Official Title: Double-arm, Randomized Study of Botulinum Toxin Injection as a Pyloric Drainage Procedure for Minimally Invasive Esophagectomy (Phase II)

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Roswell Park Cancer Institute

Study Number: **I 283516**

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Sponsor: **Roswell Park Cancer Institute**

Funding: **Roswell Park Alliance Foundation and NCI Grant P30 CA016056**

Confidentiality Statement

SYNOPSIS

Title / Phase	Double-arm, Randomized Study of Botulinum Toxin Injection as a Pyloric Drainage Procedure for Minimally Invasive Esophagectomy (Phase II)
Roswell Park Cancer Institute Study Number	I 283516
Roswell Park Cancer Institute Investigator	Moshim Kukar, MD
Sponsor	Roswell Park Cancer Institute
Funding	Roswell Park Alliance Foundation and NCI Grant P30 CA016056
Study Drug(s)	N/A
Objectives	**Primary:** • Determine if intra-pyloric botulinum toxin injection (Botox©) during a minimally invasive esophagectomy decreases postoperative occurrence of delayed gastric emptying. **Secondary:** • Determine if intra-pyloric botulinum toxin injection during a minimally invasive esophagectomy: o Reduces the number of repeat procedures for delayed gastric emptying within 90 days, o Decreases time to oral intake meeting 100% of nutritional requirements, o Reduces the incidence of pulmonary complications directly related to delayed gastric emptying, o Reduces hospital length of stay related to delayed gastric emptying and, o Increases patient quality of life.
Study Design	Double-arm, randomized, Phase II study
Target Accrual and Study Duration	A maximum of 50 evaluable patients at RPCI will be enrolled. Accrual is expected to take up to 6 years. Study participants will be followed for data collection for 90 days (routine post-esophagectomy follow-up care and surveillance, per standard of care). Data will be collected for 90 days on each patient.
Study Procedures	**Medical History, Pre-Existing Conditions (i**ncluding smoking status and diabetes): Baseline **Disease Evaluation (**Multidisciplinary evaluation and neoadjuvant therapy for esophageal carcinoma): Baseline **Hematology, Chemistry:** Baseline, Postoperative course **Performance Status:** Baseline **Physical Examination (including neurological examination, vital signs, and body weight):** Baseline, Inpatient and Outpatient Postoperative Course **Electrocardiogram, Chest x-ray, and/or Pulmonary Function tests:** At baseline, if clinically indicated.

	Pregnancy test (urine): Baseline **Gastrografin swallow or CT esophagram:** Surgery to Discharge **Nuclear Medicine Emptying Study:** Post Op Visit 2 (+/- 14 days) **Medical and Clinical Evaluation of Delayed Gastric Emptying:** Inpatient and Outpatient Postoperative Course **Clinical Events of Interest and Adverse Events:** During surgical procedure, Inpatient and Outpatient Postoperative Course **Nutrition Evaluation:** At baseline, if indicated and, Inpatient and Outpatient Postoperative Course **EORTC QLQ OES18 Questionnaire**: Outpatient postoperative course
Statistical Analysis	**Sample Size Determination:** The sample size justification is based on the primary analysis. We consider a study design with a total sample of n=50 patients (randomly assigned in a 1:1 fashion to the Botox and non-Botox treatment arms) and an interim analysis at n_1=30. The performance of this study design and decision rules (described in the primary analysis) was assessed via simulation study. **Randomization:** Patients will be randomized in a 1:1 fashion to the Botox and non-Botox treatment arms using a permuted block design. The randomization list will be developed by the Department of Biostatistics and Bioinformatics. **Primary and Secondary Analyses:** *Primary Analysis:* A recent study demonstrated that patients that received Botox had a delayed gastric emptying rate of approximately 30% as compared to a complication rate in historical controls of 70% in patients that did not receive botulinum toxin (Botox) (1). A retrospective review of patients undergoing minimally invasive esophagectomy at Roswell Park Cancer Institute indicates that the rate of postoperative delayed gastric emptying is even lower. Therefore, the primary objective is to determine if intra-pyloric botulinum toxin injection during a minimally invasive esophagectomy decreases postoperative occurrence of delayed gastric emptying. The primary outcome is delayed gastric emptying (assessed radiographically by nuclear medicine emptying study) which is treated as a dichotomous variable. Patients will be stratified by receipt of neoadjuvant chemoradiotherapy, smoking status, and diabetes; and randomized in a 1:1 to the botulinum and non-botulinum treatment arms. The primary objective will be assessed using the intent-to-treat principle and a one-sided Cochran-Mantel-Haenszel (CMH) s test about the following hypotheses: H_0:$\theta \geq 1$, H_A:$\theta < 1$ where θ is the common odds ratio (COR) for the odds of delayed gastric emptying rates for the botulinum versus non-botulinum treatment arms. A one-sided test is performed as the rate of delayed gastric emptying is expected to decrease in the botulinum arm over the non-botulinum arm; that is we expect $\theta < 1$.

The analysis will proceed in two stages using an O'Brien-Fleming alpha spending function. An interim analysis will be conducted after n_1=30 patients have completed treatment and the final analysis will be conducted after n=50 patients have completed treatment. The following decision rules will be utilized at each analysis:

Analysis	Decision Rule
Interim	• If p-value ≤ 0.011396, then reject H_0 and stop due to superiority. • If $\hat{\theta} > 1$, then stop due to inferiority. • Otherwise enroll n_2=20 patients.
Final	• Reject H_0 if p-value ≤ 0.046533

Secondary Analysis: The secondary outcomes include additional postop procedures, clinically assessed delayed gastric emptying (days to resumption of oral feeding, EORTC QLQ-30 QoL scores, and clinical symptoms of regurgitation, vomiting, and aspiration), delayed gastric emptying assessed by the gastrografin swallow exam or CT esophagram, pulmonary complications (aspiration, respiratory failure requiring reintubation, pneumonia within 3 months of surgery), and hospital length of stay. All variables will be reported by treatment arm using the appropriate descriptive statistics and graphical summaries.

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM
INCLUSION CRITERIA

Participant Name: _____

Medical Record No.: _____

Title: Double-arm, Randomized Study of Botulinum Toxin Injection as a Pyloric Drainage Procedure for Minimally Invasive Esophagectomy (Phase II)

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Esophageal carcinoma, undergoing minimally invasive esophagectomy with intrathoracic anastomosis.	
☐	☐	☐	2. Age ≥ 18 years of age.	
☐	☐	☐	3. Have an ECOG Performance Status ≤ 2. Refer to **Appendix A**.	
☐	☐	☐	4. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM
EXCLUSION CRITERIA

Participant Name: _____

Medical Record No.: _____

Title: Double-arm, Randomized Study of Botulinum Toxin Injection as a Pyloric Drainage Procedure for Minimally Invasive Esophagectomy (Phase II)

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Patients who have a history of gastrointestinal dysmotility or functional gastroparesis, including diabetic gastroparesis, central and peripheral nervous system disorders, renal failure, medication side effects, including chronic dependence of promotility agents, anticholinergic antispasmodic agents, or chronic narcotic use over 2 years due to non-cancer causes. Refer to **Appendix B** for a list of pharmacologic agents**.**	
☐	☐	☐	2. Patients who have a history of previous gastric or duodenal surgery.	
☐	☐	☐	3. Patients who have a history of duodenal ulcer or duodenal fibrosis.	
☐	☐	☐	4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	
☐	☐	☐	5. Allergy to botulinum toxin, and or egg	
☐	☐	☐	6. Pregnant or nursing female participants.	
☐	☐	☐	7. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	8. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate for study participation.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**
If "NO", do not enroll participant in study.

