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The Nature, Severity and Impact of Chronic Oropharyngeal Dysphagia following Oesophageal Cancer Surgery

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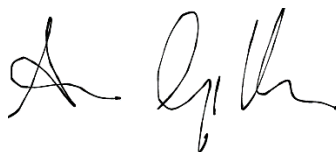
Declaration

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Two page Summary of **Methods** and **Main Findings**

The aim of this thesis was to identify 1) how chronic oropharyngeal dysphagia (COD) presents post-oesophageal cancer surgery, 2) the impact of COD and aerodigestive symptoms on quality of life throughout survivorship and 3) if there is evidence to guide oropharyngeal dysphagia rehabilitation in adults with oesophageal cancer. Forty participants consented to participate and met the inclusion criteria. Each participant attended a 60 minute session at the National Oesophageal Cancer Centre on one occasion where they underwent an instrumental evaluation of swallowing (videofluoroscopy), completed a lingual assessment, provided patient reported outcomes relevant to swallowing, quality of life, reflux, sarcopenia and oral intake status, and participated in a semi-structured interview.

The pulse and frame rates on videofluoroscopy were 25 frames per second. Barium powder was prepared to a 20% weight to volume concentration. Due to early satiety in this cohort and concerns around radiation dosage, participants self-administered just two trials of the following consistencies in the lateral position: IDDSI Level 0 (thin fluid) x5ml from a cup, IDDSI Level 0 x 10ml from a cup, IDDSI Level 0 consecutive sips from a cup, and IDDSI Level 4 Puree x5ml from a teaspoon and just one IDDSI Level 7 Regular Carr cracker with 3ml of IDDSI Level 4 puree on the surface. The anterior-posterior view protocol consisted of two trials of IDDSI Level 0 x20ml from a cup, two trials of IDDSI Level 4 Puree x 5ml by spoon, and one 13mm barium tablet.

Swallow safety and swallow efficiency were rated using the Dynamic Imaging Grade of Swallowing Toxicity v2 (DIGESTv2). Airway protection was measured using the Penetration-Aspiration Scale. Swallow physiology was measured using the MBS Impairment Profile. Oesophageal transit time (OTT) was calculated from the moment the bolus head left the pyriform sinuses and entered the oesophagus to the moment the tail of the bolus exited the lower oesophagus. The Iowa Oral Performance Instrument (IOPI) measured maximum isometric lingual strength in the anterior and posterior positions and maximum anterior lingual endurance. Based on feedback from a Patient and Public Involvement Committee, the EAT-10 and Mayo Dysphagia Questionnaire (MDQ-2weeks) were completed by participants to measure self-reported oropharyngeal and oesophageal dysphagia. The Reflux Symptom Index (RSI), SARC-F (Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls), Functional Oral Intake Scale (FOIS), MD Anderson Dysphagia Inventory (MDADI), and EORTC-QLQ-OES-18 were completed to measure self-reported reflux, sarcopenia, oral intake status, and the impact of oropharyngeal /oesophageal dysphagia on quality of life, respectively.

Fourteen (35%) participants had COD on DIGESTv2, the majority of whom (79%) had mild dysphagia. Two participants aspirated and there was a statistically significant difference in aspiration (PAS 6-8) versus no-aspiration (PAS 1-5) across the three surgical groups ($\chi^2(2)= 7.07$, $p<0.029$), with only participants from the transhiatal group aspirating. All participants had impaired pharyngeal swallow physiology to some extent on videofluoroscopy using the MBSImP; 40 (100%) had impaired swallow initiation, 36 (90%) had pharyngeal residue, 32 (80%) had reduced anterior hyoid excursion, and 28 (70%) had impaired laryngeal elevation. Tongue strength and endurance were largely within normal parameters (mean maximum posterior tongue strength, anterior tongue strength and anterior tongue endurance results on the IOPI were 39.9 kPa, 42.9 kPa and 23.5 seconds), however, 72.5% of participants had abnormal amounts of oral residue. In addition, 80% had impaired oesophageal clearance, which was worse for those who had oesophagogastric junction (OGJ) tumours ($\chi^2(2)=8.199$, $p = .017$) and/or a thoracic site of anastomosis ($\chi^2(1)= 4.339$, $p = .037$). Oesophageal transit time was also statistically higher for OGJ tumours ($\chi^2(2)=6.043$, $p = .049$). The mean OTT for IDDSI levels 0 and 4 were 26.4 seconds and 38.31 seconds, respectively.

Quantitative and qualitative results revealed that quality of life (QoL) was impacted in the long-term post oesophageal cancer surgery. The median (IQR) results for patient-reported outcomes showed a mild impact (MDADI Global: 5(4,5), MDADI Composite 77.9 (60.0,92.6), and EORTC-18 33.3 (24.1,48.2)). Subjective reports of the impact of chronic aerodigestive symptoms were, however, substantial. Key themes relating to the impact of aerodigestive symptoms on QoL, identified through reflexive thematic analysis, were isolation (being alone in managing chronic aerodigestive symptoms because of a lack of support/ understanding of community health care professionals), fear (concern that dysphagia may result in a choking episode or be a sign of cancer recurrence), altered work capacity (pain, embarrassment, discomfort, fatigue caused by chronic aerodigestive symptoms impacting the ability to return to work in the same capacity as before), and avoidance of social situations involving food (pain, embarrassment, and discomfort caused by chronic aerodigestive symptoms restricting their ability to socialise).

A systematic review found that there is a low-volume of low-quality evidence to support exercise-based dysphagia rehabilitation in adults undergoing surgery for oesophageal cancer. This consisted of a search of ten databases and three clinical trial registries which retrieved 7938 articles. Three studies met the eligibility criteria that included a total of 311 participants. Following extraction of the data using Covidence software, assessment of the risk of bias was determined using ROBINS-I and the Downs & Black Checklist. The GRADE Approach was used to identify the certainty of the entire body of evidence.

‘Let’s start at the very beginning.’

Richard Rodgers and Oscar Hammerstein II

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List of Abbreviations

AG	Anna Gillman
AJCC	American Joint Committee on Cancer
ALARA	As Low As Reasonably Achievable
ALS	Amyotrophic Lateral Sclerosis
ANOVA	Analysis of variance
APC	Argon Plasma Coagulation
ASHA	American Speech Hearing Association
BEDQ	Brief Oesophageal Dysphagia Questionnaire
BMI	Body Mass Index
BMJ	British Medical Journal
CCS	Case Control Study
CDBIMS	Completed Division of Bilateral Infrahyoid Muscles Attached to Sternum
CDC	Centre for Disease Control
CEO	Chief Executive Officer
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CK	Ciarán Kenny
COD	Chronic Oropharyngeal Dysphagia
COPD	Chronic Obstructive Pulmonary Disease
COREQ	Consolidated Criteria for Reporting Qualitative Studies
COS	Core Outcome Set
CP	Cricopharyngeal
CROSS	Chemoradiotherapy for Oesophageal Cancer Followed By Surgery
CRT	Cough Reflex Testing
CS	Case Series
CT	Computed Tomography
CVA	Cerebral Vascular Accident
DIGEST	Dynamic Imaging Grade of Swallowing Toxicity
DOF	Delayed Oral Feeding
DRS	Dysphagia Research Society
EAT10	Eating Assessment Tool - 10
EMBASE	Excerpta Medica Database
EMR	Endoscopic Mucosal Resection
EMST	Expiratory Muscle Strength Training
ENT	Ear Nose Throat
EOF	Early Oral Feeding
EORTC	European Organisation For Research And Treatment Of Cancer
EPICOT	Evidence, Population, Intervention, Comparison, Outcomes, and Time
ERAS	Enhanced Recovery After Surgery
ESD	Endoscopic Submucosal Dissection
ESMO	European Society for Medical Oncology
ESPEN	European Society for Clinical Nutrition and Metabolism
ESSD	European Society for Swallowing Disorders
FDA	Food and Drug Administration
FEES	Flexible Endoscopic Evaluation of Swallowing
FILS	Food Intake Level Scale
FLND	Field Lymphadenectomy
FOAMS	Functional Outcome Assessment in Swallowing

FOIS	Functional Oral Intake Scale
GDPR	General Data Protection Regulation
GI	Gastrointestinal
GLP	Glucagon-like Peptide
GOJ	Gastro-oesophageal Junction
GORD	Gastro-oesophageal Reflux Disease
GP	General Practitioner
GRADE	Grading of Recommendations, Assessment, Development & Evaluation
GRBAS	Grade, Roughness, Breathiness, Asthenia and Strain
GRIPP2	Guidance for Reporting of Patient and Public Involvement 2
HRM	High Resolution Manometry
HRQoL	Health Related Quality of Life
ICC	Intraclass correlation coefficient
IDDSI	International Dysphagia Diet Standardisation Initiative
IOMC	Institute of Medicine (US) Committee
IOPI	Iowa Oral Performance Instrument
IQR	Inter-quartile range
ISDE	International Society for Diseases of the Esophagus
ISRCTN,	International Standard Randomised Controlled Trial Number
IW	Irene Walsh
JR	Julie Regan
JVR	John V Reynolds
JREC	Joint Research and Ethics Committee
KAP	Kerma Area Product
LOS	Lower Oesophageal Sphincter
LOHS	Length of Hospital Stay
LPR	Laryngopharyngeal Reflux
MASA	Mann Assessment of Swallowing Ability
MBSIMP	Modified Barium Swallow Impairment Profile
MDADI	MD Anderson Dysphagia Inventory
MDQ	Mayo Dysphagia Questionnaire
MDT	Multi-disciplinary Team
MEDLINE	Medical Literature Analysis and Retrieval System Online
MESH	Medical Subject Headings
MW	Margaret Walshe
MH	Michelle Hayes
MIE	Minimally Invasive Esophagectomy
MIP	Maximum Isometric Pressure
MRI	Magnetic Resonance Imaging
NCCP	National Cancer Control Programme
NHS	National Health Service (UK)
NMES	Neuromuscular Electrical Stimulation
OGD	Oesophagogastrroduodenoscopy
OGJ	Oesophagogastric Junction
OTT	Oesophageal Transit Time
PAS	Penetration-Aspiration Scale
PBT	Proton Beam Radiotherapy
PDT	Photodynamic Therapy

PEG	Percutaneous Endoscopic Gastrostomy Tube
PEJ	Percutaneous Endoscopic Jejunostomy Tube
PHRIM	Pharyngeal High Resolution Impedance Manometry
PLOHS	Post-operative Length of Hospital Stay
POD	Post Operative Day
PPC	Postoperative Pulmonary Complications
PPI	Patient and Public Involvement
PRIMSA	Preferred Reporting Items for Systematic Reviews and Meta Analysis
PROM	Patient Reported Outcome Measure
PROSPERO	International Prospective Register of Systematic Reviews
PYY	Postprandial Peptide YY
QOL	Quality of Life
RCT	Randomised Control Trial
REC	Research Ethics Committee
ReStOre	Rehabilitative Strategies Following Oesophageal Cancer
RFA	Radiofrequency Ablation
RFS	Reflux Finding Score
RLN	Recurrent Laryngeal Nerve
RLNP	Recurrent Laryngeal Nerve Palsy
ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions
RSI	Reflux Symptom Index
RSS	Reflux Symptom Score
RTA	Reflexive Thematic Analysis
SARC-F	Strength, Assistance in Walking, Rise from Chair, Climb Stairs, Falls
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
sEMG	surface Electromyography
SEMS	Self-expanding metal stents
SJH	St James's Hospital
SLN	Superior Laryngeal Nerve
SLT	Speech and Language Therapist
SPSS	Statistical Package for the Social Sciences
SSQ	Sydney Swallow Questionnaire
StEP	Standardized Endpoints for Perioperative Medicine
SWAL-QOL	Swallow Quality of Life Questionnaire
TCD	Trinity College Dublin
tDCS	Transcranial Direct Current Stimulation
THO	Transhiatal Oesophagectomy
TIDIER	Template for Intervention Description and Replication
TNM	Tumour Node Metastasis
TOMASS	The Test of Masticating and Swallowing Solids
TOR-BSST	The Toronto Bedside Swallowing Screening Test
UOS	Upper Oesophageal Sphincter
UICC	Union for International Cancer Control
VASES	Visual Analysis of Swallowing Efficiency and Safety
VFS	Videofluoroscopic Study
WBC	White blood cells

Dissemination of Research

Published Papers as part of this PhD:

1. Gillman A, Kenny C, Hayes M, Walshe M, Reynolds JV, Regan J. Nature, severity, and impact of chronic oropharyngeal dysphagia following curative resection for esophageal cancer: a cross-sectional study. *Dis Esophagus*. 2024 Apr 27;37(5):doae003. doi: 10.1093/dote/doae003. PMID: 38266037; PMCID: PMC11060100.
2. Gillman A, Walsh, I, Hayes M, Walshe M, Reynolds JV, Regan J. Long-term Impact of Aerodigestive Symptoms on Adults with Oesophageal Cancer: a Qualitative Study. *International Journal of Speech-Language Pathology*. Accepted for publication and due to be published later in 2024 at <https://doi.org/10.1080/17549507.2024.2360065>.
3. Gillman A, Hayes M, Sheaf G, Walshe M, Reynolds JV, Regan J. Exercise-based dysphagia rehabilitation for adults with oesophageal cancer: a systematic review. *BMC Cancer*. 2022 Jan 10;22(1):53. doi: 10.1186/s12885-021-09155-y. PMID: 35012495; PMCID: PMC8751332.

Published Abstracts as part of this PhD

1. Gillman A, Reynolds JV, Hayes M, Walshe M, Regan J. The nature, severity and impact of curative esophageal resection for esophageal cancer on swallowing throughout survivorship. Preliminary Findings. ISDE 2021 Congress Supplement *Diseases of the Esophagus*, Volume 35, Issue Supplement_2, September 2022, doac051.545, <https://doi.org/10.1093/dote/doac051.545>
2. Gillman, A, Hayes, M, Walshe, M, Sheaf, G, Reynolds, J, Regan, J. Exercised Based Dysphagia Rehabilitation in Esophageal Cancer: a systematic review. Abstract at 10th ESSD Congress, 2020. *Dysphagia* 38 (Suppl 1), 1–60 (2023), S 34 <https://doi.org/10.1007/s00455-022-10457-x>
3. 12th ESSD Congress, 2022 Dysphagia Not yet Published
4. 13th ESSD Congress 2023 Dysphagia Not yet Published

Co-author on other relevant papers as part of our research team:

1. Hayes M, Gillman A, Wright B, Dorgan S, Brennan I, Walshe M, Donohoe C, Reynolds JV, Regan J. Prevalence, nature and trajectory of dysphagia postoesophageal cancer surgery: a prospective longitudinal study protocol. *BMJ Open*. 2022 Sep 22;12(9):e058815. doi: 10.1136/bmjopen-2021-058815. PMID: 36137623.

Oral Presentations (*invited):

* **British Laryngology Association ‘Cutting Edge Laryngology’ Conference** in The Royal Medicine Society in London, October 2024 on ‘SLT role in oesophageal cancer’

* **UK Swallow Research Group (UKSRG) Conference** in Birmingham in February 2024 ‘Oropharyngeal dysphagia in oesophageal cancer, can it be rehabilitated?’

13th Annual ESSD Congress 2023 2 minute oral presentation in Toulouse on ‘Long term lingual dysfunction following oesophageal cancer surgery: a cross-sectional prospective study.’

31st Annual DRS Meeting 2023 in San Francisco on ‘Nature, Predictors and Impact of Chronic Oropharyngeal Dysphagia Following Curative Resection for Esophageal Cancer: A Cross-Sectional Study’.

12th Annual ESSD Congress 2022 in Leuven on ‘Nature and Assessment of Chronic Dysphagia in Oesophageal Cancer: A preliminary cross-sectional study’.

10th Annual ESSD Congress 2020 2 minute oral presentation on Exercise-Based Dysphagia Rehabilitation for Adults with Oesophageal Cancer: A systematic review.

Poster Presentations

13th Annual ESSD Congress 2023 in Toulouse on ‘Long term lingual dysfunction following oesophageal cancer surgery: a cross-sectional prospective study.’

SJH TCD Cancer conference 2023 on ‘Nature, Severity and impact of chronic dysphagia following curative oesophageal resection: preliminary findings’.

18th ISDE World Congress 2021 on ‘Nature, Severity and impact of chronic dysphagia following curative esophageal resection: preliminary findings’.

11th Annual ESSD Congress 2021 on Exercise-Based Dysphagia Rehabilitation for Adults with Oesophageal Cancer: A systematic review.

Awards

1. Award	Four years of PhD fees and €16,500 stipend per year
Purpose	To complete a full-time PhD
Body	Trinity College Dublin Provost Award
Date	2019
2. Award	€621
Purpose	To attend and present at DRS conference 2023
Body	Trinity Research in Social Sciences (TRiSS)
Date	2023
3. Award	€450
Purpose	To attend and present at ESSD conference 2023
Body	Dysphagia Special Interest Group (Ireland)
Date	2023

1. Chapter 1 - Introduction

1.0 Context of this Research

The researcher is a clinical specialist speech and language therapist (SLT) with approximately thirteen years of experience working clinically in the assessment and management of oropharyngeal dysphagia in the acute, inpatient rehabilitative and outpatient rehabilitative settings in Ireland, the United States, New Zealand and Australia. Globally, there is a lack of guidance around how to assess and manage oropharyngeal dysphagia following oesophagectomy. Throughout the researcher's clinical practice, the researcher observed how oesophageal cancer survivors are often not referred to speech and language therapy for swallow evaluations and how, on the rare occasions when they are referred, speech and language therapists typically do not have sufficient training and knowledge to provide adequate assessment and management unless they are working in specialist centres. It is hoped that this early exploratory research will demonstrate if there is a need for SLTs to be key members of the oesophageal cancer multidisciplinary teams (MDT), will help to educate clinicians working with these patients about the nature, severity and impact of oropharyngeal dysphagia, and will create the foundation upon which experimental rehabilitative studies may be designed.

The researcher's role includes designing the research studies, obtaining ethical approval, recruiting all participants, collecting all data, analysing all the quantitative and qualitative data, interpreting the results, and disseminating the findings through publications, lectures and presentations. The researcher will be referred to as the 'main researcher' herein to avoid any confusion.

1.1 Structure of this Thesis

Chapter 2 Literature Review

This section of the thesis provides relevant background information regarding oesophageal cancer and its treatment, and normal and abnormal swallowing (dysphagia). It explores potential causes of swallowing impairment due to the cancer and/ or the cancer treatment. There will be a critical evaluation of research that has been published

on oropharyngeal dysphagia caused by oesophageal cancer and/ or its treatment and the impact of dysphagia on quality of life.

This section will highlight how little has been published on chronic oropharyngeal dysphagia (COD) following oesophageal cancer surgery. It will set up the justification for the research conducted as part of this thesis and inform the hypotheses that will be discussed later.

Chapter 3 – Theoretical Framework

The theoretical framework, which is the basis upon which this body of research is designed, is explored in this chapter.

Chapter 4 – Objectives, Hypotheses and Research Questions

The research for this thesis is broken into three main sections. For each section of this research, there will be a statement of the problem, a list of objectives, the main hypotheses, and a list of the research questions for that section.

Chapter 5 – Patient and Public Involvement Committee

This chapter discusses the involvement of oesophageal cancer survivors in this research and how they influenced the methods and research questions.

The remaining chapters of the thesis include the methods, results and discussion of the research conducted. There are three main sections (studies) to this portion of the thesis:

- The first chapter in this portion (Chapter 6) includes exploratory research of COD in oesophageal cancer. In addition, two areas that are identified as being impaired in a high proportion of participants who undergo instrumental swallow evaluation will receive special attention: the tongue and oesophageal clearance.

- The second section (Chapter 7) explores the impact of dysphagia and other aerodigestive symptoms on quality of life.
- The final section (Chapter 8) aims to identify whether there are any published studies that could guide dysphagia rehabilitation given that some survivors continue to struggle with COD for many years post-surgery.

The main research questions for each of these three sections are outlined below:

1. Nature and Severity of Chronic Oropharyngeal Dysphagia (Chapter 6)

Oropharyngeal Phase of Swallowing

- 1A. *How does COD present post oesophageal cancer surgery?*
- 1B. *What is the strength, nature, and function of the tongue post oesophageal cancer surgery?*
- 1C. *Are there surgical/treatment related variables or clinical tools that can predict COD post oesophageal cancer surgery?*

Oesophageal Phase of Swallowing

- 1D. *What is the nature and extent of oesophageal bolus flow in adults in the long-term post oesophageal cancer surgery and is it associated with any clinical/surgical/pharyngeal dysphagia variables?*
- 1E. *What are the predictors of disrupted oesophageal bolus flow post oesophageal cancer surgery?*

2. Impact of COD and aerodigestive symptoms on quality of life (Chapter 7)

- 2. *What is the impact of dysphagia and other aerodigestive symptoms on Quality of Life (QoL) post oesophageal cancer surgery?*

3. Exercised based Dysphagia Rehabilitation in Oesophageal Cancer; a Systematic Review (Chapter 8)

3. *Is there evidence to guide oropharyngeal dysphagia rehabilitation in adults with oesophageal cancer?*

To improve the flow of this thesis, two decisions were made regarding the structure of this thesis:

1) The Methods and Results relevant to each section are grouped together in the same chapter rather than having just one large Methods chapter and one large Results chapter. 2) The research questions in each section of this thesis are not necessarily grouped in the same way that they are in the published manuscripts. It was hoped that by keeping all relevant information together in the thesis it would be easier to follow. For example, the thesis groups all QoL information in one chapter however QoL is measured in two papers; the quantitative impact of dysphagia on QoL was measured in one paper and swallow-related QoL was measured qualitatively in another paper. As a result it was not possible to include the PDFs directly into each chapter.

Chapter 6- Nature and severity of COD: Methods and Results

This chapter includes the methods and results of a cross-sectional observational study focussed on the research questions outlined above.

Chapter 7 – Impact of COD and other aerodigestive symptoms on Quality of Life: Methods and Results

This research is a mixed methods design. This chapter includes the quantitative and qualitative methodology and results relating to the impact of dysphagia and other aerodigestive symptoms on QoL as outlined in the research questions above.

Chapter 8 – Exercise based Dysphagia Rehabilitation in Oesophageal Cancer; a Systematic

Review: Methods and Results

This chapter includes the methods and results of a systematic review which investigates the research question outlined above.

Chapter 9 – Discussion

In this chapter, the research will consolidate and interpret the key findings from the research questions and the existing literature, followed by a summary and recommendation of next steps, limitations and a conclusion.

Thesis Structure

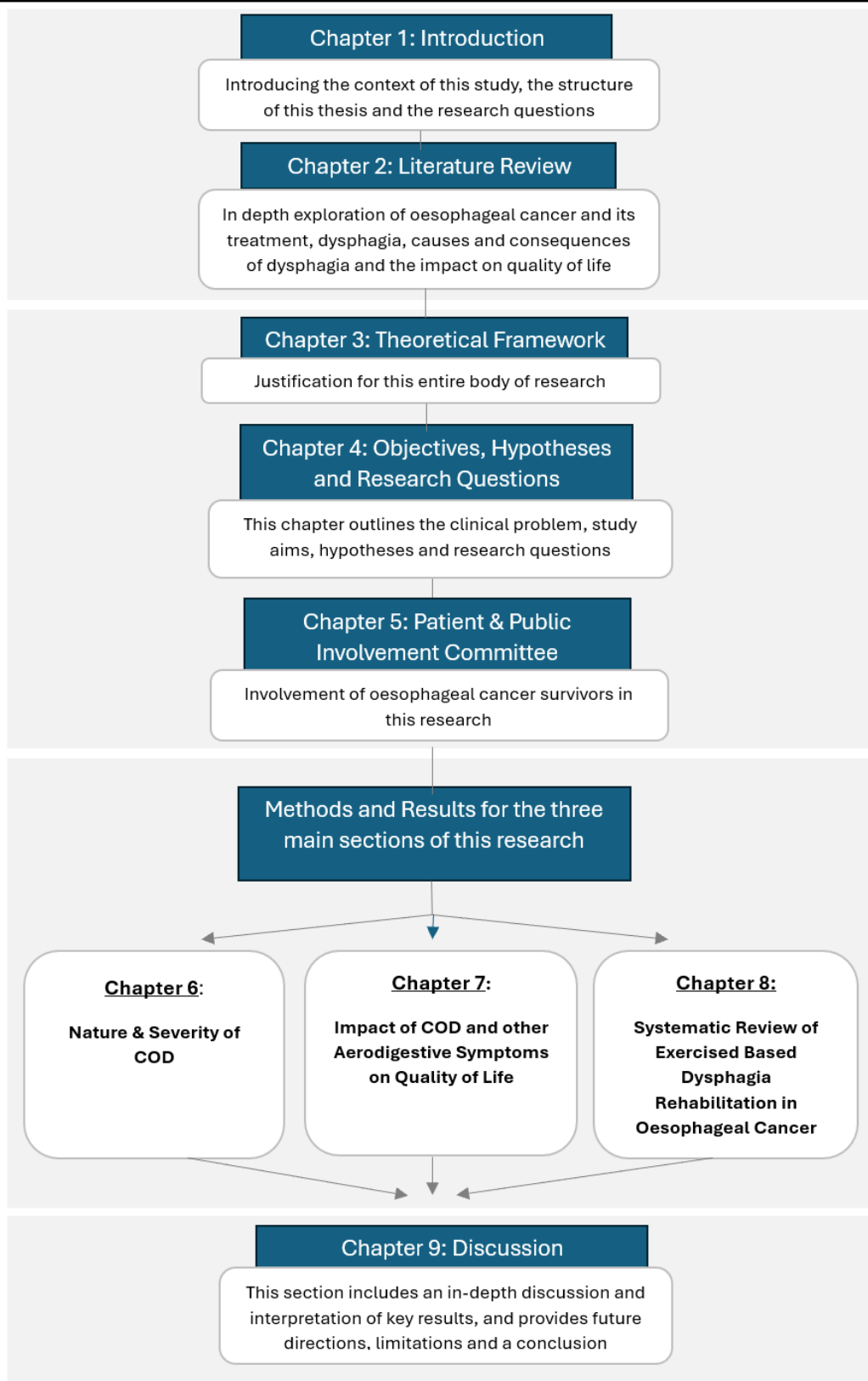


Figure 1 Thesis Structure

2 Chapter 2 - Literature Review

2.0 Introduction to Literature Review

The first section of this chapter will provide pertinent background information relevant to oesophageal cancer, its treatment, and consequences of both. The second and third sections will explain normal anatomy and normal swallowing. The fourth and fifth sections will describe abnormal swallowing and evaluation of swallowing. The sixth, seventh and eighth sections will review published research regarding dysphagia in oesophageal cancer, the causes and consequences of this dysphagia, and the impact it has on QoL. In the final two sections there will be a specific focus on the assessment and management of oropharyngeal dysphagia in oesophageal cancer.

2.1 Oesophageal Cancer

Prevalence

Cancer of the oesophagus has one of the lowest survival rates globally compared with other cancers. It is the seventh most common cancer worldwide and has the sixth most common cancer-related mortality, reportedly responsible for approximately one in every 20 cancer deaths [1-3]. In countries of higher income, recent studies have revealed an approximate five year survival rate of between 15-25% [4-6], increasing to 50% amongst patients who receive curative treatment [7], and up to 90% for patients diagnosed with Stage I cancer [2, 3, 7]. This increase is mostly due to improved patient selection, improved monitoring of Barrett's Oesophagus, technological advances enabling earlier diagnosis, the development of Enhanced Recovery After Surgery (ERAS) protocols, the use of trimodality therapy and pre- or peri-operative chemotherapy, and centralised oesophageal cancer centres with more effective and tailored treatments [8-11].

Interestingly, incidence rates vary across regions of the world. Incidence age-standardised rates by sex show that oesophageal cancer is most common in Eastern Asia, Eastern Africa, and Southern Africa [3], however further research is required to determine potential causes of this such as whether certain nutritional deficiencies may be relevant in those geographical locations [1].

Cancer Type

Squamous cell carcinoma (SCC) and adenocarcinoma are the two main histological subtypes of oesophageal cancer with SCC mostly occurring in the flat cells in the higher two thirds of the oesophagus, and adenocarcinoma, typically developing in the lower third of the oesophagus and often originating from Barrett's mucosa [4]. Worldwide SCC incidence rates are declining and adenocarcinoma rates are increasing [3].

Distribution

Oesophageal cancer is most prevalent in men and women over 70 years of age [12]. Up to 70% of oesophageal cancer diagnoses occur in men [1]. The median age of diagnosis of SCC across 20 countries was found to be 67.5 years [13] with adenocarcinoma reported in the United States to peak between 80-84 years for males, and 85 years+ for females [14]. The female to male ratios are 1:3 and 1:6 for SCC and adenocarcinoma of the oesophagus, respectively [15].

Risk factors

Oesophageal SCC risk factors include smoking, tobacco and consuming excessive alcohol [16], red meat [17], and hot or very hot foods/beverages [18]. Oesophageal adenocarcinoma risk factors include Barrett's oesophagus, male sex [19], obesity [20], and reflux [21]. Oesophageal cancer has been found to be associated with a low intake of certain nutrients which may explain diagnoses in young (14-49 years) non-smokers [12, 22-24].

Treatment

The choice of treatment depends on variables including the tumour location, disease stage, histological type, lymph node involvement, the surgeon's preference, the patient's co-morbidities, and physiological status. Some of the treatment options for superficial cancers include endoscopic mucosal or submucosal resection (EMR or ESD), photodynamic therapy (PDT), mucosal ablation using lasers (photothermal), electrocoagulation, argon plasma coagulation (APC) and radiofrequency ablation (RFA) [25-27].

Surgery alone is no longer typically considered the optimum treatment for locally advanced disease with multimodal treatment increasingly considered standard of care globally [25, 28, 29]. This typically involves neoadjuvant chemoradiotherapy or perioperative chemotherapy in addition to oesophageal resection [30].

Preoperative chemotherapy and chemoradiotherapy have been proven to reduce the likelihood of recurrence and increase the likelihood of survival when compared to oesophageal resection alone [31-33]. A treatment plan for patients receiving neoadjuvant chemoradiotherapy as part of the CROSS (ChemoRadiotherapy for Oesophageal Cancer Followed By Surgery Study) regimen was Chemotherapy (5 cycles of Carboplatin and Paclitaxel on days 1, 8, 15, 22, and 29) with concurrent radiotherapy starting when chemotherapy commenced (41.4 Gy as 23 fractions of 1.8 Gy, 5 days per week).

There are various approaches to surgical resection. Haverkamp et al (2017) conducted a survey of 478 surgeons across 49 countries to identify trends in surgical techniques and found a worldwide trend towards minimally invasive approaches for the curative treatment of oesophageal cancer [34]. 43% of participants preferred minimally invasive transthoracic oesophagectomy with a 2-field lymph node dissection and gastric conduit reconstruction [34].

The two main approaches of open surgical resection include transthoracic or transhiatal (THO) procedures with the first requiring a thoracotomy. The most common transthoracic procedures are the Ivor Lewis approach, a 2-stage en-bloc resection with incisions in the abdomen and right thoracic cavity, typically for distal oesophageal or gastroesophageal tumours, and the McKeown approach, a 3-stage en-bloc resection with incisions in the abdomen, right thoracic cavity and left cervical neck area, typically for middle and upper oesophageal tumours. The Ivor Lewis approach avoids manipulation of the upper oesophagus. The THO approach includes an incision into the abdomen and the left cervical neck area. Figure 2 illustrates the main approaches for oesophageal resection.

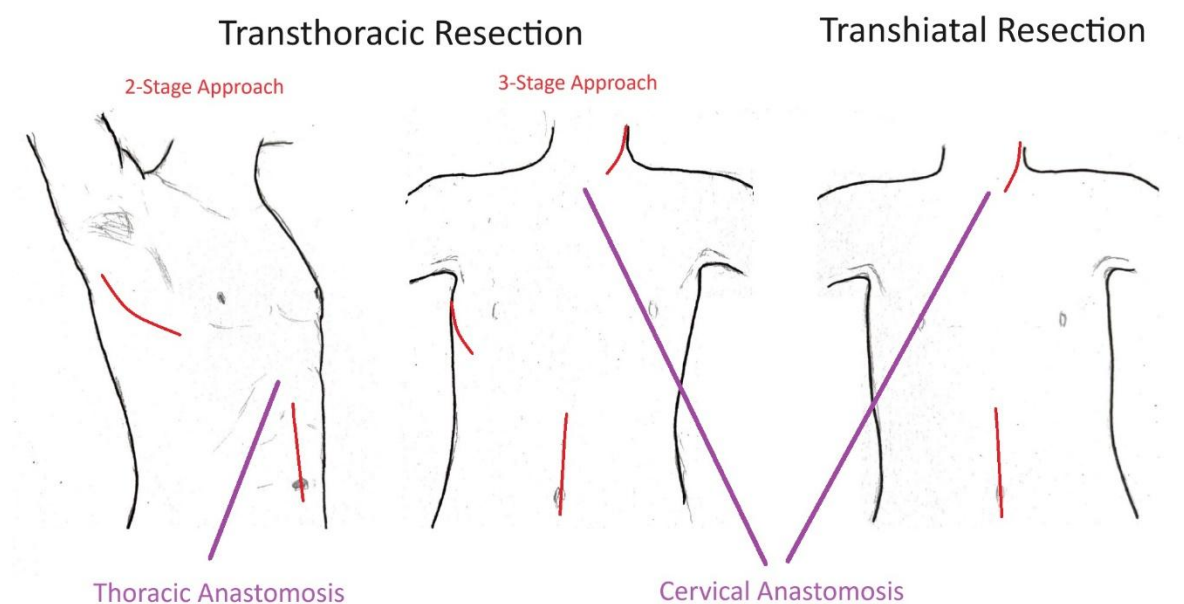


Figure 2 Main oesophageal resection approaches and corresponding sites of anastomosis

A stomach is the most common conduit in oesophageal cancer surgery because of its good vascular supply, long length, and its only needing one anastomosis however the jejunum or colon

are viable alternatives when the gastric conduit is not available [35]. See Figure 3 for an illustration of gastric pull-up following removal of the oesophageal tumour.

