Prevalence, nature and trajectory of dysphagia postoesophageal cancer surgery: a prospective longitudinal study protocol

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ABSTRACT

Introduction Dysphagia is a common problem following oesophagectomy, and is associated with aspiration pneumonia, malnutrition, weight loss, prolonged enteral feeding tube dependence, in addition to an extended in-hospital stay and compromised quality of life (QOL). To date, the prevalence, nature and trajectory of post-oesophagectomy dysphagia has not been systematically studied in a prospective longitudinal design. The study aims (1) to evaluate the prevalence, nature and trajectory of dysphagia for participants undergoing an oesophagectomy as part of curative treatment, (2) to determine the risk factors for, and post-operative complications of dysphagia in this population and (3) to examine the impact of oropharyngeal dysphagia on health-related QOL across time points.

Methods and analysis A videofluoroscopy will be completed and analysed on both post-operative day (POD) 4 or 5 and at 6-months post-surgery. Other swallow evaluations will be completed preoperatively, POD 4 or 5, 1-month and 6-month time points will include a swallowing screening test, tongue pressure measurement, cough reflex testing and an oral hygiene evaluation. Nutritional measurements will include the Functional Oral Intake Scale to measure feeding tube reliance, Malnutrition Screening Tool and the Strength, Assistance With Walking, Rise From a Chair, Climb Stairs and Falls questionnaire. The Reflux Symptom Index will be administered to investigate aerodigestive symptoms commonly experienced by adults post-oesophagectomy. Swallowing-related QOL outcome measures will be determined using the European Organisation for Research and Treatment of Cancer QLQ-18, MD Anderson Dysphagia Inventory and the Swallowing Quality of Life Questionnaire.

INTRODUCTION

The incidence of oesophageal cancer has increased markedly in the western world over the last 50 years, with the rates of the pathological subtype of adenocarcinoma linked to an increased prevalence of obesity, gastro-oesophageal reflux disease and Barrett’s oesophagus.1 The mainstay of curative treatment is surgery, often combined with preoperative combination chemoradiotherapy, or perioperative chemotherapy as per the MAGIC/FLOT or CROSS regimens.2 Surgery for oesophageal cancer is major, with up to 5% risk of mortality and over 50% risk of morbidity, irrespective of whether surgery is via open, minimally invasive or robotic-assisted approaches.3-7 Post-operative complications include pulmonary dysfunction, atrial fibrillation and anastomotic leak.5,8 Post-operative pulmonary complications (PPCs) are among the most serious postoperative challenges occurring between 15% and 40%
of patients post-oesophagectomy, impacting length of stay in critical care units, increasing overall hospital stay with significant cost implications.\cite{9,10} Malnutrition, weight loss and sarcopaenia are common after surgery or combination therapies.\cite{11,12}

Due to centralisation of services and enhanced recovery programmes, operative mortality has decreased.\cite{13} Furthermore, the 5-year survival rates among survivors of oesophageal cancer have improved in high-income countries.\cite{14} This has led to a shift in focus to improving survivorship in adults who have undergone curative treatment for oesophageal cancer.\cite{15} The health-related quality of life (HR-QOL) among oesophageal cancer survivors varies considerably. Symptoms known to impact long-term survivors and HR-QOL include coughing, reflux and deterioration in swallowing function.\cite{16}

Dysphagia is the most common presenting symptom for the majority of patients with oesophageal cancer.\cite{17} Following oesophageal resection, dysphagia continues to present post-operatively alongside other complications, which may be a result of, or further exacerbated by PPCs, recurrent laryngeal nerve (RLN) damage, neo-oesophageal strictures and gastrointestinal reflux.\cite{18-20} Interventions for oesophageal dysphagia include oesophageal dilatation, stenting and thermal and chemical ablation therapy.\cite{21} Dysphagia may be associated with aspiration pneumonia, malnutrition, prolonged feeding tube dependence and an extended inpatient hospital stay.\cite{22}

Dysphagia is highly associated with compromised quality of life (QOL) among oesophageal cancer survivors.\cite{16} One-year post-oesophagectomy, almost half of survivors’ report eating restrictions and other symptoms include dry mouth, taste problems, difficulty swallowing saliva and choking.\cite{15} At two years post-oesophagectomy, eating difficulties and reluctance to eat in front of others has been associated with psychological distress.\cite{23} In a recent cross-sectional cohort study on patient-reported outcomes post-oesophagectomy, long-term symptom burden is common in this patient group, with swallowing/conduit problems being one of the six main problems reported.\cite{24} Ten years post-operatively, swallowing difficulties persist for half of survivors.\cite{25}