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

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IN-TEXT TABLES

APPENDICES

1 BACKGROUND

1.1 Minimally Invasive Esophagectomy for Esophageal Carcinoma

Esophageal carcinoma is the 7th most common cause of death from cancer in men in the United States (U.S.). An estimated 16,910 new cases will be diagnosed in the U.S.in 2016, resulting in 15,690 deaths (2). Multimodality treatment for esophageal carcinoma includes chemotherapy, radiation, and surgery in the form of esophagectomy. During an esophagectomy, a majority of the esophagus is resected, and the stomach is narrowed to form a tube, creating a "gastric conduit" that is then relocated from the abdominal cavity into the thoracic cavity. Because both vagus nerves are resected with the specimen, it is theorized that patients may develop gastric dysmotility and pylorospasm, with resulting delayed gastric emptying or gastric outlet obstruction. These are both major complications, as they may lead to aspiration and pneumonia, inability to tolerate oral intake and maintain adequate nutrition, and the need for additional procedures.

One of the major controversial issues currently is how to prevent delayed gastric emptying. Several methods have been implemented to improve gastric emptying during open esophagectomy, with inconclusive results. In the minimally invasive setting, surgeons are utilizing intra-pyloric botulinum toxin injection to prevent pyloric spasm and thus minimize gastric outlet obstruction. Retrospective studies comparing botulinum toxin to historical controls demonstrate inconclusive results regarding the ability of botulinum toxin to decrease rates of delayed gastric emptying. This study aims to test whether it is necessary to use botulinum toxin as a pyloric drainage procedure during minimally invasive esophagectomy. We hypothesize that it is not effective in preventing delayed gastric emptying, and that performing botulinum injection adds cost and time to an already lengthy procedure, without decreasing the procedure complication rate or benefitting patient outcomes.

Improving gastric emptying is crucial to not only maintaining independent nutrition, but also in preventing devastating pulmonary complications including aspiration and subsequent pneumonia. In the era of open esophagectomy, several types of drainage procedures were employed during esophagectomy in an attempt to prevent gastric outlet obstruction. These include pyloroplasty (full-thickness longitudinal incision closed transversely), pyloromyotomy (incision through muscle only, preserving integrity of mucosal layer), and finger fracture (manual pressure on the pylorus, causing muscle disruption). Other surgeons elected not to perform any type of drainage procedure. Advocates of the "no drainage" procedure believed that surgical manipulation of the pylorus during drainage procedures leads to short-term inflammation and edema, which may *cause* gastric outlet obstruction despite that this procedure is designed to prevent such occurrence. In addition, pyloric drainage procedures may lead to dumping syndrome, bile reflux, or leak at the pyloroplasty site, leading to intra-abdominal or intra-thoracic sepsis and even death (3). Possible long-term side effects include scar or stricture formation. Alternatively, no drainage procedure may cause gastric outlet obstruction, leading to inability to tolerate oral diet, aspiration, and pneumonia. Whether or not to perform a pyloric drainage procedure is controversial.

With newer minimally invasive esophagectomy techniques, many surgeons omitted drainage procedures, as they are technically challenging to perform minimally invasively. Other surgeons use botulinum injection at the pylorus as a minimally invasive pyloric drainage procedure, with

the theory this relaxes the muscle without causing inflammation, edema, or risk of leak. Intraoperative botulism toxin injection is safe and simple to perform, without significantly adding to the total operative time. It does however add significant cost to the procedure, approximately $1,000 per treatment (1). Botulinum toxin injection into the pyloric sphincter has a pharmacologic duration of three to five months (4).

There is much controversy as to the optimal surgical management of the pylorus. A recent review of studies performed on this topic in the past ten years concluded that pyloric drainage procedures were associated with a non-significant trend towards delayed gastric emptying and biliary reflux, while not affecting the incidence of dumping (5). Two other meta-analyses supported pyloric drainage, showing decreased rates of gastric outlet obstruction and improved gastric emptying (6, 7). These meta-analyses reviewed randomized controlled trials published between 1984-2002, prior to minimally invasive technique and botulinum use. Over the past ten years significant changes were made to the way esophagectomies are performed, and these studies do not apply to our patient population today. Major changes in technique include the transition to minimally invasive technique, stapled technique for anastomosis and tissue transection, and tubularization of the stomach conduit as opposed to use of the whole stomach. With minimally invasive techniques, surgical pyloric drainage procedures are difficult to perform, and frequently omitted. When the whole stomach is used as a conduit, the conduit becomes redundant, and such a large reservoir is conducive to gastric stasis. With a narrower conduit, surgeons advocate drainage procedure is unnecessary because the occurrence of redundancy and stasis is lower. Lastly, these studies were published prior to the use of botulinum toxin.

Three retrospective reviews comparing botulinum to pyloric drainage procedures versus no drainage procedure during open esophagectomy have found a significant benefit of botulinum in preventing gastric outlet obstruction, with varying effect on rate of aspiration events and other comorbidities (1, 3, 8). However, a fourth retrospective review of patients undergoing open esophagectomy, patients receiving botulinum injection experienced *higher* rates of gastric outlet obstruction, requiring additional procedures for pyloric dilation compared to patients undergoing pyloromyotomy or pyloroplasty (9). Although these studies were performed using the open esophagectomy technique, they highlight the issues with the data we currently base our practice on. These studies have all been underpowered or flawed, are retrospective in nature, and lack objective criteria in determining requirement for secondary intervention. We are unable to determine if botulinum toxin as a pyloric drainage procedure is a necessary step in an already complex operation. Standardized reporting of postoperative gastric outlet obstruction with delayed gastric emptying and thresholds for intervention are necessary to determine if botulinum toxin as a pyloric drainage procedure is a necessary step in an already complex operation. No prospective randomized study has been published, or to the author's knowledge is in process, to assess the use of intra-pyloric botulinum toxin in the minimally invasive setting as a pyloric drainage procedure.

1.2 Risks and/or Benefits

Risks:

By omitting the pyloric botulinum toxin injection, there is a risk of delayed gastric emptying causing nausea, vomiting, aspiration, pneumonia, prolonged nasogastric decompression, inability

to tolerate oral diet and lengthening hospital stay. Delayed gastric emptying is a known complication after esophagectomy, and a common complication. This complication occurs even with botulinum injection in about 30% of patients (7). One published study concluded that patients receiving botulinum toxin injection experienced higher rates of delayed gastric emptying (9). In most cases of delayed gastric emptying, symptoms may be treated with medications and if severe, by endoscopic procedures, such as botulinum toxin injection or balloon dilation. Therefore, if a patient who did not receive pyloric botulinum toxin injection develops gastric outlet obstruction, he may undergo an endoscopic procedure to alleviate his symptoms. Rarely, severe delayed gastric emptying with complete obstruction may require a return to the operating room.

The drug used in this study is OnabotulinumtoxinA (botulinum toxin type A, Botox©). When injected intramuscularly, botulinum toxin inhibits the release of acetylcholine from nerve endings at neuromuscular junctions in the local muscle (10). Without release of acetylcholine, neurotransmission between peripheral nerve endings and muscle fibers cannot occur, and the muscle becomes weak or paralyzed (10). Botulinum toxin is used for cosmetic procedures, and is also FDA-approved to treat cervical dystonia, strabismus, and primary axillary hyperhidrosis (11). Off-label uses of botulinum toxin in the gastrointestinal tract include achalasia and refractory anal fissure, in addition to pyloric injection during esophagectomy.

Benefits:

We hypothesize that pyloric botulinum toxin injection does not prevent delayed gastric emptying and is an unnecessary portion of the minimally invasive esophagectomy. If it is found that botulinum toxin injection does not lead to lower rates of delayed gastric emptying, then this procedure may be omitted, saving cost and side effects associated with the medication, and potential side effects of employing a pyloric drainage procedure, including pyloric edema, dumping syndrome and bile reflux. Pyloric edema from receiving botulinum toxin injection may actually cause delayed gastric emptying. The current rates of pyloric edema, dumping syndrome, and bile reflux are unclear at this time, and will be directly assessed in this study during the nuclear medicine emptying study.