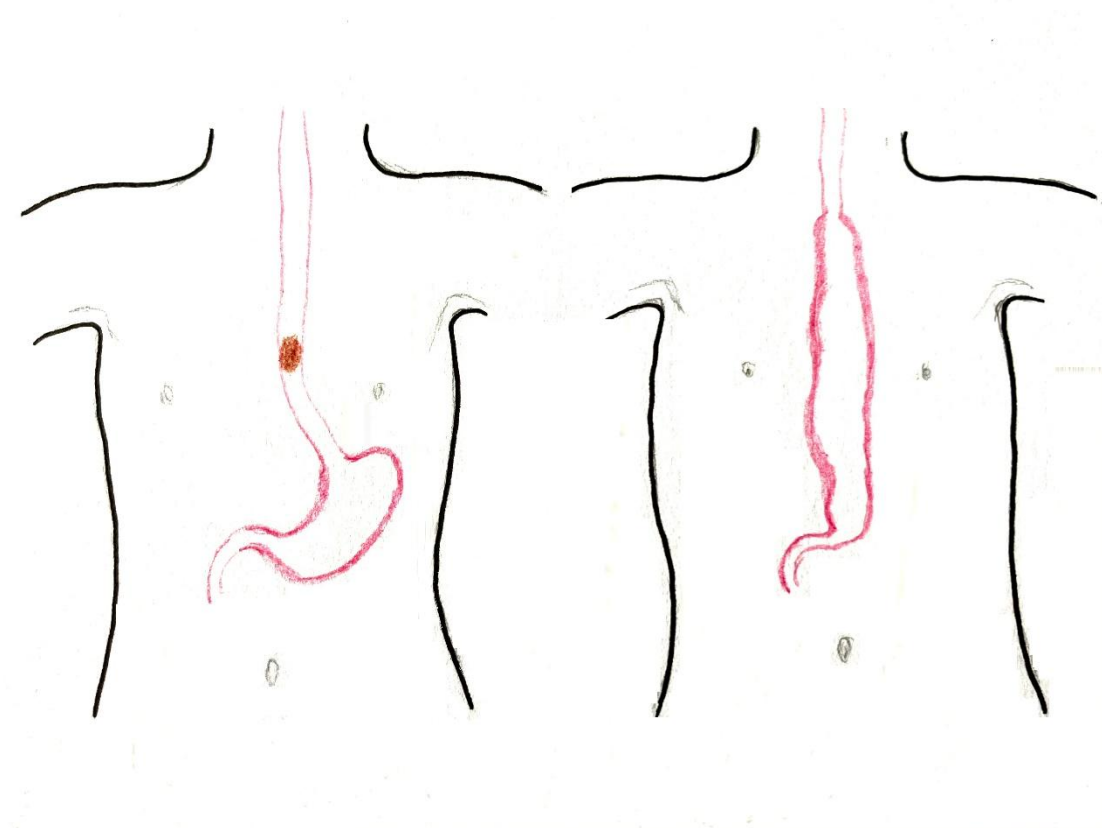


Figure 3 Tumour in oesophagus (A). Gastric pull-up post oesophageal resection (B).

A 3-field lymphadenectomy consists of the dissection of lymph nodes around the neck, mediastinum and abdomen during an oesophagectomy [36]. A 2-field lymphadenectomy includes dissection of lymph nodes around the mediastinum and abdomen [37].

Incision, dissection and anastomosis in the cervical region can provide the benefit of a more extensive oesophageal resection [38], however, it has a higher likelihood of leaking [39, 40]. Although these leaks can result in serious consequences, especially if they are upper mediastinal leaks, they generally tend to be less morbid than leaks in the thorax [41, 42]. Recurrent laryngeal nerve (RLN) damage is possible when the cervical anastomosis takes place and when the lymph nodes are removed from the cervical oesophagus [43].

The procedure for thoracic anastomosis is associated with lower rates of RLN trauma than the procedure for cervical anastomosis [40]. Transthoracic surgery enables direct visualisation of the thoracic oesophagus which can improve oncological outcomes [44], however transthoracic surgery is often avoided in adults with pulmonary co-morbidities, or with smaller tumours, given the risks associated with thoracic anastomotic leak such as cardiopulmonary complications and sepsis [28]. RLN trauma is still possible during a right thoracotomy when the nerves are exposed and the bilateral intrathoracic recurrent nerve chain nodes are dissected [45].

The purpose of the Minimally Invasive Esophagectomy (MIE) approach is to reduce the physiological stress response to trauma and to reduce postoperative complication rates [46, 47]. Other research has indicated that these reductions in complications only become evident after the surgeon undergoes a steep learning curve [41, 48]. There are also hybrid surgical approaches, where an open procedure is combined with laparoscopy and thoracoscopy, and robot-assisted surgeries [27].

For patients deemed appropriate candidates for curative treatment, the typical treatment options and relevant timelines are displayed below in Figure 4.

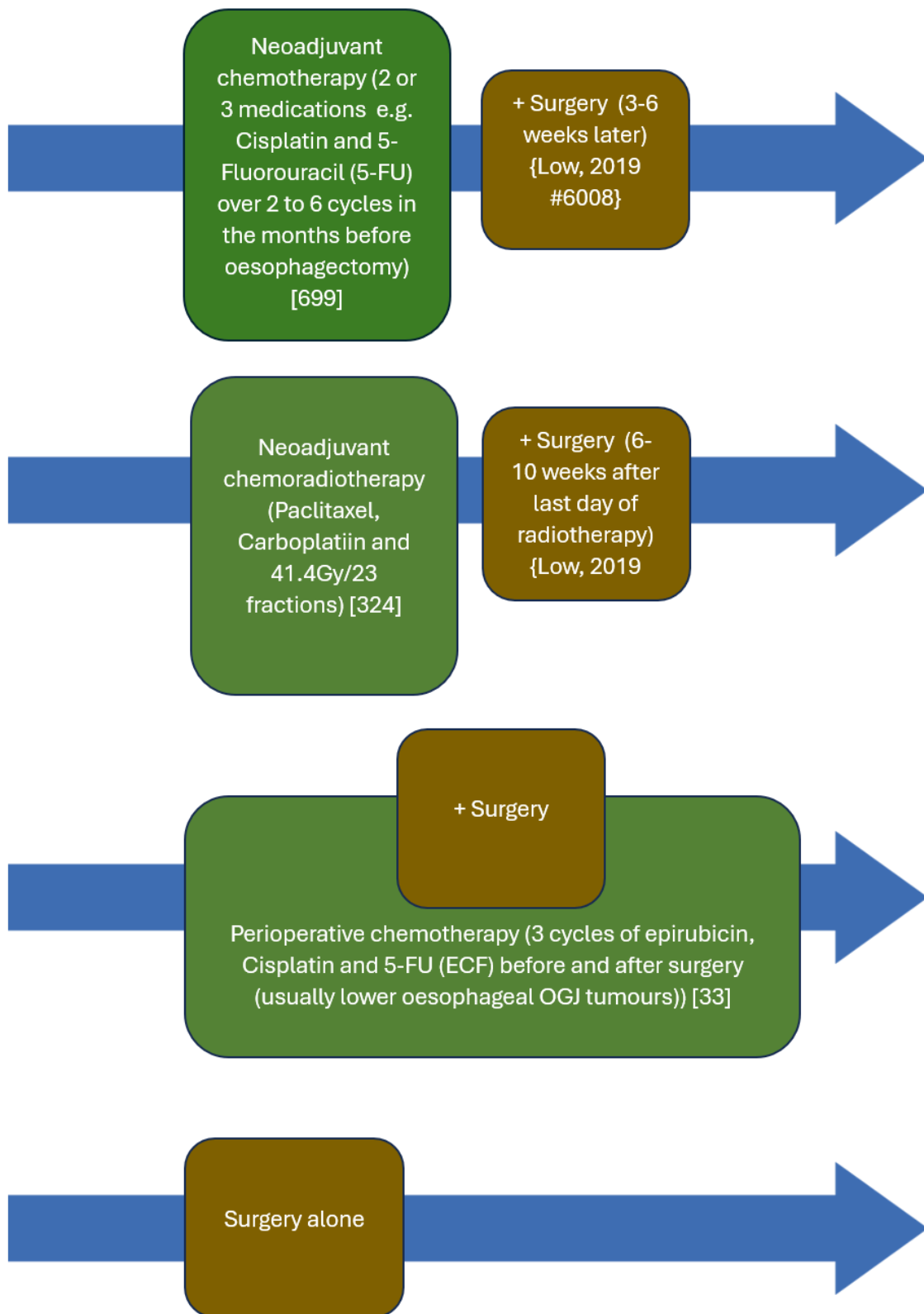


Figure 4 Typical options for oesophageal cancer treatment with curative intent

Complications Post-Surgery

Oesophagectomy surgery is highly invasive and post-operative complications are very common [49, 50], reported to occur in 40-60% of patients [50-52], with major complications consisting of pulmonary complications [50, 53], anastomotic leak and/or stricture [42, 54-56], RLN impairment [57-59], dysphagia [60, 61], and reflux [62, 63].

Pulmonary Complications

The most frequent complication of surgery for oesophageal cancer is postoperative pulmonary complications (PPCs), meaning any type of respiratory compromise that occurs within a month of surgery [64-66]. Survivors of surgery are particularly vulnerable to pulmonary complications [50] because of potential damage to the thoracic wall and intercostal muscles during surgery which may result in alveolar collapse, pulmonary oedema, RLN damage, and poor ventilation [67].

PPCs have been specifically reported in 6% of patients post 3-field lymphadenectomy (3FLND) [53], 7.4% after 3-stage MIE [68], 12% post thorascopic oesophagectomy [69] and ranging from 11% to 28% when multiple types of surgical procedures were conducted (28% [70], 14% [71, 72], 11% [73], and 23% [74]).

In particular, pneumonia has been argued to be the most important complication post oesophagectomy [65]. It has been cited in the literature as occurring in approximately 25% of patients post-operatively and being the most common cause of death [64, 65, 75]. In a study by Atkins et al (2006), which included 379 participants post Ivor Lewis, transhiatal and other surgical approaches, the incidence of death in those participants who developed pneumonia was 20%, compared to 3.1% in those who did not develop pneumonia [65]. Pneumonia was the main cause of death in 54.5% of people who died, and respiratory failure secondary to pneumonia was reported in 81.8% of deaths [65].

There are a variety of screening tools and definitions for identifying pneumonia in the literature [76]. For example, there is the Utrecht Pneumonia Scoring System [77] which considers temperature, leukocyte count and pulmonary radiography in people with oesophageal cancer. There is the definition established by the Center for Disease Control (CDC) which is “new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which include the new onset of fever, purulent sputum, leucocytosis, and decline in oxygenation” [78-81]. There is also the Standardized Endpoints for Perioperative Medicine (StEP) collaborative network’s definition [82] which includes one sign/symptom or laboratory result indicating infection, two or more serial chest images with new or progressive changes (infiltrate/ consolidation/ cavitation) or an organism seen on gram stain or evidence of abscess/ infection on anatomical or histopathologic examination. These varying definitions of pneumonia can cause confusion when measuring pulmonary outcomes in oesophageal cancer research [9] as well in other clinical specialties including dysphagia research.

Intra-thoracic surgery has a higher likelihood of pulmonary complications. Minimally invasive, hybrid and robotic-assisted hybrid approaches have reduced PPCs compared to open approaches [46, 83, 84]. Radiation dose greater than 50Gy may potentially result in increased pneumonitis and fibrosis [85, 86]. Patients with oral bacteria have been found to have a significantly higher rate of PPCs [87] and dental brushing before oesophageal cancer surgery can reduce the incidence of pneumonia most surgery [88].

Anastomotic leak

Anastomotic leaks, where there is a leakage of content from the anastomosis, which can occur at the site of the cervical or thoracic anastomoses, have been reported to occur in approximately 30% of adults post oesophagectomy (n=155) [54]. The cause of anastomotic leak is multifactorial however it is mostly caused by ‘inappropriate ischemia of the gastric fundus’ which is often the site of anastomosis, and issues with the surgical technique used [42]. The consequences of

anastomotic leaks post oesophagectomy can be significantly worse than other gastrointestinal anastomoses because of the contents within the gastric fluid and oral secretions that reach the anastomosis [42]. In addition, the negative intrapleural pressures can facilitate the spread of bacteria throughout the pleural cavity [42]. Most anastomotic strictures are benign however occurrence of an anastomotic stricture more than 12 months post operation may be local cancer recurrence [89].

Recurrent Laryngeal Nerve Damage

RLN damage can occur during the cervical or thoracic surgical procedures [57-59], in particular during lymphadenectomy [90]. Vocal fold paralysis is one of the most commonly reported symptoms when there is damage to the RLN, and it may result in insufficient vocal fold closure and impaired laryngeal sensation [60]. Studies evaluating dysphagia found that RLN damage and/or vocal fold paralysis ranged from 7.6%-65.6% [36, 53, 57, 60, 61, 68-70, 73, 74, 91-94] and in other non-dysphagia studies it was rated similarly from 10-50% [95-100]. One study by Lee et al (2016) found a probability of 42.3% of aspiration if vocal fold paralysis was present [61]. Vocal fold palsy was found to be predictive of aspiration in the acute phase post oesophageal cancer surgery in two studies [49][61]. Vocal fold palsy is also significantly associated with post-operative pneumonia ($p<0.001$) [61][104, 105].

Malnutrition

Oesophageal cancer results in the highest median weight loss before diagnosis compared to other cancer types, with up to 80% of patients malnourished [101-103]. Adults with oesophageal cancer are particularly vulnerable to malnutrition and cachexia, often stemming from an inadequate volume of oral intake due to the tumour impacting the oesophagus, particularly when the disease is more advanced. Oral intake can be further reduced during chemoradiotherapy because of mucosal inflammation, odynophagia, nausea and vomiting [104]. If energy intake is deemed to be insufficient (i.e. less than 60% of energy requirements for more than 10 days), enteral nutrition

will be commenced [104]. Pre-operative nutritional intervention can be recommended as reduced weight loss and reduced nutritional status can impact upon tolerance of neoadjuvant treatment and surgery risk [105-108]. Similarly, post surgery, artificial supplementary nutrition is recommended to minimise bacterial translocation and cytokines which prevent postoperative complications [105, 109]. Participants in a study by Elliott et al (2017) (n=252) had a five-fold increase in sarcopenia identified via computer tomography (CT) 12 months after surgery compared to at the time of diagnosis, with incidence reported in 25% of patients [110]. The authors highlighted that sarcopenia deteriorated independent of postoperative complications suggesting that dietary intake is likely to be a large cause. Enteral nutrition options include percutaneous endoscopic or surgical gastrostomy or jejunostomy tubes (PEG or PEJ). Parenteral nutrition can be used instead if there is not a functioning digestive tract or in addition to the enteral nutrition, and is administered using a catheter and venous access [104].

Other nutritional related consequences include reduced appetite [111, 112], altered taste [113, 114], diarrhoea [113], nausea and vomiting [114], dumping syndrome (when the food is transferred from the stomach before it is inadequately digested) [115, 116], pyloric dysfunction (thickening of pyloric muscles impacting the ability of the stomach to empty food into the intestine) [117], refeeding syndrome (this includes clinical complications such as imbalanced electrolytes caused by rapid introduction of foods after a time of inadequate nutrition, which can be fatal) [112, 118], and reflux [114, 119]. There may also be early satiety caused by altered enteroendocrine physiology such as increased postprandial peptide YY (PYY) and total glucagon-like peptide 1 (GLP-1) levels (small intestinal gut hormones that are secreted as a response to luminal contents such as glucose and fatty acids etc.) which exist two years after surgery, and one of which, GLP-1, is also predictive of weight loss 12 months post-surgery [120]. Unintended weight loss has been detected with an average weight loss of 13% at three years post-surgery [121] and greater than 15% at 5 years post-surgery [122], with a five-fold increase in loss of muscle mass one year post surgery [110]. In addition, malabsorption, an inability to fully absorb certain

nutrients has been reported postoperatively secondary to exocrine pancreatic insufficiency, which is associated with postoperative morbidity [123].

It is worth noting that malnourished patients are also at higher risk of poor compliance with neo-adjuvant treatments [124].

Enhanced Recovery After Surgery Protocol

Enhanced Recovery After Surgery (ERAS) guidelines aim to reduce post-operative risks, morbidity rates and mortality rates associated with oesophagectomy surgery [125]. It consists of a multidisciplinary method for improving care and maximizing recovery through the incorporation of the following key components: a nutritional assessment at diagnosis, multidisciplinary decision making regarding surgery, physical and nutritional prehabilitation [101, 126], surgery being completed 3-6 weeks after chemotherapy and 6-10 weeks after chemoradiotherapy. In addition, there are recommendations specifically for surgery (regarding surgical approach, conduit, pyloroplasty, lymphadenectomy, anastomotic and chest drains, NG tube for decompression), for anaesthetic management and ventilation, early enteral feedings (with target rate by day 3-6), early mobilisation, preoperative counselling and cessation of smoking/alcohol, management of hypothermia, postoperative glycemic control, nausea and vomiting, bowel stimulation and catheters. These recommendations have been found to reduce overall non-surgical and pulmonary complications and reduce length of stay in hospital with no consequential impact on readmission rates [2, 101, 127]. These guidelines have acknowledged that adults with dysphagia post oesophagectomy may have a moderate risk of post-operative complications and those with severe dysphagia may have a high risk of complications [88].

A protocol for the reintroduction of food and fluids post oesophagectomy surgery at Ireland's National Centre for Oesophageal Cancer, St James's Hospital (SJH), which is based on international evidence, is outlined below in Figure 5:

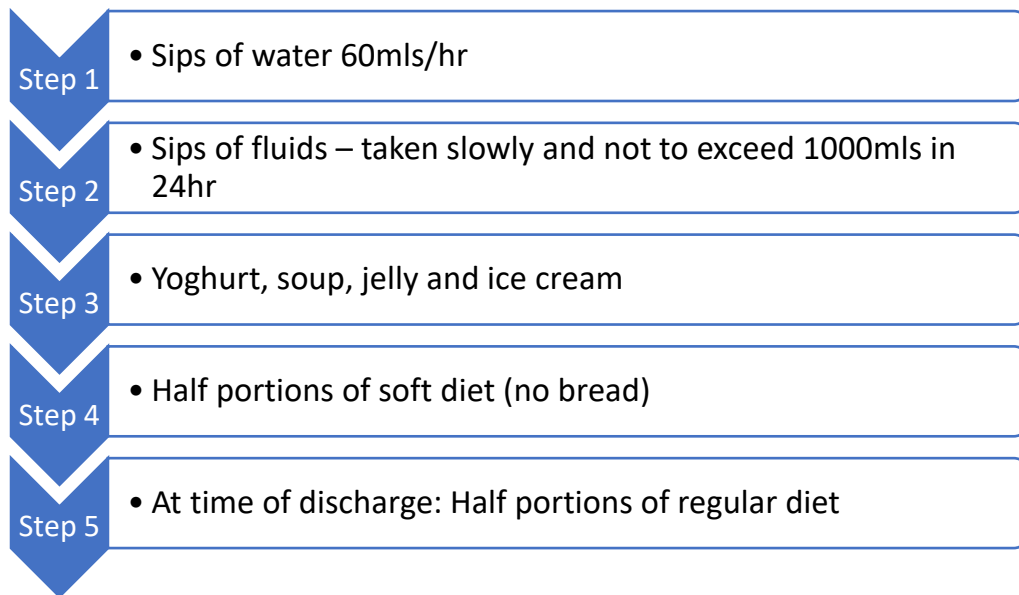


Figure 5 St James's Hospital protocol for introducing food and fluids post oesophagectomy

Step 1 usually commences at day 4 or 5 postoperatively. The rate of progression is advised by the surgical team, with progression through the steps every 24 hours if there are no contraindications such as the presence of chyle leakage in the surgical drains or anastomotic leakage during the water contrast swallow evaluation. Patients are typically discharged on an IDDSI Level 7 regular diet. The SLT may modify the diet consistency if oropharyngeal dysphagia is present. An example of the SLT Enhanced Recovery Pathway at Guys' and St Thomas' in London is included in Figure 6:

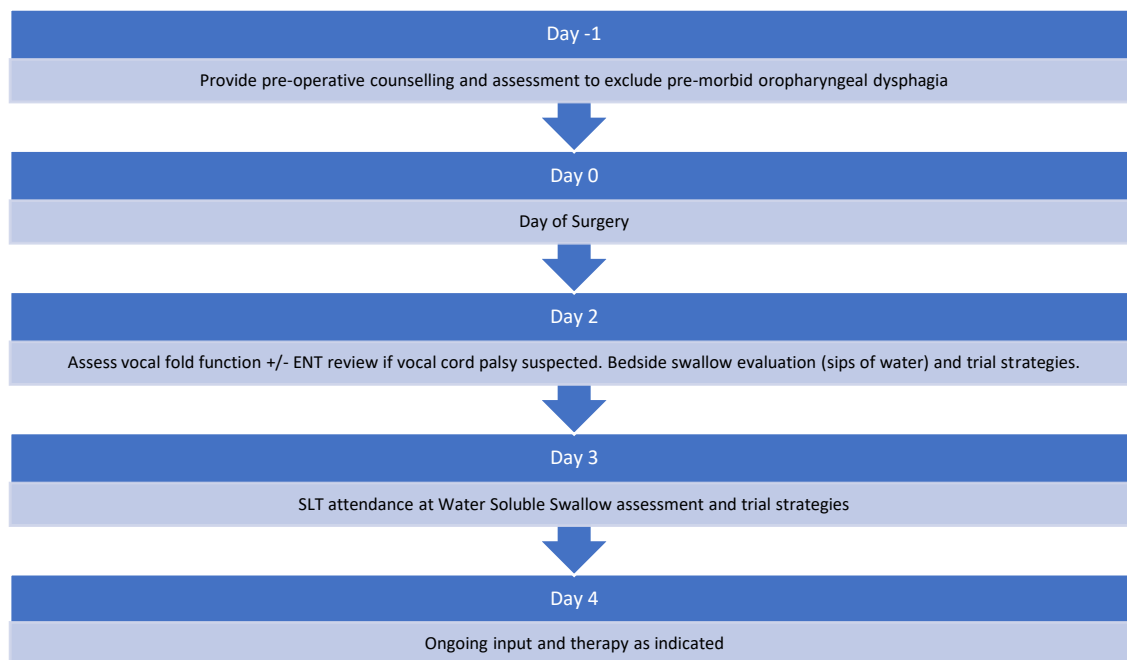


Figure 6 SLT Enhanced Recovery Pathway at Guys' and St Thomas's Hospital, London

2.2 Swallowing Anatomy

This section will outline normal swallowing anatomy.

The oral cavity is the first part of the digestive system. It contains the lips, tongue, dentition, gingivae, buccal mucosa, velum, hard palate, and other associated structures such as salivary glands.

The pharynx is divided into three segments (see Figure 7 below):

- 1) The nasopharynx, posterior to the nasal choanae, contains the eustachian tubes and pharyngotympanic tubes and is bordered inferiorly by the velopharyngeal port [128].
- 2) The oropharynx, posterior to the oral cavity and inferior to the nasopharynx, extends from the soft palate to the pharyngoepiglottic fold and includes the posterior third of the tongue, lateral and posterior pharyngeal walls and the tonsils [129]. The lateral walls are marked by the palatopharyngeal arches and palatine tonsils [130].

3) The hypopharynx is located between the oropharynx and the upper oesophageal sphincter (UOS). Alongside the pharyngeal walls are the epiglottis, valleculae, larynx, and pyriform sinuses [129, 131]. The tongue, oropharyngeal area and UOS consist of striated muscle [132].

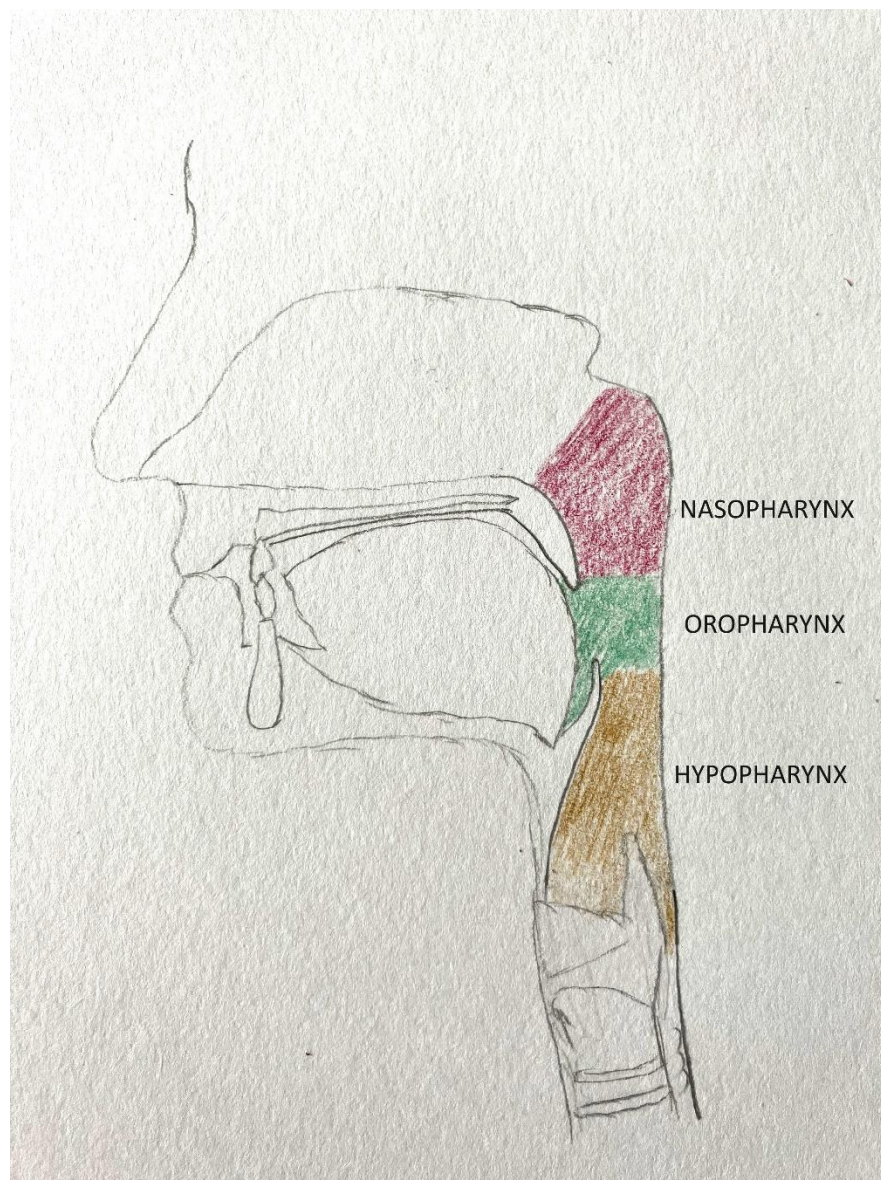


Figure 7 Pharynx

The oesophagus is a muscular tube connecting the cricoid cartilage at C6 to the oesophagogastric junction (OGJ) at T11 [133]. It ranges from approximately 21-28cm in length and approximately 0.6-1.5cm in width while at rest, widening during bolus transport to 2.5cm x 1.6cm and 2.5cm x 2.4cm (for the upper/middle and lower oesophageal regions, respectively) [133]. It is divided into

three anatomical areas; the cervical, thoracic and abdominal sections, with each measuring approximately 4cm, 20cm and 1.5cm, respectively. (See Figure 8.) The oesophagus contains four layers: inner mucosa, submucosa, muscularis and adventitia. The superior third of the muscularis consists of striated muscle, the inferior third is smooth muscle including the lower oesophageal sphincter, and a combination of the two muscle types comprise the middle third [132]. At the location where the striated and smooth muscle portions of the oesophagus meet, there is a transition zone [134-136] of mixed muscle in between, with the proximal striated muscles being more rigid and more sensitive [137]. The transition zone is typically located between 4 and 11 cm below the peak pressure in the UOS and its distance is approximately 20% of the length of the oesophagus [137]. Because of the position of the oesophagus in the thorax and abdomen, there are naturally occurring constrictions and indentations which are most apparent on barium swallow, for example, at 23 cm from the upper incisor teeth, the oesophagus is crossed by the aortic arch and left main bronchus at approximately T4/T5 before entering the posterior mediastinum. In addition, at 40 cm from the upper incisor teeth, the oesophagus traverses the right crus of the diaphragm into the abdominal segment to the fundus at the level of the 10th thoracic vertebra [138-141]. At approximately 4-5 cm below the carina there can be an indentation due to the pulmonary vein into the left atrium and this is also considered normal [142]. Barium coating on videofluoroscopy (VFS) is expected at the level of the aortic arch and the transition zone where the proximal oesophageal contraction ends and distal oesophageal contraction begins [143]. The OGJ is located between the oesophagus and the stomach and is composed of the lower oesophageal sphincter and crura diaphragm [144, 145].

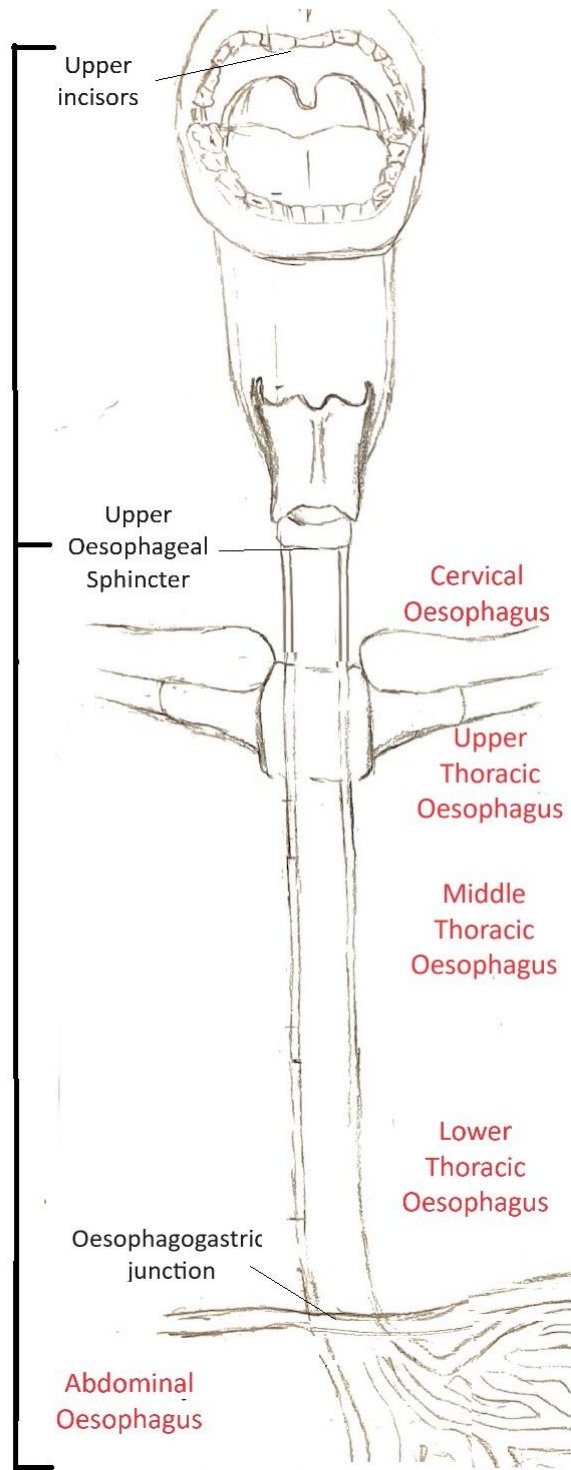


Figure 8 Oesophagus

2.3 Swallowing Physiology

Swallowing is a highly complex process including volitional and reflexive movement of over 30 muscles in the oral cavity, pharynx, larynx and oesophagus [146]. There are five phases of

swallowing: the pre-oral phase (anticipatory), oral preparatory phase, oral phase, pharyngeal phase and the oesophageal phase [147]. The pre-oral phase of swallowing initiates when an electrical signal travels to the sensory cortex, for example, at the sight or smell of food. This message travels through the brain's association cortices, the limbic system, the insular cortex and the frontal lobe before arriving at the nucleus tractus solitarius in the dorsal medulla oblongata and moving on to the nucleus ambiguus in the ventral medulla oblongata, from where a motor response is formed [148]. Secretions in the oral cavity are produced by the sublingual and submandibular glands in anticipation of food [149] when the motor fibres of the chorda tympani branch (facial nerve) are activated. During the oral preparatory phase, food or drink are received and manipulated into a bolus via the masticatory muscles, such as anterior digastric belly, mylohyoid, temporalis, masseter and pterygoid muscles (trigeminal nerve), facial muscles such as risorius, zygomaticus and quadratus labii superioris (facial nerve), and intrinsic and extrinsic lingual muscles (hypoglossal nerve). After which the oral phase commences, which is when the bolus is transferred from the oral cavity to the pharynx via feedback from the sensory components of the maxillary and mandibular branches of the trigeminal nerve and the glossopharyngeal nerve [148]. The motor component of oral transfer is activated by the hypoglossal nerve which controls the lingual transfer of the bolus and initiates bolus propulsion, and by relaxing the palatoglossus muscle (innervated by the pharyngeal plexus) [148].

The glossopharyngeal nerve is triggered during the oral phase of swallowing to induce the pharyngeal phase; the hyoid bone moves superiorly and anteriorly through contraction of the suprahyoid muscles (anterior and posterior digastric belly, mylohyoid, stylohyoid and geniohyoid muscles innervated by the trigeminal and facial cranial nerves and Ansa Cervicalis) to enable opening of the UOS. Epiglottic deflection is a biomechanical event that occurs passively as a result of hyoid elevation and excursion. Airway closure has multiple levels of protection including closure of the vocal folds, false vocal folds, epiglottic deflection and consequential squeezing of the quadrangular membrane [150]. Almost all intrinsic laryngeal muscles are innervated by the RLN

[150]. The bolus is rapidly propelled through the pharynx towards the UOS with the help of both sensory and motor information. The pharyngeal plexus controls pharyngeal shortening and contraction through innervation of the superior pharyngeal constrictor, palatopharyngeus and salpingopharyngeus. The glossopharyngeal nerve innervates the stylopharyngeus. These muscles assist with bolus propulsion through the pharynx [148]. The superior, middle and inferior pharyngeal constrictors, innervated by the pharyngeal plexus, squeeze the bolus through the entire length of the pharynx. The kinematic propulsion which initiated in the oropharynx pushes the bolus from the hypopharynx through the UOS and into the oesophagus when the UOS is relaxed. A resting pressure exists in the UOS due to myogenic tone whilst also existing secondary to the anatomical and structural components themselves as demonstrated in cadaver studies [151]. It takes approximately 1 second for the pharyngeal phase of swallowing to be completed [152].

