests.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part, you are still free to withdraw at any time without giving a reason. A decision to withdraw at any time or a decision not to take part will not affect the standard of care you receive.

What will happen to me if I take part?

The same as all patients who are having the Ivor Lewis gastro-oesophagectomy, you will receive standard preoperative and postoperative care. The additional tests are as follows:

- Preoperatively, you will be required to complete an 8-questioned questionnaire.

- Postoperatively,
  1. On day 3, additional test will be performed on one routine blood samples taken from you for gut hormone tests.
  2. Between days 4 and 6, you will be given a test meal of ice-cream followed by blood sampling from a line. The sampling will occur every 30 minutes for up to 2 hours. Breath samples will also be taken every 30 minutes but for 4 hours. The breath test assesses the amount of carbon exhaled during each breath.

3. If you develop delayed gastric emptying and require an intervention (balloon dilatation, which is stretching of the outlet of the stomach with a balloon), the tests mention at no. 2 will be repeated.
4. At 4 weeks and 4 months after the operation, we will perform the breath test with a test meal and questionnaire again. If you are selected for further gut hormone tests (only the first 20 with delayed gastric emptying and the first 20 without delayed gastric emptying will be selected), then further blood samples will be taken from you. For the out-patient breath test and gut hormone tests, we will require you to be fasted for 6 hours prior to the test. This time you will be given a sandwich test meal.
5. All information will be kept on NHS computers in locked NHS offices. For traceability, your information will be pseudo-anonymised with a study ID, until completion of the study. All your samples will be anonymised and be sent to external labs for analysis, usually, at the end of the study. No research samples can identify you unless cross referenced with information on our system. Any identification will occur only if a serious clinical reason arose. All information will be stored for 5 years, for NHS auditing, and be destroyed thereafter.
6. Your samples will be stored in NHS laboratories until time for analysis. Analyses will be performed in Plymouth University and Imperial College London. Excess samples, if any, will be stored at secured Plymouth University laboratories and be destroyed at 5 years. Any further analysis maybe performed on those samples in concordance to your consent and study protocol. Other analysis will only be performed with your additional consent.

What are the side effects of taking part?

We do not foresee any severe side effects as a result of the study. Blood test will be taken using a needle or a cannula (plastic tube with a removable needle) and may result in mild discomfort or bruising. The ice-cream test meal contains octanoic acid which is a medium-chain fatty acid found in palm oil, coconut oil or milk in humans and cows. Octanoic acid can cause some side effects of nausea, bloating and diarrhoea. You should not take octanoic acid if you have been diagnosed with medium-chain acyl-CoA dehydrogenase deficiency.

What are the possible benefits for taking part?

There are no benefits to you by taking part. However, results of the study will benefit future patients undergoing the procedure in terms of diagnosis and management of delayed gastric emptying.

What if new information becomes available?

Sometimes during the course of a research study, new information becomes available about the investigations being studied. If this happens, your research doctor will tell you all about it and discuss whether you want to continue in the study. If you decide to continue with the study, you will be asked to sign an updated consent form or withdraw from the study. Your treatment and management will continue as usual.

What happens when the research study stops?
Once the study has finished, the results of the study can be made available to you and/or your GP should you wish. If you have any problems immediately following the study, then you should contact the research team on the numbers provided below. Your anonymised clinical details and samples will be kept for 5 years and be destroyed thereafter. This is for research auditing purposes. Additionally, during that time, if further development in research occurs, your clinical details and samples may be used for analysis in future research.

What if something goes wrong?
In the unlikely event that you are harmed by taking part in this research study, you are covered by Plymouth Hospitals NHS Trust indemnity. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study, then you should immediately inform the Chief Investigator: Mr Ji Tham through the research registrar's office (01752430011) or through the Derriford Hospital Switchboard (01752202082). If you have a medical emergency, please either contact your GP or attend the Accident and Emergency department and quote that you are under this study if the problem is related to the study. The normal National Health Service complaints mechanism (NHS South Devon and Torbay CCG, 01803652578) and Patients Advice and Liaisons Service (PALS at 01752432564) are also available to you. If you are still dissatisfied with the response, you may contact the Research Governance Manager at Plymouth Hospitals NHS Trust (01752431045).