2 RATIONALE

This study will help clarify if a pyloric drainage procedure is necessary in patients undergoing minimally invasive esophagectomy. Over the past ten years significant changes were made to esophagectomy technique including transition to minimally invasive technique, stapled technique for anastomosis and tissue transection and tubularization of the stomach conduit as opposed to use of whole stomach. With a narrower conduit, a drainage procedure may be unnecessary since the occurrence of redundancy and stasis is lower.

3 OBJECTIVES

3.1 Primary Objective

- Determine if intra-pyloric botulinum toxin injection (Botox©) during a minimally invasive esophagectomy decreases postoperative occurrence of delayed gastric emptying.

3.2 Secondary Objectives

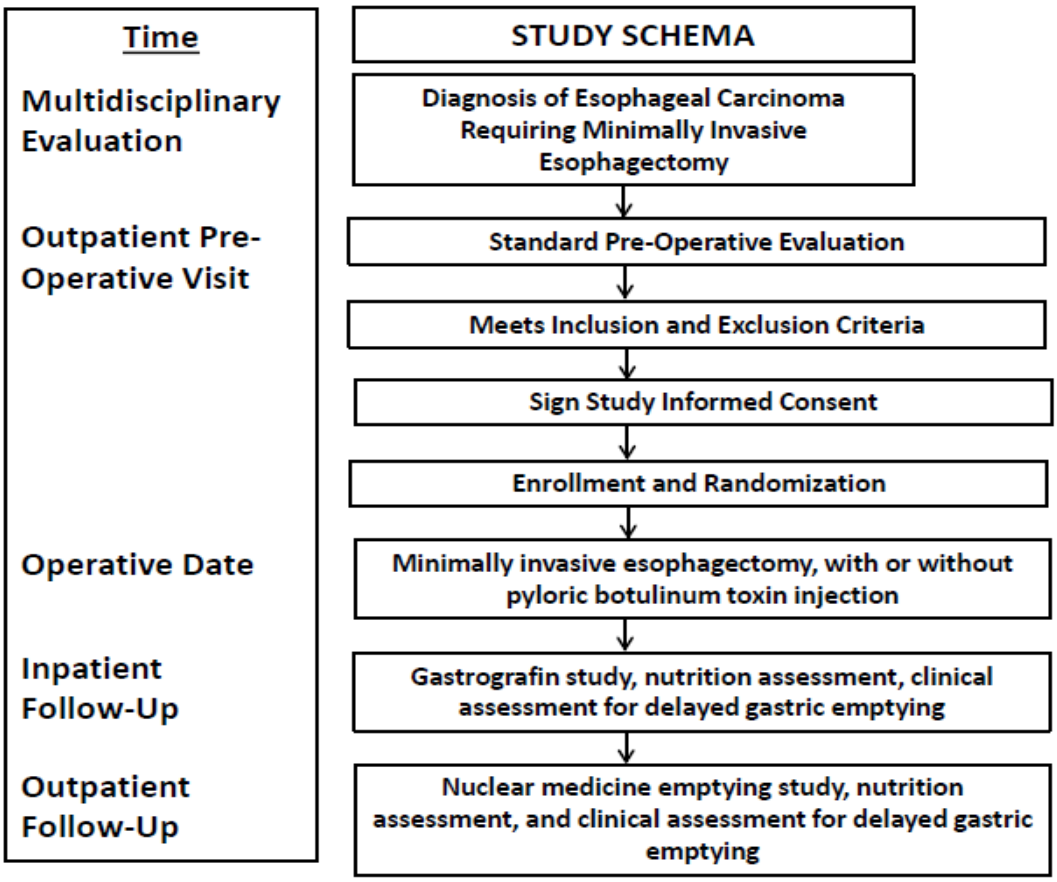
- Determine if intra-pyloric botulinum toxin injection during a minimally invasive esophagectomy:
    - Reduces the number of repeat procedures for delayed gastric emptying within 90 days,
    - Decreases time to oral intake meeting 100% of nutritional requirements,
    - Reduces the incidence of pulmonary complications directly related to delayed gastric emptying,
    - Reduces hospital length of stay related to delayed gastric emptying and,
    - Increases patient quality of life

4 METHODOLOGY

4.1 Study Design

This is a double arm, single-blinded randomized trial evaluating the use of botulinum toxin injection as a pyloric drainage procedure. The study is expected to accrue patients over 4 years. The study schema is depicted below in **Figure 1**.

Figure 1 Study Schema



All patients considered for minimally invasive esophagectomy in our surgery practice will receive routine work-up and multidisciplinary evaluation and care for esophageal carcinoma, which may include neoadjuvant therapy. Patients will be given a patient consent form that will inform them of the possible risks and benefits of this study. Patients will undergo the standard of care preoperative work-up, during which it will be determined if they meet the inclusion and exclusion criteria summarized in **Section 5.1** and **Section 5.2** prior to enrollment in the study. If criteria are met, patients will be randomized by the study coordinator, per methods determined by the statistician. The randomization allocation will be shared with the surgical team from the study coordinator to the surgeon prior to the surgery and discussed during the surgical time-out. The next 50 patients who meet the study criteria will be randomized to either the intrapyloric botulinum injection arm or the non-botulinum treatment arm. All participants will sign a surgical consent prior to minimally invasive esophagectomy.

All patients will undergo routine minimally invasive esophagectomy. If randomized to the botulinum arm, patients will undergo the standard minimally invasive esophagectomy performed at RPCI, including intra-pyloric botulinum injection. If randomized to the no botulinum arm, patients will undergo the standard minimally invasive esophagectomy performed at RPCI **excluding** the pyloric drainage procedure with botulinum injection. The patient and radiologist

will be blinded to the treatment arm. The surgeon, due to the nature of the intervention, will not be blinded to the treatment arm.

The standard of care for minimally invasive esophagectomy at RPCI is outlined in the following postoperative pathway. **All patients follow this pathway unless clinical status dictates otherwise**:

- Patients leave the operating room with a nasogastric tube (NGT) tip at or beneath the esophago-gastric anastomosis, and a feeding jejunal-tube (j-tube).
- Unless prohibited by medical condition, tube feeds are started through the j-tube at 20 mL/hour. Tube feeds are advanced to goal after return of bowel function.
- The NGT is removed.
- If there is no concern for aspiration-such as hoarseness, altered mental status, or limited mobility, and the patient is alert and able to protect the airway, oral diet is started with sips of clear liquids.
- Diet is advanced to full liquids. The nutritional goal, which continues at hospital discharge, is for the oral full liquid diet to meet 50% of calculated caloric needs, and the remaining 50% given as supplemental tube feeds through the j-tube. Patients remain on a full liquid diet for two weeks postoperatively.
- A gastrografin swallow study or CT esophagram is performed to evaluate for any signs of anastomotic leak.
    - This study may also be used to assess gastric emptying. A single radiologist will evaluate the gastrografin study/CT esophagram (1):
    - Quantifying gastric emptying by gastrografin swallow or CT esophagram will allow comparison of our results to previous nonrandomized studies (1).
- Patients are discharged from the hospital if they are medically stable and tolerating 100% of nutritional needs as a combination of orally or through j-tube. Any clinical signs of delayed gastric emptying causing regurgitation, vomiting or aspiration will delay hospital discharge until the risk of aspiration is low.
- The day that the first nutritional goal is met will be recorded, when 50% nutritional needs are met with oral full liquid intake and 50% supplemental tube feeds.
- Hospital length of stay attributed to delayed gastric emptying: If patients have intractable nausea and vomiting, or experience a pulmonary event related to aspiration, this will be recorded as attributed to delayed gastric emptying. Prolonged hospital length of stay will be defined as hospital admission past Postoperative Day #14 attributed to delayed gastric emptying.
- If it is uncertain whether a pulmonary event is related to delayed gastric emptying, a formal swallow evaluation will be performed by a speech language pathologist.