The function of the oesophagus is to facilitate the transit of food from the pharynx to the stomach during the oesophageal phase of swallowing. The UOS, composed of the cervical oesophagus (specifically the muscularis mucosae), the cricopharyngeus muscle and the inferior pharyngeal constrictor, relaxes briefly to enable food to enter the oesophagus, or to allow gas/emesis to exit the oesophagus. The cricopharyngeal muscle is innervated by the RLN and the external branch of the superior laryngeal nerve (SLN) [153]. The SLN is responsible for relaxation of the cricopharyngeal muscle [148, 154]. The bolus descends from the upper oesophagus via primary peristalsis. If the primary sensory neurons, both vagal and spinal afferents, detect bolus stasis in the oesophagus, then a secondary peristaltic motion is activated with an intention to propel the bolus to the stomach [155, 156]. The lower oesophageal sphincter (LOS) relaxes to allow transit of the bolus into the stomach, while its natural tonic state prevents the retrograde flow of gastric materials into the oesophagus. The oesophageal phase of swallowing is involuntary, and takes approximately 6-8 seconds for the peristaltic wave to be completed [132].

The opening of the LOS is triggered during oesophageal peristalsis. It does not consist of specific sphincter muscles however relaxation is supported by the angle at which the oesophagus enters the stomach, by the positive intra-abdominal pressure compressing the oesophageal walls, and by the shape of the fibres of the diaphragm's right crura resulting in what has been described in the literature as a 'pinch-cock' effect [157].

2.4 Swallowing Pathophysiology (Dysphagia)

One definition of dysphagia that has been frequently referred to in the literature is 'an inability to voluntarily pass fluids or food from the mouth to the stomach' [158]. A breakdown in swallowing can occur at any of the five phases of swallowing discussed above [147]. Abnormal swallowing in the oral and pharyngeal phases is most often caused by alterations in the musculoskeletal, respiratory or nervous systems which can be due to a wide variety of conditions and diseases such as stroke, traumatic brain injury, head and neck cancers, progressive neurological conditions, respiratory diseases etc. [159-161]. Oesophageal dysphagia can be caused by mechanical dysfunction involving the myenteric plexus, for example achalasia, or alterations to the lumen, for example smooth muscle changes caused by scleroderma [132]. In addition, dysphagia can be caused by treatments such as antipsychotic medication [162], surgery which may cause nerve damage or alter anatomy, and radiotherapy potentially inducing early inflammatory damage to mucosa (xerostomia, mucositis) or delayed fibrosis or atrophy [163, 164]. This can cause wide ranging short-term and long-term implications in terms of functional and psychosocial impact, health related quality of life (HRQoL), medical issues and prolonged hospital stay [160]. Normal changes to swallowing that occur with ageing, termed presbyphagia, does not typically cause dysphagia, but may exist with an underlying age-related pathophysiology such as sarcopenia that may cause dysphagia.

Signs of abnormal swallowing:

Overt and more subtle signs of oropharyngeal dysphagia may include [161, 165]:

- Coughing during eating/drinking
- Choking when eating/drinking
- Throat clearing when eating/drinking
- Change to vocal quality when eating/drinking
- Odynophagia (pain when swallowing)
- Inadequate mastication
- Shortness of breath when eating/drinking
- Oxygen desaturation >2% while eating/drinking
- Difficulty managing saliva
- Nasal regurgitation
- Inability to initiate the swallow
- Residue in the oral cavity
- Anterior spillage of food/fluid
- Sensation of food getting stuck in mouth/throat
- Multiple swallows to clear a bolus
- Loss of weight/malnutrition
- Recurrent respiratory tract infections

Signs of oesophageal dysphagia can include[132]:

- Odynophagia
- Regurgitation of ingested materials
- Pyrosis (heartburn)
- Chest pain
- Belching
- Halitosis
- Rumination
- Sensation of food sticking in the oesophageal or pharyngeal regions
- Loss of weight/malnutrition
- Dehydration

Complications of dysphagia can include [166-171]:

- Aspiration pneumonia
- Dehydration
- Malnutrition
- Sudden death
- Feeding tube reliance
- Reduced QoL including embarrassment and reduced socialising
- Weight loss
- Increased hospital readmissions
- Reduced oral intake
- Psychiatric symptoms including anxiety and depression

2.5 Swallow Evaluation

Swallow evaluations can be categorised into screening tools, clinical assessments, and instrumental evaluations.

Screening Tools

Swallow screening tools have been developed to enable swallow specialists and the multidisciplinary team to identify patients at risk of dysphagia using patients' clinical history, clinical examinations, or self-reported symptoms [172]. There are a range of questionnaires, observations and rating tools that can be administered with various populations [173], however it is important that they are validated and reliable with good diagnostic performance for identifying the outcome (e.g. dysphagia or aspiration) in the relevant population [174]. An example of a swallow screen is the Toronto Bedside Swallowing Screening Test (TOR-BSST) [175] and examples of self-reported dysphagia questionnaires are the EAT-10 [176], Swallow Disturbance Questionnaire [177], Sydney Swallow Questionnaire (SSQ) [178], and Mayo Dysphagia Questionnaire [179, 180]. Additional questionnaires to identify oral intake status/tube

reliance, laryngopharyngeal reflux, sarcopenia and health/swallow related QoL outcomes are the (Functional Oral Intake Scale) FOIS [181], Reflux Symptom Index (RSI) [182], Reflux Symptom Score [183]), SARC-F (Strength, Assistance in Walking, Rise from Chair, Climb Stairs, Falls) [184, 185], Mini Sarcopenia Risk Assessment [186] , MDADI (MD Anderson Dysphagia Inventory) [187], EORTC-QLQ-OES-18 [188], and the Swallow Quality of Life questionnaire (SWAL-QOL) [189].

Clinical Assessment

A clinical evaluation of swallowing aims to identify people with dysphagia and may consist of an oro-facial assessment including a cranial nerve examination, case history, and swallow trials. It can be useful to establish an initial hypothesis and to determine candidacy for a more robust instrumental assessment. Instrumental assessments are not available in all clinical locations [166, 174] and in such cases, a bedside clinical swallow evaluation may be the most reliable option available to identify a swallowing impairment and guide management. The position statements of ESSD (European Society of Swallowing Disorder) advises that people with dysphagia on clinical exam should have an instrumental evaluation [190]. There is currently a lack of international consensus around the use of bedside swallow tests [161], as despite some studies revealing high sensitivity and specificity for detecting dysphagia when compared with Flexible Endoscopic Evaluation of Swallowing (FEES) [191], a systematic review by O'Horo and colleagues, which evaluated 38 studies, found that the sensitivity of clinical assessments was still not accurate enough [161]. There are also few standardised protocols available resulting in inconsistent and subjective assessment behaviours globally [175, 192], and the research that has been validated includes few populations, mostly people with stroke. An important consideration when using the clinical swallow evaluation is its poor sensitivity in identifying silent aspiration (when swallowed material enters below the vocal folds without a response to try to clear it) [193, 194]. Examples of clinical evaluation tools includes the Mann Assessment of Swallowing Ability (MASA) [192] and The Test of Masticating and Swallowing Solids (TOMASS) to evaluate solid bolus ingestion [195].

There are three swallow screening tests; the Yale Swallow Protocol [196, 197], the 3 ounce Water Swallow Test [196], and the Timed Water Swallow Test [198]. There are adjunct tools which can be used in conjunction with a clinical swallow evaluation such as the IOPI (Iowa Oral Performance Instrument) which measures lingual pressures [199, 200], Cough Reflex Testing (CRT) which can provide insight into laryngeal sensation and potential risk of aspiration [201, 202], cervical auscultation [203], and pulse oximetry [204].

Instrumental evaluation

An instrumental swallow evaluation can be completed to identify the presence, severity, nature and cause of dysphagia [205], and to guide appropriate treatment of the dysphagia or dysphagia symptoms. Assessment of the oesophagus is usually conducted by the upper GI team using oesophagogastroduodenoscopy (OGD) and/or contrast imaging [159, 206]. Radiographic means of assessment have proven valuable; a barium oesophagogram is a widely used test of functional and structural diseases of the oesophagus [207]. This barium swallow evaluation or upper gastrointestinal endoscopy are typically the initial evaluations for suspected oesophageal dysphagia [132]. Barium swallow has the advantage of detecting diverticula and motility disorders in 70-95% of cases which may be missed on endoscopy [208] whereas endoscopy provides a clear image of lesions which may enable biopsy.

Oropharyngeal dysphagia is typically assessed and treated by speech and language therapists and laryngologists using VFS or FEES [159, 209]. A VFS is a modified barium swallow evaluation which focuses on the oral and pharyngeal phases of swallowing and should include a standardised and validated screen of the oesophagus [210]. VFS enables evaluation of the timing, extent and duration of the movement of key physiological components as well as the movement of the barium containing bolus, however drawbacks of its use include exposure to ionising radiation, barium can alter taste and viscosity, and that patients' medical status must be adequate for transfer to the radiology suite [211-213]. FEES consists of a comprehensive evaluation of

swallowing during nasendoscopy [214]. Nasendoscopy allows direct visualisation of the oropharynx and hypopharynx to identify anatomical or physiological abnormalities, including observation of vocal fold adduction during non-swallow tasks, something that is not possible during VFS. FEES also has the benefit of not exposing patients to radiation and being portable for easy access to patients at their bedsides if needed. Limitations of FEES include a ‘whiteout’ period during swallowing which inhibits the view of real-time penetration or aspiration, an absence of an oral evaluation, an inability to conduct an oesophageal screen, and as the volume of material aspirated on FEES can be ambiguous [215]. Examples of tools that exist for rating swallowing on instrumental evaluation include: MBS Impairment Profile [216], Dynamic Imaging Grade of Swallowing Toxicity v2 (DIGESTv2) [217], Penetration-Aspiration Scale (PAS) [218], Swallow tail, [219], and Visual Analysis of Swallowing Efficiency and Safety (VASES) [220]. The ESSD published a White Paper in 2022 which emphasised that there currently lacks expert consensus regarding measurement tools for analysis given inadequate psychometric evidence to prove validity or reliability [174].

High resolution impedance manometry is highly effective in diagnosing oesophageal motor disorders such as achalasia and nutcracker oesophagus [132], and in more recent years has been applied to the pharyngeal phase of swallowing to objectively and non-radiographically measure pharyngeal pressures [221]. The clinical value of emerging metrics are still being investigated [222-224].

2.6 Dysphagia in Oesophageal Cancer – A review of the literature

People with oesophageal cancer often report experiencing dysphagia from before diagnosis to long beyond treatment and this may be secondary to the tumour obstructing the oesophagus, from tumour related dysmotility, and from the treatment itself [225, 226]. Dysphagia with solids is often one of the first symptoms, and the predominant symptom, to present in oesophageal cancer due to the mechanical obstruction of the oesophagus [27, 227, 228]. It can progress to

dysphagia with fluids, and even saliva, as the growing tumour occupies more space in the oesophagus [27, 133, 229]. Dysphagia symptoms reported by people with oesophageal cancer prior to surgery include odynophagia, retrosternal sticking of solid food, regurgitation of undigested food, coughing during/after meals, reflux, and the need to modify or avoid certain food textures [227]. Swallowing issues may present at any stage from diagnosis through to many years postoperatively [230], however, as symptoms often present at a late-stage, cancer may not be diagnosed until palliative intervention is the only option. Swallowing symptoms have a reported incidence of up to 85-95% [231, 232]. Examples of medical treatments that can relieve symptoms of dysphagia in palliative patients are listed in Table 2.1 [233, 234].

Table 2-1 Medical treatments to relieve dysphagia in palliative oesophageal cancer

Treatment	Definition
Oesophageal stents	A metal, silicone or plastic tube placed in the oesophagus to maintain patency during an invasive procedure such as gastroendoscopy (e.g. self expanding stents) [235, 236].
Oesophageal dilatation	Stretching of a narrowed part of the oesophagus to achieve improved patency using either a push dilator (bougie) or a balloon dilator [237].
Intraluminal brachytherapy	A type of internal radiotherapy that can deliver high doses of radiation with excellent precision to the oesophageal wall [238].
External beam radiation therapy	Radiation therapy where the machine is exterior to the body [239].

Treatment	Definition
Systemic chemotherapy	Drugs spreads through the blood to cells around the body because of the likelihood of metastases in advanced oesophageal cancer [240].
Concurrent chemoradiotherapy	Chemotherapy and radiotherapy provided in parallel [241, 242].
Thermal and chemical ablative techniques (including laser and photodynamic therapy (PDT))	Photodynamic therapy – the tumour site is irradiated with light consisting of a particular wavelength which generates an oxygenating response that kills cancer cells [243]. Endoscopic laser ablative therapy is a form of tumour destruction/vaporisation using light amplification by stimulated emission of radiation [244, 245].

Despite the wealth of research referring to ‘dysphagia’ as a symptom post oesophageal surgery, there is little distinction made between the different phases of dysphagia so it is possible that they are referring to oropharyngeal dysphagia or oesophageal dysphagia or both [15, 246, 247].

A comprehensive review of the literature has been conducted below. Our research team also completed a scoping review of dysphagia in oesophageal cancer, for which the PhD candidate was involved and will be a named author when it is submitted for publication. This scoping review was completed after the review included in this thesis and therefore served as verification that no relevant studies had been omitted.

The following subsections will explore the literature that has been published on oropharyngeal dysphagia in patients with oesophageal cancer at various timepoints throughout their cancer journey; preoperatively, acutely following surgery, the sub-acute period, and in the long-term.

This review conveys how the majority of the research that does refer to oropharyngeal dysphagia in this population refers to the acute postoperative period following oesophageal surgery completed with curative intent. This highlights a gap in the literature and a need to investigate COD in this population

This review found 26 studies with key information listed in Table 2-3.

Five of the studies included THO surgical resection (total n= 115) [57, 91, 227, 229, 248], four studies included the open 3-stage approach (total n=121) [36, 53, 93, 249], two included 3-stage MIE (total n=53[68] [69], five studies included a variety of approaches in their analysis (total n=172) [60, 70, 71, 250, 251], and eight studies did not clearly name their surgical approach (n=1623) [61, 72-74, 92, 150, 252-254].

Presentation of oropharyngeal dysphagia pre-operatively

Two studies evaluated swallowing pre-operatively. In a case-control study, Okumura et al (2016) [69] measured swallowing in 26 participants who were due to undergo thorascopic oesophagectomy with cervical anastomosis, rated via VFS and the Functional Outcomes Assessment Measure of Swallowing (FOAMS) Scale. Neo-adjuvant chemotherapy was received by 11 participants however it is not clear whether this was prior to or following the FOAMS assessment. Authors reported that all participants had FOAMS scores of 7/7 prior to surgery, indicating efficient swallowing abilities. Martin et al (2001) evaluated dysphagia symptoms prior to THO in an pre- and post- observational study [227]. None of the 10 participants in their study received neo-adjuvant treatment. 9/10 experienced a mild oral-preparatory dysphagia and 10/10 experienced at least a mild oral and mild pharyngeal dysphagia on VFS. The following symptoms were reported: abnormal bolus formation (9/10 – mild/moderate), posterior leakage (8/10 - mild/moderate), hesitancy (10/10 - mild/ moderate), abnormal tongue movement (10/10 - mild/moderate), oral residue (10/10 - mild/ moderate), delayed initiation (8/10 mild/ moderate), reduced peristalsis (6/10 - mild), pharyngeal residue (10/10 - mild/ moderate), penetration/

aspiration (2/10 - mild), impaired UOS opening (4/10 - mild), oesophageal obstruction (2- severe, 8 mild- moderate) [227]. The quality of this study is limited by the small sample size and a lack of validated rating scales for measuring outcomes.

An observational QoL study by Scarpa et al (2013) (n=126) found that self-reported dysphagia using the EORTC-QLQ-OES-18, EORTC-QLQ-OES-C30 and EORTC IN-PATSAT32 improved following neoadjuvant therapy but fell significantly after surgery ($p > 0.001$), before improving again later. They also revealed that global Health-related HRQoL was independently associated with dysphagia at the time of diagnosis and following neoadjuvant therapy.

Presentation of oropharyngeal dysphagia in the acute post-operative phase

Oropharyngeal dysphagia is reported to be at its worst in the first three weeks following surgery [252]. There appears to be consensus in the literature that oropharyngeal dysphagia exists acutely post oesophagectomy for a high proportion of adults, which is unsurprising given the invasiveness of the surgery. The prevalence of dysphagia was reported directly in three observational studies which used VFS (total of 50 participants across the studies), as 75% [150], 90% [252], and 90% [73].

Regarding the oral phase, reduced tongue strength [253], with a significant decrease in tongue pressure acutely post oesophageal resection [253, 255], has been found to be associated with postoperative aspiration and pneumonia, independent of RLN palsy or age [253, 255]. These two studies had a prospective observational design (n=39) and a retrospective observational design [255] (n=216). One limitation is that Yokoi et al (2019) do not clarify when the pre-surgical outcomes were measured [253].

Regarding the pharyngeal phase, the following were reported: premature spillage posteriorly [57] vallecular residue [93, 256], pyriform sinus residue [91, 93, 227], pharyngeal residue [57, 254], reduced base of tongue to posterior pharyngeal wall approximation [250, 256], reduced laryngeal

sensation [250], incomplete or absent epiglottal deflection [71, 91, 229, 256], reduced laryngeal elevation [36, 60, 227, 229], reduced anterior excursion of the hyoid [71, 91, 251], reduced pharyngeal contraction [227, 250, 252], reduced laryngeal closure [60, 71, 252], prolonged pharyngeal time [249], reduced UOS opening [91, 251, 252], penetration/aspiration [36, 227, 229] penetration [68, 254], aspiration [57, 60, 61, 71, 72, 74, 91, 249, 252, 254], silent aspiration [61], and overt aspiration [68].

Focussing more closely on penetration and aspiration, the prevalence of aspiration/ penetration was reported in between 11-60% of participants as displayed in Table 2-2.

Table 2-2 Prevalence of aspiration/penetration across studies in acute post-op period

Author	Study Design	No of participants	Aspiration rates	Comment
Blakely et al, 2021 [71]	Retrospective chart review	50	22% aspirated	When the 3 stage approach was considered in isolation, 40% aspirated
Martin et al, 2001 [227]	Pre- and post-op observational	10	60% penetrated/ aspirated	
Kumai et al, 2017[36]	Observational	25	56% penetrated/ aspirated	
Kato et al, 2007 [57]	Longitudinal	27	52% aspirated	
Lewin et al, 2001[250]	Experimental cohort	26	81% of patients referred for a dysphagia assessment aspirated	Silent aspiration in 71% of these n= 15/21
Ben-David et al, 2015 [68]	Observational	27	45% aspirated	30% silent aspiration, 15% overt aspiration
Lee et al, 2016[61]	Observational	118	32% aspirated	14% silently aspirated
Berry et al, 2001 [72]	Retrospective observational	779	12% aspirated	
Takatsu et al, 2021 [74].	Retrospective case control study	276	11% had a high risk of aspiration, 11% had a medium	

				risk of aspiration, 29% had a low risk of aspiration		
Sugase et al 2022 [256]	Retrospective observational	304	53% (108/304) aspirated	85 silently aspirated		

The incidence of aspiration post-operatively varied across studies, having been reported in 12% of participants following a variety of surgeries including both open surgeries and MIE, and both cervical and thoracic approaches [72], and up to 81% of patients post a variety of 2-stage and 3-stage surgeries [250]. One study found that 40% of patients whose surgery was completed using the 3-stage MIE approach presented with aspiration/ dysphagia post-operatively compared to only 13.3% of patients who underwent the 2-stage MIE approach, however, this difference was not statistically significant [71]. Thus, there is a strong rationale for further research to investigate how to minimise aspiration and aspiration pneumonia in this cohort [65]. Penetration/ aspiration was found to be significantly worse following 3-field lymphadenectomy (FLD) (70%) compared to 2-FLD (20%) ($p=0.025$) [60]. This is potentially due to high levels of surgical stress in the cervicothoracic region impacting upon laryngeal elevation [60]. Impaired laryngeal elevation was significantly associated with aspiration ($p=0.021$) in a study after 3-FLD [36]. Additionally, when surgeons implemented a CDBIMS (completed division of bilateral infrahyoid muscles attached to sternum) approach to the 3-FLD group, penetration and aspiration dropped from 70 to 25% ($p=0.018$) [60], demonstrating the importance of protecting the sternohyoid and sternothyroid muscles during surgery ‘given their opposing action required for laryngeal elevation’ [60].

Yasuda et al (2013) found that aspiration occurred in participants who had recurrent laryngeal nerve palsy (RLNP) if they also had reduced laryngeal elevation resulting in incomplete laryngeal vestibule closure [60]. Being over 70 years of age was also associated with aspiration and/or dysphagia on VFS ($p=0.019$) [71].

It is hypothesised that reducing aspiration pneumonia rates in this population could reduce surgical complications, sarcopenia and malnutrition, treatment-related morbidity, hospital length of stay and readmissions [72, 257, 258].

One study [259] found a significantly smaller cross-sectional area of the geniohyoid muscle on computed tomography (CT) in those with dysphagia on postoperative day (POD) 7, and in those with preoperative sarcopenia, however, this was a published abstract and limited information was provided on how swallowing was rated on VFS.

The two studies which compared swallowing before and after surgery, found that in general, the oral phase did not deteriorate post-operatively however the pharyngeal phase was worse with at least one new additional impairment, for example, delayed swallow initiation [69, 227].

Presentation of oropharyngeal dysphagia in the sub-acute phase

Improvements to swallow function over time have been reported in a number of studies [61, 71, 229, 252] with dysphagia spontaneously resolving one month post-op in two studies [61, 229] and within 5.5 weeks in one study [71]. These results are limited, however, by the absence of validated rating tools [252], minimal information on the volumes and consistencies of trials on VFS [252], only two bolus trials on VFS [61], and small sample size [252]. 41.7% of aspiration had fully resolved after 1 month in one study [61] and Easterling et al (2000) [91] found no evidence of aspiration in their follow up time point which ranged from 42-105 days post-op. Okumura et al (2016) found significant improvements ($p < 0.001$) in efficiency of swallowing at time of discharge (32.4 $\pm$ 12.2 days post-op) [69] however non-validated swallow evaluation methods were used and little information was provided on statistical analysis conducted.

Presentation of oropharyngeal dysphagia in the chronic stage

Three studies referred to dysphagia in the long term which for this review is considered to be greater than 3 months post oesophageal cancer surgery, in line with dysphagia research in head and neck cancer [260].

Yuen et al (2019) reported chronic mild to moderate pharyngeal dysphagia in 29 participants a mean of 4.3 years post operatively in their well-designed observational study which used the Videofluoroscopy Dysphagia Scale, a validated rating tool, and provided adequate detail on the number and consistency of trials and how analyses were conducted [70].

From an oral dysphagia perspective, Yuen et al (2019) reported inadequate bolus formation in two (7%) participants, inadequate mastication in one (3%) participant, impaired tongue to palate seal in five (17%) participants and greater than 50% of bolus spillage prematurely in two (7%) participants.

From a pharyngeal perspective, Yuen et al identified delayed swallow initiation in 26 (90%) participants, greater than 50% vallecular residue in four (14%) participants, 10-50% of residue in pyriform sinuses in seven (24%) participants, pharyngeal coating in 17 (59%) participants, pharyngeal transit time greater than one second in two (7%) participants, aspiration in eight (28%) participants, and penetration in 13 (45%) participants on VFS. Yuen et al revealed that 29 survivors without a history of dysphagia, who were mean 3.5 years post oesophagectomy, continued to present with a mild to moderate pharyngeal dysphagia on VFS.

Interestingly, Koh et al (2004) reported that the pharyngeal swallow was relatively intact on VFS a median of 18 months (range 6-40 months) post-surgery [248], however, the quality of their study was limited by a number of factors for example, no information was provided on the number and consistency of trials provided on VFS or the frame rate used, a validated rating tool was not used to measure the dysphagia outcomes, and there was a small sample size of nine. Dysphagia was

reported in 5/9 participants, however, none had any identifiable anatomical cause, for example, all anastomotic diameters were within normal limits and no tumours were visualised by endoscopy or barium swallow. The authors further probed using provocative balloon distension oesophageal manometry and revealed hypertensive peristalsis (i.e. mean oesophageal pressures over 100mmHg) in the cervical oesophagus in 80% of those complaining of this otherwise unidentifiable dysphagia.

Finally, the third study by Sugase et al (2022) did not actually measure dysphagia as an outcome at their long-term timepoint (a median of 37 months (range 1-76) after discharge) however they did report that there were significantly higher rates of pneumonia more than 12 months post oesophagectomy in the group who presented with acute dysphagia on VFS compared to the non-dysphagia group [256]. Unfortunately, this research group did not use a validated VFS rating tool and did not describe the consistency or volume of trials provided or the VFS frame rate used.

Table 2-3 Key studies identified in a literature review

Author	Study design	Surgical Approach +/- Technique	Anasto-mosis site	N=	Neo-adjutant tx	Swallow Ax	Post-operative timing of swallow evaluation	Dysphagia-Related Findings	Other Relevant Findings
Easterling et al 2000 [91]	Case controlled observational study	THO	Cervical	8	Not mentioned	VFS	Day 7-10	100% (n=8) had pharyngeal dysphagia. PS residue (n=5), Incomplete or absent epiglottal descent (n= 5), Significantly reduced UOS opening compared to healthy controls, and reduced anterior excursion of hyoid in those who aspirated v those who did not. 63% (n=5) aspirated. No pts aspirated in follow up between day 42-105 post op.	2/8 vocal cord paralyses
Martin et al 2001 [227]	Pre- and post op observational study	THO	Cervical	10	0	VFS	Final VFS Day 42-105 Day 2-21 preop 44-134 POD	Pre-Op: 100% (n=10): mild oropharyngeal dysphagia. 2 had severe oesophageal obstruction. Abnormal bolus formation (9/10 mild/mod), posterior leakage (8/10 mild/mod), hesitancy (10/10 mild/mod), abnormal tongue movement (10/10 mild/mod), oral residue (10/10 mild/mod), delayed initiation (8/10 mild/mod), reduced peristalsis (6/10 mild), pharyngeal residue (10/10 mild/mod), pen/asp (2/10 mild) impaired UOS opening (4/10 mild), oesophageal obstruction (2 severe, 8 mild-mod) Post-op: No significant difference in the oral phase. 100% (n=5) at least a mild oropharyngeal swallowing impairment. Pharyngeal residue (n=5) and penetration/asp (n=3). 4/5 had at least 1 new abnormality e.g. reduced pharyngeal contraction (n=3) or reduced laryngeal elevation (n=2).	
Leder et al 2007 [57]	Prospective observational cohort	THO	Cervical	73	Not mentioned	FEES	POD 5	15/73 aspirated. 24/73 penetrated. Premature spillage: 4/73 Pharyngeal residue: 19/73. Pooling : 9/73 Authors: Underlying pathophysiology of aspiration is from premature bolus loss, lack of laryngeal rise during the pharyngeal swallow, resulting in aspiration before the vocal folds are fully adducted	Vocal fold immobility not correlated with dysphonia VF palsy is predictive of aspiration in acute phase post op (p=0.012)
Koh et al 2004 [248]	Prospective observational study	THO	Cervical	9	Not mentioned	VFS (Functional Dysphagia Measure) FEES Oes. manometry	6-40 months post operatively, median 18 months	Pharyngeal phase of swallowing relatively normal. Incomplete pharyngeal contraction with pooling in valleculae (n=2) with no functional impact on swallow). Significant impact on global QOL. Authors: Dysphagia caused by hypertensive peristalsis in cervical oesophagus.	No early or late anastomotic strictures
Heitmiller et al, 1991 [229]	Abstract	THO	Cervical	15	Not mentioned	VFS	1 week (6-10 days) 1 month (18-52 days)	Laryngeal pen/asp 7 (47%), incomplete laryngeal elevation 5 (33%), abnormal epiglottic tilt 2 (13%) 1 month post op, all dysphagia had resolved	
Kim et al 2016 [249]	Observational controlled study (excl controls)	3 Stage	Cervical	47	10	VFS	8.2 days +/-1.6	Aspirated n=23, did not aspirate 24, Decreased Maximal anterior displacement of the hyoid, Decreased maximal rotation of the epiglottis, prolonged pharyngeal delay time	3 incomplete vf palsy, 4 complete vf palsy
Sadanaga 2016[53]	Abstract	3 FLND		35		VFS	7	Not mentioned	RLNP in 10 (29%). Post op pneumonia:2
Yuen et al, 2019 [70]	Observational study			29	14(48%)	VFS using (PAS and VDS) and EORTC-18	Means 4.3 years post op	Mild to mod pharyngeal dysphagia mean of 4.3 years post op. Inadequate bolus formation: 2 (7%), inadequate mastication: 1 (3%), impaired tongue to palate seal: 5 (17%), premature bolus spillage: <10% = 11 (38%), >50% = 2 (7%), delayed swallow initiation 26 (90%), vallecular residue: <10% = 9 (31%), >50% = 4 (14%), residue in pyriform sinuses 10-50% 7 (24%), 3 (10%),	VC palsy 5 (16%), pulmonary complications 8 (28%), anastomotic leak 4 (14%)

Author	Study design	Surgical Approach +/- Technique	Anastomosis site	N=	Neo-adjuvant tx	Swallow Ax	Post-operative timing of swallow evaluation	Dysphagia-Related Findings	Other Relevant Findings
			Cervical Thoracic	23 (79%) 6 (21%) 16 (55%) 3 (10%) 8 (28%) 1 (3%) 1 (3%)				pharyngeal coating 17, (59%), pharyngeal transit time >1s 2 (7%), aspiration 8 (28%), penetration 13 (45%)	
Blakely et al 2021 [71]	Retrospective chart review	MIE 3 phase Lewis Tanner THO Transthoracic		50	39 (78%)	VFS	Average (13-19)	17 (8) patients had OP dysphagia or aspiration on VFS 17 days post op: reduced hyolaryngeal excursion, reduced laryngeal closure, incomplete epiglottic deflection, dysphagia, 22% aspiration.	Asp pneumonia in 7 (14%). Anastomotic leak in 6%
								40% of McKeon patients had asp +/- dysphagia post op versus 13.3% of Ivor Lewis (both were MIE). Did not reach statistical significance. >70 years of age associated with asp and/or dysphagia in VFS (p=0.0185). Dysphagia and post-op aspiration were associated with pneumonia (p=0.027) Resolution of dysphagia on VFS 5.5 weeks (median). 13.3% aspiration 40% aspiration	
Lewin et al, 2001 [250]	Experimental cohort design	Ivor Lewis McKeown	Thoracic Cervical	45 5 26	12	Ba swallow and VFS	Day 13 (range 6-43)	Aspiration in 21/26 (81%). Mild reduction in pharyngeal contraction (5/26). Reduced base of tongue to posterior pharyngeal wall opposition (4/26). Authors: Impaired elevation and anterior movement of hyolaryngeal complex resulted in aspiration during the swallow of all cases (100%) and aspiration after the swallow in 10 of 21 patients (48%) due to spillage of residue from the pyriform sinuses. Reduced or absent laryngeal sensation, as indicated by an inconsistent or absent cough response to aspiration, was observed in 15/21 (71%)	Not mentioned
		3 stage 2 stage THO		5 5 16 40					
Yasuda et al 2013 [60]	Prospective controlled experimental study					VFS	Average Day 13	Significantly worse pen/asp in 3FL (70%) compared to 20% of 2FL (p=0.025). The additive CDBIMS decreased the frequency of laryngeal penetration and aspiration compared to 3FL from 70 to 25 % and from 40 to 10 %, respectively. Reduced total laryngeal elevation impeded laryngeal vestibule closure resulting in aspiration if RLN palsy present. Authors: sternohyoid and sternothyroid muscles are subjected to considerable damage in cervical LN dissection, because of retraction and partial division for visualization of the cervicothoracic area.	
		3FLND 2FL 3 FL CDBIMS	Cervical Cervical	10 10 20 27	5 5 7				
Kato et al 2007 [251]	Longitudinal observation study					VFS	Between Day 14-21	Significantly reduced hyoid elevation and excursion following intrathoracic surgery and surgery via the posterior mediastinal route. Following restrosteral route surgery, there was reduced cricopharyngeal opening, and hyoid excursion and elevation. Authors: The reason for the postoperative swallowing abnormalities is a result of postoperative adhesion due to the lymph node dissection, scarring at the anastomosis, inflammation (not just neural damage given the 2 stage patients had reduced hyoid movements too), adhesion of the gastric tube to the trachea and incarceration of the gastric tube in the thoracic inlet. Damage of neural pathways of pharyngeal or cervical oesophagus.	RLNP = 3, anastomotic leak = 1 RLNP = 3, anastomotic leak = 1 RLNP = 2, anastomotic leak = 1

Author	Study design	Surgical Approach +/- Technique	Anastomosis site	N=	Neo-adjuvant tx	Swallow Ax	Post-operative timing of swallow evaluation	Dysphagia-Related Findings	Other Relevant Findings
		McKeown route	RS Cervical	8					
		McKeon route	PM Cervical	8					
		Ivor Lewis IT route	Thoracic	11					
Kumai et al 2017 [36]	Observational	3 FLND	Cervical	25		VFS with PAS	2-3 weeks	10 of the 18 with VFP had pen +/- asp. 1 of 6 with normal vf penetrated, none aspirated. Impaired laryngeal elevation was significantly associated with aspiration (p=0.021) after 3 field lymphadenectomy. Authors: damage to infrahyoid muscles in cervical LN dissection. May be scar formation due to surgical procedures around the trachea circumferentially at the level of cervical to thoracic areas.	18 had unilateral vf paralysis. 1 bilateral vf paralysis and did not aspirate.
Kumai et al 2017(chintuck) [93]	Intervention cohort	3 FLND	Cervical	14		VFS	Day 14.8+/-0.4 d	Residue in valleculae and pyriform sinuses.	Unilateral vocal fold paralysis = 6 (42.9%)
Ben-David et al 2015 [68]	Observational study	3 stage MIE	Cervical	27		VFS with PAS		8/27 had silent aspiration, 4/27 had overt aspiration. All patients with vfp aspirated. PAS score of 2 (n=1), 3 (n=1), over 6 (n=12). 8 of these scored above 3 on PAS 5 days later (any penetrated material does not reach level of vocal folds).	Post-op pneum: 2 (7.4%) RLNP: paresis (4) & paralysis (2) Anastom leaks: 3 (11%)
Okumura et al 2016 [69]	Case control study	Thorascopic oesophagectomy MIE	Cervical	26 Control group (n=12)	5	FOAMS rating	4.7 days post op. 26 days post op	Control group's FOAMS score was significantly reduced from 7 to 4.7 +/-1.4 (p<=0.01) post op, recovering after 26+/-15days to 5.5+/- 1.3 at time of discharge.	Aspiration pneumonia 3 RLNP 4 Anastomotic leak 2
Lee et al 2016 [61]	Observational study	Unclear		118	24	VFS Bedside swallow test	7-10 days 1 month	38 aspirated on VFS. Bedside test yielded positive results in 26 of these 38 (32.2%). Silent asp: 17. Change in voice quality detected aspiration with 68.4% sensitivity and 70% specificity. Cough after swallow detected aspiration with 55.3% sensitivity and 67.5% specificity, therefore not sufficient to detect subglottic aspiration. 41.7% showed spontaneous recovery of aspiration 1 month post op on VFS. Authors: Vocal fold paralysis is most likely due to insufficient glottic closure and impaired laryngeal sensation. There may also be temporary postoperative oedema of laryngeal structures.	Anastomotic leak 1 (0.8%), VFP 15 (12.7%) Operation time of > 6 hours significantly increased risk of aspiration to 3.22 (p=0.007) VF palsy is predictive of acute asp (p<0.001)
		Unclear	Cervical	33					
		Unclear	Thoracic	85					
Mafune et al 2019 [150]	Observational study	MIE	Cervical	32				Dysphagia in 24 (75%), impaired pharyngeal reflexes in 8 (25%) No relation between hoarseness and postoperative dysphagia. Authors: Dysphagia in this study affected very little by RLNP but greatly by inclusion of cervical lymph node dissection.	RLNP 65.6% (21/32) had, 19 of whom had hoarseness, 9 of whom were nil oral.
Scarpa et al 2013 [92]	Observational study	Unclear		126				Self-reported dysphagia significantly deteriorated after surgery (p<0.01).	Anastomotic leak: 8 (8.6%), RLN lesions: 7 (7.6%).
			Cervical Thoracic	25 (25%) 69 (75%)					
Hambreus et al 1987 [252]	Observational study	Unclear		9/26 included here		VFS	3 weeks post op	At least 1 type of pharyngeal dysfunction in 8/9 participants. Most notable : reduced hyolaryngeal elevation (not excursion). N=6: paresis of pharyngeal constrictor muscles. In pts who also had reduced closure of laryngeal vestibule, there was gross aspiration. Defective relaxation of the CP muscles was not present in any patient. Improvements to pharyngeal dysphagia noted after a few weeks.	Some cervical anastomotic pts experienced recurrent pneumonia caused by aspiration. 3 patients had paresis of recurrent nerve resulting in vf immobility.
			Cervical	21					
Yokoi et al 2019 [253]	Observational study	Unclear		58	39		JMS tongue pressure measurement system	Tongue pressure reduced significantly from before oesophagectomy: 35.6+/-7.3 kPa, to 2 weeks post-op: 4.2+/-7.3 kPa (p=0.011) in 37 participants (62.7%).	