Despite the prevalence of dysphagia post-oesophagectomy as well as its impact on QOL, the prevalence, nature and trajectory of dysphagia has been poorly studied in oesophageal cancer. Some small studies have identified impairment of oropharyngeal structures post-operatively during videofluoroscopy (VFS). Swallowing impairment following resection have been reported to include a reduction in tongue pressure, delayed initiation of the pharyngeal swallow, impaired biomechanics, RLN palsy and increased pharyngeal residue, which may increase the patients’ risk of aspirating, silently aspirating and developing pneumonia.\cite{26-28} To date there has been no systematic research using a prospective longitudinal study design in this patient group. By determining the prevalence, nature and trajectory of dysphagia post-oesophagectomy the researchers anticipate that this would inform future research and guidelines in prevention and management of dysphagia, including exercise-based dysphagia interventions, which may optimise clinical and QOL outcomes.

**Study objectives**

The primary objectives of this study are:

1. To establish the prevalence, nature, severity and trajectory of dysphagia post-oesophagectomy among adults who have undergone a transthoracic (2-stage or 3-stage) or a transhiatal oesophagectomy (THO).
2. To determine the impact of oropharyngeal dysphagia on HR-QOL in this population across short and long-term time points.

The secondary objectives of this study are:

1. To determine the risk factors for post-operative dysphagia among adults post-oesophagectomy.
2. To identify the post-operative complications of dysphagia within this clinical population.

**METHODS AND ANALYSIS**

**Study design**

This is a proposed prospective longitudinal study which will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology checklist (see online supplemental appendix A).\cite{29}

**Study setting**

The study will take place in a National Oesophageal Centre (NOC) where patients with a diagnosis of oesophageal cancer who are scheduled for oesophagectomy, including curative oesophageal cancer surgery within the study setting will be invited to participate in this study by an independent gatekeeper. This prospective research study will assess patients across four time points: (1) A preoperative assessment of swallow will be recorded using the Functional Oral Intake Scale (FOIS) at time of consent for this study prior to their surgery,\cite{30} (2) on day 4 or 5 post-oesophagectomy resection, (3) 1-month post-surgery and (4) 6-months post-surgery. The research team will evaluate swallowing-related outcome measures across these four time points. Risk factors and post-operative complications have been selected based on research in this clinical population to date. This will create a large resource of original data, which will inform further studies targeting prevention, early detection and intervention in dysphagia.

**Patient and public involvement (PPI)**

PPI in research has evolved over the past decade demonstrating a positive impact on health-related research.\cite{31} Early collaboration is known to enhance the quality and relevance of research when setting research priorities important to both the researcher and PPI, while also guiding further research.\cite{32} This prospective longitudinal
Study has two PPI representatives (one male (SD); one female (BW)) involved on the research team, both of whom have undergone curative oesophageal cancer treatment. The PPI representatives are participating throughout the research study from the research design to dissemination. The PPI committee initially reviewed resource materials including the consent forms, patient information leaflet and patient-reported outcome measures (PROMs) for their relevance and ease of use. PPI involvement will be recorded using the Guidance for Reporting Involvement of Patients and the Public 2 form, ensuring quality and consistency throughout the research. The PPI will be an integral part of the Knowledge Exchange and Dissemination scheme plan.

### Study participants

Eligibility criteria are listed below.

#### Inclusion criteria

- A diagnosis of oesophageal cancer as confirmed by biopsy.
- Treated with curative intent involving surgery, which may be either open or minimally invasive.
- +/- neoadjuvant/adjuvant therapy.
- Scheduled for either a transthoracic (2-stage or 3-stage) or THO.
- Adults (>18 years).
- Ability to provide informed consent as per ethical approval obtained.

#### Exclusion criteria

- Known metastatic disease.
- Unable to complete VFS due to post-operative complications on POD 4 or 5.
- Patients who experience prolonged intubation beyond enhanced recovery after surgery (ERAS) protocol (>2 days).
- Patients who have a tracheostomy inserted due to failed extubation, secondary to prolonged intubation or reintubated post-operatively.
- Premorbid conditions potentially causing oropharyngeal dysphagia such as an acute or progressive neurological disease, history of head and neck cancer.
- 2-stage oesophagectomy with a confirmed anastomotic leak based on failed water-soluble swallow study at POD 5.

### Patient recruitment

The proposed study will recruit 60 adults with oesophageal cancer undergoing oesophagectomy for curative intent. Participants will be recruited from the NOC, at St. James’s Hospital (SJH). Details on recruitment and data collection can be viewed in figure 1.