Will my taking part in this study be kept confidential?
All information collected about you during the course of the research will be kept strictly confidential. Your GP will only be informed about your participation with your consent.

What will happen to the results of the research study?
The results are likely to be published in 2 years from the study commencement. Your confidentiality will be ensured at all times and you will not be identified in any publication. At the end of the study, the results of the study can be made available to you and/or your GP should you wish.

Who is organizing and funding the research?
This study is organised by the Plymouth Oesophago-Gastric Cancer Centre and is sponsored by Plymouth Hospitals NHS Trust and funded by Plymouth Hospitals Charitable funds.

Who has reviewed the study?
This study has been reviewed by the London BromleyResearch Ethics Committee.

Contact for further information

If you experience any problems during the study, you may withdraw at any stage. The doctors involved in the study, Mr Tham can be contacted through the research registrar's office at 01752430011.

Appendix II: Consent Form

Consent, Version 1.3, 30th October2017

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CONSENT FORM

IRAS ID: 228439

Chief Investigator: Mr Ji Chung Tham
Co-Investigators: Mr Grant Sanders, Mr Tim Wheatley, Dr Stephen Lewis.

Plymouth Oesophago-Gastric
Cancer Centre
Derriford Hospital
Derriford Road
Plymouth PL6 8DH
Tel: 01752432070

Participant Identification Number for this trial:.....

Title of Project: **Delayed gastric emptying after Ivor Lewis gastro-oesophagectomy**

Name of Researcher: .....

Please initial box

1. I confirm that I have read the information sheet dated 30th October 2017 (version 1.3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Derriford Hospital, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research, I give permission for these individuals to have access to my records. ☐
4. I understand that the information collected about me (clinical data and samples) will be used to support other research in the future, and may be shared anonymously with other researchers. ☐
5. I agree to my General Practitioner being informed of my participation in the study including any necessary exchange of information about me between my GP and the research team. ☐
6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Researcher	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 to be kept in medical notes.

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Appendix III: Enhanced recovery protocol

	Day of operation (Day 0)	1st day after operation (Day 1)	2nd day after operation (Day 2)	3rd day after operation (Day3)	4th day after operation (Day 4)	5th day after operation (Day 6)	6th day after operation (Day 6) - discharge
Monitoring	Hourly obs Heart monitor attached Humidified O_2 via mask TED™ stockings in situ	2 – 4 hourly obs Hourly urine output TED™ removed and legs checked	4 – 6 hourly obs			Stop O_2	6 hourly obs
Pain Control	PCA and local anaesthetic infusion IV paracetamol	Diclofenac PR if required and eGFR normal				Stop PCA and local anaesthetic infusion Switch to oral analgesia	
Exercise	Supported to lie upright in bed Sit out in chair Leg movements in bed Breathing exercises using incentive spirometer	Sit out in chair Support patient to mobilise 4 times/day Other exercise as per day 0					
NG Tube	In place			Spigot with 4 – 6 hourly aspiration	Consider removal if: 1. oral intake >1L 2. Oral intake and NG output difference >50% 3. conduit <50% on chest x-ray Else 8 hourly aspiration	As per day 4; else DGE present. Book pyloric dilatation from day 7 onwards	As per day 4 and 5
Chest Drains	In place				Consider removal of 1	Consider removing others	
Urinary Catheter	In place					Consider removal	
Central Line	In place					Consider removal	
IV Fluids	6 hourly litre bags				Consider reducing rate	Consider stopping	
Eating and Drinking	Sips of water ≤ 100 ml/hour – consider supplements (Fortips Compact Protein)			Free fluids		Pureed food (half portions)	
Wound Care		Change drain dressings and check surgical wound if necessary				Leave surgical wound undressed if dry and healing well	
Investigations	Chest x-ray in recovery	Chest x-ray		Chest x-ray		Chest x-ray	
		FBC, U&E, CRP, Mg^{2+}	FBC, U&E, CRP	FBC, U&E, CRP	FBC, U&E, CRP	FBC, U&E, CRP	FBC, U&E, CRP

Appendix IV: Modified symptomology questionnaire

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Modified Quality of life questionnaire

This questionnaire is for the DGE after Ivor Lewis gastro-oesophagectomy study.