Author	Study design	Surgical Approach +/- Technique	Anastomosis site	N=	Neo-adjuvant tx	Swallow Ax	Post-operative timing of swallow evaluation	Dysphagia-Related Findings	Other Relevant Findings
Mayanagi et al 2021 [254]	Experimental case series	Thoracotomy Thoracoscopy 3FLND mostly MIE	Cervical	8 51 187	187	VFS (using and FILS) FEES	7-15 POD	Laryngeal penetration, aspiration, post-swallow residue in pharynx.	
Berry et al 2010 [72]	Retrospective observational study	Early era operations (379) included thoracotomies, late era operations (420) were MIE and/or transhiatal.	Cervical Non-cervical	779 469 330 9	50%	VFS and then Barium swallow	Unclear: Prior to starting oral intake, when pts had adequate respiratory support and appropriate return of bowel function.	Aspiration in 96 (12%) significantly increased from 7% to 16% in the later era (p<0.0001) however incidence of postop pneumonia was significantly reduced in later era (11% v 18% p=0.003) (Could this be due to improved SLT testing with VFS protocol in late era?). Early era: 23 of 27 episodes of aspiration detected during barium swallow to evaluate anastomotic integrity. Later era: 58/69 episodes of aspiration detected during VFS before barium swallow to evaluate aspiration. Early era, Cervical anastomosis and aspiration independently predicted pneumonia. Later era: neither anastomotic location nor aspiration predicted pneumonia.	14% pneumonia post-op (18% in early era, 11% in late era), anastomotic leak in 15% (in both eras), anastomotic stricture in 22% (25% early era reduced to 20% later era) Cervical anastomosis reduced from 76%-40% and thoracic anastomosis reduced from 58% to 22%.
Tsubosa et al 2005 [73]	Case Series	Thoracotomy with 3 FLND With 2 FLND	Cervical Thoracic	8 1 276		MWST Swallow screen	After POD 5/6.	N=30 high risk of aspiration (for VFS), n=30 mediate risk of aspiration, n=107 (low risk of aspiration).	Postoperative pneumonia: n=64, Anastomotic leak n=30, RLNP = 56
Takatsu et al 2021 [74]	Retrospective case control study	Thorascopic Open 3 FLND 2 FLND		85 (78%) 24 (22%) 89 (81.7%) 20 (18.3%)					
Sugase et al 2022 [256]	Retrospective	Transthoracic 2 Field	Thoracic	304	CT n = 147, CRT n = 49	VFS	8-9 days post, follow up median , At time of discharge (19 days range 13-122) post surgery. Outpatient median 37 months (range 1-76) months after discharge	112 (37%) had postoperative dysphagia, 11 of which were severe. 108 (36%) aspirated, including silent aspiration in n=85. 136 (45%) had residue in pyriform sinuses or valleculae. Abnormal epiglottic deflection in 92	At discharge 37 (33%) with postoperative dysphagia developed pneumonia. 24 (21%) of those with postop dysphagia developed pneumonia. Significantly more pneumonia in post-op dysphagia group >1 year post op compared to no post-op dysphagia group. Post op dysphagia is an independent risk factor for out of hospital pneumonia. Age ≥ 70 and low BMI are independent risk factors for postoperative dysphagia. Age ≥70, RLNP, and postoperative dysphagia were independent risk factors for acute pneumonia

Author	Study design	Surgical Approach +/- Technique	Anastomosis site	N=	Neo-adjuvant tx	Swallow Ax	Post-operative timing of swallow evaluation	Dysphagia-Related Findings	Other Relevant Findings
Kokima et al 2023	Retrospective observational study	Thorascopic-Laparoscopic oesophagectomy	Cervical	216	CRT = 153	VFS	1 day before surgery POD 6	Median Preoperative tongue pressure 37.1 kPa (32.9–45.0 kPa), postoperative tongue pressure 35.6 kPa (29.7–41.3 kPa), and perioperative change in tongue pressure – 2.5% (– 8.8 to 3.7%). Non-aspiration (n = 187, 86.6%) and aspiration (n = 29, 13.4%). Significantly lower geniohyoid muscle size on CT in the dysphagia group, and geniohyoid muscles was significantly smaller in those with preoperative sarcopenia.	Recurrent laryngeal nerve palsy was demonstrated to be an independent risk factor for postoperative dysphagia. Postoperative complications included recurrent laryngeal nerve palsy in 47 patients (21.8%), and pneumonia in 44 patients (20.4%)
Katsumata et al 2019 (only abstract available)	Retrospective observational study	Unclear	Unclear	54	Unclear	VFS	POD 7		

KEY: THO: Transhiatal Oesophagectomy, POD: Post-operative day, CDBIMS: complete division of the bilateral infrahyoid muscles attached to the sternum, RS route: retrosternal route, PM route: posterior mediastinal route, IT route: intrathoracic route, pts: participants, OP: oropharyngeal, Tx: treatment, Ax: Assessment, Dx: Diagnosis, Pen: penetration, Asp: aspiration, Post-op: postoperative, vf: vocal fold, vfp: vocal fold paralysis, RLNP: Recurrent laryngeal nerve palsy, CP: cricopharyngeal, Pneum: pneumonia, Oes: oesophageal, PS: pyriform sinuses, MWST: Modified Water Swallow Test, FLND: field lymphadenectomy

2.7 Causes and Consequences of Oropharyngeal Dysphagia in Oesophageal Cancer

Dysphagia, the most common first symptom to present in people with oesophageal cancer, typically does not present until the oesophagus is 80-90% occluded by a tumour [261]. This explains how many patients report swallowing difficulties that progress from solids to fluids as the tumour grows.

Potential causes of oropharyngeal dysphagia in oesophageal cancer

This section will discuss in more detail some of the most pertinent potential causes of chronic dysphagia in people with oesophageal cancer.

Chemotherapy and radiotherapy

Combined modality treatment, consisting of neoadjuvant chemotherapy, radiotherapy and surgical resection is the main approach for the curative treatment of locally advanced oesophageal disease [262]. Chemotherapy and radiotherapy are known to impact upon swallowing with even a small alteration to the oesophageal lumen significantly impacting upon the severity of dysphagia experienced [263]. Head and neck cancer research has shown that COD can exist following chemoradiotherapy (CRT) because of inflammatory cytokines related to oxidative stress, inflammation and hypoxia of tissues [209]. Interestingly, a study published by Kenny and his team in 2024 [264] found associations between Oxaliplatin chemotherapy and certain dysphagia symptoms for solid tumours outside the head, neck and upper gastrointestinal tract. Chemoradiotherapy can result in worse toxicities than radiotherapy alone [265] which can result in worse dysphagia outcomes particularly when anti-metabolites are used, such as 5-fluorouracil, which are associated with symptoms of oral, pharyngeal, and oesophageal dysphagia [266, 267]. A study conducting videofluoroscopies following head and neck cancer treatment found that

concomitant chemotherapy resulted in increased epiglottic changes compared to those who just had radiotherapy (66.7% versus 30.8%; $p = .05$) [268]. Dysphagia can occur due to tissue atrophy associated with reduced capillary flow, fibrosis, mucositis and strictures [209]. Mucositis was found to be the biggest cause of dysphagia in patients receiving treatment for oesophageal cancer and it is found to be correlated with the use of chemotherapy drugs Cisplatin and the addition of Melphalan [269]. Conversely, chemotherapy may actually improve symptoms of oesophageal dysphagia as the tumour shrinks and is therefore a potential treatment in palliative care [269].

Regarding the impact of radiotherapy, the oesophagus contains radiosensitive mucosa resulting in acute radiation-induced oesophagitis consisting of discrete ulcers, granular mucosa and a narrowing of the oesophagus which can cause severe odynophagia and dysphagia [270]. Radiation-induced oesophageal strictures may appear between 3-18 months following radiation therapy [270, 271]. Mucositis is particularly common in normal cells that divide rapidly such as mucosa surfaces in the oesophagus and oral cavity [265]. 47.8% of cancer patients receiving radiotherapy experience xerostomia irrespective of the primary location. Early post-radiation damage such as mucositis can have long-term 'consequential effects' but there can also be 'generic effects' such as fibrosis, meaning the thickening of the submucosal wall, or atrophy which happen later regardless of early symptoms [164]. Pseudomembranous inflammation is experienced in the oesophagus in response to irradiation [265]. Radiation-induced chronic inflammation or fibrosis can result in loss of elasticity and pain or difficulty swallowing in the acute or late stages following treatment [146]. Radiation to the oesophagus can cause noticeable soft tissue malformations such as strictures and stenosis of oesophageal muscles [164], which can be severe and require dilatation [249, 270, 272]. Radiation-induced oesophageal strictures may appear between 3-18 months following radiation therapy [270], and have been reported to occur in between 12-37% of patients after oesophageal treatment [273, 274]. Mucositis and rigidity of the mucosa may appear between 6 months – 5 years post treatment [275]. Additionally, striated muscle, which is situated in the proximal oesophagus, is known to contract with high-dose

radiation. Type II fibres of skeletal muscles, such as in the outer layer of the inferior pharyngeal constrictors are at most risk of radiation damage [164]. Muscle and nerve electrophysiology can also be affected by inflammation and fibrosis and messages may be disrupted which can lead to hyposensitivity. Extensive research demonstrates the negative impact of radiation therapy on swallow function when it is used for head and neck cancer [146, 164, 275, 276]. The impact of oesophageal radiation therapy on the oropharyngeal swallow warrants further exploration. With the development and improvement of Proton Beam Radiotherapy (PBT) and lowered total body integral doses, patients experience lower toxicities resulting in reduced postoperative pulmonary complications following oesophageal cancer surgery [277] giving rise to hope that there may be less severe swallowing difficulties as PBT becomes more accessible.

In one study, 1248 out of 2610 (48%) cancer patients reported experiencing xerostomia (dry mouth) throughout and following their cancer treatment (range 7 days to 18 months post operatively), most of whom were treated with chemotherapy and radiotherapy and/ or surgery for various cancer locations [278]. Xerostomia can result in difficulty swallowing at the oral and pharyngeal levels [279].

One study of 97 participants found a significant association between a higher T stage and self-reported dysphagia after neo-adjuvant therapy ($p=0.002$) [92], where more than half (56.7%) received combined chemoradiotherapy and 42.4% underwent just chemotherapy.

Surgical-related Consequences

Oesophageal Strictures

Further to radiation-induced strictures mentioned above, it is normal for patients to experience scarring at the anastomosis site which is less elastic compared to the elasticity throughout the oesophagus. The surgery itself can cause the anastomotic strictures or stenosis [206]. An additional potential cause of stricture-induced dysphagia can be an anastomotic leak [119].

Dilatation can improve scar contractures but can make severe anastomotic leak-induced strictures worse, therefore it is vital that surgeons ascertain whether the patient is experiencing a radiation or scar contracture stricture, a fistula-induced stricture (anastomotic leak) or a functional dysphagia prior to performing dilatation [119].

Altered oesophageal and gastric anatomy

Reflux can occur as a result of the altered position and shape of the stomach following gastric pull up, which no longer has the 'angle of His' or the 'spring action of the diaphragm' at the lower oesophagus [119], or can be caused by the positive pressures within the abdomen, the negative intrathoracic pressure or because of delayed gastrointestinal motility which can be a result of bilateral vagotomy as mentioned in the previous point [280]. Reflux has been shown to be associated with impairment of the pharyngeal swallow [281, 282] including UOS hypotonicity [283].

Dysphagia might occur due to the new shape of the stomach which consequently has poor peristalsis [117]. There can also be pyloric dysfunction preventing the stomach from emptying, both of which can result in hold-up in the oesophagus [117]. It is plausible that people whose entire oesophagus has been removed would also suffer dysphagia given the speed at which the bolus would exit the pharynx and enter the conduit of choice, usually the gastric organ. Hiatus hernia can form following surgery in up to 19% of survivors, often when an extensive hiatal resection is required, and can present with symptoms of dysphagia [117].

Finally, it has also been hypothesised that a short remnant results in reduced muscle strength in the oesophagus, [119] which may potentially impact upon oesophageal clearance.

Pulmonary damage

Damage to the thoracic wall and intercostal muscles during surgery can result in pulmonary oedema and poor ventilation [67]. Given the close relationship between swallowing and

breathing, it is possible that should there be prolonged respiratory complications, these may continue to impact upon the timing and coordination of swallowing [284].

Nerve injury

Surgically-induced damage or inflammation of key nerve pathways that provide sensory and motor neurons to the pharynx and oesophagus may also occur [251].

RLN paralysis can occur during the surgery [206] and impact upon glottic movement and airway protection [285]. It has been reported in up to 65.6% of patients as observed on laryngoscopy in 21 patients on post-operative day 1 [150]. It is thought to be one of the most common causes of aspiration after oesophagectomy [257] and an independent risk factor of dysphagia [256, 286]. It can occur during a thoracotomy and intrathoracic anastomosis, particularly when bilateral recurrent nerves are exposed during dissection of lymph nodes surrounding the bilateral intrathoracic laryngeal nerves but is significantly more likely to occur during a cervical anastomosis because of the location of the nerves [43, 97]. The RLN is located in the tracheoesophageal groove and can be damaged when the cervical oesophagus and stomach are reconstructed, and during the lymphadenectomy in the cervical area [43].

A thoracotomy could also result in more extensive damage to the intercostal nerves and pulmonary vagus, which may modify the swallowing reflex [287]. Damage to this branch of the vagus nerve may impact upon cricopharyngeal opening and glottic adduction [50, 133]. One group reported that RLNP had little impact on swallowing but that cervical lymph node dissection was more strongly associated with dysphagia [36].

The Ansa Cervicalis is a component of the cervical plexus and innervates the geniohyoid and infrahyoid muscles (excluding the thyrohyoid muscle) [60, 288] so damage to this may impact upon hyolaryngeal excursion and depression, and closure of the quadrangular membrane. The inferior root of Ansa Cervicalis has numerous cervical combinations, extending from the primary

rami of C2 and/or C3 and occasionally C1 or C4, making its descending route variable from that point, potentially placing it at risk of injury during cervical surgery and during the removal of deep cervical lymph nodes [90, 289].

The pharyngeal plexus is formed by the pharyngeal branches of the glossopharyngeal and vagus nerves. It innervates all muscles of the velum and almost all muscles of the pharynx [288]. Damage may impact upon glossopalatal approximation, base of tongue to posterior pharyngeal wall approximation, laryngeal elevation, pharyngeal contraction and pharyngeal shortening. Much of the pharyngeal plexus lies exterior to the middle pharyngeal constrictors extending to the inferior pharyngeal constrictors [288]. It enters the posterior pharyngeal wall at the C2-C4 levels within 10mm of the greater horn of the hyoid bone [289]. Damage to the pharyngeal plexus does not appear to be commonly reported however it has been identified as a potential risk of injury during cervical surgery [252].

Surgically removing the nerve and vascular supply to the oesophagus can result in altered pathophysiology, for example, dumping syndrome and delayed gastric emptying [119]. 45% of patients have dumping one year post surgery [116]. Delayed gastric emptying has been reported to result in self-reported dysphagia in 30% of survivors [290].

Additional possible surgical related injuries

Brain remapping occurs following limb amputation so does the brain remap after a key organ such as the oesophagus has been removed? Research has shown that humans experience significant neuroplastic changes following injury to the peripheral and central pathways. In particular stroke research has shown cortical reorganisation in response to ongoing activity and skill relearning. In monkeys, there has been extensive reactivation of the somatosensory cortex of face and hand regions over the space of a month resulting in rapid functional improvement [291]. When a digit was removed from a monkey, there was expansion of the stump cortical representation in the brain [292]. This has since been expanded upon in other mammals and to the visual, auditory and

motor system, and subcortical regions including the lower brain stem [293]. There is also evidence for reorganisation at the subcortical and brainstem levels in response to injury peripherally [294]. In adults post total laryngectomy, MRI research has shown that patients had reduced olfactory bulb representation in the brain when compared to healthy controls [295]. In addition, phantom limbs, which are hypothesised to be a reorganisation of parts of the brain, have also been reported following laryngectomy; as a phantom larynx [296]. Given these findings in the literature, it is plausible that brain reorganisation occurs to some extent following removal of key organs such as the oesophagus.

An additional surgical injury may be trachea scarring and reduced blood flow to the trachea which have been reported as consequences of surgery and may reduce the cough reflex [297].

Age

Oesophageal cancer is typically diagnosed in older adults across the globe, for example, the mean age was 65.7 ± 10 years in the US population between 2004- 2015 [298], the median age ranged from 66 to 75 years across multiple countries in Europe, Australia, New Zealand and Canada [299], and the majority of Japanese patients were found to be in their sixties or seventies [300, 301].

Between 15% and 33.7% of community dwelling adults over 65 have been reported to have dysphagia [302-306]. Presbyphagia, normal age-related swallow changes, include reduced speed of oropharyngeal and oesophageal swallowing, prolonged oral transit time, weak tongue propulsion, delayed onset of airway protection and UOS opening, reduced lingual pressure, increased oesophageal transit duration, delayed UOS opening, reduced oesophageal contraction amplitude without altered function, reduced occurrence of secondary peristalsis, and a higher frequency of reflux [166, 305, 307]. It has been suggested that some of these changes may be due to reduced muscle fibres in older adults, reduced excitation impulses, or reduced timing/coordination [303, 308].

Being older than 69 years of age has been identified as an independent risk factor of postoperative dysphagia following oesophagectomy [256]. Similarly, Mann et al found a correlation between dysphagia post MIE and older age in 129 adults with oesophageal cancer [309].

Sarcopenia

Sarcopenia, characterized by decreased muscle mass, and low muscle strength and function [310], can exist following oesophageal cancer treatment. Preoperative sarcopenia has also been reported to occur in 49.9% to 74.9% of oesophageal cancer patients depending on the cut off values used to define sarcopenia, and was associated with anastomotic leak and postoperative pulmonary complications [311, 312]. Sarcopenia has been found to be associated with an increased risk of postoperative complications [110], including postoperative dysphagia after oesophagectomy surgery [254]. Malnutrition has been reported in as high as 78.9% of people with oesophageal cancer and is significantly associated with negative surgical consequences including morbidity so it is important that patients are as nourished as possible prior to surgery [313]. Oesophagectomy patients are particularly vulnerable to malnutrition and weight loss and ultimately sarcopenia because of the obstruction within the oesophagus prior to surgery and because of a potential catabolic state caused by the cancer [314]. Sarcopenia has been reported in 35% of people with oesophageal cancer 12 months after surgery [110]. It has been associated with reduced tongue strength and dysphagia in healthy adults over 65 years of age ($p < 0.001$) [315]. Additionally, a significant association was found between low hand grip strength and postoperative aspiration and reduced airway protection after thorascopic-laparoscopic oesophagectomy [316]. A systematic review and meta-analysis showed that sarcopenia also increases the odds of aspiration pneumonia by 4.06 [317]. Dysphagia caused by sarcopenia, sarcopenic dysphagia, may be caused by sarcopenia of the entire body including the swallow related muscles [318]. Dysphagia may then cause or exacerbate sarcopenia [319] and if sarcopenia

can be prevented or minimised by improving swallowing, it should be considered. Theoretically, resistance training may be an appropriate treatment for sarcopenic dysphagia [316, 320].

Further research exploring sarcopenic dysphagia in people with oesophageal cancer is warranted given that a recent systematic review of three studies evaluating dysphagia in oesophageal cancer found that there was reduced tongue pressure in survivors acutely post oesophageal surgery [253], that reduced geniohyoid muscle mass causes dysphagia [259], and that patients who were sarcopenic preoperatively developed postoperative dysphagia [254].

Given that sarcopenia impacts upon maximum inspiratory pressure, forced expiratory volume and forced vital capacity in older adults, it is possible that these deficits may potentially limit the respiratory requirements of swallowing [110], such as swallowing at the ideal moment in the expiratory phase (at mid-to-low lung volume) and having adequate support for a respiratory pause that can protect the airway during swallowing [284].

Weight loss can be attributable to multiple factors such as cachexia which is an elevated basal metabolism that results in reduced skeletal muscle and/ or fat [102]. Cachexia, meaning cancer related muscle mass wasting which results in functional impairment, could potentially place oesophageal cancer patients at risk of dysphagia given that cachexia has been found to be associated with severe dysphagia in cancer patients [321]. In addition, general fatigue, which is common in cancer has also been associated with laryngeal penetration and impaired mastication in other conditions such as Amyotrophic Lateral Sclerosis [322].

Psychological-related maladaptive behaviours

Any of the above mentioned symptoms of dysphagia may instil anxiety and/or maladaptive swallowing behaviours, for example, a fear of choking. Although there is limited research on this topic in the literature, maladaptive compensatory strategies have been hypothesised to be a potential cause of abnormal swallowing presentation on VFS in head and neck cancer [323].

Phagophobia, fear of swallowing, may be present in some participants in this study given that fear of choking was mentioned on multiple occasions during the interviews. In addition, many participants reported that when they experienced a sign of dysphagia, they felt a fear of cancer recurrence, which is in itself an important theme discussed in the cancer literature [324]. Studies have shown how phagophobia and anxiety or other psychological stresses can impact upon the ability to swallow food and fluids [325, 326]. It is plausible that participants were perhaps altering their swallow in anticipation of unpleasant symptoms such as odynophagia, GORD, globus sensation, nausea etc. [325].

Premorbid dysphagia

A further potential cause of abnormal swallowing could be attributable to a pre-morbid unrelated dysphagia of an unknown or idiopathic aetiology. This research aimed to minimise this risk by excluding comorbidities that may be associated with dysphagia such as stroke, head and neck cancer and COPD.

Potential consequences of oropharyngeal dysphagia in oesophageal cancer

Section 2.4 lists potential consequences of oropharyngeal dysphagia. Those most pertinent to oesophageal cancer which are discussed in the literature are further explored here:

Nutrition

The presence of dysphagia can result in weight loss and is associated with malnutrition, sarcopenia and cachexia [327-330]. A retrospective observational study of 304 participants, published by Sugase et al in 2022, found that patients with dysphagia acutely post-oesophagectomy experienced severe long-term risk of malnutrition [256]. Pre-operative malnutrition, loss of skeletal muscle, and weight loss severity are associated with diminished post-operative outcomes including lower survival rates in people with oesophageal cancer [101, 331], with patients

continuing to struggle to return to their preoperative weight at 3 years following oesophagectomy [332].

Sarcopenia, a loss of both muscle mass and strength, that is associated with frailty and impaired QoL [333], can be due to age (primary sarcopenia) or lack of muscle use, disease or poor nutrition (secondary sarcopenia). People with oesophageal cancer are particularly vulnerable to both types of sarcopenia pre-operatively and post-operatively as they are typically older and as nutrition is often compromised by dysphagia [312, 319]. As discussed in section 2.1.1 of the literature review, sarcopenic dysphagia is a difficulty swallowing caused by weakness to skeletal and swallowing muscles [330]. An observational study by Elliott et al (2017) which included 250 participants with oesophageal cancer, found that sarcopenia, identified on CT, increased significantly from 16% pre-operatively to 31% after neo-adjuvant treatment, and that 35% of participants had sarcopenia 12 months after surgery [110].

One study found that surgical patients greater than or equal to 50 years of age had a greater chance of being dysphagic, and that those with dysphagia and frailty had increased risk of poor outcomes including increased length of stay in hospital and surgical complications [334]. Preoperative dysphagia risk has also been found to be associated with malnutrition and sarcopenia risk in community settings [335]. A catabolic state resulting in the breakdown of muscle tissue and energy storage may occur in patients following surgery depending on the extent of surgical stress or trauma [336]. It is also possible that dysphagia prevents patients from reaching their full potential from a nutrition perspective. Malnutrition can then give rise to poor wound healing, prolonged recovery time, infection, reduced immune response, further impaired nutritional status, morbidity, mortality, increased hospital length of stay and hospital costs [337]. Malnutrition has been reported to occur in 78.9% of oesophageal cancer patients prior to surgery compared to 9.1% with breast cancer [338].

Finally, there was a significant association between tube feeding post discharge and postoperative sarcopenia with 30% requiring tube feeding at discharge, according to one observational study of 134 participants who underwent open thoracic oesophageal resection [339].

Respiratory Complications

After oesophagectomy, postoperative dysphagia was found to be an independent risk factor of short term (inpatient) and long term (after 1 year) pneumonia [72, 227, 256], and dysphagia and aspiration have been proven to be risk factors for aspiration pneumonia ($p=0.027$ and $p=0.003$ [71, 72]). Sugase et al (2022) evaluated long term pneumonia in patients who were acutely dysphagic and found that 33% of patients with postoperative dysphagia developed pneumonia after discharge from the acute setting. After 1 year post surgery, significantly more patients from the post-operative dysphagia group (21%) developed pneumonia compared to the non-dysphagic group, demonstrating that post-operative dysphagia could be associated with long-term pneumonia. Those participants who developed pneumonia had significantly worse swallow results on barium swallow and VFS than those who did not develop pneumonia [65]. Dysphagia has also been found to be most significantly associated with aspiration post oesophagectomy in those with severe dysphagia [72].

The presence of dysphagia postoperatively is an independent risk factor of pneumonia [340]. Berry et al (2010) [340] found that 12% of patients had evidence of aspiration, hence approaches that minimise aspiration and aspiration pneumonia are clinically of great relevance to achieving optimum outcomes for these patients. Improving swallowing may potentially reduce aspiration, reduce pneumonia and PPCs, and may impact on sarcopenia and malnutrition, treatment-related morbidity, hospital length of stay and readmissions [257, 258, 340, 341].

Further research is needed to explore the other consequences of oropharyngeal dysphagia in this population.

2.8 Impact of Oropharyngeal Dysphagia on Quality of Life in Oesophageal Cancer

It is important to consider HRQoL, which despite there being no consensus among experts on the definition [342], has been referred to in the literature as the impact of a person's health status/health treatment on their 'physical, emotional, mental, and social functioning' [343]. In recent years there has been extensive research investigating HRQoL following surgical treatment of oesophageal cancer [344-346]. Consideration of QoL outcomes is needed during cancer treatment decision making, [347] with a reliable evaluation tool being necessary in order to fully appreciate the impact of a health condition [348, 349] and to try to improve quality of care [350]. Patients' QoL can be negatively impacted acutely and chronically post oesophagectomy due to the consequences of the invasive and complex treatment received [27, 351, 352].

A significant volume of research has revealed the extent of the impact of oropharyngeal dysphagia on HRQoL in people with various conditions such as head and neck cancer and neurological diseases [343] [353-361]. A lesser but still substantial volume of research has also shown that swallow/eating-related QoL is impacted in people with oesophageal cancer [352, 362-369] and symptoms that impact oral intake such as dysphagia, dumping syndrome and malabsorption were found to be significantly associated with impaired HRQoL [370]. Patients continue to report chronic dysphagia related symptoms, for example 'eating problems', choking, and trouble swallowing saliva for many years [52, 101, 362, 371, 372]. HRQoL was associated after both open oesophagectomy and MIE across many domains including dysphagia, reflux, eating difficulties, oesophageal pain, trouble swallowing saliva, choking, dry mouth and taste problems, with eating difficulties being one of the most outstanding problems [373, 374]. Lagergren et al (2007) evaluated HRQoL using the EORTC-QLQ-OES-18 with 47 long-term oesophageal cancer survivors within six weeks before surgery and 36 months (+/- 50 days) post-operatively [375]. Dysphagia improved from 17 (9-26) to 10 (3-17) ($p=0.18$), reflux deteriorated from 12 (5-18) to 32 (22-43) ($p=0.001$), with minimal changes reported for eating restrictions, oesophageal pain,

choking or cough. General emotional function does appear to improve at the three year time point compared to baseline (69 (61-77) to 80 (73-87) ($p=0.008$)) which perhaps correlates with some studies that have shown that swallow related QoL improved three years post surgery [376]. However in contrast, others reported that QoL is impacted up to five years post treatment with subjective rating of swallowing difficulties being a pertinent factor [377], and even up to 15 years post surgery with eating difficulties, dysphagia and reflux being the most severe ongoing symptoms demonstrating that this is a chronic issue in need of addressing [246, 378].

A small qualitative study identified the following five key themes when it explored the impact of dysphagia on QoL: 1) recognising dysphagia, 2) the physical experience 3) the emotional side of things, 4) significantly limited socialising, and 5) treatment of dysphagia [379]. The impact of a swallowing difficulty on HRQoL for a person with oesophageal cancer can be devastating, leading to anxiety during meals and limiting participation in family mealtimes and social occasions [380]. Other research has also found that ongoing symptoms such as choking, nausea and diarrhoea can result in reduced socialising behaviours [342] and reduced work capacity [381].

Despite this research which refers generically to 'dysphagia' impacting upon HRQoL, no studies have specifically investigated the impact of oropharyngeal dysphagia on HRQoL following oesophageal cancer surgery until this time. With increased survival rates, there is a need for a greater focus on recovery throughout survivorship to improve HRQoL [101, 382]. Further studies exploring this are warranted.

2.9 Evaluation of Oropharyngeal Dysphagia in Oesophageal Cancer

There is limited research published regarding best practices for oropharyngeal swallow evaluation in this population. There are currently no validated protocols. One study found that maximum phonation time of less than 15 seconds was predictive of late aspiration pneumonia in patients acutely post oesophagectomy [383]. A study by Leder et al [57] found that 44.7% of patients

(n=73) who aspirated acutely post THO did so silently, therefore bedside clinical swallow assessment is not considered adequate for determining a patient's suitability to initiate oral intake. A study by Lee et al revealed only 68.4% sensitivity and 70% sensitivity in identifying aspiration with a clinical swallow evaluation [61]. Comprehensive swallowing evaluation including instrumental assessment was found to detect aspiration prior to commencing oral feeding after oesophagectomy surgery, and this significantly reduced the incidence of pneumonia, especially aspiration pneumonia associated with cervical anastomosis [72].