### ERAS protocol

All participants will be treated according to standardised ERAS care pathway (see online supplemental appendix B), involving either multimodal therapy (pre-operative chemotherapy alone or combined with radiation therapy), as per the MAGIC/FLOT or CROSS regimens, respectively, or surgery only. Surgical resection is typically performed at least 6 weeks post neoadjuvant therapy. Date of expected discharge from hospital is POD 9 as per the local oesophagectomy integrated care pathway.

### Study protocol

#### Videofluoroscopy

The prevalence, nature and trajectory of oropharyngeal dysphagia post-oesophageal resection will be examined using VFS, a reference standard instrumental evaluation of oropharyngeal dysphagia and the evaluation of aspiration risk. Two VFS examinations will be completed on patients undergoing transthoracic (2-stage or 3-stage) and THO across two time points, immediately post-operatively (POD 4 or 5) and at 6-months post-oesophagectomy. Where a water-soluble contrast swallow study is required for inpatients post 2-stage oesophagectomy, the VFS will be completed immediately after this study, once the radiologist has ruled out an anastomotic leak. If an anastomotic leak is determined in this test, the participant will be withdrawn from the research study and the UGI clinical team informed.
Tongue pressure evaluation

To investigate the nature of oropharyngeal dysphagia within this population, tongue pressure will be measured at three study time points. The Iowa Oral Performance Instrument (IOPI) is a handheld device frequently employed in clinical dysphagia research which will be used to measure tongue pressure. This evaluation will be conducted at the bedside (POD 4 or 5) and in outpatient clinics (1-month and 6-month time points) before the VFS examination, where relevant. Participants will be instructed to insert an air-filled bulb into the oral cavity and to use their tongue to press this bulb against their hard palate. Measures of anterior peak tongue pressure (kPa) and tongue endurance (s) will be obtained.

Cough reflex testing

To evaluate laryngeal sensation, a dose–response method of cough reflex testing (CRT) will be measured across two of the study time points (prior to VFS POD 4 or 5 and at the 6-month clinic). CRT involves inhalation of a single concentration of a tussive agent (citric acid) via a facemask nebuliser for a fixed period (within 15s of starting the nebuliser). For best sensitivity and specificity to detect silent aspiration risk and impaired laryngeal sensation, a dosage of 0.4–0.8 mol/L of citric acid in 0.9% saline solution is recommended. In this study, various increments of citric acid in conjunction with a placebo 0.9 normal saline will be administered. A cough response will be considered positive if two (C2) or more consecutive strong coughs are triggered within the time period where citric acid is induced. A weak cough will be determined as a cough that does not appear strong to clear material from the airway and is deemed substantially weaker than their own volitional cough. Patients who do not cough may indicate a greater silent aspiration risk and will be documented as a negative result. The findings of the test will be marked as a pass or fail result.

Aerodigestive symptoms

Based on feedback from the patient representatives, aerodigestive symptoms including cough and reflux are commonly experienced post-oesophagectomy and, given their strong association with swallowing, will be captured alongside swallow status in this study. The Reflux Symptom Index has been selected to address this and will be administered to participants across three time points (POD 4 or 5, 1-month and at 6-months) within the research study.

Patient-reported outcome measures

Based on feedback from PPI representatives, the PROMs selected for this study include the MDADI and the SWAL-QOL. The MDADI and the SWAL-QOL are validated dysphagia-specific QOL measure which is commonly used in dysphagia research. The EORTC-18 is another PROMs developed specifically for oesophageal cancer which is frequently used to evaluate HR-QOL in oesophageal cancer research (see table 1).

Primary outcome measures

VFS analysis

The primary researcher, an experienced SLT, will complete the VFS analysis. Modified Barium Swallow Impairment Profile (MBS-Imp) ratings will be used to rate the presence, severity and trajectory of any swallow pathophysiology. Fifteen randomly selected VFS studies (25%) will be rerated by blinded researchers to minimise bias (AG and JR).

The following validated VFS analysis measures will be obtained:

1. MBS-Imp ratings to identify the presence, severity and nature of any swallow pathophysiology.

The VFS images will be analysed frame by frame and graded using...
the standardised MBS-Imp to identify the presence, severity and nature of swallow pathophysiology across 17 components. The components closely examine physiological components including the oral, pharyngeal and oesophageal phases of swallowing via lateral and AP radiological positioning during VFS. Please see table 2.

2. Penetration-Aspiration Scale (PAS) ratings to measure swallow safety and cough response to aspiration across all swallows. The validated PAS will be used to evaluate aspiration and cough response to penetration and aspiration. This is an 8-point ordinal scale, which characterises the depth and response to airway penetration/aspiration during a VFS study.

3. Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) score will be used to stratify participants into dysphagia and non-dysphagia subgroups.

### Secondary outcomes

#### Risk factors

The data on risk factors and post-operative complications will be obtained from participants’ medical charts and from a local research database. Potential predictor variables will include: (1) age, (2) gender, (3) pre-surgical chemo/radiation, (4) tumour staging, (5) tumour type (squamous cell carcinoma/adenocarcinoma), (6) surgery type, (7) surgery duration (measured in hours), (8) RLN damage, (9) presence/degree of sarcopaenia using the Strength, Assistance With Walking, Rise from a Chair, Climb Stairs, and Falls; SWAL-QOL, Swallowing Quality of Life questionnaire.

#### Post-operative complications

Post-operative complications data will be collected from medical records and post-oesophagectomy database at outpatient appointments (1-month and 6-month clinic). Data will be obtained on (1) length of stay in the Intensive Care Unit (ICU) (days >3 days); (2) time to oral intake (days >5-POD); (3) tube feeding duration (days >30 days post discharge); (4) presence of pneumonia as per American Thoracic Society (ATS) post-operative pneumonia score (as per local UGI database) (yes/no); (5) oesophageal strictures±dilatation/stenting; (6) mortality/survival rates; and (7) other complications as per the Esophageal Complications Consensus Group definitions.

### Table 1: Swallowing, nutritional and QOL measurements across all time points

| Instrument | Time point 1: baseline function and consent | Time point 2: POD 4/5 | Time point 3: 1 month | Time point 4: 6 months |
|------------|-------------------------------------------|----------------------|----------------------|----------------------|
| 1. Swallow screening tool (TOR-BSST) | x | x | x | x |
| 2. Cough reflex testing (CRT) | x | x | x | x |
| 3. Tongue pressure measurement (IOP) | x | x | x | x |
| 4. FOIS, IDDSI, SARC-F, MST, weight and BMI | x | x | x | x |
| 6. QOL measures: | x | x | x | x |
|   ► MDADI | | | | |
|   ► SWAL-QOL | | | | |
|   ► EORTC-18 | | | | |

### Table 2: Modified Barium Swallow Impairment Profile analysis components

| Number | Physiological component |
|--------|-------------------------|
| 1      | Lip closure             |
| 2      | Tongue control during bolus hold |
| 3      | Bolus preparation/mastication |
| 4      | Bolus transport/lingual motion |
| 5      | Oral residue            |
| 6      | Initiation of pharyngeal swallow |
| 7      | Soft palate elevation   |
| 8      | Laryngeal elevation     |
| 9      | Anterior hyoid excursion|
| 10     | Epiglottic movement     |
| 11     | Laryngeal vestibular closure |
| 12     | Pharyngeal stripping wave |
| 13     | Pharyngeal contraction (AP view) |
| 14     | Pharyngoesophageal segment opening |
| 15     | Tongue base retraction  |
| 16     | Pharyngeal residue       |
| 17     | Oesophageal clearance (AP view) |
| AP     | anterior–posterior       |
Pneumonia

PPCs, primarily pneumonia, is a common post-operative complication, which may be infection associated or complicated by respiratory failure or acute respiratory distress syndrome (ARDS). The risk is greater in patients with existing chronic obstructive pulmonary disease or in current smokers. Other risk factors include age, gender, total number of lymph nodes resected and operation approach (transsthoracic extended). The ATS post-operative pneumonia score will be used to determine pneumonia in post-oesophagectomy patients. The ATS define hospital-acquired pneumonia as a pneumonia not incubating at the time of hospital admission, occurring >48 hours post hospital admission whereas ventilated-acquired pneumonia is determined >48 hours post endotracheal intubation. Pneumonia is suspected if the patient has radiographic infiltrates that is new or progressive in association with the following clinical findings suggestive of a pneumonia include: (1) new onset of fever, (2) purulent sputum, (3) leukocyosis and (4) a decline in oxygenation. As pneumonia is the most prevalent complication post-oesophageal resection, research supports assessing patients for any swallowing dysfunction or predisposition to aspiration prior to commencing oral intake to reduce risk of post-operative complications and mortality. As the prevalence, nature and trajectory of oropharyngeal dysphagia has not been determined in a prospective longitudinal study, its link and impact on pneumonia rates post-oesophageal cancer surgery are relatively unknown.

Study size

This is an exploratory longitudinal study in an area with limited previous research or group comparisons and no reporting of effect size. Based on previous literature in this cancer cohort to estimate an effect size 0.5 at a significance level of 0.05 and a power of 0.8, a sample size of 60 is calculated for repeated measures. This sample estimate is consistent with other publications in this area.