- Patients will receive non-opiate and opiate pain relief medications in the postoperative period. Opiate pain medications should only be administered if adequate pain control is not met with non-opiate pain medications.

As a participant in this study the patient will undergo a ***nuclear medicine emptying study*** to assess for conduit function. This study will be obtained within the window of Postoperative Visit #2 (±14 days). *Prior to the nuclear medicine emptying study*, the patient must be fasting for at least 6 hours; including oral intake and any supplemental j-tube feeds. The fasting glucose should be measured and less than 275 mg/dL. Patients should be off all narcotic pain medications for the 48 hours prior to the nuclear medicine emptying study.

- 120 mL of liquid egg white product (Egg Beaters) will be radiolabeled with 1 mCi of Tc99m, cooked and then scrambled. The patient will be instructed to ingest the meal within 10 minutes. Images will be obtained every 15 minutes for up to four hours. If the patient vomits part of the meal at any time during the test, it will be recorded on the study report.
- During the study, for the time between the images, the patients may be sitting, standing, or walking, but should remain in close proximity to the nuclear medicine facility. Patients will be monitored for any symptoms of delayed gastric emptying during this time. Participants will answer a questionnaire to assess for gastrointestinal symptoms during the nuclear medicine study (See **Appendix C)**.

A single nuclear radiologist, who is blinded to the randomization group, will assess gastric emptying on the nuclear emptying study. There is no standardized method for reporting conduit emptying by this method. Two published studies on this topic have used time to 50% gastric emptying as an endpoint (8), and categorized 50% gastric emptying into ranges, with >180 minutes categorized as "delayed," within 180 minutes as "intermediate," and immediate emptying as "rapid" (12). We will measure time to 50% gastric emptying in all patients, and categorize similar to the above description, as follows:

Table 1 50% Gastric Emptying Times and Definitions:

Definition	50% Emptying Time
Rapid	Immediate emptying, no radiotracer seen on first image obtained at 15 minutes
Intermediate	< or = 150 minutes
Delayed	> 150 minutes

This time modification is based on the current guidelines and normal limits for gastric retention assessed by nuclear scanning (13). The report will also include the percentage of tracer retained the following times after meal ingestion: 1, 2, 3, and 4 hours.

To ensure the radiologist interpreting the nuclear medicine and gastrografin studies/CT esophagram remains blinded, the radiologist should not open the "operative note" documents in

the electronic medical record. During study interpretation, if the radiologist requires clarification regarding the operative procedure, he should contact the operating surgeons directly. The randomization group will not be listed in any other part of the electronic medical record.

Primary Endpoint

- Postoperative delayed gastric emptying assessed radiographically as "severe" by nuclear medicine emptying study compared to "intermediate," and "rapid" emptying. "Severe" delayed gastric emptying will be defined as scoring of "delayed" on nuclear emptying study. Patients assessed as "intermediate" or "rapid" on nuclear medicine emptying study will be considered to have normal conduit function.

Secondary Endpoints

- Postoperative delayed gastric emptying assessed radiographically by gastrografin swallow /CT esophagram.
- Postoperative delayed gastric emptying assessed clinically by the following:
    1. Quality of life score assessed by EORTC QLQ-C30 OES18.
    2. Pulmonary events directly related to delayed gastric emptying, as assessed by the operating surgeon. Pulmonary events include pneumonia, acute aspiration, and respiratory failure requiring intubation.
    3. Gastrointestinal and nutritional status: Requirement of NGT past Postoperative Day #7, or need to reinsert NGT, witnessed nausea, vomiting, or regurgitation directly related to delayed gastric emptying. This does not include postoperative ileus. Tolerance of full liquid diet at hospital discharge and meeting nutritional goals of time to resumption of 50% caloric needs orally by Postoperative Day #7, 75% caloric needs orally by Postoperative Day #21, and 100% caloric needs orally by Postoperative Day #35.
        - "Moderate" delayed gastric emptying will be defined as clinical symptoms requiring medical therapy.
        - "Severe" delayed gastric emptying will be defined as clinical symptoms requiring secondary procedure.
    4. Hospital length of stay attributed to delayed gastric emptying.
    5. Number of secondary procedures within 90 days due to delayed gastric emptying. Secondary procedures include endoscopic or operative procedures for delayed gastric emptying.
        - Requirement of secondary procedure will be graded as "Severe" delayed gastric emptying

4.2 Target Accrual and Study Duration

A maximum of 50 evaluable patients at RPCI will be enrolled. Accrual is expected to take up to 6 years.

This target accrual and study duration is highly feasible based off the high volume of patients with esophageal carcinoma undergoing minimally invasive esophagectomy at RPCI. An interim analysis will occur after 30 patients have been enrolled.

Study participants will be followed for data collection for 90 days (routine post-esophagectomy follow-up care and surveillance, per standard of care).

A patient will be replaced on study if the following deviations from the original surgical plan occur:

- the surgical procedure is converted to open technique or,
- a cervical anastomosis is performed or,
- a patient does not complete the postoperative evaluation through the nuclear medicine emptying study obtained within ± 14 days of post-operative visit #2.

5 PARTICIPANT SELECTION

5.1 Inclusion Criteria

To be included in this study, participants must meet the following criteria:

1. Esophageal carcinoma, undergoing minimally invasive esophagectomy with intrathoracic anastomosis.
2. Age ≥ 18 years of age.
3. Have an ECOG Performance Status of ≤ 2. Refer to **Appendix A**.
4. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

5.2 Exclusion Criteria

Participants will be excluded from this study for the following:

1. Patients who have a history of gastrointestinal dysmotility or functional gastroparesis, including diabetic gastroparesis, central and peripheral nervous system disorders, renal failure, medication side effects, including chronic dependence of promotility agents, anticholinergic antispasmodic agents, or chronic narcotic use over 2 years due to non-cancer causes. Refer to **Appendix B** for a list of pharmacologic agents**.**
2. Patients who have a history of previous gastric or duodenal surgery.
3. Patients who have a history of duodenal ulcer or duodenal fibrosis.
4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
5. Allergy to botulinum toxin, and or egg.
6. Pregnant or nursing female participants.

7. Unwilling or unable to follow protocol requirements.
8. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate for study participation.

5.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

6 STUDY PROCEDURES

The study-specific assessments are detailed in this section and outlined in **Table 2** (Schedule of Procedures and Observations). Standard preoperative screening assessment and multidisciplinary evaluation must be performed up to 6 weeks prior to minimally invasive esophagectomy. The nuclear medicine emptying study may occur within the window of Postoperative Visit #2 (± 14 days) unless contraindicated per physician's discretion**.** Unless otherwise defined in the written protocol text, all procedures/assessments will be conducted in accordance with RPCI Clinical Research Services Standard Operating Procedures. All procedures and evaluations listed are our post-esophagectomy standard of care at RPCI except for Nuclear Medicine Emptying Study, EORTC QLQ OES18 Questionnaire, and *routine* postoperative outpatient assessment by our dietician.

6.1 Participant Randomization and Registration

Eligibility of each participant will be established prior to randomization.

Informed consent ***MUST*** be completed prior to receiving any study related procedures.

Participants will be randomized in a 1:1 fashion to the botulinum and non-botulinum treatment arms using a permuted block design. The randomization list will be developed by the Department of Biostatistics and Bioinformatics, and randomization procedure as outlined in **Section 9.2**.

6.2 Baseline Evaluations

Preoperative workup and multimodality therapy for esophageal cancer as standard of care at RPCI, based upon the NCCN guidelines for esophageal cancer. Standard presurgical assessment with full medical history and physical examination, laboratory tests, cross-sectional imaging and cardiopulmonary assessment as determined by the operating surgeon or the Preoperative Anesthesia Clinic based upon RPCI established guidelines.

The following will be performed prior to the participant's scheduled minimally invasive esophagectomy and will be confirmed before surgery:

- Informed consent for study. Must be completed prior to receiving any study-related procedures.
- Medical history with preexisting conditions, including all neoadjuvant therapy related to esophageal carcinoma, smoking status and, diabetes.

- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure), body weight and height; with emphasis on the neck, thoracic, and abdominal cavities.
- Multidisciplinary evaluation and neoadjuvant therapy if indicated for esophageal carcinoma. Multidisciplinary evaluation will be documented in the outpatient preoperative office visit note.
- Pregnancy test (urine) in females of childbearing potential. The standard operating procedure for all females of childbearing potential in the Ambulatory Surgical Center (ASC) pre-op holding area is to obtain a urine HCG. This study protocol does not deviate from the standard operating procedure of the ASC/pre-op holding area at RPCI. If the pregnancy test is positive, the patient is excluded from the study.
- Nutritional status assessment by a dietician, as clinically indicated.

The following will be performed if indicated by the anesthesia pre-op assessment (standard operating procedure for the pre-op clinic at RPCI). These tests are not strictly required to support eligibility for this study, but if indicated and performed, may exclude the patient from receiving a general anesthetic and thereby excluding the patient from this study.

- Hematology: CBC with automated differentials (WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % lymphocyte, absolute lymphocyte, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated).
- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- 12-lead electrocardiogram, chest x-ray, pulmonary function tests, and cardiac stress test, if indicated.

6.3 Treatment

- If criteria are met, patients will be randomized by the study coordinator, per methods determined by the statistician. The randomization allocation will be shared with the surgical team from the study coordinator to the surgeon prior to the surgery.
    - If randomized to the botulinum arm, patients will undergo the standard minimally invasive esophagectomy performed at RPCI, including botulinum injection. The intraoperative procedure for botulinum toxin injection is as follows: 100 units of botulinum toxin is dissolved in 10 mL normal saline. After preparation of the gastric conduit, including mobilization and transection, the 10 mL of botulinum toxin solution is injected with a thoracoscopic needle intramuscularly at the anterior pyloric ring, in 2-3 separate areas.

  - If randomized to the no botulinum arm, patients will undergo the standard minimally invasive esophagectomy performed at RPCI **excluding** the pyloric drainage procedure with botulinum injection.

- Standard Post Anesthesia Care Unit (PACU) protocols for patient recovery from surgery. Patients will be continuously monitored both intraoperatively and during the recovery period.
- Clinical Events of Interest and Adverse Events will be recorded throughout the time of entry into the operating room until the post-operative follow-up. Refer to **Section 7.1.3** for method of recording clinical events of interest and adverse events.

6.4 Inpatient Postoperative Follow-Up Evaluations

The following evaluations will be performed during the **inpatient postoperative course (surgery to discharge), unless otherwise clinically indicated.**:

Patients will follow Roswell Park standard of care postoperative pathway for minimally invasive esophagectomy (refer to Section 4.1), unless otherwise clinically indicated. This includes:

- Initial postoperative care in the intensive care unit or intermediate care unit, based on clinical status, with nursing care and vital signs per hospital unit standard:
- At the minimum daily physical examination (including vital signs).
- Laboratory analysis, including hematology (CBC with automated differentials) and chemistry (CMP), at least on a daily basis until Postoperative Day 6.
- Standard inpatient postoperative evaluations after minimally invasive esophagectomy include daily chest x-ray for at least four days postoperatively, and occasionally a CT scan of the chest if clinically indicated.
- Gastrografin swallow study/CT esophagram is obtained to evaluate for any signs of anastomotic leak.
- Clinical evaluation of symptoms will be evaluated by the participant's care team, including inpatient nurses, mid-level providers, surgical fellows, operating surgeon, speech therapist, occupational or physical therapists, dieticians, and documented in the RPCI electronic medical record (EMR).
- Speech therapy evaluation for any dysphagia or signs of aspiration.
- Nutritional assessments will be performed by a dietician familiar with the study. The initial evaluation will be performed in the outpatient setting if there are signs of malnutrition or inability to tolerate oral intake at the preoperative visit. Otherwise the standard is to perform the initial nutritional assessment in the immediate postoperative period. Patients will be monitored by the dietician Monday-Friday while an inpatient, and then at each subsequent follow-up office visit, and assessment documented in the RPCI EMR.
- Nutritional goals are as follows: By hospital discharge, patients are expected to meet 50% of their total nutritional requirements orally and 50% by supplemental j-tube feeds. On

Postoperative Day #6, ± 1 day, patients will undergo a 24-hour calorie count, to objectively assess oral intake. By Postoperative Day #21, patients should meet 75% nutritional requirements orally and 25% j-tube feeds, and by postoperative week #5, 100% oral calories. The postoperative day that each of these goals are met will be recorded (Day tolerating 50% oral feeds, 75% oral feeds, 100% oral feeds).

- Concomitant medication: List any ongoing medications with dose changes, as applicable. Patients may take opiates in the postoperative period, including on the day of the gastrografin swallow study/CT esophagram, and type and dosage will be recorded.
- Clinical Events of Interest and Adverse Events

Patients will be discharged from the hospital if they are medically stable and tolerating 100% of nutritional needs with a combination of orally and supplemental through j-tube:

- Any clinical signs of delayed gastric emptying causing regurgitation, vomiting, or aspiration will delay hospital discharge until the risk of aspiration is low.
- Hospital length of stay attributed to delayed gastric emptying: If patients have intractable nausea and vomiting, or experience a pulmonary event related to aspiration, this will be recorded as attributed to delayed gastric emptying.

6.5 Criteria for Retreatment

- Patients with “severe” delayed gastric emptying assessed radiographically or clinically at any time will be considered for endoscopic procedures for gastric outlet obstruction, including pyloric botulinum toxin injection or balloon dilation, or operative procedure. This is irrespective of whether a patient was initially treated with botulinum toxin at the minimally invasive esophagectomy; patients randomized to the botulinum toxin group may undergo additional botulinum toxin injection endoscopically. The maximum dose of botulinum toxin a patient may receive for this study in the three-month period is 300 units. Each of these procedures- when a patient undergoes a therapeutic endoscopic procedure or returns to the operating room- will be defined as a secondary procedure.
- Development of “severe” delayed gastric emptying as assessed by nuclear medicine study will be considered a failure of the experimental procedure and will be included in the primary analysis. Requirement for secondary procedure or development of “severe” delayed gastric emptying as assessed by parameters other than the nuclear medicine study will be included in the secondary analysis.
- Patients with “moderate” delayed gastric emptying assessed radiographically or clinically at any time will be considered for initiation of promotility agents. Development of “moderate” delayed gastric emptying will be included in the secondary analysis.

6.6 Outpatient Postoperative Follow-Up Visits

Study participants will be followed for data collection for 90 days (routine post-esophagectomy follow-up and surveillance, per standard of care). The following evaluations will be performed during the outpatient postoperative course, unless otherwise clinically indicated:

- In the postoperative period, patients return to office for outpatient follow-up approximately one to three weeks after discharge ("Postoperative Visit #1"). This visit is standard of care and can be scheduled per PI discretion. Physical exam and vital signs will be conducted at this visit. The dietician will assess oral intake, and supplemental tube feeds adjusted accordingly. Day until patient tolerates 75% and 100% of nutritional needs orally will be recorded as per nutritionist assessment.
- As a participant in this study, patients in both randomization groups will undergo a nuclear medicine emptying study The nuclear medicine emptying study may occur within the window of Postoperative Visit #2 (± 14 days) to assess dynamic conduit function. This test can be extended beyond post-operative Visit #2 at PI's discretion. Patients will be monitored for any symptoms of delayed gastric emptying during this time by questionnaire (See **Appendix C)**, to determine if nuclear medicine study findings correlate with concurrent clinical symptoms.
    - Prior to the nuclear medicine emptying study, the patient must be fasting for at least 6 hours, including oral intake and any supplemental j-tube feeds. If the patient is a diabetic, the glucose level should be measured and less than 275 mg/dL within 2 hours of the study. Opiates must be held for 48 hours prior to the study. Patients should not be on any of the medications listed in **Appendix B** within the 48 hours prior to the study. Patients will remain in the nuclear medicine suite during this time, and will be required to sit upright, and may walk around the room. During the study, for the time between the images, the patients may be sitting, standing, or walking, but should remain in close proximity to the nuclear medicine facility.
- Post-surgical symptom evaluation based on clinical factors during the outpatient follow-up visits, and additionally by phone conversation between outpatient follow-up appointments if clinically indicated.
- At Postoperative Visit #2, patients will be assessed for quality of life as measured by EORQLQ-C30 OES18 questionnaire (**Appendix D**). This will usually occur in the office around postoperative week six to eight. However, if the patient remains hospitalized during this time point, the questionnaire will be administered once between Postoperative Days 35-42.
- Concomitant medications: List any ongoing medications with dose changes, as applicable.
- Clinical Events of Interest and Adverse Events