A combined VFS and barium swallow procedure, involving radiologists and speech and language therapists, has been reported as a useful approach to developing an understanding of the patient's oropharyngeal swallow physiology and risk of aspiration, whilst also assessing for anastomotic leaks [71]. Routine use of water-soluble contrast swallow tests are often utilised to assess anastomotic integrity during the first week post oesophageal resection in an effort to reduce morbidity associated with undetected oesophageal leaks [384]. There is, however, some debate in the literature regarding the appropriateness of using contrast oesophagograms in this population, given its inherent risk of aspiration and poor sensitivity (35%) [385, 386]. High rates of specificity (up to 97% [385]) nevertheless reinforce its utility in patients for whom there is clinical suspicion of a leak.

Berry et al's study, published in 2010, revealed that conducting a VFS immediately prior to barium swallow can reduce the risk of short term aspiration post oesophagectomy [72]. Lewin et al (2001) also conducted a joint procedure however, contrasting Berry and colleagues, they implemented the barium swallow prior to the VFS in their study [250]. Informal conversations with SLTs at Guy's and St Thomas' NHS Foundation Trust in the United Kingdom, a high volume oesophageal cancer surgery centre, revealed that they attend the water-soluble studies for all 3-stage and THO patients. These studies are led by the radiologist, whom the SLT asks to trial various fluid volumes and strategies with the patient, while the SLT observes for aspiration. As part of a research project

taking place at TCD and St James's Hospital [81], a VFS is now being conducted following a contrast swallow for 3-stage and THO patients, where the SLT (researcher) leads the procedure, once anastomotic integrity has been confirmed by the radiologist. It is worth noting Berry et al's criteria for referring a patient for this combined study [72]. Patients were referred if they presented *without* overt signs of aspiration at bedside, or if overt signs of aspiration were eliminated with strategies (cup sip or chin tuck). Aspiration was detected in 16% (n=69) of their total participants (n=420), 319 (76%) of whom had a cervical anastomosis.

It is important that clinicians conducting VFS perform a screen of the oesophagus when assessing any population, including oesophageal cancer, so as not to miss a potential cause of oropharyngeal dysphagia that may otherwise go undetected, and to refer to relevant multidisciplinary team members for further investigation if needed [387]. Allen and colleagues found that VFS had 62.8% sensitivity and 100% specificity in identifying oesophageal impairments when compared to oesophagram findings as the gold standard. Sensitivity increases to 71% with the inclusion of a barium capsule [387].

2.10 SLT Intervention in Oesophageal Cancer

It is understood that people with head and neck cancer can experience short-term and long-term dysphagia reducing their QoL [388], and that dysphagia rehabilitation may improve their QoL and dysphagia outcomes, for example, severity of aspiration and pharyngeal efficiency [389-395]. However, with regard to adults with oesophageal cancer, there is limited research exploring oropharyngeal swallowing intervention. A systematic review by Kaneoka et al [257] identified three small studies (N=45) of low/inadequate quality which evaluated the effectiveness of compensatory strategies acutely post oesophagectomy. The studies found that when a chin tuck was implemented there were significant improvements to airway protection, UOS opening duration, and pyriform sinus residue [93, 250, 396]. Since this systematic review was published, an additional study found that chin-down-plus-larynx-tightening manoeuvre during swallowing

reduced a 'choking cough' during oral trials [397]. This study did not include an instrumental evaluation of swallowing.

A consideration of sarcopenic dysphagia is recommended for SLTs during their swallow evaluations given the high prevalence of sarcopenia in people with/post oesophageal cancer [297].

Finally, two further considerations relevant to swallowing professionals are detailed below which may improve respiratory and nutritional outcomes for people with oesophageal cancer:

Timing of Oral Intake

There is a high risk of complications in patients who are malnourished and/or at risk of malnutrition and have severe dysphagia (tolerating puree/fluids only) therefore early introduction of nutrition is recommended [101]. Nutritional support can be provided enterally or parenterally. Enteral nutrition is often preferred over parenteral means to maintain the strength and function of the gastrointestinal tract and may be received via a nasojejunal tube or a jejunostomy tube in the acute post-operative period [398, 399]. Early initiation of nutritional support is paramount to prevent postoperative complications and to maintain physical and nutritional status achieved during prehabilitation [400]. Early oral intake has been reported to result in reduced calorie intake when compared to nutrition provided enterally [401]. Surgeons are also often reluctant to initiate oral intake because of concerns around gastric emptying issues, aspiration and anastomotic leak [399]. Research has shown the detrimental consequences of aspiration events and pneumonia in this population and the importance of focusing post-treatment care on preventing these outcomes [402]. A multicentre prospective study including 50 participants found that it was feasible to initiate a liquid oral diet immediately post minimally invasive oesophagectomy for 62% of participants who did not have complications with non-significant reductions in pneumonia rates and anastomotic leak rates and no difference in mortality [401]. Patients discharged with enteral feeds have a higher association with increased hospital admissions [403]. A Cochrane review

including 37 randomized controlled trials (N = 5711) demonstrated that the absence of nasogastric tubes that assist with drainage reduced pneumonia [404]. The ERAS Society guidelines for pre- and post- oesophagectomy care recommend multi-disciplinary nutritional intervention [101, 405]. To increase the safe return to oral intake as quickly as possible, there is a need to focus on reducing the barriers to oral intake. Ashok et al (2020) suggest using endoscopy, contrast swallow, and CT to assess anastomotic integrity, and suggest that it is unclear yet which is superior [400]. Unfortunately many institutions continue to rely on clinical assessment for the initiation of oral intake.

Early oral intake may be superior to enteral intake given the risk of complications associated with the surgery and the reoperation risk including entry site leakage and infection, tube dislocation, gastrointestinal complaints and due to the potential atrophy of swallow muscles [399].

Sun et al (2013) evaluated liquids one day after surgery following endoscopy to test vocal cord function and evaluated semi-solids two days after surgery and found no increase in complications, and an earlier return of bowel function with improved short term QoL [406]. A systematic review and meta-analysis in 2020 included 14 studies and found that in the open-oesophagectomy subgroup, early oral feeding (EOF) was 2.89-fold more likely to be associated with an anastomotic leakage compared with delayed oral feeding (DOF). In the MIE subgroup there was no significant difference in the anastomotic leakage rate between EOF and DOF. In the cervical anastomosis subgroup, anastomosis leakage may be less in the DOF group than the EOF group. In the thoracic subgroup, anastomosis leakage showed no obvious difference between DOF and EOF. There was no significant difference in pneumonia rates between the EOF group and the DOF group. Studies published since then found significantly reduced hospital stays following a MIE with no associated increase in postoperative complications in EOF group compared to standard care (nil-by-mouth for 5 days) [125, 407]. It is important for swallowing clinicians to understand this information as part of the wider MDT team involved in dysphagia management.

Oral Care

Interestingly, 69.2% of 232 patients assessed by a dentist in a retrospective study had periodontitis pre-oesophagectomy [408]. Dental plaque pre-operatively has been shown to be a risk factor for postoperative pneumonia following thoracic oesophagectomy [409]. Another large study of 775 patients across 25 hospitals found that increased frequency of oral care before and following oesophageal cancer surgery was significantly associated with reduced postoperative pneumonia [410] likely due to the removal of pathogenic microorganisms in saliva which may be aspirated [411, 412].

Concluding Paragraph:

This chapter has summarised the literature to date on oropharyngeal dysphagia in people with oesophageal cancer from diagnosis through survivorship. Further information is needed to better understand the nature and severity of dysphagia in this cohort, in particular throughout the chronic stages in order to optimise outcomes for this increasing group of survivors. Once this is identified, the data will assist researchers to develop rehabilitation studies and will aid clinicians to develop appropriate assessment and management plans for this patient group who can continue to struggle for many years following their curative surgery.

3 Chapter 3 - Theoretical Framework

The theoretical framework for this body of research lies around four prominent themes.

1) Limited evidence to support dysphagia management in oesophageal cancer

It is not currently possible for researchers or clinicians to identify appropriate treatments for adults with COD after oesophageal cancer surgery [413] because key information such as the nature, severity and impact of this dysphagia has not yet been identified. Once this information is known, these findings will form the basis upon which future intervention research can be designed aiming to optimise long term QoL amongst those in the community.

Interventions prior to, during and following oesophageal cancer treatment may reduce the extent of COD experienced by survivors similar to physiotherapy and dietetics peri-rehabilitative research which found statistically significant and clinically meaningful gains to physical functional performance and HRQoL [414]. Improvements to dysphagia symptoms would be important given that this cohort is particularly vulnerable to malnutrition because of anatomical changes to the digestive tract [400]. Given that sarcopenia places patients at a lower probability of survival three years post-operatively [415], improvements to swallowing may have a vital role to play in rehabilitation, survival and overall HRQoL.

Similarly, understanding the nature, severity, and impact of COD may guide dysphagia clinicians to provide and advocate for adequate services, and may potentially assist surgeons with decision making regarding appropriate surgical approaches.

2) Impact on quality of life

For some survivors of oesophageal cancer surgery, long-term QoL is severely impacted [416, 417]. Research, which has evaluated the HRQoL of people following oesophageal cancer surgery, has consistently identified that patient reported symptoms of dysphagia such as pain and choking

when eating continue to impact QoL even 15 years after surgery [352, 362-369, 416]. Further research is needed to more specifically understand the impact of dysphagia on QoL. It is now widely understood that cancer care is more than just anti-cancer treatment, but it must also consider supportive care needs, including the improvement of QoL from diagnosis throughout survivorship. QoL outcomes are important in cancer treatment decision making [347].

3) Increased Survivorship

The Irish National Cancer Strategy 2017-2026 highlights how increased survival rates require a greater focus on survivorship [418] and a need to ensure that QoL is improved for this growing cohort [101, 382, 419]. The Irish National Cancer Strategy promotes the importance of focusing on survivorship so patients not just survive but thrive [420].

Survivorship has been defined as commencing at the time of diagnosis or once treatment has begun with consensus that it continues until the end of life [421, 422]. Healthcare services are needed to manage long-term post treatment consequences to ensure that survivors are supported and to provide appropriate routine monitoring of cancer recurrence [103].

The National Cancer Control Programme's (NCCP) survivorship programme aims to reduce health inequalities and ensure that patients receive the required care at the right time from an expert clinical team in the optimal location, including appropriate follow up and support throughout survivorship [423].

Aziz and Rowland (2003) indicate that research is needed to determine physiological outcomes of interest and to develop diagnostic criteria for assessing the impairments, to identify late symptoms experienced by cancer survivors, to identify the patients' perspectives, and to ultimately improve function and QoL [424]. Survivorship research should aim to understand and reduce adverse effects of cancer and its treatment [422] for example radiation-induced dysphagia or psychological distress experienced as a result of altered swallow anatomy [422]. Therefore it is

essential that dysphagia research is conducted to prove whether there is a need for this service to be provided.

Long term health issues are of public concern given the significant increase in survival rates [424, 425]. The World Cancer Research Fund specifically identifies that maintenance of body weight is an important factor for all cancer survivors [426] highlighting the importance of identifying COD to minimise the risk of unintentional weight loss.

Few communities globally provide community services for individuals in the community who have had oesophageal cancer surgery [427].

4) Importance of MDT access in the community

There is a need for specialists and primary care providers who can ensure that all survivors' health needs are met [422, 428]. As per the ESMO Clinical Practice Guidelines, multidisciplinary practice in long-term follow up clinics should be prioritised [429]. Specialised survivorship clinics where multidisciplinary care is offered at one site is important to ultimately improve outcomes for cancer survivors and their families [422, 424, 427]. This will enable multidisciplinary rehabilitation which can optimise overall functioning and ideally improve patients' self-management and psychosocial wellbeing [420, 430]. Pre-operative and peri-operative nutritional and exercise programmes have resulted in a reduction in perioperative morbidity secondary to pulmonary complications, improved physical and nutritional status, and improved perception of care [427, 431]. Dysphagia intervention may also be valuable in this cohort as certain patients cannot be deemed appropriate for curative treatments due to their poor physiological and nutritional status [432]. Evidence is required to justify speech and language therapy involvement.

New models of multidisciplinary care in the community should be a health care priority to meet the needs of cancer survivors [433, 434]. If experts are not based in the community, there needs to be a transfer of knowledge from specialists to primary care team members [435, 436]. It is clear

that there are ongoing unmet needs in cancer survivorship as a result of current service delivery models [437].

Oesophageal cancer ERAS guidelines also recommend multidisciplinary practice using a standardised pathway [101]. The Irish National Oesophageal Cancer Clinical Guidelines (No 19) advises the consideration of a referral to speech and language therapists post oesophageal cancer surgery [26]. There may also be a role for dysphagia education and evaluation pre-operatively [72]. Once more is understood about the nature, severity and impact of COD, swallowing specialists may be included in future referral pathways throughout survivorship.

Access to adequately skilled health care professionals in the community is also in line with Ireland's healthcare reform, Sláintecare, which aims to improve primary and community care services [438].

Framework

The following diagram conveys the four pillars which underpin the theoretical framework behind this research, with this research placed at the centre. Interestingly, each of these themes are relevant to seven of the nine domains of survivorship that patients in existing survivorship research identified as most important to them including treatment complications, physical function, social function, relationships and family, employment and finance, mental health, and self-care [439].

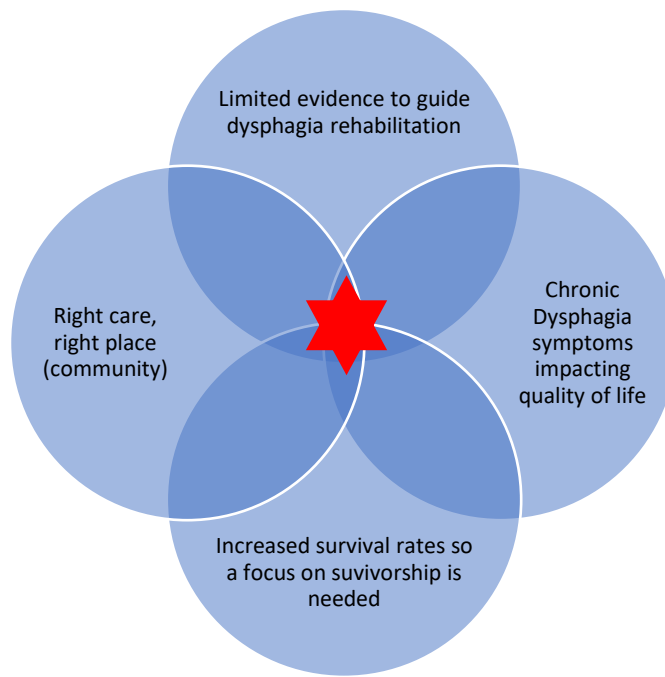


Figure 9 Four pillars underpinning theoretical framework

4 Chapter 4 - Objectives, Hypotheses and Research Questions

The majority of the research herein focusses on one important time-point that has received little attention in the literature: the *long-term* effects of curative treatment for oesophageal cancer on swallowing, and the impact that *chronically* altered swallowing has on QoL post oesophagectomy.

This body of research will evaluate the nature of swallowing a minimum of 12 months post oesophageal cancer surgery completed with curative intent. There are three main sections depicted in blue, orange and green throughout this thesis.

1. Nature and Severity of Chronic Oropharyngeal Dysphagia

Question 1A

How does COD present post-oesophageal cancer surgery?

Question 1B

What is the strength, nature and function of the tongue in the long-term post-oesophageal cancer surgery?

Question 1 C

Are there surgical/ treatment related variables or clinical tools that can predict COD post-oesophageal cancer surgery?

Question 1D

What is the nature and extent of long-term oesophageal bolus flow and is it associated with any clinical/ surgical/ pharyngeal dysphagia variables?

Question 1E

What are the predictors of disrupted oesophageal bolus flow in the long-term post-oesophageal cancer surgery?

2. Impact of COD and aerodigestive symptoms on quality of life

Question 2

What is the impact of COD and other aerodigestive symptoms on QoL in the long-term post-oesophageal cancer surgery?

3. Exercised based Dysphagia Rehabilitation in Oesophageal Cancer

Question 3

Is there evidence to guide oropharyngeal dysphagia rehabilitation in adults with oesophageal cancer?

Figure 10 Sections of this Research

The first part of the first section focuses on the presence, nature and severity of oral and pharyngeal phases of swallowing. Following a broad evaluation of oropharyngeal swallowing, this section will then elaborate in more detail on one particular area of impairment that is identified in this research, lingual function, as components of lingual dysfunction were identified in high numbers of participants in this study as well as having been identified in other published studies, as discussed in the literature review above. Following this, there will be a clinical focus aiming to identify surgical and treatment related variables that might be predictive of COD which will be relevant to clinicians working with this cohort. The remainder of the first section will broadly explore the nature of oesophageal swallowing, more specifically the nature of bolus flow through the oesophagus, as impairment of this swallowing component was also identified in a high proportion of participants during the oesophageal screen of this study. Although oesophageal bolus flow is related to oesophageal dysphagia and not oropharyngeal dysphagia, it will be considered within this section because clinicians conduct an oesophageal screen as part of their

swallow evaluation during VFS and findings may provide information that is of clinical relevance. It is also an important topic to explore given that dysmotility in the oesophagus is known to be a potential cause of oropharyngeal dysphagia [440]. This section will then conclude with another clinical focus aiming to identify predictors of impaired oesophageal bolus flow.

The second section of this research will discuss the impact that dysphagia and other aerodigestive symptoms have on HRQoL using both quantitative and qualitative methods of analysis.

The third section will aim to identify whether any published studies have evaluated the efficacy of exercise-based dysphagia rehabilitation in oesophageal cancer in order to guide clinical practice or direct future research.

Each section will provide a statement of the main problem relating to that section, followed by the objectives of this research (which attempt to combat that problem). Subsequent to this, hypotheses will be stated, justifying the selection of variables. Given the lack of existing dysphagia research in oesophageal cancer, hypotheses have been established based on the literature review findings above, existing research on dysphagia in other populations or in consultation with experts in the field of oesophageal cancer. Finally, each section will conclude with a list of the research questions for that section.

Section 1: Nature and Severity of Chronic Dysphagia

4.0.1 Oropharyngeal Phase of Swallowing

Chronic Oropharyngeal Dysphagia

Statement of problem

The literature review in Chapter Two highlighted the paucity of published research evaluating COD following oesophageal cancer surgery completed with curative intent, and how the only studies that have been published found conflicting results. Therefore prior to this body of research, it was not yet clear if or how COD presented and without this knowledge, it is not possible to develop

intervention studies or to make clinical recommendations. A study by Takatsu et al (2020) found that oropharyngeal dysphagia improved with rehabilitation exercises including jaw opening, tongue exercises, the Shaker exercise, thermal-tactile stimulation, and voice therapy however this study did not conduct instrumental evaluation of swallowing and used a blanket approach for rehabilitation instead of selecting exercises that would target specific biomechanical components of swallowing. It is therefore not known what the impaired areas of swallowing were or what exactly improved with therapy, so it is unclear whether they received an appropriate treatment [441, 442]. Guidance regarding specific areas to target in rehabilitation are hence lacking in the literature.

Objectives:

This research intended to determine the nature and severity of COD as this might lay the groundwork for future research such as a randomised controlled trial implementing rehabilitation exercises that target a specific biomechanical impairment. A second objective was to compare differences in dysphagia outcomes across various cancer/ treatment groups (cancer location, cancer type, age, site of anastomosis and whether radiotherapy was received or not) to determine if certain patients may be more likely to experience dysphagia. This information may be relevant for surgeons, patients and dysphagia therapists.

Hypotheses:

Based on the findings from the two studies which previously evaluated COD [70, 248], it was expected that some participants who participated in this study would present with at least mild COD. It was also hypothesised that the participants who received cervical incisions would present with more severe symptoms of dysphagia, evident on instrumental assessment and from self-reported swallowing symptoms questionnaires, when compared with those participants who had thoracic incisions given that cervical anastomosis is more strongly associated with RLNP compared to thoracic anastomosis [443]. It was hypothesised that there may be differences in COD based

on: cancer location, for example, a cancer higher in the oesophagus results in a shorter neo-oesophagus post resection which may more significantly impact the pharyngeal phase of swallowing than an intact long oesophagus; based on age given that altered swallowing can exist in healthy older adults [444]; and based on whether radiotherapy was received or not as radiotherapy is known to cause dysphagia in head and neck cancer patients [164]

Research Question

1A. How does COD present post oesophageal cancer surgery?

- i. What is the nature and severity of COD?

Nature of lingual strength, endurance and function

Statement of problem

A previous study by Yokoi et al published in 2019 found that tongue strength was significantly reduced two weeks post oesophageal cancer surgery compared to pre-surgery [253]. Reduced tongue strength has been shown to be associated with incidence of dysphagia, postoperative aspiration and postoperative pneumonia [253, 255]. It is not known whether adults with oesophageal cancer continue to experience chronic lingual impairments. The components of impaired lingual function that were previously referred to in studies investigating lingual function post oesophagectomy include poor bolus formation, premature posterior spillage (which can be due to reduced tongue control/positioning during bolus hold), and oral residue. It is not clear why these issues exist however they may potentially be caused by reduced lingual strength [445] or from muscle fatigue due to reduced lingual endurance [446].

Objective

The findings from Research Question 1A illustrated abnormal levels of oral residue deficits in a high proportion of participants (72.5%) therefore this study aimed to further explore lingual

strength and endurance to potentially guide future peri-rehabilitation research. In addition, this research aimed to identify associations between lingual variables and clinical variables to get closer to understanding a cause for reduced strength and endurance as this would be pertinent information when forming an appropriate rehabilitation plan for clinical practice or for directing future research.

Hypothesis

As per previous acute research [253], it was hypothesised that participants would have reduced tongue strength [447-450] when compared to healthy norms, and that this was likely to impact upon lingual function. No research has previously explored lingual function on the Modified Barium Swallow Impairment Profile (MBSImp) with this population however the components that are deemed most relevant to lingual function have been selected as variables for analysis (Component 2: Tongue control during bolus hold, Component 4: Bolus Transport, Component 5: Oral residue).

It was hypothesised that tongue strength might be associated with age (as has been demonstrated with healthy adults [451]), sarcopenia (as per healthy adults [452]), radiotherapy (as found in people with head and neck cancer [453]), and FOIS scores (as per research in Amyotrophic Lateral Sclerosis [454]). It was hypothesised that tongue strength would potentially be associated with 'months since surgery' in line with research investigating grip strength and physical strength at various intervals up to 6 months post-oesophagectomy [455]. Theoretically, it was hypothesised that days in ICU/hospital post-surgery might indicate a severe acute dysphagia which could potentially be associated with long-term tongue strength [253] that may or may not have completely improved.

Research Questions

1B What is the strength, nature and function of the tongue in the long-term post oesophageal cancer surgery?

- i. What is long-term lingual function post-surgery on MBSImP?
- ii. What is the long-term lingual strength and endurance post-surgery?
- iii. Is there an association between lingual strength and function (strength, endurance, function on MBSImP) and clinical variables (age, months since surgery, sarcopenia, radiotherapy, days in ICU, days in hospital after surgery, FOIS)?

Clinical Context – Predictors of Chronic Oropharyngeal Dysphagia

Statement of problem

The findings in Section 1 demonstrate that COD exists in this population however despite this, as per the review of the literature in Chapter 2, there is a lack of published studies which can guide clinicians on how to assess and manage this [117].

Objective

To assist clinicians on the ground, this research will attempt to identify surgical and/or treatment related predictors of oropharyngeal dysphagia and/or clinical tools that could predict oropharyngeal dysphagia. This information may also improve referrals to swallowing clinicians, it may assist therapists in prioritising patients and it may even guide surgeons with their decision making when selecting treatments.

Hypotheses

It was expected that site of anastomosis would be a significant predictor of COD given similar findings in acute research [70, 248]. Similar to the rationales for Question 1A, the following

variables were hypothesised to be predictors of COD: site of anastomosis [70, 248], cancer location, age [444]; and radiotherapy [164]. Acute research has previously found associations between tongue strength and dysphagia [253], therefore it was hypothesised that tongue strength may predict COD (DIGESTv2). It was hypothesised that complications such as RLN injury, responsible for laryngeal sensation and airway protection, and anastomotic leak, which can cause anastomotic strictures over time [456], may impact upon the pharyngeal phase of swallowing and be predictive of dysphagia. Days in ICU and days in hospital post-surgery were hypothesised to be predictive of dysphagia for the same reason as mentioned previously; perhaps a longer stint in hospital may indicate that a person was medically unwell for longer which potentially resulted in weakened swallowing muscles. It was plausible that perhaps swallowing may not have not fully improved for some participants, given existing research which shows an association between dysphagia and length of stay in hospital [457]. SARC-F results can detect a risk of sarcopenia and it was hypothesised that SARC-F might predict dysphagia as sarcopenia detected on CT has been found to predict dysphagia in cancer patients [458]. If patients experienced sarcopenic dysphagia, malnutrition or weakness post-surgery, it was hypothesised that this might improve with time so 'months since surgery' will be included as a predictor variable. The status of oral intake (FOIS) may theoretically predict dysphagia if patients are modifying consistencies because of dysphagia symptoms, therefore it will be included as a predictor variable.

Research Question

1C. Are there surgical/treatment related variables or clinical tools that can predict COD post oesophageal cancer surgery?

- i. Are there clinical and treatment-related variables predictive of COD?

4.0.2 Oesophageal Phase of Swallowing

Nature of oesophageal bolus flow

Statement of problem

To date it appears that no research has evaluated oesophageal bolus flow in this population. As mentioned previously, oesophageal motility disorders (including altered oesophageal peristalsis post oesophageal surgery) can impact upon the oropharyngeal phase of swallowing so it is therefore plausible that a relationship exists between altered oesophageal bolus flow (including retrograde flow) and oropharyngeal dysphagia. Laryngopharyngeal reflux in particular is a significant issue following oesophageal resection [62, 459]. Consequential pharyngolaryngitis reportedly occurs in up to 70% of patients with cervical anastomoses and 68% with thoracic anastomoses [460]. Discomfort in the oesophageal area after swallowing may potentially also be associated with abnormal bolus flow in the oesophagus [62] and therefore this topic warrants further investigation.

Objective

The aim of this section is to better understand the movement of the bolus beyond the oropharyngeal phase of swallowing throughout the oesophagus (i.e. the presence of oesophageal retention and the oesophageal transit duration). An oesophageal screen was included during the instrumental evaluation of swallowing for this purpose. There is international consensus in recent years that individuals with swallowing difficulties should have all phases of swallowing assessed and that clinicians should consider an oesophageal cause of dysphagia in their differential diagnosis [210, 461, 462].

Hypotheses

It was hypothesised that there would be oesophageal retention and prolonged oesophageal transit in some participants because of dysmotility induced by radiation [463] or that retrograde flow of the bolus might be present because of peristaltic changes and/or anatomical changes (i.e. no lower oesophageal sphincter, and/or surgically-induced nerve damage) [280].

Oesophageal clearance has been selected as a variable to measure as research has shown how altered lower oesophageal sphincter function can impact upon peristaltic contractions within the oesophagus resulting in stasis [464]. Reduced force of peristaltic contraction can occur when there is reduced basal pressures at the lower oesophagus inhibiting the transfer of foods through the oesophagus, particularly solid foods, and may promote gastroesophageal reflux [464]. It was therefore hypothesised that delayed oesophageal transit time and retrograde flow of the bolus may be present in the participants in this study, as they have had their lower oesophagus removed.

It was hypothesised that oesophageal clearance would be associated with relevant pharyngeal components of the MBSImP. It was hypothesised that: *Anterior hyoid excursion* and *Laryngeal elevation* would be impaired as they may potentially be tethered if there is reduced UOS opening given the inter-connection between these flexible structures. *UOS opening* might be altered given that it is impacted by other oesophageal motility conditions such as achalasia [465] and given the discovery of long-term hypertensive peristalsis in the cervical oesophagus (i.e. mean oesophageal pressures over 100mmHg) in 80% of nine participants who underwent oesophageal resection a median of 18 months prior [248]; *Pharyngeal stripping wave* and *Pharyngeal contraction* would likely be altered given the known inter-relationship that exists between oesophageal dysmotility and issues with pharyngeal contraction and speed of pharyngeal transit [440, 466]; *Tongue base retraction* might theoretically be associated with oesophageal clearance given that it provides the bolus with the initial thrust of its journey through the pharynx and oesophagus [467, 468] and previously mentioned studies detected reduced anterior tongue strength acutely post oesophagectomy [253]. It was also hypothesised that oesophageal clearance would be associated with months since surgery given that motility of the newly positioned gastric organ and oesophagus may improve over time following oesophageal surgery [469, 470]. Theoretically, it was hypothesised that an anatomically higher location of cancer may result in worse oesophageal clearance given that there would typically be less of the original oesophagus remaining, which is

associated with impaired bolus flow as per manometric findings [471]. The type of neo-adjuvant treatment was selected as a variable to assess as it was hypothesised that radiation to the oesophagus might result in fibrosis and impact upon oesophageal clearance [472]. Site of anastomosis was selected as a variable in order to analyse its correlation with oesophageal clearance as this information may be relevant to surgeons when making decisions about the most appropriate technique to use. It was hypothesised that the cervical anastomosis would result in worse oesophageal clearance given the greater risk of vagus nerve damage. As mentioned, given that oesophageal motility disorders have been proven to have an inter-relationship with the pharyngeal phase of swallowing, it was hypothesised that there would be an association between oesophageal clearance and dysphagia on DIGESTv2. It is understood that sarcopenia is mostly associated with striated muscle but recent research has shown an association with smooth muscle fibres [473], therefore it was anticipated that there would be an association between SARC-F and oesophageal clearance given that the oesophagus contains both striated and smooth muscle fibres. Finally it was hypothesised that there would be an association between reflux identified on the RSI and retrograde flow of the bolus identified through the Component 17 of the MBSImp Oesophageal Clearance.

Surgical variables that were found to have statistically significant correlations with oesophageal clearance (location of cancer, site of anastomosis and neo-adjuvant treatment) were then selected as potential predictors of oesophageal clearance to clinically assist clinicians with identifying at risk patients. Given the presence of delayed gastric emptying (i.e. retention of barium in the gastric conduit [474]) in certain patients, it was hypothesised that oesophageal transit duration might also be delayed in some participants [475]. It was hypothesised that a shorter oesophagus (which has a cervical surgical site and typically higher anatomical location of cancer) would be associated with slower transit as per manometric findings that revealed reduced peristalsis in shorter remnants [471]. Finally, it was hypothesised that there would be differences in oesophageal transit time depending on age (as per previously published data on healthy adults

[476]), and neo-adjuvant treatment given that radiotherapy may result in fibrosis and strictures and consequential slower transit of the bolus [472].

Research Questions

1D What is the nature and extent of oesophageal bolus flow in adults in the long-term post oesophageal cancer surgery and is it associated with any clinical/surgical/pharyngeal dysphagia variables?

Clinical Context – Predictors of disrupted oesophageal bolus flow

Statement of problem

Most research relevant to oesophageal bolus flow following oesophagectomy includes radiological and manometric studies that refer to functional disorders such as delayed gastric emptying and dumping syndrome [477] with minimum mention of altered oesophageal motility [471]. If swallowing specialists do not know which patients are at a higher risk of impaired oesophageal bolus flow and/or laryngopharyngeal reflux (LPR), patients presenting with consequential oropharyngeal dysphagia may be missed. In addition the opportunity to identify the appropriate cause of relevant symptoms may be missed which could be targeted with appropriate treatments.

Objective:

This study aimed to identify variables that may predict abnormal bolus flow and LPR as this may identify at-risk patients and may potentially guide surgical decision making.

Hypotheses:

For the same rationales above under nature of oesophageal bolus flow, it was hypothesised that clinician/surgical variables which were found to have statistically significant correlations with

oesophageal clearance might be predictive of oesophageal clearance: age >65, location of cancer, neo-adjuvant treatment, pathological stage.

Research Questions

1E: What are the predictors of disrupted oesophageal bolus flow in the long-term post oesophageal cancer surgery?

- i. Are surgical and clinical variables predictive of abnormal oesophageal clearance?

Section 2: Impact of COD and other Aerodigestive Symptoms on Quality of Life

Statement of problem

Published studies have revealed how some participants' HRQoL is severely impacted post-oesophagectomy for many years with comments from participants including "eating problems", "choking", and "trouble swallowing saliva" [362, 364] having strong negative effects on HRQoL measures [15]. Quantitative findings from QoL questionnaires in this study revealed that QoL is mildly impacted. Throughout the clinical career of the main researcher, some oesophageal cancer survivors have anecdotally reported significant long-term swallowing difficulties and consequential daily struggles and it was therefore felt that the quantitative data from this study did fully not capture this.

Objective

This study aimed to quantitatively identify the impact of chronic aerodigestive symptoms including dysphagia on HRQoL. To supplement this, a qualitative study was conducted to better understand the perspective of those participants whose QoL continues to suffer chronically from ongoing aerodigestive symptoms.

Hypotheses

It was hypothesised that in line with existing research, participants might not feel well supported in the community [478, 479], they might experience a lower quality of sleep, a higher risk of financial problems, reduced social participation, and a change in their perceived role in the family [480]. It is expected that findings from this research would differ from existing research because these chronic symptoms would be directly reported to be occurring secondary to aerodigestive symptoms.

It was hypothesised that patients would report that QoL is chronically impacted by dysphagia given the ongoing “eating problems” and “difficulty swallowing” symptoms reported in research up to 15 years after surgery [246].

Theoretically, it was hypothesised that more invasive surgery, more complications post surgery, higher age and radiotherapy would result in worse dysphagia and hence reduce QoL. Therefore the following variables were considered for sub-group analysis: surgical approach, RLN injury, age, radiotherapy.

It was hypothesised that worse dysphagia outcomes would correlate with reduced QoL therefore the following variables were included for assessment of correlation with QoL: dysphagia on DIGESTv2, MBSImP Total scores for oral, pharyngeal and oesophageal swallowing. It was hypothesised that tongue strength scores might be associated with QoL as per existing research on people with Parkinson’s Disease [481]. It was hypothesised that number of days in ICU/hospital post-surgery may potentially be associated with worse dysphagia acutely as mentioned above, which may be correlated with QoL. It was hypothesised that if dysphagia improved gradually over time QoL would correlate with months since surgery [482]. Given that cervical anastomosis has been shown to predict pneumonia [72], and has a higher incidence of anastomotic leak [483], and that thoracic anastomosis has lower rates of RLN injury [40], it was hypothesised that site of anastomosis and anastomotic leak, and location of cancer which can determine the site of anastomosis, would all be associated with QoL.