Patient ID: _____

Date: _____

Please circle one option:

Pre-operative	Week 4	Week 16

For each question, please only tick one response.

During the past week:	Not at all	A little	Quite a bit but not troublesome	Quite a bit and troublesome	Very much
1. Have you felt full up too quickly?					
2. Have you had trouble with eating?					
3. Have you had trouble enjoying your meals?					
4. Have you had trouble eating in front of other people?					
5. Have you felt nauseated?					
6. Have you vomited?					
7. Have you had acid indigestion or heartburn?					
8. Have you had pain in your stomach when you eat?					

Thank you for your time and patience.

Glossary of Abbreviations

%C13	Percentage excretion of Carbon-13 against Carbon-12 Carbon Dioxide
^{13}COABT	Carbon-13 Octanoic acid breath test
95%CI	95% Confidence interval
AJCC	American Joint Committee on Cancer
ASA	American Society of Anaesthesiology grade
AUC	Area under the curve
AUGIS	Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
BMI	Body mass index
BSG	British Society of Gastroenterology
C12	Carbon-12 isotope
C13	Carbon-13 isotope
cm	Centimetre
CO_2	Carbon dioxide
CONSORT	Consolidated standards of reporting trials
CROSS	Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study
CRP	C-Reactive protein

CT	Computed tomography
CXR	Chest X-ray
DES	Delayed gastric emptying symptoms
DGE	Delayed gastric emptying
EBUS	Endobronchial ultrasound
ECCG	Esophagectomy Complications Consensus Group
eGFR	Estimated glomerular filtration rate
EMIOTT	European Minimally Invasive Oesophagectomy Think Tank
EMR	Endoscopic mucosal resection
EORTC	European Organisation for Research and Treatment of Cancer
ESD	Endoscopic submucosal dissection
EUS	Endoscopic ultrasound
FBC	Full blood count
GB	Gastric band
GH	Gut hormone
GHP	Gut hormone profile
GIQLI	Gastrointestinal quality of life index
GLP-1	Glucagon-like peptide-1

GOJ	Gastro-oesophageal junction
GOO	Gastric outlet obstruction
GP	General Practitioner
IBM©	International Business Machines Corporation
IGLE	Intra-ganglionic Laminar Endings
ILGO	Ivor Lewis Gastro-oesophagectomy
IV	Intra-venous
JCC	Japanese Joint Committee
LOS	Length of Stay
Mg^{2+}	Magnesium
MIO	Minimally invasive oesophagectomy
NG	Nasogastric tube
NHS	National Health Service
NOGCA	National Oesophago-Gastric Cancer Audit
Obs	Observations
OGD	Oesophagogastroduodenoscopy
p	Probability value
PACS	Picture Archiving and Communication System

PCA	Patient Controlled Analgesia
PET	Positron Emission Tomography
ρmol	picomole
PODRS	Post-Operative DGE-related symptoms
PR	Per Rectal
PYY	Peptide Tyrosine Tyrosine
QALY	Quality-adjusted Life Year
QOL	Quality of Life
QLQ-C30	Quality of Life Questionnaire for Cancer, 30(+3) items
QLQ-OES18	Quality of Life Questionnaire for Oesophageal cancer, 18 items
R&D	Research and development
RCT	Randomised controlled trial
ROC	Receiver Operating Characteristics
ROMIO	Randomised Oesophagectomy: Minimally Invasive or Open Trial
RYGB	Roux-en-y Gastric Bypass
SG	Sleeve Gastrectomy
SPSS	Statistical Package for the Social Sciences
$t_{½}$	Half Emptying Rate

TED	Thrombo Embolus Deterrent
TNM	Tumour Node and Metastasis Classification for solid cancers
U&E	Urea and Electrolytes
UICC	International Union Against Cancer
UK	United Kingdom
VATS	Video-Assisted Thoracoscopy