Participants who are unavailable for follow-up evaluations should be classified as lost to follow-up for one of the following reasons:

- Lost to follow-up: For a participant to be considered lost to follow-up, the investigator must make two separate attempts to re-establish contact with the participant. The attempts to re-establish participant contact must be documented (e.g., certified letter).

- Death: Date and cause of death will be recorded for those participants who die within 30 days of surgery (telephone verification is acceptable).

6.7 End of Study Visit

- At day #90 (± 7 days), an end of study phone call will be conducted by the study coordinator. The purpose of this call is to inquire about any subsequent procedures the patient may have undergone related to delayed gastric emptying or esophagectomy, nutrition assessment to determine if the patient continues to require supplemental jejunal feeds, any persistent clinical symptoms of delayed gastric emptying, including any subsequent pneumonia, aspiration events, respiratory failure, nausea, vomiting, ability to eat solid food or drink liquids or having any trouble eating, early satiety, difficulty swallowing saliva, noticing bile or green staining on pillow while sleeping, experiencing acid indigestion or heartburn, or pain with eating, concomitant medications and Clinical Events of Interest and adverse events will be assessed. If the patient indicates continued use of tube feeds, the study coordinator will alert the dietician to call the patient for further evaluation of the percentage of tube feeds versus oral intake. If the patient is no longer using jejunal feeds, the study coordinator will mark down “100% oral intake.

The schedule of procedures and observations for this study is summarized in **Table 2** below.

Table 2 Schedule of Procedures and Observations

Evaluation	Baseline[1]	Day of Surgery	Inpatient Postoperative Course[2] (Surgery to Discharge)	Postoperative Visit #1[3] ± 14 days	Postoperative Visit#2[3] ± 14 days	End of Study phone call Day#90 (± 14 days)
Medical History, Pre-Existing Conditions (including smoking status, diabetes)	X					
ECOG Performance Status	X					
Multidisciplinary Evaluation and neoadjuvant therapy for esophageal carcinoma	X					
Physical Examination, including vital signs[4]	X	X	X	X	X	
Hematology[5]	X		X		X	
Chemistry[6]	X		X		X	
Sign study informed consent, if eligible based on above factors	X					
Minimally invasive esophagectomy with or without pyloric drainage procedure		X				
Fasting glucose				X As indicated)		
Chest X-Ray, CT chest			X (As indicated)		X (As indicated)	

Evaluation	Baseline[1]	Day of Surgery	Inpatient Postoperative Course[2] (Surgery to Discharge)	Postoperative Visit #1[3] ± 14 days	Postoperative Visit#2[3] ± 14 days	End of Study phone call Day#90 (± 14 days)
Gastrografin swallow evaluation[12] /CT esophagram			X[12a]			
Nuclear Medicine Emptying Study[10, 11]				X[11] (**Phone call prior to give instructions**)		
Clinical Evaluation of Symptoms			X	X[11]	X	X
Medical evaluation (signs of pneumonia, aspiration)			X	X	X	
Nutrition evaluation[13]	X (As indicated)		X[14]	X	X	X (As indicated)
EORTC QLQ OES18 Questionnaire[10] See Appendix D					X	
Pregnancy Test[7](Urine)	X					
Electrocardiogram, Chest x-ray, and/or Pulmonary Function tests	X (As indicated)					
Speech therapy evaluation			X (As indicated)			
Concomitant Medications	X[8]	X	X	X	X	X
Clinical Events of Interest and AEs		X[9]	X	X	X	X

Evaluation	Baseline[1]	Day of Surgery	Inpatient Postoperative Course[2] (Surgery to Discharge)	Postoperative Visit #1[3] ± 14 days	Postoperative Visit#2[3] ± 14 days	End of Study phone call Day#90 (± 14 days)
Fasting glucose (for patients with diabetes)					X (As indicated)	

1 Baseline evaluations will be performed prior to the participant's scheduled minimally invasive esophagectomy and will be confirmed before surgery (Preoperative workup and multimodality therapy for esophageal cancer as standard of care at Roswell Park and based upon the NCCN guidelines for esophageal cancer. Refer to Section 6.2).

2 Patients will follow the standard of care postoperative pathway for minimally invasive esophagectomy.

3 Initial Standard of Care postoperative follow-up visit (Postoperative Visit #1) after hospital discharge, and then again at Postoperative Visit #2 if the postoperative course is uncomplicated. If complications arise, patients may be seen more often in follow-up. Patients will be followed for data collection for 90 days following surgery.

4 Vital signs (temperature, heart rate, respiratory rate, blood pressure), body weight and, height. Height collected at baseline only.

5 If indicated by the anesthesia pre-op assessment- Hematology: CBC with automated differentials (WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, , % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % lymphocyte, absolute lymphocyte, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated).

6 If indicated by the anesthesia pre-op assessment - Chemistry: CMP (chloride, CO2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap), as clinically indicated.

7 To be performed < 1 week prior to scheduled surgery,

8 Medications ongoing, or discontinued, within 1 week prior surgery.

9 To be recorded from the time of entry into the operating room until the post-operative follow up. Clinical Events of Interest and SAEs will be recorded in the electronic medical record, and found in the patient's operative note, anesthesia records, daily progress notes, consult notes, nutrition notes, and outpatient visit notes.

10 All procedures and evaluations listed are our post-esophagectomy standard of care at RPCI except for Nuclear Medicine Emptying Study, EORTC QLQ OES18 Questionnaire, and routine postoperative assessment by dietician. See Table 1 for definitions, section 4.1. If contraindicated per investigator's discretion, the nuclear medicine emptying study can be extended beyond post-operative Visit #2 at PI's discretion.

11 Evaluation as documented in Appendix C, Nuclear Medicine Questionnaire.

12 CT esophagram or gastrografin swallow.
12[a]: As inpatient when clinically indicated.

13 Nutritional goals as defined in Section 6.4: Day tolerating 50% oral feeds, 75% oral feeds, 100% oral feeds.

14 Nutrition assessment will include a 24-hour calorie count on Postoperative Day #6 ±1 day.

6.8 Compliance

The patient must attend his/her post-operative appointments in the ninety days after surgery to evaluate for any signs of delayed gastric emptying.

7 SAFETY EVALUATION

7.1 Clinical Events of Interest and Adverse Events

Clinical events of interest (captured in REDCap) include, but are not limited to: patient continues to require supplemental jejunal feeds, persistent clinical symptoms of delayed gastric emptying (delayed gastric emptying assessed by the gastrografin swallow exam/CT esophagram), subsequent pneumonia, aspiration events, respiratory failure requiring reintubation, nausea, vomiting, ability to eat solid food or drink liquids or having any trouble eating, early satiety, difficulty swallowing saliva, bile or green staining on pillow while sleeping, experiencing acid indigestion or heartburn, pain with eating, additional postop procedures, EORTC QLQ-30 QoL scores, and hospital length of stay.