Research Questions

Question 2: What is the impact of COD and other aerodigestive symptoms on QoL?

- i. What is the impact of oropharyngeal and oesophageal dysphagia on QoL and are there differences in QoL impact across various clinical/treatment subgroups?
- ii. What dysphagia, clinical and surgical variables are associated with reduced QoL?
- iii. What is the impact of chronic aerodigestive symptoms on QoL post curative oesophageal cancer surgery?

Section 3: Exercised based Dysphagia Rehabilitation in Oesophageal Cancer

Statement of problem

A limited number of studies have implemented exercise based dysphagia rehabilitation in adults with oesophageal cancer [413, 484, 485], meaning that patients with COD may potentially be receiving no dysphagia rehabilitation or inappropriate interventions as often SLTs are unaware of any evidence base in this relatively new field.

Objective

This study aimed to determine the effectiveness of dysphagia rehabilitation in improving clinical outcomes (oral intake status, pneumonia and swallow) and HRQoL outcomes in adults with oesophageal cancer across time points and to determine elements of rehabilitation (delivery, dose, intensity, timing, adverse events and fidelity) which may inform future research of dysphagia rehabilitation in oesophageal cancer.

Hypothesis

It was hypothesised that there would be a small number of relevant studies on the topic which would provide very limited/ no information that could guide dysphagia rehabilitation in clinical practice and in future research.

Research Question

Question 3. Is there evidence to guide oropharyngeal dysphagia rehabilitation in adults with oesophageal cancer?

- ii. What evidence exists to guide oropharyngeal dysphagia rehabilitation in adults with oesophageal cancer?
- iii. What is the effectiveness of dysphagia rehabilitation in improving clinical outcomes (oral intake status, pneumonia and swallow) and health related QOL outcomes in adults with oesophageal cancer across time points?

The methods and results for each of the three sections will be detailed in Chapters 6, 7 and 8.

5 Chapter 5 - Patient and Partnership Involvement (PPI)

A PPI committee of people at various stages of their oesophageal cancer journeys was created and consulted for this research to ensure that this research would be relevant, high quality, accountable and transparent. The National Institute for Health Research's National Advisory Group, INVOLVE, defined public involvement in research as research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them [486]. The GRIPP-2 SF international reporting guidelines were considered in the development and implementation of this committee to improve the quality of our PPI reporting [487, 488]. The invaluable feedback from oesophagectomy survivors in our PPI group assisted with the development of materials for our studies that are deemed more appropriate for participants. Two individuals participated in a collaborative fashion, reviewing questionnaires and providing feedback and suggestions.

Three important suggestions made by the PPI committee are listed in Table 5-1. One key finding from this initiative was how the individuals involved found it difficult to distinguish symptoms of oropharyngeal dysphagia from symptoms of the entire aerodigestive tract (including cough, reflux, voice alterations). This aligns with a study that has compiled closely related cancer symptoms into clusters [489]. Aktas et al (2018) analysed symptoms reported from 1000 patients with advanced cancers and identified seven clusters using multiple types of analysis [489]. They confirmed that cough, dysphagia, dyspnoea, hoarseness and wheeze were all closely connected in terms of patient reported symptoms. Guo et al (2019) found that three months following oesophageal cancer surgery, digastric issues including reflux and bloating were clustered with shortness of breath [490]. They also found that difficulty swallowing and QoL were negatively associated which is important for clinicians to be aware of. Similarly, the American Speech Hearing Association (ASHA) has compiled a list of aerodigestive disorders of the upper digestive tract (oesophagus) which result in swallowing difficulties; this list includes gastroesophageal reflux which is in line with the feedback from our PPI members [491]. A study by Pereira et al (2003),

similarly reported on the presence of upper aerodigestive symptoms in patients following bilateral thyroidectomy which included dysphagia, ‘neck strangling’ and voice changes [492]. Given the impact of all of these symptoms on a patient’s experience of swallowing, and given that patients have reported that it is difficult to consider symptoms in isolation, it is therefore important for health professionals to contemplate the patient’s symptoms holistically to fully understand their presentation. For example, a speech and language therapist may learn additional information about a patient’s swallowing through asking questions about their reflux/ cough/ voice that also relate to the experiences that they ‘cluster’ with swallowing symptoms. Thus, this study has ensured that additional information is collected from patients regarding changes to their voice, cough and reflux through the questionnaires used and interview questions asked.

The GRIPP-2 Reporting Checklist has been adhered to [487].

Table 5-1 PPI groups’ three key suggestions which have been implemented in this research

	PPI Comment	PPI’s Suggestion Implemented
1	It is difficult to distinguish symptoms of swallowing from symptoms of entire aerodigestive tract (cough/reflux/voice etc.).	Questionnaires and interview questions were selected that incorporate symptoms of the entire aerodigestive tract.
2	The Reflux Symptoms Index was recommended by both participants.	This is included in the protocol.
3	The EORTC-OES-QLQ-18 was reported to be a valuable tool.	This is included in the protocol.

6 Chapter 6 - Nature & Severity of COD: Methods and Results

Results of this chapter are published in:

Gillman A, Kenny C, Hayes M, Walshe M, Reynolds JV, Regan J. Nature, severity, and impact of chronic oropharyngeal dysphagia following curative resection for esophageal cancer: a cross-sectional study. *Dis Esophagus*. 2024 Apr 27;37(5):doae003. doi: 10.1093/dote/doae003. PMID: 38266037; PMCID: PMC11060100.

6.0 Introduction

The literature review in Chapter 2 has conveyed how some people with oesophageal cancer experience oropharyngeal dysphagia throughout their cancer journey from before diagnosis through to survivorship and how this can have a significant impact on malnutrition, weight loss, tube feeding reliance, aspiration pneumonia and QoL. Further research in this area is warranted given the limited evidence published to date. A patient's ability to eat and drink was listed as one of the ten outcomes (out of 68 domains) in a Core Outcome Set (COS) for oesophageal cancer surgery research published in 2019, highlighting the importance of further research in this area [493]. This COS was developed by experts and patients from the CONSENSUS Esophageal Cancer Working Group to ensure that the most pertinent outcomes would be measured and reported on in future trials following oesophageal cancer surgery in order to increase homogeneity.

Our research team, lead by the main researcher, published a study on this topic which is available to read at Appendix C.

6.1 Methods

6.1.1 Ethical Approval

Ethical approval was received from the St James's Hospital/Tallaght University Hospital Joint Research and Ethics Committee (JREC): Reference Submission number 315, Approval Date 24/11/2021. Ethical approval was granted for the recruitment of up to 40 participants. The Ethics form is included in Appendix D. The letter of approval from the REC is included as Appendix E.

6.1.2 Study Design

A cross-sectional prospective observational study was designed. The STROBE Statement guidelines were used to report on findings from this study, and have been implemented where possible in this report, as per the Checklist in Appendix F [494].

As no research has ever previously investigated COD a minimum of 12 months post oesophageal cancer treatment completed with curative intent, this research was intended to be exploratory in nature hence an observational study was designed to determine whether dysphagia exists, and if so, how it presents and what impact it has on QoL. Exploratory research is typically utilised to identify patterns and gain insight about an issue [495]. It is hoped that this body of work will lay the groundwork that may guide future research on oropharyngeal dysphagia in oesophageal cancer.

6.1.3 Recruitment and Sampling

Sample Size

A sample size could not be calculated as this is exploratory research [496]. A target of 40 participants was selected as this number of participants would provide adequate data for initial exploration of dysphagia to inform a larger scale research study. The number was based on existing exploratory cross-sectional research investigating chronic dysphagia in other health conditions; Van den Berg et al's cross-sectional study evaluated dysphagia in 32 patients with head and neck cancer [497], and Waito et al's cross-sectional study evaluated swallowing in 19 ALS patients [498]. An additional factor in selecting this number of participants was the availability of

videofluoroscopy access (30 minutes per week over 12 months). A higher number of participants may have resulted in unnecessary radiation exposure.

Sampling

Purposive sampling was selected as it is an adequate method for recruiting participants experiencing a particular healthcare related phenomena [499], it is appropriate for both quantitative and qualitative research [500] [501], and it enables the researcher to select a particular perspective to explore in great detail [499]. The researcher intended to recruit roughly equal numbers of participants who had cervical or thoracic anastomoses as part of their surgery so that differences in dysphagia outcomes could be evaluated between these anastomotic site groups. Seventy-eight participants were contacted and 40 participants wished to participate.

Recruitment

Recruitment took place at a single site, St James's Hospital, the national oesophageal cancer centre in the Republic of Ireland. At the time of recruitment, all surgical approaches that had been conducted at the hospital were transhiatal resections, 2-stage en-bloc resections (Ivor Lewis approach) or 3-stage en-bloc resections (McKeown approach) with either 1- or 2-field lymphadenectomies completed. A jejunostomy tube was typically inserted during surgery with a nasogastric tube later inserted for gastric decompression. The main researcher obtained access to the SJH Upper Gastrointestinal Cancer Registry database which listed all oesophageal cancer surgeries completed at SJH. Eligible participants were then chronologically identified from this database and electronic medical records using the following eligibility criteria:

Inclusion Criteria:

- First time diagnosis of oesophageal cancer.
- Transhiatal or transthoracic resection.
- Chronic (defined as minimum 12 months post surgery).

- All TNM stages of oesophageal cancer.
- Medical approval received from upper GI surgeon to participate in the study.
- Written consent provided by participant to participate in study.
- Adequate language comprehension / cognition to participate.

Rationales:

The decision was made to exclude individuals prior to 12 months post-surgery as the neural activity of the stomach begins to return to normal function 12 months following oesophagectomy [502], suggesting that a new state of normal may begin to emerge at this time. In addition, the longitudinal study being conducted by a fellow PhD colleague on our research team, Michelle Hayes, is collecting data at the six-month time point and it was hoped that the findings from our studies would compliment each other.

Exclusion Criteria:

- History of neurological impairment including but not limited to cerebral vascular accident (CVA) and progressive neurological conditions such as Parkinson's Disease.
- Known history of oral or pharyngeal dysphagia due to a cause other than oesophageal cancer diagnosis.
- History of head and neck cancer.
- Evidence of metastatic or recurrent disease.
- Formal diagnosis of Chronic Obstructive Pulmonary Disease (COPD).
- Pregnancy.
- Receiving palliative treatment.

Rationales:

The above exclusion criteria were selected to minimise the presence of a premorbid dysphagia from an existing cause (e.g. previous oesophageal cancer, neurological impairment [503], head and neck cancer [504], COPD [505]). This study focussed only on cancer that was targeted with curative intent surgery therefore patients undergoing palliative treatment were not included.

Eligible patients received a cover letter and patient information leaflet in the post (Appendix G), followed by a phone call seven days later. At the end of an in-depth conversation with the main researcher by telephone regarding the purpose and risks of the study, it was suggested that the patient could make contact with the researcher by telephone or post should they wish to participate in the study. Those who wished to participate were provided with the next available appointment time.

A one hour radiology slot was available each week in the radiology department at SJH, a large acute hospital, to complete a VFS for this research project. Patients attended the hospital on just one occasion where the main researcher elaborated further on the information provided in the patient information leaflet. Written consent was obtained. A Covid-19 declaration form was completed.

6.1.4 Data Collection

Data collection commenced in October 2021 and was completed in September 2022. Data was collected from a VFS, a tongue function assessment tool, a range of questionnaires and an interview. Data was also collected regarding patient characteristics, surgical outcomes and clinicopathological information from the patient, electronic patient records and from the data manager's dataset as detailed in Table 6-1:

Table 6-1 Background and Surgical Information

Background Information	Surgery/Acute information	Patient-reported information

Name	Surgical approach	Presence of swallowing difficulty
Age	Anastomosis site	Recent chest infections
Sex	Additional procedures	Recent admissions to hospital
Date of Birth	Surgical duration	No of anastomotic dilatations
Relevant Medical history (e.g. Barrett's, GORD etc)	Surgical complications e.g. RLNP	Current food and fluid consistencies being consumed
Type of Cancer	Field of lymphadenectomy	If modifying these, since when
T-N-M factors	Length of stay in ICU	Tube reliance
Stage of cancer	Length of stay in hospital	Current height
Location of cancer		Current weight

All data were entered on a password protected Microsoft Surface Book 3, Intel(R) Core(TM) i5-1035G7 Processor using Windows 11 v22. (See Figure 11.) Data was stored on the Trinity College Dublin's (TCD) One Drive.

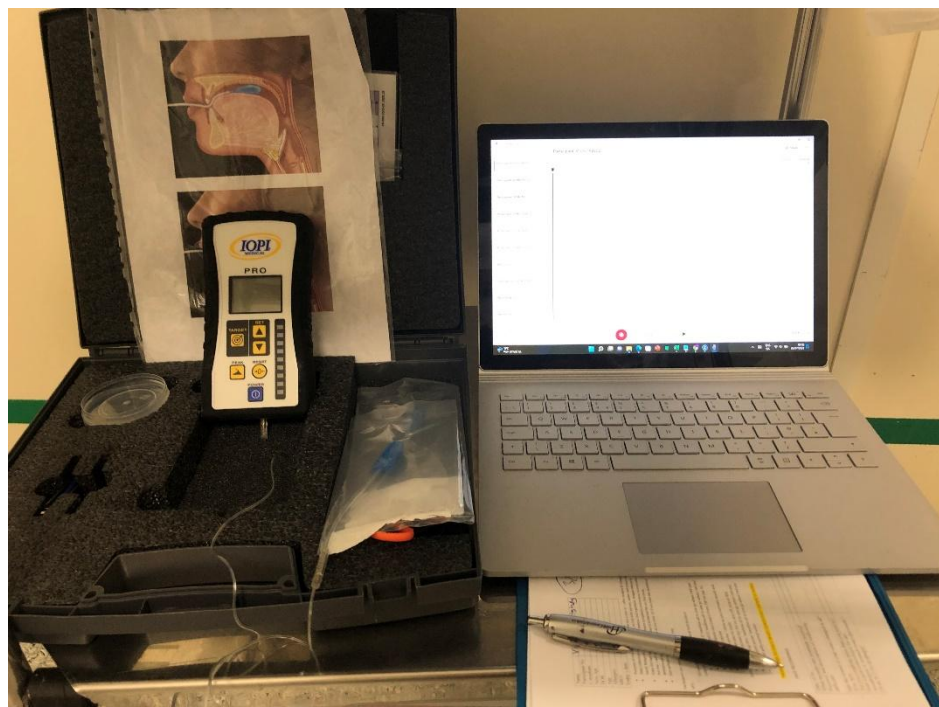


Figure 11 Computer Set-up

Storage of Data

All data were immediately pseudonymised and stored only on password encrypted Microsoft files on the lead researcher's password protected computer, on TCD's One Drive, and on SJH computers. Data were entered in an Excel database which was located in the TCD One Drive. Audio files were recorded using the Microsoft Sound Recording App and immediately transferred to the TCD cloud. Audio files were transcribed by two researchers manually and using Microsoft Word's transcript function within seven days of recording. Audio files from interviews were deleted after transcription to ensure anonymity. Transcripts were reviewed to ensure any identifiable information was deleted. No data were stored locally on the laptop. Codes with alphanumeric keys were accessible by the main researcher only. All data will be deleted after seven years. Data was collected and stored securely as per the ethical approval and GDPR regulations. No identifiable information has ever or will ever be published.

6.1.5 Study Setting

Participants were invited to attend a single testing session at SJH. They were provided with an appointment time in the SJH radiology suite with the radiographer present. When there were two videofluoroscopies booked in to the 30 minute slot, or if there were other personnel present, the participants went to a clinical room with the main researcher after the VFS to complete the remainder of the session. Otherwise the entire session took place in the radiology suite.

The session lasted approximately 60 minutes. The set-up in the radiology suite is illustrated in Figure 12 below.

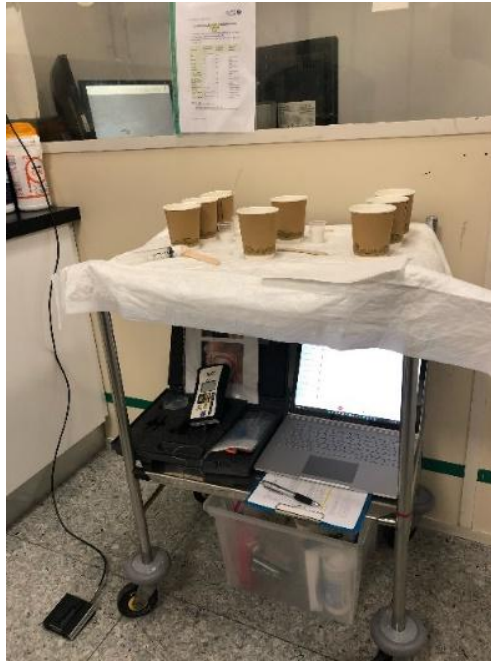


Figure 12 Set-up in videofluoroscopy suite

6.1.6 Study Details (Equipment, Protocol, Outcomes & Data Analysis)

Due to the number of tools used, it was decided to group the tools together in their own section below, within which, the equipment, protocol, outcomes, data analysis, and inter-rater reliability for each will be discussed. The study protocol is outlined in Figure 13.

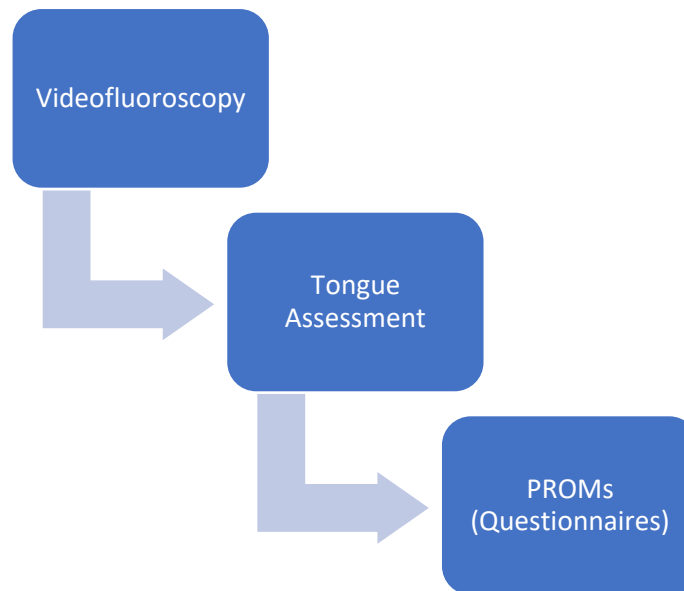


Figure 13 Study Protocol

Videofluoroscopy

Equipment

A VFS is a widely used instrumental study of swallowing. It was selected for this research as although it requires radiation exposure [506], it provides the benefits of viewing the safety and efficiency of swallowing from the oral cavity through the oesophagus with an option to screen the oesophagus which is not possible during FEES, and as penetration and aspiration can be observed in real-time compared to FEES when a white-out occurs [215, 507]. Fluoroscopy refers to the collection of a continuous series of x-rays in real-time, thereby enabling a view of moving structures. The machinery used for this particular research included an X-ray tube with a tilt-table

positioned in an erect position. X-rays were emitted from the x-ray tube and beamed directly and continuously across to the fluoroscope with the patient positioned in-between. The fluoroscope was repositioned depending on the desired anatomical locations to be examined. As the x-rays passed through various tissues, some were more absorbed than others resulting in the pattern referred to as the radiation image which was projected as a visible form using an image intensifier [508]. The frame rate refers to the number of images generated per second and corresponds to the upper temporal resolution achievable for the video recording system. For this study, it was set at 25 frames per second, the maximum available at the data collection centre, and a standard video frame rate in Europe [507]. The pulse rate was set to 25 per second. This is the rate at which the machine is emitting rays compared to the frame rate which is the rate at which images are caught. Pulse rate should match the frame rate to prevent the patient being exposed to radiation that is not being captured. A digital video capture system was then used to view and save the images on a computer. The researcher independently recorded the images to the TIMS DICOM computer system (TIMS Medical by Foresight Imaging LLC) using a foot-pedal. The researcher instructed the radiographer on which anatomy to view during each recording, and when to commence and cease screening. The configuration of the equipment has been drawn in Figure 14.

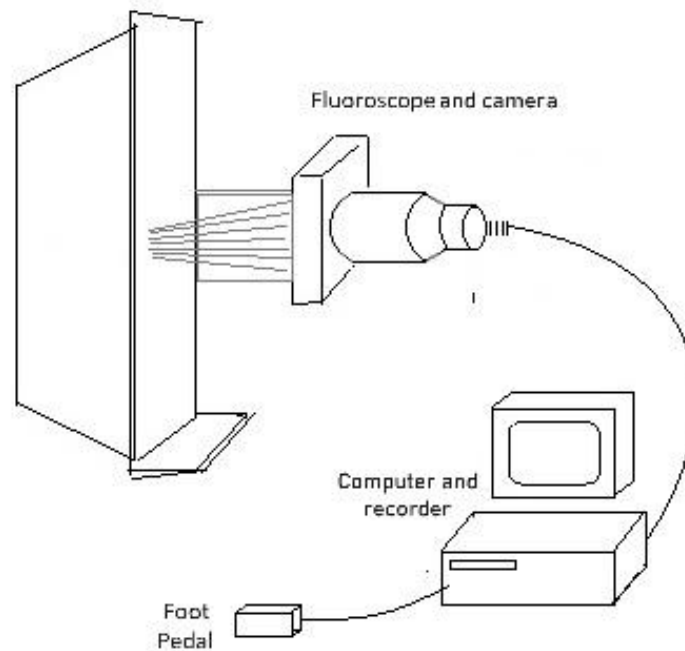


Figure 14 Set-up of videofluoroscopy equipment

To reduce the risk of radiation-induced cancer in the future, the Food and Drug Administration (FDA) in the United States advised that fluoroscopic equipment must display the cumulative exposure time and that there will be an audible signal after five minutes of fluoroscopy [509]. Fluoroscopy exposure time was limited to a maximum of five minutes in our study as per other dysphagia research [510]. Other personnel including the main researcher and radiographer had to wear protective clothing including lead aprons and thyroid shields as depicted in Figure 15 and stand behind protective screens where possible to minimise exposure to scattered radiation [511]. The main researcher stood six feet away from the x-ray tube. Exposure was monitored via an ionizing radiation badge worn over the lead gown.



Figure 15 Protective gear

Barium solution

Materials such as bone or barium are more radiopaque and appear darker on fluoroscopy, enabling visualisation of the movement of the oral, pharyngeal, laryngeal and oesophageal structures in real-time during the swallow [507]. An online barium calculator [512] was used to prepare barium powder to a 20% weight to volume (w/v) concentration using Maxibar™ (98.45% powder w/v for oral suspension). Concentration is a term used to describe the amount of one compound in reference to another conveyed as w/v [507]. Higher concentrations are more radiopaque on videofluoroscopy. The ideal balance of barium allows the bolus movement to be visualised on images but does not leave a coating on the oropharynx which may be interpreted as residue [507]. The addition of barium to food and fluid can alter the consistency therefore standardised recipes were adhered to as per the International Dysphagia Diet Standardisation Initiative (IDDSI) framework [513]. This framework is a global standard that consists of eight levels for describing food and fluid textures/ thickness to enable consistent production and measurement of consistencies. (See Figure 16 below.)

The IDDSI Framework

Providing a common terminology for describing food textures and drink thicknesses to improve safety for individuals with swallowing difficulties.



© The International Dysphagia Diet Standardisation Initiative 2019 @ <https://iddsi.org/framework/>
 Licensed under the Creative Commons Attribution Sharealike 4.0 License <https://creativecommons.org/licenses/by-sa/4.0/legalcode>.
 Derivative works extending beyond language translation are NOT PERMITTED.

Figure 16 The International Dysphagia Diet Standardisation Initiative

20% w/v was selected for this study as a higher concentration, for example 40%, is unlikely to be a true thin liquid, with Fink and colleagues reporting that 20% may be most appropriate [514].

Below Figure 17 is an image of aspiration of IDDSI Level 0 fluid.

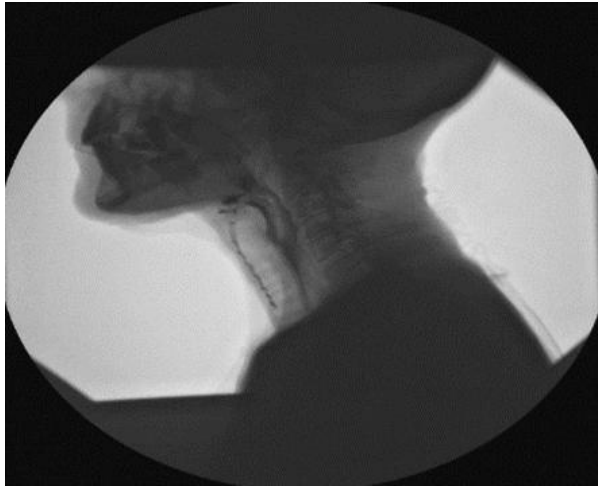


Figure 17 Aspiration of IDDSI Level 0 thin fluid on Videofluoroscopy

VFS Protocol

Participants attended the VFS suite where the VFS was performed in the lateral and anterior-posterior positions. The protocol is outlined in Table 6-2 below. Following discussions with the Upper Gastrointestinal Consultant and PPI representatives, a decision was made for the protocol to be limited to just two bolus trials of each consistency due to early satiety, regurgitation and abdominal discomfort in this cohort. In the lateral view, the participant self-administered two trials of IDDSI level 0 thin fluids x5ml by cup, two trials of IDDSI Level 0 x 10ml by cup, unspecified volume consecutive sips from a cup of IDDSI Level 0 fluids, two trials of IDDSI Level 4 (pureed consistency made from water, thickening agent and barium) x5ml from a teaspoon and one IDDSI Level 7 Carr cracker with 3ml of IDDSI Level 4 puree spread on top. The anterior-posterior view protocol consisted of two trials of IDDSI Level 0 thin fluids x20ml from a cup, two trials of IDDSI Level 4 puree x 5ml by spoon, and one 13mm barium tablet.

Table 6-2 VFS Protocol

Position	IDDSI Level	Quantity	Volume	Method of delivery	Administered by
Lateral	0	2	5ml	Cup	Participant
	0	2	10ml	Cup	Participant
	0	1	Unspecified	Cup	Participant
			consecutive sips		
	4	2	5ml	Teaspoon	Participant
	7	1	1 Carr water	Fingers from	Participant
A-P			cracker with 3ml	plate	
			IDDSI 4 barium on		
			top		
	0	1	20ml	Cup	Participant
	4	2	5ml	Teaspoon	Participant
	Tablet	1	13 mm barium	Fingers	Participant
			tablet		

Key: A-P : Anterior-posterior

The prepared volumes can be viewed in Figure 18 below. The small number of trials (max two) of each bolus volume was selected to allow for a greater variety of consistencies to be evaluated within the limited timeframe available for each videofluoroscopy, and because of the early satiety experienced by individuals post curative oesophageal resection due to their altered upper gastrointestinal anatomy [515]. A number of leading international researchers have designed reputable studies using two or less trials in their dysphagia research [197, 216, 217, 516, 517] however it is still considered that this is a limitation of this research given that an increased number of trials would have increased the likelihood of identifying signs of aspiration. A Carr

Cracker was selected as it has previously been used as the Irish equivalent of a dry biscuit in international research which compared swallow-related outcomes across many countries [195].



Figure 18 Consistencies Trialled

Participants were initially seated laterally with the anterior oral cavity, cervical spine, soft palate and proximal cervical oesophagus in view. Participants were then asked to stand to visualise the anterior-posterior plane with the hypopharynx located superiorly and the oesophagus in the centre.

For the oesophageal screen, fluid, puree and a barium tablet were trialled in the anterior-posterior position and followed from the oral cavity through the LOS as per the protocol in a study by Miles and colleagues [476]. Once the participant placed the barium tablet in their mouth, before swallowing they were provided with a cup of 100mls of water and encouraged to swallow 'all in one go'. After 15 seconds (s) of screening, there was a pause for 15s, after which the screening continued every 15s until the bolus was cleared or until 60s had passed to minimise radiation exposure. 15s was selected as a healthy adult's oesophageal transit time is usually less than 15s [476]. The researcher instructed the radiographer on the anatomy to view during each recording, and when to start/stop screening. Radiation exposure was controlled by a radiographer through modifying the field of view and/or limiting the time of exposure. Radiation is measured using

millisieverts (mSv). The shared goal of the radiographer and researcher is to maximise the clinical assessment and number of images collected whilst minimising the risk, duration and dose of radiation (i.e. adhering to ALARA: as low as reasonably achievable) [518, 519].

To minimise exposure to radiation, the patient was positioned by the radiographer before commencing fluoroscopy. The x-ray field was collimated to the region of interest throughout the procedure, while the study was kept as short as possible. As per the local policy, additional medical clearance was required for female participants under 55 years of age who were less than ten days into their menstrual cycle.

Outcomes and Data Analysis

DIGEST

The Dynamic Imaging Grade of Swallowing Toxicity v2 (DIGESTv2) was selected as it is a validated tool for rating the presence and severity of pharyngeal dysphagia in head and neck cancer [217]. There are, as of yet, no swallow-related tools validated in people with oesophageal cancer. This tool differs slightly to the original version of the DIGEST which is widely used in clinical and research practice [520-522]. The DIGESTv2 is an updated version which looks at two important markers of swallowing performance on videofluoroscopy; **swallow safety and swallow efficiency**. The safety classification score is determined using the maximum Penetration-Aspiration Score (PAS) and the frequency/amount of penetration/aspiration. The efficiency classification score is determined using the estimated maximum percentage of pharyngeal residue. An overall grade of pharyngeal dysphagia is retrieved from a provided matrix using both scores and is rated on an overall five point ordinal scale where 0 = no pharyngeal dysphagia, and 4 = life threatening pharyngeal dysphagia [217]. Although this test refers to pharyngeal dysphagia, the term 'chronic oropharyngeal dysphagia' is used when referring to DIGESTv2 findings throughout this thesis.

The Penetration-Aspiration Scale (PAS)

The PAS rates an individual's risk of compromised **airway protection** on videofluoroscopy. The rater considers the depth of airway invasion, material present post-swallow, and how a patient responds to airway invasion. The overall score was determined using an eight point ordinal scale where the worst score for each consistency was recorded [218]. For this study, results were grouped categorically into safe (1), penetrating (2-5), and aspirating (6-8). This tool was selected as it has high inter-rater reliability following sufficient rater training, and is used widely across clinical practice and research and with many different populations [523-525].

MBS Impairment Profile

The MBS Impairment Profile (*MBSImP™*©) is a standardised tool used to quantifiably rate **swallowing physiology** on videofluoroscopy. This tool was selected as it has external validity, favourable inter- and intra-rater reliability and is widely used for both research and clinical purposes [216]. There are 17 components which cover the oral, pharyngeal and oesophageal phases of swallowing. Each component is rated on a three to five point ordinal scales from 0-2, 0-3 or 0-4 (for which 0 is normal). For components 1 (lip closure), 5 (oral residue), 15 (tongue base retraction), and 16 (pharyngeal residue), a score of 1 is also considered normal [526]. The highest (worst) result for each consistency formed the Overall Impression Score. The Total Oral Score and Total Pharyngeal Score were comprised of the sum of the Overall Impression Scores for all oral components (1-6) and all pharyngeal components (7-16), respectively, where a higher score indicates worse physiological performance. Results were also converted into dichotomous results 'normal' versus 'abnormal' as per existing research using MBSImP [527]. Raters were two certified MBSImP™© clinicians meaning that they had previously completed training and passed an assessment with minimum 80% success.

Oesophageal Transit Time (OTT)

A number of oesophageal screen protocols have been published [216, 387, 461, 476, 528-530] with various methodologies [210]. Oesophageal transit time has been defined in existing research as the moment the bolus head leaves the pyriform sinuses and enters the oesophagus to the moment the tail of the bolus flows exits the lower oesophageal sphincter [529]. A timer on the VFS images enabled this to be measured in minutes, seconds, and milliseconds. Imaging was ceased after 15s and recommenced after 15s to minimise radiation exposure up until a maximum of 60s [476]. The protocol for this research included a 13 mm barium tablet as it has been shown to increase sensitivity in detecting dysphagia from 63% to 71% with specificity of 100%. Further information on the tools, means of assessment, rationales and relevant research questions are provided in Table 6-3.

Table 6-3 Outcomes for Dysphagia Safety, Efficiency, and Physiology

Outcome	Measurement Tool	Means of completion	Rationale	Research Question
Pharyngeal dysphagia (safety & efficiency)	DIGESTv2 (Dynamic Imaging Grade of Swallowing Toxicity) Version 2 safety and efficiency rating tool [217, 531]	VFS	COD has been reported in the oesophageal cancer literature [70, 230, 256].	1a, 1c, 2
Swallow safety	Penetration-Aspiration Scale (PAS) [525]	VFS	Aspiration has been reported in some participants with COD [70].	1A, 1C, 2

Swallow	Modified	Barium	VFS	Chronically	altered	1A,	1C,
physiology	Swallow	Impairment		oral and	pharyngeal	1D, 1E, 2	
	Profile			swallow	physiology		
	(MBSImpP)[216]			have been reported			
				with	limited		
				information provided			
				[70].			
	Oesophageal	transit		OTT has been shown		1D, 1E, 2	
	time [476]			to vary across			
				populations	[529]		
				and is likely to be			
				altered given the			
				treatment received			
				which may impact			
				upon	overall		
				swallowing and oral			
				intake.			

Inter-rater reliability

Inter-rater reliability was calculated to reduce a risk of bias throughout this research. There were two raters who were clinical specialist speech and language therapists with extensive experience analysing VFS and both were MBSImpP certified. Raters were blinded to all background information. The main researcher analysed all images and 25% of participants' images on VFS were reviewed and rated by a second rater to determine inter-rater reliability of swallow safety, efficiency and physiology outcomes. Any differences were resolved through discussion until consensus was reached or through the involvement of a third party.

There was 82.2% agreement on the MBSImP, 93.75% agreement on PAS, and 94.9% agreement on DIGESTv2 scores. See Table 6-4 for more information.