Data analysis

SPSS V.22.0 will be used for statistical analyses. Variables will be tested for normality using the Shapiro-Wilks test. Normally distributed variables will be summarised as mean and SD. Non-normally distributed data will be summarised as median and IQR. Categorical variables are presented as frequency (percentage). To establish changes in participant swallow outcomes across time points, repeated measures will be performed using repeated measures analysis of variance or Friedman tests.

To identify independent risk factors, multiple logistic regression will be performed. To identify complications of dysphagia, mean/median (depending on distribution of data) differences in length of hospital stay, pneumonia, sarcopaenia, tube-feeding reliance, mortality and QOL will be compared across dysphagia and non-dysphagia subgroups. The VFS protocol outlined includes a robust system of validated measures to detect oropharyngeal dysphagia in this patient group. A strict data management plan includes data being stored securely, anonymously and processed in adherence to the general data protection regulator best practice guidelines in line with ethical approval.

Ethics and dissemination

Ethical approval has been obtained from the SJH-Tallaght University Hospital (TUH) Joint Research Ethics Committee (J-REC) (2021-Jul-310), alongside the SJH Research and Innovation (R&I) committee. The patient will be formally enrolled into the research study if meets the research criteria and informed consent has been obtained. The primary researcher (MH) involved will eliminate any potential risks to the participant. During the procedure, the patient may be at risk of aspiration if oropharyngeal dysphagia post-oesophagectomy is present. The researcher will inform the patient, refer to inpatient Speech and Language Therapy and Physiotherapy team and notify the UGI Surgeons. The Radiology department where the VFS will take place is located within SJH and is covered by the hospital response team. All adverse events will be documented, and any serious adverse incidences will be immediately reported to the patients’ surgical team and to the research ethics committee.

Findings of the prospective longitudinal study will be disseminated via conference presentations including the World Dysphagia Summit, Dysphagia Research Society, The European Society of Swallowing Disorders and the International Society of Diseases of the Esophagus conference. The findings will be published in peer-reviewed academic journals. Study participants will be informed of study results.

DISCUSSION

Data collection and analysis will be completed at a NOC, where approximately 55–60 curative oesophageal resections are completed annually. This research study has not received any specific grants from funding agencies, and no known competing financial interests or personal conflict that could appear to influence the nature of this research has been declared.

As survival rates are improving among adults with oesophageal cancer, there has been a shift in research and clinical focus to optimise HR-QOL among survivors. Dysphagia is strongly associated with HR-QOL in this population, but relatively understudied in terms of prevalence and modifiable intervention target, and the studies proposed will provide comprehensive data on this cohort and inform further research and clinical advances in this context. Physiological changes impacting the oropharyngeal swallow across four separate time points will be determined using rigorous reference standard and validated swallowing assessment tools. A robust study design will be implemented, using a broad range of clinical swallowing outcomes. This will be examining the prevalence, nature
and trajectory of oropharyngeal dysphagia following oesophagectomy.

PPI will be a key strength in this research study. Patients’ previous experience of the oesophageal cancer journey will provide invaluable insight and guidance across different time points in the study. Furthermore, the collaboration between the researcher and committee members will strengthen research priorities set out and aim to meet at different intervals throughout the research cycle within this study.

This study has some limitations that we acknowledge. Firstly, the risk of post-operative complications including ARDS, pneumothorax, risk of re-intubation, delirium, anastomotic leak who require medical interventions, will prevent recruitment into this study. Failure to collect data on patients with complex post-operative needs who may potentially present with an oropharyngeal dysphagia is recognised as a limitation. Patient retention may be challenging due to the increased risk of cancer recurrence in this population, ultimately impacting their ability to participate during the different time points. For this reason, it was decided to recruit patients up to 6-months post-resection rather than 1-year following oesophagectomy. The author acknowledges that the 6-month timeframe may not fully capture swallowing impairment and QOL measures following surgery, however this research group is also conducting another major study, examining the prevalence, nature and impact of dysphagia 1-year post-oesophagectomy and into survivorship.

This longitudinal study will create a large database encompassing detailed information about the presence, nature and trajectory of dysphagia in the post-oesophagectomy setting, its link to other complications and its impact on recovery of QOL. The database will inform the development of intervention programmes tailored to the unique needs of people with oesophageal cancer. The results will provide a large resource of original data and inform further studies targeting prevention and early intervention. Furthermore, the findings may target development of swallowing compensatory strategies and rehabilitation therapy to optimise swallow function and safety. The results may further inform current clinical practice and provide direction for future research.

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