7.1.1 Definition of Adverse Events

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of ‘unrelated’, ‘unlikely’, ‘possible’, ‘probable’, or ‘definite’).

An AE is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

7.1.1.1 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

7.1.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF. Pain will not be considered an adverse event at any point, given the nature of the intervention (surgical procedure).

7.1.1.3 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated blood potassium level of 7 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

7.1.1.4 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

7.1.2 Drug Information- Botulinum toxin

OnabotulinumtoxinA (botulinum toxin type A, Botox©) inhibits the release of acetylcholine from nerve endings at neuromuscular junctions in the local muscle (10). Without the release of acetylcholine, neurotransmission between peripheral nerve endings and muscle fibers cannot occur, and the muscle becomes weak or paralyzed (10). The inhibitory effect of botulinum toxin is temporary, and muscle function recovers at 3 months after administration. The effect is not immediate, and rather occurs within 1-3 days.

With intramuscular injection at a dose of 100 units, botulinum toxin is not expected to be in contact with the peripheral blood (10). In rare instances, botulinum toxin may spread from the area of injection and produce symptoms consistent with botulinum toxin effects (13). These unanticipated symptoms may include asthenia, diplopia, ptosis, dysphagia, dysphonia, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection.

Incidence of side-effects depends on injection site location. For example, patients treated with botulinum toxin injection into the sternocleidomastoid muscle for cervical dystonia are more likely to have the side-effects of swallowing difficulties, due to local diffusion. Swallowing and breathing difficulties may be life-threatening, and there have been reports of death (11). Patients with history of underlying conditions predisposing to muscle weakness have an increased risk of these side effects occurring (11). However, due to the nature of this study, patients with underlying muscle weakness are excluded from this study.

The maximum recommended dose of OnabotulinumtoxinA, regardless of the indication, is 400 units over three months (10). Cervical dystonia is treated with doses ranging from 198-300 units, divided among the affected muscle, with maximum dose 50 units per site. Our proposed dosage, 100 units in divided doses into the pyloric muscle, is within the range used among other high-volume esophagectomy centers (2, 3, 8, 9).

Absolute contraindications to botulinum toxin injection include previous hypersensitivity to the product (10). Mild to moderate side effects are generally mild transient, and include swelling or bruising at the injection site, and the small possibility of infection at injection site (10). Anaphylaxis/hypersensitivity reactions have occurred (11). Higher doses or more frequent administration may result in neutralizing antibody formation and loss of efficacy (10). This summary of the US FDA boxed warning may also be found at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM176360.pdf

7.1.3 Grading and Relationship to Study Procedure

The descriptions and grading scales found in the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 4 of the CTCAE is identified and located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology and documented according to the grading scales provided in the CTCAE Version 4.

The relationship of event to study procedure will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.

- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

7.1.4 Reporting Adverse Events

Table 43 Guidelines for Routine Adverse Event Reporting for Phase 2 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Routine AEs occurring between the starting date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

7.2 Serious Adverse Events

7.2.1 Definition

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does **NOT** include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.2.2 Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 90 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The RPCI SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 90 day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs that are unexpected and possibly, probably or definitely related must be reported as an Unanticipated Problem. Please refer to **Section 7.4** for details on reporting Unanticipated Problems.

7.3 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

7.4 Unanticipated Problems

7.4.1 Definition

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
    a) The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
    b) The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized or if in relation to an AE is deemed **Serious** per **Section 7.2**.

7.4.2 Reporting Unanticipated Problems

The Reportable New Information (RNI) Form will be submitted to the CRS Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, the CRS QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to the QA Office with an updated Reportable New Information Form. The site

Investigator or designated research personnel will report all unanticipated problems to the **IRB in accordance with their local institutional guidelines**.

8 DATA AND SAFETY MONITORING

The Roswell Park Data Safety Monitoring Committee will assess the progress of the study, the safety data, and critical efficacy endpoints (Phase I studies will be reviewed quarterly; Phase II, III and pilot investigator-initiated studies will be reviewed semi-annually). The DSMC will review the study and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) suspension of or (d) termination of the study

9 STATISTICAL METHODOLOGY

The primary objectives of this study are:

- Determine if intra-pyloric botulinum toxin injection during a minimally invasive esophagectomy decreases postoperative occurrence of delayed gastric emptying, as assessed radiographically by nuclear medicine emptying study.

The secondary objectives of this study are:

- Determine if intra-pyloric botulinum toxin injection during a minimally invasive esophagectomy reduces the number of repeat procedures for delayed gastric emptying within 90 days, decreases time to oral intake meeting 100% of nutritional requirements, reduces the incidence of pulmonary and gastrointestinal complications directly related to delayed gastric emptying, reduces hospital length of stay related to delayed gastric emptying, and increases patient quality of life.

9.1 Sample Size Determination

The sample size justification is based on the primary analysis. We consider a study design with a total sample of n=50 patients (randomly assigned in a 1:1 fashion to the Botox and non-Botox treatment arms) and an interim analysis at n_1=30. The performance of this study design and decision rules (described in the primary analysis) was assessed via simulation study.

If the true rates of delayed gastric emptying are 0.30 and 0.70 in the Botox and non-Botox treatment arms, then the study design achieves 85.0% power to detect a significant change in the delayed gastric emptying rates at a significance level of 0.05. The chance of stopping early for superiority is 42.8%, while the chance of stopping early due to inferiority is only 1.0%.

If the true rate of delayed gastric emptying is 0.70 in both treatment arms, then there is a 4.3% chance of falsely identifying the Botox arm as superior (observed type I error rate), a 0.9% chance of stopping early for superiority, and a 42.1% chance of stopping early for inferiority.

9.2 Randomization

Patients will be randomized in a 1:1 fashion to the Botox and non-Botox treatment arms using a permuted block design. Participants will be stratified on the receipt of neoadjuvant chemoradiotherapy, smoking status, and diabetes. Participants will be randomized prior to the

minimally invasive esophagectomy, after signing consent for the surgical procedure. The randomization list will be developed by the Department of Biostatistics and Bioinformatics and provided to the study coordinator, who will then relay the information to the surgical team at the start of the procedure.

9.3 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

9.4 Primary and Secondary Analyses

Primary Analysis: A recent study demonstrated that patients who received Botox had a delayed gastric emptying rate of approximately 30% as compared to a complication rate in historical controls of 70% in patients that did not receive botulinum toxin injection (7). A retrospective review of patients undergoing minimally invasive esophagectomy at Roswell Park Cancer Institute indicates that the rate of postoperative delayed gastric emptying is even lower, however, this rate is based on very stringent criteria for delayed gastric emptying- requirement of a secondary procedure. Therefore, the primary objective is to determine if intra-pyloric botulinum toxin injection during a minimally invasive esophagectomy decreases postoperative occurrence of delayed gastric emptying. The primary outcome is delayed gastric emptying (assessed radiographically by nuclear medicine emptying study) which is treated as a dichotomous variable.

Patients will be stratified by receipt of neoadjuvant chemoradiotherapy, smoking status, and diabetes; and randomized in a 1:1 to the botulinum and non-botulinum treatment arms. The primary objective will be assessed using the intent-to-treat principle and a one-sided Cochran-Mantel-Haenszel (CMH) s test about the following hypotheses:

H_0:$\theta \geq 1$,
H_A:$\theta < 1$

where θ is the common odds ratio (COR) for the odds of delayed gastric emptying rates for the botulinum versus non-botulinum treatment arms. A one-sided test is performed as the rate of delayed gastric emptying is expected to decrease in the botulinum arm over the non-botulinum arm; that is, we expect $\theta < 1$.