An additional quality control measure was introduced for DIGESTv2, MBSImP and PAS ratings, whereby two blind raters jointly rated two entire VFS studies together prior to both independently blindly rating 25% of all studies.

Given the altered gastrointestinal anatomy following surgery, which included complete or partial removal of the oesophagus and occasional removal of part of the stomach, as well as the repositioning of the stomach conduit, the point at which the oesophagus ended was sometimes unclear on imaging. To determine the reliability of the main researcher's mapping of anatomy in the anterior posterior view on videofluoroscopy, ultimately ensuring that the oesophageal transit of the bolus was correctly calculated, a radiology registrar was recruited to map the anatomy on 20% of the images, specifically the location of the UOS and the end of the neo-oesophagus. When compared with the researcher's mapping, 100% inter-rater agreement was achieved without any deliberation required.

Agreement was estimated by kappa statistics where values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 were indicative of poor, moderate, good, and excellent reliability, respectively [532].

Table 6-4 Inter-rater reliability of videofluoroscopy ratings

Test for inter-rater reliability		% of inter-rater agreement
MBS-ImP ratings,	Retrospective blind rating by	82.2% (i.e. ICC 2,2 = .822) on
DIGESTv2, PAS	second reviewer of random	MBSImP (98.8% of responses
	sample of 25% of	were within one point
	videofluoroscopies	(MBSImP, difference or less), and 93.75%

	DIGESTv2, PAS, and oesophageal clearance measures)	and 94.9% on PAS and DIGESTv2 scores, respectively.
Mapping of oesophageal anatomy on Anterior Posterior plane of VFS images	A radiology registrar, blind to protocol results and the researcher's mapping, reviewed 20% of participants' images. 100% inter-rater agreement	

IOPI (Iowa Oral Performance Instrument)

The IOPI was selected for measuring lingual strength and endurance. The equipment consists of a handheld device which is connected to a 11.5cm long plastic tube that connects to an air-filled plastic tongue bulb which is approximately 3.5cm long and with an internal volume of approximately 2.8ml. The handheld device contains a computer and display screen which has buttons and a row of lights that turn green when pressure reaches a specified target. (See Figure 19).



Figure 19 IOPI Device (Image included with permission from IOPI)

Following the swallow screen, maximal isometric pressure was measured by placing an air-filled bulb in the participant's anterior and posterior oral cavity. (See Figure 20). The participant was educated on what would happen using visual aids, after which, the bulb was placed in the correct position by the researcher. Posterior position was at the midpoint of the soft palate and the anterior position was at the centre of the alveolar ridge extending to the hard palate [533]. The patient was encouraged to squeeze their tongue against the bulb and the roof of the mouth 'as hard as possible' for two seconds in each position three times each [534]. The pressure (in kilopascal, KPa) produced by the tongue was indicated on the instrument's display screen and recorded automatically. The highest value of three trials was considered the maximum isometric pressure (MIP) [535]. To calculate maximum anterior endurance, the device target was manually set to 50% of the anterior MIP [536] and the participant was encouraged to squeeze their tongue against the bulb until the top light on the device turned green, indicating that the participant has reached the target. The participant was encouraged to 'keep the light green for as long as possible'. The results were recorded on the device and the maximum of the three endurance results was selected [453].

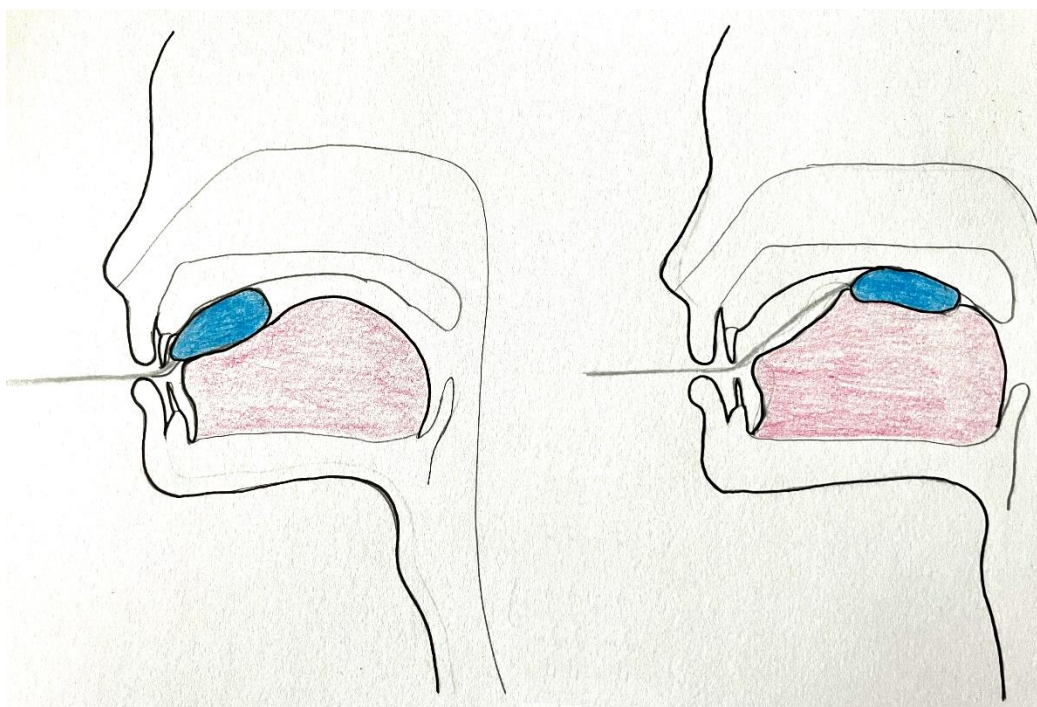


Figure 20 Anterior and posterior placements of IOPI bulb

Outcomes and Data Analysis

Lingual strength and endurance

The IOPI has been used clinically and in research, and it is reported to be a valid and reliable tool to measure lingual strength and endurance in a variety of populations such as elderly individuals and stroke [534, 536-538]. Lingual pressure was selected as an outcome measure for this study as previous research found that patients experience significantly reduced lingual strength acutely post oesophagectomy and that this was associated with incidence of dysphagia and pneumonia [253]. No published research had evaluated chronic lingual strength or function more than 12 months post oesophageal cancer surgery. The maximum isometric pressure in the anterior and posterior positions was recorded from three attempts as per existing research across various populations [536]. Lingual endurance refers to the tongue's ability to maintain muscle contraction against resistance for a time [539]. This outcome, lingual endurance, is correlated with oral residue in dysphagic patients [540]. A PhD thesis submitted at Trinity College Dublin by Professor Ciarán Kenny found significantly reduced lingual endurance ($n=10$) in patients undergoing

chemoradiotherapy treatment for solid tumours outside of the head, neck and upper GI areas when compared to healthy adults using a novel tongue pressure assessment tool, the OroPress. Given that these patients did not experience radiotherapy to the oral phase, this tongue endurance change may potentially be consequential to the systemic effects of chemotherapy. The maximum lingual endurance in the anterior position was recorded from three attempts, as per existing protocols in head and neck cancer research [453]. Data were automatically stored on the IOPI device and were also registered manually in case of equipment breakdown.

Table 6-5 Lingual Outcomes

Outcome	Measure	Means of completion	Rationale	Research Question
Anterior lingual strength	IOPI (Iowa Oral Performance Instrument)[199, 200]	IOPI measured by main researcher	Lingual pressure has been shown to significantly decrease acutely following oesophageal resection and is associated with postoperative aspiration and pneumonia [253, 255]. It is unknown if this is a chronic issue.	1B, 1C, 2

Patient Reported Outcome Measures

Equipment/ Protocol

Participants were provided with a pen to complete the questionnaires. If a participant was unable to hold the pen or read the questions independently, questionnaires were available which contained visual cues and extra large font or the researcher could read the questions aloud or circle the desired responses. The questions and questionnaires are included in Appendix H.

Outcomes and Data Analysis

Self-reported outcomes

Patient Reported Outcome Measures (PROMs) in dysphagia management are considered an important method of collecting patient-centred data which are easy to compare across time points or with other participants' results as well as being a meaningful outcome when the ultimate goal is to improve QoL [541]. The EAT-10, Mayo Dysphagia Brief Oesophageal Questionnaire- 2 week version (MDQ-2), Reflux Symptom Index (RSI), and QoL questionnaires are detailed below.

Self- reported oropharyngeal dysphagia (EAT-10)

The EAT-10 was selected as it is a tool that has proven validity and reliability in identifying oropharyngeal dysphagia in head and neck cancer [176]. Significant correlations have been found between EAT-10 scores and the MBS Impairment Profile (pharyngeal component) and PAS scores in the head and neck cancer population [542, 543]. A score of >2 on the EAT-10 has been found to indicate abnormal swallowing in older adults [176]. It is a tool for identifying patient reported dysphagia not for identifying swallow related quality of life. It is a concise tool that is easy to administer.

Self-reported oesophageal dysphagia (Mayo Dysphagia Questionnaire – 2 weeks)

The Mayo Dysphagia Brief Oesophageal Questionnaire 2 week version (MDQ – 2) captures dysphagia symptoms over the prior two weeks. It was selected as it is a short tool which has been shown to have validity, reproducibility, internal consistency and validity for oesophageal dysphagia [179]. Its selection over the longer Mayo Dysphagia Questionnaire [180] is appropriate for brief interactions and when symptoms are recurring frequently [179]. Given the high number of tasks that participants were required to complete during this data collection process, the shorter version was preferred.

Risk of Reflux

The RSI was included as it is validated with voice disordered patients where a score of >13 is indicative of laryngopharyngeal reflux [544]. The tool contains only nine questions, is easy to administer [544], and was also selected because our team's PPI members felt it encompasses the aerodigestive symptoms, is very clear to the point, is relevant to the topic in question, and is a "peachy" assessment.

Risk of Sarcopenia

Lower body mass index (BMI) has been found to be predictive of postoperative dysphagia in the acute phase post oesophagectomy for oesophageal cancer [256], with 90% of patients experiencing five percent weight loss at three months postoperatively [314], and with ongoing chronic weight loss reported even three years post-surgery [332], which may signify significant malnutrition [545]. Sarcopenia was found to be five times higher 12 months after surgery compared to at the time of oesophageal cancer diagnosis with incidence reported in 25% of patients [110]. The SARC-F is a 5-item screening questionnaire used by health care professionals to identify a risk of sarcopenia, and is validated with adults in the community [185], where a score of greater than or equal to four can identify a risk of sarcopenia [546].

Status of Oral Intake

The Functional Oral Intake Scale (FOIS) is used to record an individual's status of oral intake/tube dependency. It is a seven point scale where Level 1 indicates tube reliance and Level 7 indicates complete oral intake (normal foods and drinks being consumed without modifications or restrictions). Levels 1-3 refer to tube dependency that also includes minimal attempts at eating/drinking (Level 2) or consistent oral intake of food/fluids (Level 3). Levels 4-6 refer to oral diets ranging from one consistency only (Level 4), to multiple consistencies that require preparation/ compensations (Level 5) to multiple consistencies requiring no special preparation but limited to certain foods (Level 6). This tool has been found to be reliable and validated with various populations and in multiple languages [181, 547-549]. The FOIS was also selected as previous research has found that patients with dysphagia on MBSImP caused by various aetiologies had significantly lower FOIS scores [543].

Hazelwood and colleagues identified associations between physiologic swallowing impairment, functional swallowing ability, and swallow related QoL which shows that each of these contribute independently to the overall profile of a person with dysphagia, therefore each item was included in this study to ensure a comprehensive assessment of dysphagia was conducted [550].

Additional information relating to self-reported outcomes is included in Table 6-6.

Table 6-6 Self-Reported Outcomes

Outcome	Measure	Means of completion	Rationale	Research Question
Self-reported oropharyngeal &	EAT-10 [176]	Questionnaire completed by participant	Self-reported dysphagia has been reported post-surgery	1A

oesophageal	Mayo	Questionnaire	[248]	however	Participant
dysphagia	Dysphagia Questionnaire- 2 weeks/ Brief Oesophageal Questionnaire [179, 180]	completed by participant	by further research is needed to clearly distinguish between the phases of dysphagia.		Demographics
Risk of Reflux	Reflux Symptom Index [182]	Questionnaire completed by participant	Reflux is a common symptom due to the altered lower oesophagus [119]		1D
Risk of Sarcopenia	SARC-F (Strength, Assistance in Walking, Rise from Chair, Climb Stairs, Falls) [184, 185]	Questionnaire completed by participant	OC patients are vulnerable to reduced nutritional intake for many years due to altered anatomy [551]. Preoperative sarcopenia is a risk factor for postoperative dysphagia and no research has explored an association with long-term dysphagia [254]		1B, 1C, 1D

Oral	intake	FOIS	Questions asked	Some	individuals	1A, 1B
Status	/ Tube	(Functional	by	main	continue	modifying/
Reliance		Oral Intake	researcher		avoiding certain foods	
		Scale)[181]			for many years post-	
					surgery [112, 552,	
					553]	

6.1.7 Statistical Analysis

Oropharyngeal Phase of Swallowing

Analysis of data was completed using IBM SPSS Version 24.0 (SPSS, Inc, Chicago, IL, USA). Descriptive analyses analysed participant demographics and treatment data (age, sex, type of cancer, stage of cancer, location of cancer, surgical approach, site of anastomosis, RLN injury, anastomotic leak, type of neo-adjuvant treatment, days in ICU, days in hospital post-surgery, months since surgery), and outcomes from evaluation tools (self-reported dysphagia (EAT-10 and MDQ-2 weeks), risk of sarcopenia (SARC-F), oral intake status (FOIS), tongue strength and endurance (IOPI), QoL (MDADI, EORTC-QLQ-OES-18), swallowing pathophysiology (MBSImP), dysphagia (DIGESTv2), penetration-aspiration (PAS), reflux (RSI), oesophageal transit time). These data were summarised using frequency counts, percentages, means, ranges, standard deviations, medians, and interquartile ranges.

The distribution of data was examined to establish the need for parametric or non-parametric testing using the Shapiro-Wilk test and the Levene statistics was used for homogeneity of variance tests. The Shapiro-Wilk test was selected as the sample size is less than 50. Where sig >0.05 and plots are normal on histogram, then the variable is deemed to be normally distributed [46].

Continuous variables are presented as means (standard deviation and range) when normally distributed and as medians (interquartile range) when not normally distributed [554]. Medians are the most appropriate measure of central tendency for non-parametric or skewed data and for ordinal data and means should not be used for ordinal data, however, may be converted to ranks [555]. Categorical variables are displayed as counts and percentages.

The types of tests chosen for inferential statistics depends on the variable type. For subgroup analyses, variables are compared using t-tests and one-way analysis of variance (ANOVA) when data are parametric, and using Mann-Whitney U and Kruskal Wallis Tests when data are non-parametric [554, 556]. Mann-Whitney U tests are used when data contains ordinal variables. A Kruskal-Wallis H test can be used when independent variables have two or more categories and is also appropriate for subgroup analysis of ordinal data (dependent variables) [557]. If distributions of each group do not have the same shape, Kruskal Wallis 'means ranks' are provided instead of 'medians'. This means that data has been converted from scores into ranks rather than a dichotomous option of above or below the median (e.g. it will explain which subgroup performed higher or lower relative to another instead of providing means/ medians related to the original scores) [558]. When establishing a difference between a variable of two categories (two nominal variables), or most data falls into two responses with the odd outlier, the Chi Squared Test is used [559]. However, if assumptions are not met, for example, observed versus expected counts, small sample size, or non-parametric data, then a Fisher Freeman Helton Exact Test is used [556, 560]. For this research, all reported p values are two-sided and $P < 0.05$ was considered significant. A type I error exists when the null hypothesis is rejected when it is true and a type II error exists when the null hypothesis is accepted when it is false [561].

Bivariate analysis measures associations between two variables and the direction of this relationship. Pearson's r correlation, a parametric test, is used when variables are normally distributed, and Spearman's ρ rank correlation, a non-parametric test, is selected for non-normally

distributed data and is appropriate for use when the variables are measured on a scale that is at least ordinal. Odds ratios and 95% confidence intervals were applied. 95% confidence intervals are recommended for use when estimating parameters in populations [554]. The magnitude of the r is determined using a conventional approach (i.e. where 0.0 – 0.1 = negligible correlation, 0.1-0.39 is a weak correlation, 0.4 – 0.69 is a moderate correlation and 0.7 – 0.89 is a strong correlation) however these results are interpreted with caution given the potential for chance in statistics and/ or misinterpretation if these parameters are considered too rigidly [562].

Univariate binary logistic regression analysis was conducted to determine whether clinical and early surgical variables (age, months since surgery, surgical approach, location of cancer, RLN palsy, site of anastomosis, radiotherapy, days in ICU, self-reported dysphagia (EAT-10), oral intake status (FOIS)) were predictors of COD (DIGESTv2). Binary regression analysis, a type of univariate or multivariate analysis, was chosen as data was split into dichotomous variables because of the small sample size (in order to keep a larger number in each group); aspirators versus non-aspirators, dysphagia versus no dysphagia (DIGESTv2), self-reported dysphagia was normal (0/1/2) versus abnormal (>2) (EAT-10), functional swallowing/oral intake was normal (7) versus abnormal (<7) (FOIS). The intention was for multivariate regression analysis to be conducted in addition to univariate analyses however this was not possible given that only one variable was statistically significant with univariate regression analysis and due to the small sample size of less than 250 [563].

The statistical analysis relating to each research questions is outlined below:

Chronic Oropharyngeal Dysphagia

Question 1A. How does COD present post oesophageal cancer surgery?

- i. What is the nature and severity of COD?

Descriptive analysis was conducted. Median (IQR) results are provided from MBSImP, DIGESTv2, PAS, EAT-10, and FOIS.

What are the differences in COD across subgroups?

Subgroup analyses examined differences in 1) background and surgical information across anastomotic groups, and 2) dysphagia-related results (DIGESTv2, PAS, MBSImP Total Oral and Total Pharyngeal Scores) across various cancer/treatment related subgroups (cancer location, age, site of anastomosis, radiotherapy received).

Data were not normally distributed, therefore, a Kruskal-Wallis H test, the non-parametric equivalent of the one-way ANOVA was chosen because it should be used with non-parametric data, and as it is an alternative to the Mann-Whitney U when independent variables have two or more categories, and as it is appropriate for subgroup analyses of ordinal data (dependent variables). Because the distributions of each group did not have the same shape, Kruskal Wallis 'means ranks' are provided instead of 'medians'.

Given the small number of aspirators in the cohort (n=2), analysis was conducted using a dichotomous variable (aspirators (PAS 6-8) versus non-aspirators (PAS 1-5)) to determine if there was a statistically significant difference between surgical groups for this variable. Counts and percentages of penetration/ aspiration were provided across surgical groups.

Nature of lingual strength, endurance and function

Question 1B What is the strength, nature and function of the tongue in the long-term post oesophageal cancer surgery?

- i. What is the nature of lingual function chronically post-surgery on VFS?

Descriptive analyses were conducted to provide counts and median (IQR) results from the MBSImP (Component 2: Tongue control during bolus hold, Component

4: Bolus Transport, Component 5: Oral residue). Regarding Component 2, tongue control during bolus hold was rated from 0-3 (where 0 = cohesive bolus between tongue to palatal seal, 1 = escape to lateral buccal cavity/ floor of mouth, 2 = posterior escape of less than half of bolus, 3 = posterior escape of greater than half of bolus). Component 4 bolus transport/ lingual motion was rated from 0-4 where 0 = brisk tongue motion, 1 – delayed initiation of tongue motion, 2 = slowed tongue motion, 3 = repetitive/ disorganised tongue motion, 4 = minimal to no tongue motion. Component 5 oral residue after first swallow was rated from 0-4 (where 0= complete oral clearance, 1 = trace residue lining oral structures (considered normal), 2 = residue collection on oral structures, 3 = majority of bolus remaining, 4 = minimal to no clearance).

ii. What is long-term lingual strength and endurance post-surgery?

Descriptive analyses were conducted to provide mean, standard deviations and range results from the IOPI (mean maximum anterior lingual strength, mean maximum anterior lingual endurance and mean maximum posterior lingual strength).

iii. Is there an association between lingual strength and function (strength, endurance, function on MBSImP) and clinical variables?

Spearman's Rank-Order Correlation tests, Spearman's correlation for short, were conducted because the data was non-normally distributed to measure associations between tongue results (anterior tongue strength, posterior tongue strength, anterior tongue endurance, and relevant tongue components on MBSImP (tongue control, bolus transport and oral residue)), and clinical/treatment-related variables (age, months since surgery, site of anastomosis, radiotherapy, number of days in ICU, days in hospital post-surgery, risk of sarcopenia on SARC-F, and oral intake status (FOIS)).

Clinical Context

Question 1C Are there surgical/treatment related variables or clinical tools that can predict COD post oesophageal cancer surgery?

- i. What are the clinical and treatment-related predictors of COD?

Spearman's correlation tests were completed because non-normal distribution of data was identified to measure the associations between dysphagia (DIGESTv2) and surgical / clinical variables (age, months since surgery, cancer location, surgical approach, site of anastomosis, recurrently laryngeal nerve injury, radiotherapy, days in ICU, days in hospital postsurgery, risk of sarcopenia (SARC-F), and oral intake status (FOIS)).

Univariate binary logistic regression analyses were then conducted to determine whether there may have been a linear relationships between independent variables (predictor variable i.e. age, months since surgery, cancer location, dysphagia reported at time of cancer diagnosis, surgical approach, site of anastomosis, radiotherapy, time in hospital / ICU after surgery, sarcopenia risk, modified oral intake) and dependent variables (outcome variable i.e. COD or no COD based on DIGESTv2 findings). Binary analysis is the type of univariate/multivariate analyses used when the dependent variable has two categories (dysphagia or no dysphagia on DIGESTv2) and the independent variable is continuous or categorical. Multivariate analyses were not completed as there were not multiple statistically significant results.

Oesophageal Phase of Swallowing - Nature of oesophageal bolus flow

Question 1D What is the nature and extent of oesophageal bolus flow in adults in the long-term post oesophageal cancer surgery and is it associated with any clinical/surgical/pharyngeal dysphagia variables?

- i. What is the nature and extent of disruption to oesophageal bolus flow chronically post-surgery and is it associated with any clinical/surgical/ pharyngeal dysphagia variables?

Descriptive statistics analysed the MBSImP Component 17 results and provided counts and percentages of oesophageal clearance results. Scores were categorised into 'normal' (score =0) -v- 'abnormal' (score >0) and into groups depending on the degree of retrograde flow 'no retrograde flow' (score = 0, 1), 'retrograde flow within the oesophagus' (score = 2), 'retrograde flow into the pharynx' (score = 3), 'no/minimal oesophageal clearance' (score = 4).

Inferential statistical analyses were completed to measure associations between the MBSImP Component 17 (Oesophageal clearance) and relevant clinical/surgical/ pharyngeal dysphagia variables (all relevant pharyngeal MBSImP components – Component 8 Laryngeal elevation, Component 9 Anterior hyoid excursion, Component 12 Pharyngeal Stripping Wave, Component 13 Pharyngeal Contraction, Component 14 UOS Opening, Component 15 Tongue Base Retraction, Component 16 Pharyngeal Residue), location of cancer, site of anastomosis, neo-adjuvant treatment, months since surgery, dysphagia on DIGESTv2, risk of sarcopenia and reflux symptoms). Spearman's correlation test was completed to measure the strength and direction of association between variables which were measured on ordinal scales (MBSImP Components 8, 9, 12, 13, 14, 15, 16) or continuous scales (months since surgery). Fisher's Exact Test was used when participants fell entirely or mostly into two categories (location of cancer, site of anastomosis, type of neo-adjuvant treatment, dysphagia on DIGESTv2, risk of sarcopenia and reflux symptoms). The Kruskal Wallis H test can also be used when there are more than two groups (i.e. with neo-adjuvant treatment) [564].

Descriptive analyses calculated mean oesophageal transit durations for each consistency. A bar chart will display the breakdown of mean OTT for each consistency across surgical approaches.

A Kruskal Wallis H test was selected, as data were non-parametric, to compare differences in OTT for each consistency (IDDSI Levels 0, 4 and tablet) across clinical and surgical groups (location of cancer, age, surgical approach, site of anastomosis, neo-adjuvant treatment).

A Kruskal-Wallis H test was conducted to identify differences in oesophageal clearance results (MBSImp 17) across the following surgical groups which had statistically significant correlations with oesophageal clearance (location of cancer, site of anastomosis, neo-adjuvant treatment).

The distributions of each group did not have the same shape therefore 'means ranks' Kruskal Wallis tests were used instead of 'medians'.

Clinical Context

Question 1E What are the predictors of disrupted oesophageal bolus flow in the long-term post oesophageal cancer surgery?

- i. Are surgical and clinical variables predictive of abnormal oesophageal clearance?

Univariate binary logistic regression analysis was conducted to determine whether clinical/surgical variables (age > 65, location of cancer, type of neo-adjuvant treatment, pathological stage) are predictive of abnormal oesophageal clearance (MBSImp 17 score > 0).

6.1.7.1 Missing Data

One of the 40 participants had missing data as the VFS assessment revealed a likely recurrence of disease resulting in immediate readmission to hospital for further investigations. As a result, the remaining data were not collected from this participant for this study and the gaps were excluded from all analyses.

This concludes the Methods for the first section. The Results will be explored below.

6.2 Results: Participant Demographics

A total of 40 patients (30 males and 10 females) were recruited over a 12 month period, with a mean age of 66 years (age range 43-84). The breakdown for cancer types were 23 (58%) adenocarcinoma, 12 (30%) SCC, three (8%) high grade dysplasia, and two (5%) intramucosal carcinoma. Tumour locations were 24 (60%) at the OGJ, 10 (25%) in the lower oesophagus, and six (15%) in the middle oesophagus. Participants underwent a radical 2-stage en-bloc oesophagectomy (21 participants (53%)), a radical 3-stage en-bloc resection (10 participants (25%)), and a transhiatal resection (nine participants (23%)), all with gastric conduit reconstruction. 3-field lymphadenectomies were not conducted at this oesophageal cancer surgical centre where data recruitment took place. Minimally invasive oesophagectomy procedures had not been carried out there at the time of this study. Therefore, 19 (48%) received cervical anastomoses and 21 (53%) received thoracic anastomoses. (See Figure 21).

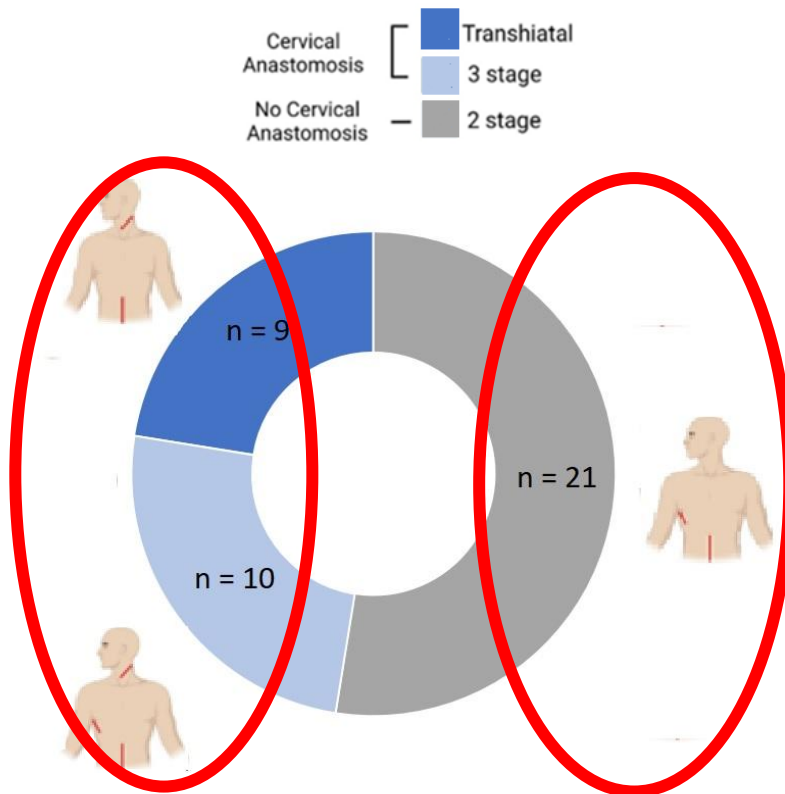


Figure 21 Representation of surgical groups

The mean time since surgery was 52 months (range 13-125 months). Figure 22 below demonstrates the proportion of participants who were 65 years of age or older when participating in this study.

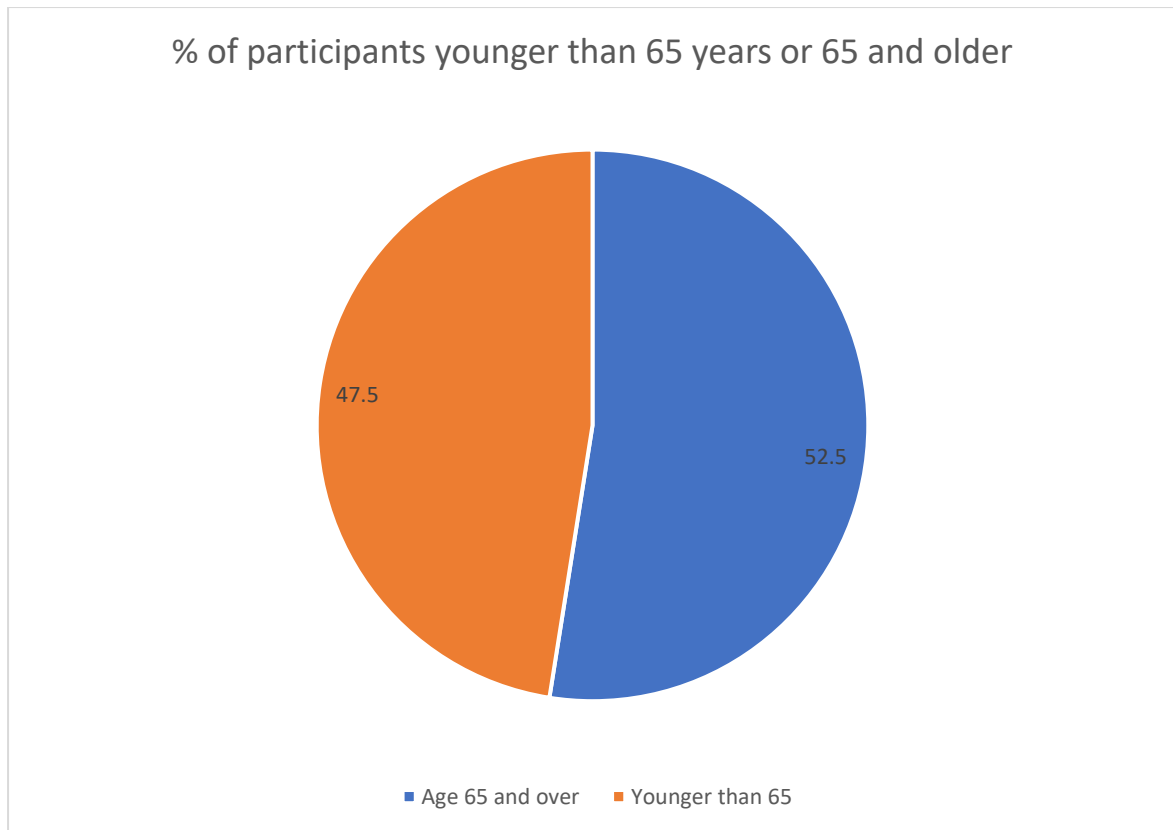


Figure 22 Proportion of participants over 65 years of age

A breakdown of the number of participants at each pathological stage of cancer is outlined below in Figure 23.

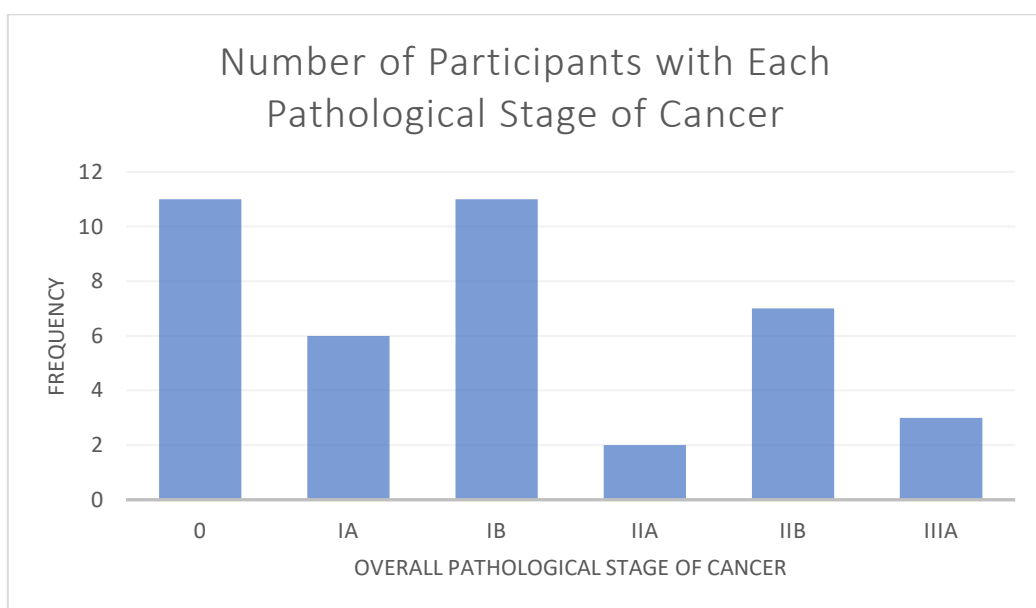


Figure 23 Pathological Stages of Cancer

Further information on the breakdown of age, cancer types, pathological stages of cancer, location of cancer and surgical groups/site of anastomosis can be found in Table 6-7 below.