The analysis will proceed in two stages using an O'Brien-Fleming alpha spending function. An interim analysis will be conducted after n_1=30 patients have completed treatment and the final analysis will be conducted after n=50 patients have completed treatment. The following decision rules will be utilized at each analysis:

Analysis	Decision Rule
Interim	• If p-value ≤ 0.011396, then reject H_0 and stop due to superiority. • If $\hat{\theta} > 1$, then stop due to inferiority. • Otherwise enroll n_2=20 patients.
Final	• Reject H_0 if p-value ≤ 0.046533

Secondary Analysis: The secondary outcomes include additional postop procedures, clinically assessed delayed gastric emptying (days to resumption of oral feeding, EORTC QLQ-30 QoL scores, and clinical symptoms of regurgitation, vomiting, and aspiration), delayed gastric emptying assessed by the gastrografin swallow exam/CT esophagram, pulmonary complications (aspiration, respiratory failure requiring reintubation, pneumonia within 3 months of surgery), and hospital length of stay. All variables will be reported by treatment arm using the appropriate descriptive statistics and graphical summaries.

The days to resumption of oral feeding, QoL scores and, hospital length of stay will be compared between treatment arms using the two sided independent-sample, stratified T-test. Normality will be assessed using the Anderson-Darling test and transformations (such as Box-Cox) will be applied, as appropriate. Bootstrap or non-parametric methods will be applied if no normalizing transformations can easily be applied. The rates of moderate clinical delayed gastric emptying (clinical signs of regurgitation, vomiting, and aspiration), moderate delayed gastric emptying (score of 2 or 3 on the gastrografin swallow test/CT esophagram), severe delayed gastric emptying (score of 4 or 5 on the gastrografin swallow test/CT esophagram), and pulmonary complications will be compared between treatment arms using the two-sided CMH exact test.

A previous study demonstrated that the rate of additional postoperative procedures may be lower for patients treated with botulinum (3.9%) as compared to those without botulinum (15.9%). Therefore, the rates of additional postop procedures within 3 months of the original procedure will be compared between treatment arms using a one-sided CMH exact test.

All analyses will be performed in SAS v9 (Cary, NC).

9.4.1 Adverse Events

The adverse events will be reported by grade using frequencies and relative frequencies. Additionally, the study will be monitored by the RPCI Data and Safety Monitoring Committee, which will assess the progress of the study, the safety data, and critical efficacy endpoints.

9.5 Interim Analysis and Criteria for Early Termination of the Study

An interim analysis will be conducted after n_1=30 patients have completed treatment and will consider the following decision rules:

Analysis	Decision Rule
Interim	1. If p-value ≤ 0.011396, then reject H_0 and stop due to superiority. 2. If $\hat{\theta} > 1$, then stop due to inferiority. 3. Otherwise enroll n_2=20 patients

10 ETHICAL AND REGULATORY STANDARDS

10.1 Ethical Principles

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

10.2 Informed Consent

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant or the participant's legally authorized representative in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The

participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

11 STUDY RESPONSIBILITIES

11.1 Data Collection

Data entry into the REDCap database is to be completed in a timely fashion (within 30 days) after the participant's clinic visit. If an AE is considered serious it is captured on the Serious Adverse Event Source Form, which is handled in an expedited fashion.

Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. eCRF data will be collected in REDCap, but Adverse Event data will be collected in Advarra EDC for DSMC reporting.

11.2 Maintenance of Study Documents

Essential documents will be retained per RPCI's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with RPCI.

12 ADMINISTRATIVE RULES

12.1 Revisions to the Protocol

RPCI may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

12.2 Termination of the Study

It is agreed that, for reasonable cause, either the RPCI Investigators or the Sponsor, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, RPCI may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

12.3 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

13 APPENDICES

Appendix A ECOG Performance Status Scores

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

Appendix B Ineligible Pharmacologic Agents

- Daily use of medications that delay or enhance gastric emptying:
- Prokinetic agents, including erythromycin, metoclopramide, tegaserod, domperidone
- Anticholinergic antispasmodic agents, including: dicyclomine, hyoscyamine, glycopyrrolate
- Other agents, including atropine, nifedipine, progesterone, octreotide, theophylline, benzodiazepine, phentolamine, opioids

Appendix C Nuclear Medicine Questionnaire

1. Did you have trouble eating the entire meal within the time allotted?

2. Did you have trouble eating the solid component?

3. Did you experience acid indigestion or heartburn at any point during the study?

4. Did you experience nausea or reflux at any point during the study?

5. Did you vomit at any point during the study?

6. Did you have pain related to eating at any point during the study?

7. Did you feel too full at any point during the study?

8. What medications did you take in the past 48 hours (2 days)?

_____

Patient Signature: _____ Date: _____

Appendix D EORTC QLQ- OES18

Patient Signature: _____ Date: _____

EORTC QLQ – OES18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Could you eat solid food?	1	2	3	4
32.	Could you eat liquidised or soft food?	1	2	3	4
33.	Could you drink liquids?	1	2	3	4
34.	Have you had trouble with swallowing your saliva?	1	2	3	4
35.	Have you choked when swallowing?	1	2	3	4
36.	Have you had trouble enjoying your meals?	1	2	3	4
37.	Have you felt full up too quickly?	1	2	3	4
38.	Have you had trouble with eating?	1	2	3	4
39.	Have you had trouble with eating in front of other people?	1	2	3	4
40.	Have you had a dry mouth?	1	2	3	4
41.	Have you had problems with your sense of taste?	1	2	3	4
42	Have you had trouble with coughing?	1	2	3	4
43.	Have you had trouble with talking?	1	2	3	4
44.	Have you had acid indigestion or heartburn?	1	2	3	4
45.	Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
46.	Have you had pain when you eat?	1	2	3	4
47.	Have you had pain in your chest?	1	2	3	4
48.	Have you had pain in your stomach?	1	2	3	4

Appendix E Pre-Procedure Instruction Handout for Patients:

Your doctor has ordered a test that will permit evaluation of how food moves through your new stomach conduit. This test is called a Nuclear Medicine Gastric Emptying Study. This study will be performed in the nuclear medicine department.

Preparation for the Gastric Emptying Study:

- You should not consume any liquids or food after midnight the night before the test. You should turn off your jejunal tube feeds at midnight as well.
- If you smoke, do not smoke any time after midnight and throughout the time you are having the study pictures recorded. You may smoke after you are instructed that the test is completed.
- Some medications are stopped for this test. This should be discussed with your doctor. The following medications must be stopped for 48 hours (2 days) before the test: Reglan (metoclopramide), erythromycin, benzodiazepines (Ativan, Valium, Xanax), and opioids (Lortab, Norco, Percocet, Dilaudid, Methadone, Morphine, Oxycontin, Oxycodone). Do not take any laxatives on the day before or any time during your study.
- Unless otherwise directed by your physician, you may continue your normal medications that could be taken with a small amount of water or juice up to 2 hours prior to your study. You should not drink coffee or tea.
- If you have diabetes, skipping breakfast may affect your need for diabetic medication. If you are a diabetic and on insulin, we request that you bring your regular morning dose of insulin with you. You can take this with the meal that will be given to you. We may reduce your insulin dose to adjust for the small size of the breakfast. Often half of your insulin is taken with the test meal. If you take oral hypoglycemic medications, generally these are taken with the meal in the nuclear medicine department. If there are any questions concerning your dose of insulin this should be discussed with your study coordinator or surgeon.
- If you have diabetes, we also ask you to bring your glucose monitoring equipment to the test. We will ask you to check your glucose before the test and possibly during or after the test.

Description of the Gastric Emptying Study:

- For this test, you will be asked to eat an egg meal that consists of the equivalent of one egg together with water. The meal has been labeled with an isotope that will permit pictures to be taken as the meal passes through the stomach conduit.
- Pictures of short duration are acquired with you standing in front of the nuclear medicine department's gamma camera. Between the images you will be permitted to walk about and continue normal activities. It is suggested that you bring some reading material and/or personal music device. These studies try to simulate normal daily activities. The nuclear medicine department's rooms may be cooler than the rest of the hospital, and you may want to bring a sweater with you.
- The study generally takes 4 hours once it is started.

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