Table 6-7 Participants' Background Information

Participant Demographics (N = 40)	
Age:	66.03 +/- 9.58 Range 41: 43-84
Mean+/- Std Dev Range	
Sex	10 females 30 males
Type of Cancer	Adeno = 57.5% (n = 23) Scc 30% (n=12) Other 12.5% (n=5)
Location of Cancer	Middle: 15% (n= 6) Lower: 25% (n= 10) OGJ: 60% (n= 24)
Pathological Stages of Oesophageal Cancer (The American Joint Committee on Cancer (AJCC) tumour/node/metastasis (TNM) classification system). Please refer to Appendix I for explanation of the pathological stages and to Figure 23 for a visual display of this data.	0: 27.5% (n=11) IA: 15% (n = 6) IB: 27.5% (n=11) IIA: 5% (n=2) IIB: 17.5% (n = 7) IIIA: 7.5% (n=3) IIIB: 0 IVA: 0 IVB:0
Neo-adjuvant treatment	Chemotherapy: 18 Radiotherapy: 0 Chemoradiotherapy: 16
Surgical Approach	Transhiatal: 22.5% (n=9) 2 stage: 52.5% (n=21) 3 stage: 25% (n=10)

Time since surgery (months)	51.73 +/- 30.29 Range 112: 13-125
Mean +/- Std Dev Range	
RLNP	1 participant (2.5%)
Length of stay in hospital post-surgery (days)	
Mean +/-Std Dev Range	19.5 +/-11.934 Range 56: 6 – 62
Median (IQR)	16.5 (10.5)
Length of stay in ICU (days)	
Mean +/- Std Dev Range	2.4 +/-3.5 Range 13: 0-13
Median (IQR)	.00 (4.75)
Oral Intake Status (FOIS)	
Mean +/- Std Dev Range	6.49 +/--.683 Range 2: 5-7
Median (IQR)	7/6-7
Patient Reported Oropharyngeal Dysphagia	
Outcome (EAT-10) (n=39)	
Mean +/- Std Dev Range	7.79 +/- 9.163 Range 30: 0-30
Median (IQR)	3/0-14
Patient Reported Oesophageal Dysphagia	
Outcome (MDQ-2 week) (n=39)	
Frequency Mean +/- Std Dev Range	3.54 +/- 5.266 Range 18: 0-18
Frequency Median (IQR)	1.00
Severity Mean +/- Std Dev Range	1.77 +/- 2.311 Range 8: 0-8
Severity Median (IQR)	.00

Key: adeno = adenocarcinoma, scc = squamous cell carcinoma, other = other carcinoma types, EGJ = oesophagogastric junction, RLNP = Recurrent Laryngeal Nerve Palsy

53% (n=21) of participants reported that they had ongoing swallowing difficulties. 53% of participants scored >2 on the EAT-10 which indicates abnormal swallowing [176], and 43% of participants scored below 7 on the FOIS indicating either avoidance (30%) or modification of certain/all food consistencies (13%). See Figure 24 below for more detailed information on this.

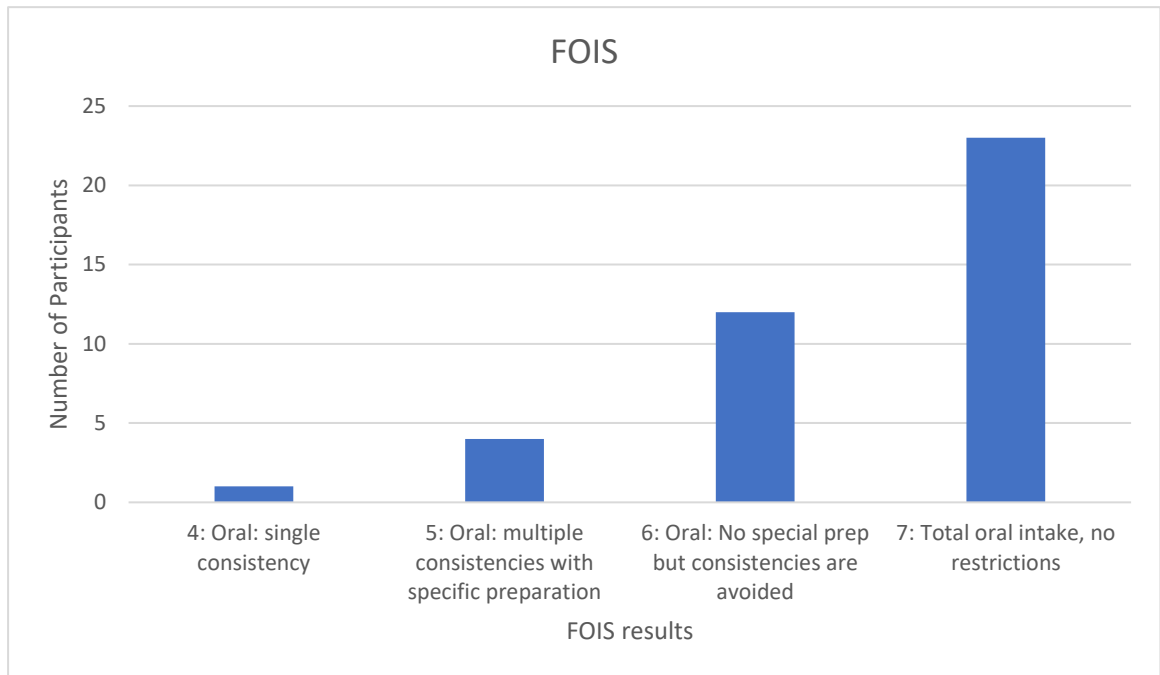


Figure 24 FOIS Results

Background information across thoracic and cervical (2 stage / 3 stage) groups is outlined in Table 6-8.

Table 6-8 Comparison of background and surgical information across surgical groups

	Thoracic Group	Cervical group		
	2 stage n=21 (52.5%)	3 stage n=10 (25%)	Transhiatal n=9 (22.5%)	$\chi^2(2), p$
Age: Mean rank	19.88	16.85	26	3.037
(mean)	(65.1)	(62.8)	(71.7)	.219
Sex	3 females	4 females	3 females	2.749
	18 males	6 males	6 males	.253
Cancer Type	Adenocarcinoma =18	Adenocarcinoma =2 scc =8	Adenocarcinoma =3 scc =2	13.73
	scc =2		High Grade Dysplasia =3	.001
	Intramucosal =1		Intramucosal =1	
Recurrent nerve palsy	0	1	0	ns
Location of cancer in oesophagus	Middle:0	Middle :5	Middle: 1	13.053
	Lower:3	Lower:2	Lower:5	.001
	OGJ:18	OGJ:3	OGJ:3	

Months since surgery	12	28.9	31	23.552
Mean Rank (Mean)	(44)	(79)	(76)	<0.001
Neo-adjuvant treatment	Chemotherapy: 14 Radiotherapy :0 Chemoradiotherapy :9	Chemotherapy: 2 Radiotherapy:0 Chemoradiotherapy: 7	Chemotherapy: 2 Radiotherapy:0 Chemoradiotherapy: 0	14.389 <0.001

Key: scc = squamous cell carcinoma, OGJ = oesophagogastric junction, ns = not significant

6.3 Results: Nature and Severity of COD

6.3.1 Results: Oropharyngeal Phase of Swallowing

Question 1A How does COD present post oesophageal cancer surgery?

i. What is the presence, nature and severity of COD?

Presence, nature and severity of COD

COD was present in 14 (35%) participants on the DIGESTv2 (score >0). Mild COD was present in 11 (27%) participants, moderate COD was present in one (3%) participant, and severe COD was present in two (5%) participants.

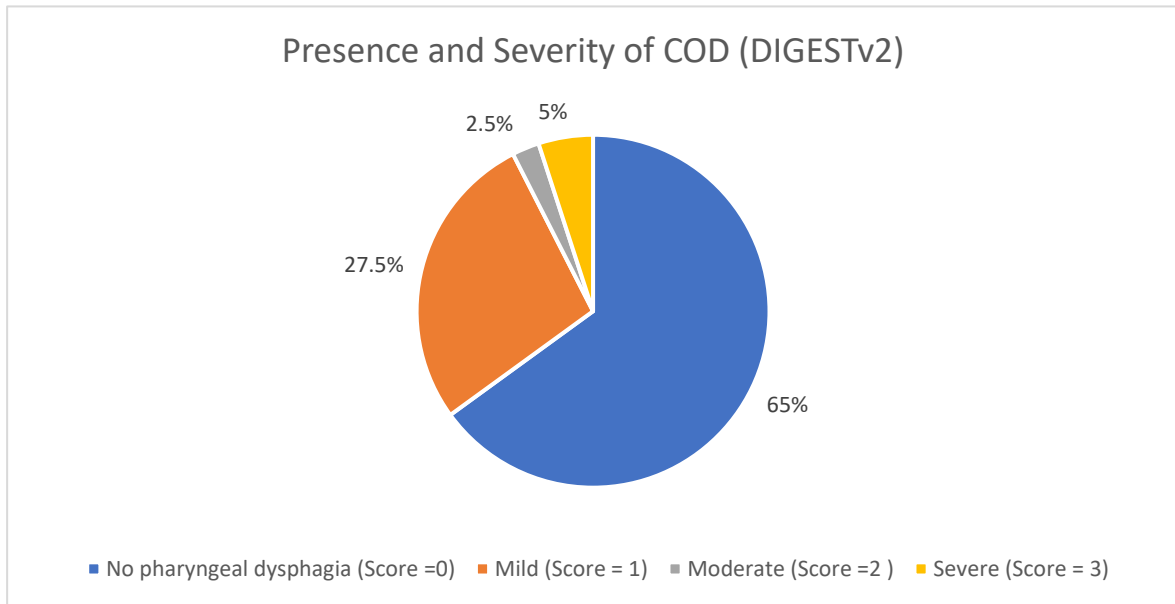


Figure 25 Presence and Severity of Chronic Pharyngeal Dysphagia

Pathophysiology of COD

All participants had at least one impaired component on MBSImP. Impaired swallow initiation was present in 40 (100%), pharyngeal residue was present in 36 (90%), reduced anterior hyoid excursion was present in 32 (80%) and impaired oesophageal clearance was present in 32 (80%). The frequency of impairment across components is shown in Figure 26. Bars are highlighted when frequency is $\geq 70\%$ to visually convey the six most frequently impaired components (oral residue, swallow initiation, laryngeal elevation, anterior hyoid excursion, pharyngeal residue, and oesophageal clearance). Median (interquartile range (IQR)) results for impaired components (score >0) include oral residue 2(0,2), swallow initiation 2(2,3), laryngeal elevation 1(0,1), anterior hyoid excursion 1(1,1), pharyngeal stripping 1(1,1), UOS opening 1(1,1), tongue base retraction 1(1,2), pharyngeal residue 2(1,2), and oesophageal clearance 1.5(1,2).

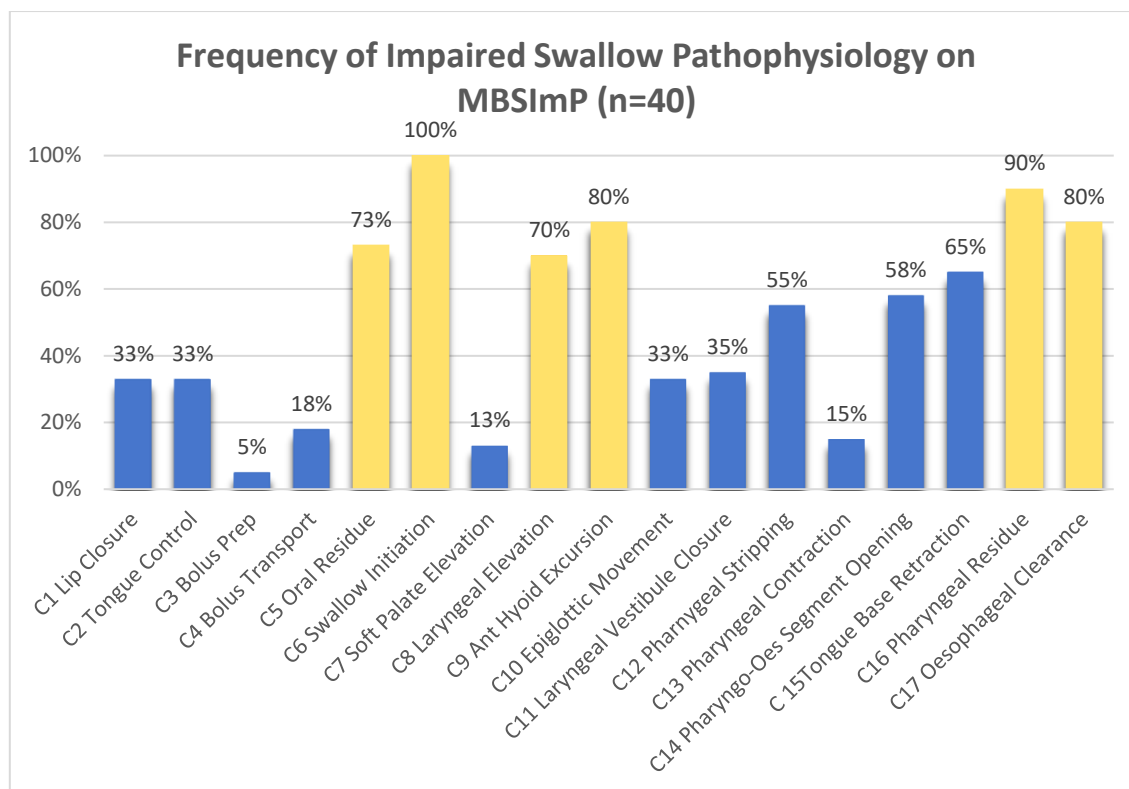


Figure 26 Frequency of Impaired Swallow Pathophysiology on 17 MBSImP Components

The median scores for each MBSImP Component are presented in Fig 27.

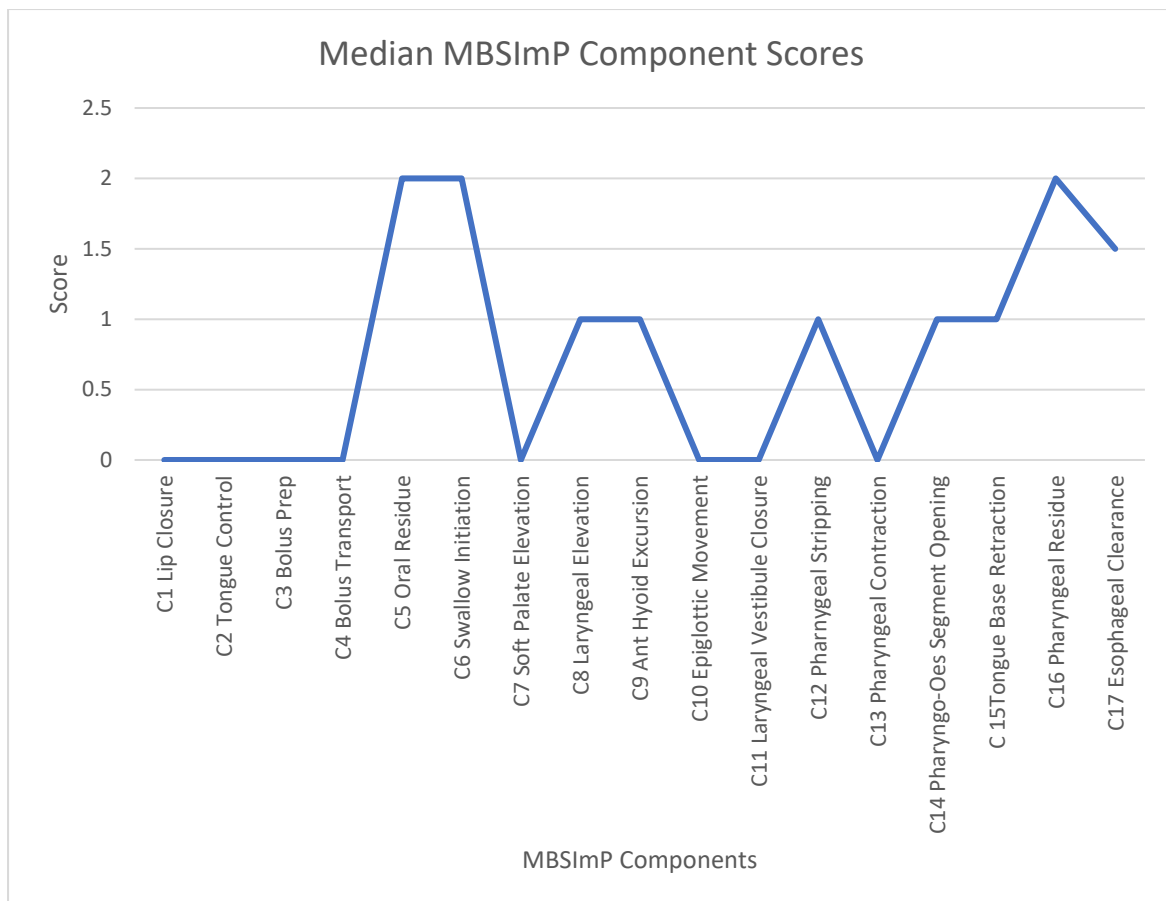


Figure 27 The Median Scores for MBSImP Components

The median (IQR) scores for dysphagia and swallow physiology are: DIGESTv2: 0 (0,1), PAS: 1(1,1), MBSImp Total Oral Score: 4(3,6) and Total Pharyngeal Score: 7(3.25,9). 21 (54%) participants scored >3 on the EAT10 which indicates abnormal swallowing [176]. Table 6-9 provides descriptive results (mean, SD, range, median, and IQR) for the entire cohort regarding dysphagia and aspiration outcomes, swallow pathophysiology, and patient-reported outcomes (relating to oral intake status and dysphagia). Individual participant level breakdown of each of these scores is shown in Appendix J.

Table 6-9 Dysphagia, aspiration and QoL results across the entire cohort

(n =40)	Mean +/- Std Dev Scores	Median/IQR	Range
DIGESTv2	.49+/- .79	.00/ 0-1	0-3
PAS	1.54 +/- 1.502	1/1-1	1-8
MBSImP Total Oral	4.82 +/- 2.293	4/3.0-6.0	1-10
MBSImP Total Pharyngeal	6.36 +/- 3.004	7/3.25-9.0	1-11

With respect to aspiration, 2 (5%) participants had uncleared penetration on the PAS, 2 (5%) had uncleared laryngeal aspiration, 4 (10%) effectively cleared laryngeal penetration, and 32 (80%) did not have laryngeal penetration or aspiration.

The two aspirators both had collections of pharyngeal residue, both aspirated level 0 fluids, both had RSI over 12 (scores of 15 and 21), both had low IOPI scores (anterior lingual strength of 24.9 and 43.3kPa), low posterior lingual strength (29.3 and 35.8kPa), and varied anterior lingual endurance of 26 and 4.6 seconds.

Of all the aspirators and penetrators within the penetration/ aspiration subgroup (n=8), five had impaired oral residue, pharyngeal stripping, UOS opening and oesophageal clearance (MBSImP Component 17). All eight had reduced tongue base retraction, initiated the swallow when the bolus was already beyond the valleculae at the posterior laryngeal surface of the epiglottis, and had pharyngeal residue. Six had abnormal EAT-10 scores (scores of 27, 14, 28, 12, 19, 8).

There was no aspiration or penetration observed on IDDSI Level 4 (puree consistency), only on IDDSI Level 0 (thin fluid), and mostly with uncontrolled volumes of fluid. One person transiently penetrated on IDDSI Level 7 (regular food).

Differences in COD across clinical and surgical subgroups

Comparing cervical versus thoracic anastomotic cohorts (Table 6-10 below), the median (IQR) results for dysphagia (DIGESTv2) are .00 (.0,1) -v- .29 (.0,1) ($p = .246$). The median (IQR) results for penetration versus aspiration (PAS) are 1(1,1) -v- 1(1,1) ($p=.816$). The median (IQR) results for oral and pharyngeal pathophysiological impairments (MBSImP Total Oral and MBSImP Total Pharyngeal Scores) are 4(3,5) -v- 5(3.5,7) ($p=.098$) and 7(5,8) -v- 7(3,10) ($p=.935$), respectively. The Kruskal Wallis H test was used to identify statistically significant differences in dysphagia related variables between surgical groups.

Table 6-10 Median (IQR) and mean rank dysphagia and aspiration results across the cervical and thoracic subgroups

Median (IQR) Mean rank,	Site of Anastomosis		Kruskal Wallis H (df), p-value
	Cervical (n = 19)	Thoracic (n=21)	
DIGESTv2	.00 (.0,1) 22.39	.29 (.0,1) 18.79	$\chi^2(1)= 1.349$, $p = .246$
PAS	1(1,1) 20.82	1(1,1) 20.21	$\chi^2(1)= .054$, $p = .816$
MBSImP Total Oral	4 (3,5) 17.34	5 (3.5,7) 23.36	$\chi^2(1)= 2.731$, $p = .098$
MBSImP Total Pharyngeal	7(5,8) 20.34	7 (3,10) 20.64	$\chi^2(1)= .007$, $p = .935$

There were no statistically significant differences for other dysphagia or aspiration outcomes across surgical approach, location of cancer, age, or radiotherapy. Mean ranks results are provided in Table 6-11 below.

Table 6-11 Differences (Mean ranks) for dysphagia and aspiration across subgroups

Mean rank Kruskal Wallis H (df), p value	Location of Cancer			Age		Site of Anastomosis		Radiotherapy	
	Mid oesoph n = 6	Lower oesoph n = 10	OG Junction n=24	65 or older n = 21	<65 n = 18	Cervical n = 19	Thoracic n = 20	Radiotherapy n = 13	No radiotherapy n = 26
DIGESTv2	24	15.35	21.77	22.43	18.37	22.39	18.79	21.86	19.77
PAS	$\chi^2(2)=3.919, p = .141$			$\chi^2(1)=1.707, p = .191$		$\chi^2(1)= 1.349, p = .246$		$\chi^2(1)= .412, p =.521$	
	23.25	18.3	20.73	21.55	19.34	20.82	20.21	19.29	21.15
MBSImP Total Oral	$\chi^2(2)= .1.427, p = .49$			$\chi^2(1)=.729, p = .393$		$\chi^2(1)= .054, p = .816$		$\chi^2(1)= .477, p =.49$	
	11.17	23.7	21.5	21.43	19.47	17.34	23.36	23.93	18.65
MBSImP Total Pharyngeal	$\chi^2(2)= .4.911, p = .086$			$\chi^2(1)=.288, p =.591$		$\chi^2(1)= 2.731, p =.098$		$\chi^2(1)=1.916, p =.166$	
	22.92	14.9	22.23	19.21	21.92	20.34	20.64	24.18	18.52
	$\chi^2(2)= .3.124, p = .21$			$\chi^2(1)=.543, p =.461$		$\chi^2(1)= .007, p = .935$		$\chi^2(1)= 2.166, p =.141$	

Key: scc = squamous cell carcinoma, adeno = adenocarcinoma, other = other carcinoma types, oesoph = oesophagus, OGJ = oesophagogastric junction

Four (44.4%) participants who had undergone a transhiatal resection had dysphagia on the DIGESTv2 compared to six (28.5%) 2-stage and four (40%) 3-stage resection participants ($\chi^2(2)=.823$, $p=.663$). Seven (77.7%) in the transhiatal cohort scored below 7 on the FOIS, compared with three (33.3%) 2-stage and three (30%) 3-stage participants ($\chi^2(2)=5.796$, $p=.055$). Regarding self-reported oropharyngeal dysphagia using the EAT-10, six (66.7%) participants in the transhiatal cohort had abnormal swallowing compared with 10 (47.6%) 2-stage and five (50%) 3-stage ($\chi^2(2)=.754$, $p=0.686$) participants.

As aspiration was only evident in patients who had undergone a transhiatal resection, a subgroup analysis was conducted using Kruskal-Wallis H test to further explore whether the surgical approach might have been relevant. Results revealed a statistically significant difference ($\chi^2(2)=7.07$, $p<0.029$) in aspiration PAS (6-8) versus no aspiration (PAS 1-5) across the three surgical groups. No one from the transhiatal group penetrated but four (19%) participants who had a 2-stage resection, and two (20%) who had a 3-stage resection showed penetration ($\chi^2(2)=.039$, $p=.981$). The breakdown of penetration/aspiration across surgical groups is displayed in Table 6-12.

Table 6-12 Worst Penetration/Aspiration scores on any consistency by surgery type

	PAS Score n (%)		
	1: No penetration or aspiration	2-5: Penetration	6-8: Aspiration
2 stage (n = 21)	17 (80%)	4 (19%)	0
3 stage (n = 10)	8 (80%)	2 (20%)	0
Transhiatal (n= 9)	7 (78%)	0	2 (22.2%)

6.3.2 Results: Nature of Lingual Strength, Endurance and Function

Question 1B What is the strength, nature and function of the tongue in the long-term post oesophageal cancer surgery?

i. What is the nature of long-term lingual function post surgery on MBSImP?

Regarding component 2 (Tongue Control During Bolus Hold), 2/40 (.05%) participants were impaired. One participant presented with escape to floor of mouth, and one had posterior escape of >50%. For component 4 (Bolus Transport/ Lingual Motion), 7/40 (17.5%) were impaired. Three presented with delayed initiation of the tongue and four presented with slowed tongue movement. For Component 5 (Oral Residue after first swallow), 29/40 (72.5%) had abnormal amounts of oral residue: 27 had a collection of residue and two had the majority of the bolus remaining in the oral cavity. These results are displayed in Figure 28.

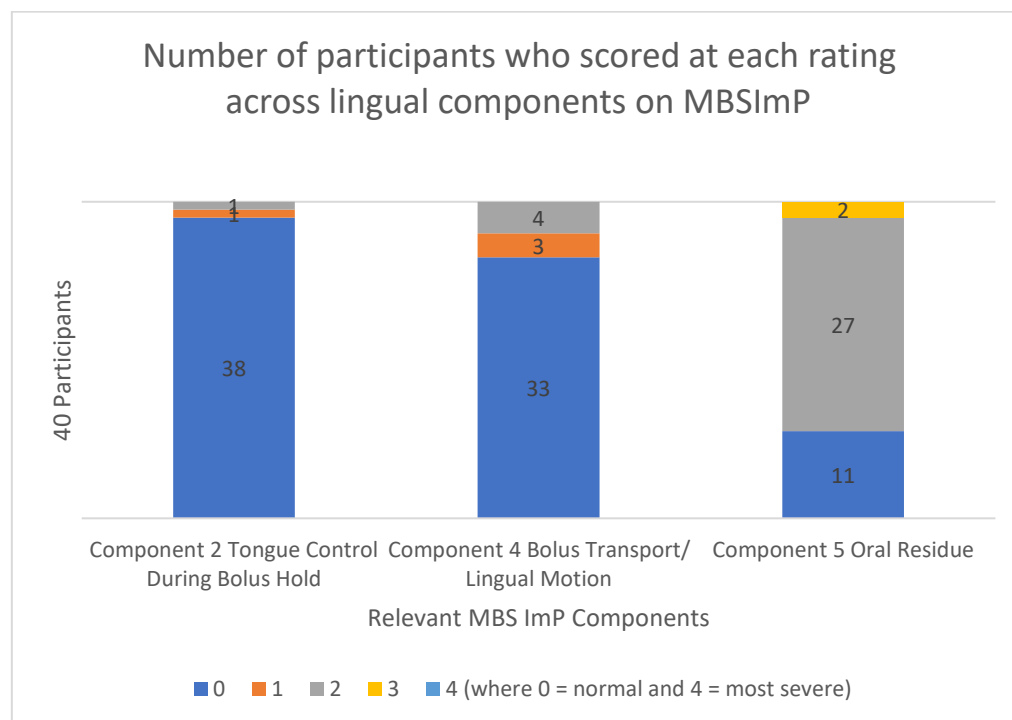


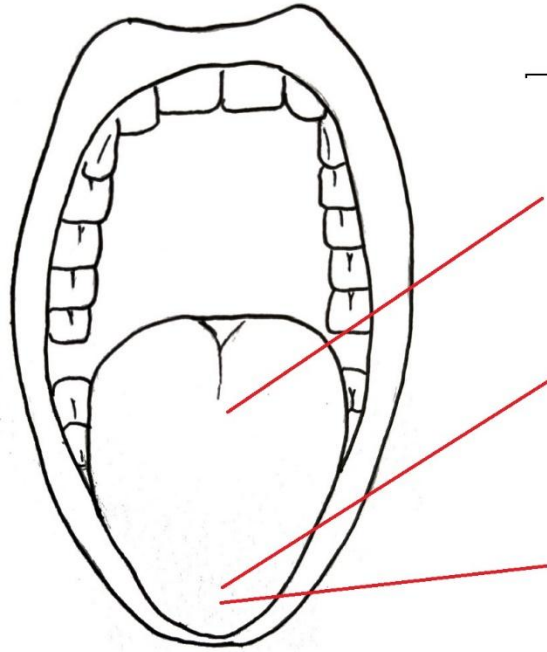
Figure 28 Number of participants at each rating across lingual components (MBSImP)

Median (IQR) scores for MBS Imp Components 2, 4 and 5 (Components Bolus Hold, Bolus Transport, and Oral Residue) are: .0 (1), .0 (.0), 2 (2.0), respectively.

ii. What is the long-term lingual strength and endurance post oesophageal cancer surgery?

Mean maximum posterior tongue strength, anterior tongue strength and anterior tongue endurance results on the IOPI were 39.9 kPa, 42.9 kPa and 23.5 seconds. See Table 6-13 below.

Table 6-13 Lingual strength and endurance results



IOPI (n=39)	Overall Mean +/- Std Dev (Range)
Mean maximum posterior tongue strength	39.977 +/-11.193 kPa (Range 47: 15.7-62.7)
Mean maximum anterior tongue strength	42.9991 +/-10.98256 kPa (Range 51.6: 23.1 – 74.7)
Mean maximum anterior endurance	23.4713 +/-29.9033 seconds (Range 180.2: 1.4-181.6)

Of the participants who had abnormal oral residue (i.e. more than coating) (n=22), nine had anterior tongue strength below 40kPa but there was no statistically significant correlation using Chi square test ($X(1) = .128, p=.721$), and 11 had posterior tongue strength below 40kPa but there was also no statistically significant correlation ($X(1) = .033, p = .855$).

iii. Is there an association between lingual variables and clinical/surgical variables?

There was a moderate significant negative association between anterior tongue endurance and days in hospital post-surgery ($r_s(37) = -.405, p = .01$), meaning that as days in hospital post-surgery increased, long-term anterior tongue endurance decreased. There was a significant weak negative association between months since surgery and bolus transport (MBSImP Component 4) ($r_s = -.385$,

$p = .014$), meaning that as months since surgery increased, MBSImP component 4 scores decreased (improved). See Table 6-14 for further information.

Table 6-14 Associations between lingual outcomes and clinical/treatment related variables

	Mean maximum posterior tongue strength	Mean maximum anterior tongue strength	Mean maximum anterior tongue endurance	MBSImP Component 2 (Tongue control during bolus hold)	MBSImP Component 4 (Bolus Transport/ Lingual motion)	MBSImP Component 5 (Oral residue)
Age	$r_s(37) = -.123, p = .454$	$r_s(37) = -.069, p = .678$	$r_s(37) = .062, p = .709$	$r_s(38) = .017, p = .916$	$r_s(38) = .082, p = .615$	$r_s(38) = -.122, p = .452$
Months since surgery	$r_s(37) = -.132, p = .422$	$r_s(37) = -.043, p = .793$	$r_s(37) = -.092, p = .576$	$r_s(38) = .062, p = .703$	$r_s(38) = -.385, p = .014$	$r_s(38) = -.03, p = .856$
Radiotherapy received	$r_s(37) = -.019, p = .911$	$r_s(37) = -.044, p = .793$	$r_s(37) = -.012, p = .942$	$r_s(38) = .168, p = .299$	$r_s(38) = .065, p = .689$	$r_s(38) = -.03, p = .856$
No of days in ICU	$r_s(37) = -.06, p = .717$	$r_s(37) = .184, p = .263$	$r_s(37) = -.053, p = .75$	$r_s(38) = -.035, p = .83$	$r_s(38) = .039, p = .811$	$r_s(38) = .067, p = .683$
Days in hospital	$r_s(37) = -.02, p = .905$	$r_s(37) = .096, p = .559$	$r_s(37) = -.405, p = .01$	$r_s(38) = -.315, p = .047$	$r_s(38) = -.278, p = .811$	$r_s(38) = -.57, p = .725$
Sarcopenia (SARC-F)	$r_s(37) = -.055, p = .739$	$r_s(37) = -.210, p = .199$	$r_s(37) = .031, p = .849$	$r_s(38) = .134, p = .409$	$r_s(38) = -.295, p = .065$	$r_s(38) = .182, p = .262$
Oral intake status (FOIS)	$r_s(37) = -.014, p = .934$	$r_s(37) = .110, p = .505$	$r_s(37) = -.253, p = .12$	$r_s(38) = -.088, p = .588$	$r_s(38) = -.021, p = .896$	$r_s(38) = -.123, p = .448$

RLN = Recurrent Laryngeal Nerve, FOIS = Functional Oral Intake Scale, dx = time of cancer diagnosis

6.3.3 Results: Clinical Context – Predictors of COD

Question 1C Are there surgical/treatment related variables or clinical tools that are predictive of COD post oesophageal cancer surgery?

i. Are there clinical and treatment-related variables predictive of COD?

Oral intake status (FOIS) is associated with dysphagia as rated on the DIGESTv2: the odds ratio of dysphagia (DIGESTv2) for participants who scored <7 on FOIS (i.e., abnormal) was 4.05 (95% CI 1.03-16.00 $p = .046$). This means that participants were four times more likely to have dysphagia on the DIGESTv2 if they were modifying their diet/ avoiding foods. The remaining variables (age over 65, location of cancer, months since surgery, dysphagia at time of cancer diagnosis, radiotherapy, surgical approach, site of anastomosis, days in ICU and hospital post-surgery, and clinical results: IOPI, abnormal scores (≥ 0) on SARC-F) were not found to be predictors of pharyngeal dysphagia as illustrated in Table 6-15.

Table 6-15 Univariate regression model representing factors associated with pharyngeal dysphagia (DIGESTv2).

Predictor of Pharyngeal Dysphagia	p-value	Odds Ratio	95% CI
Age >65	.666	.75	.203 – 2.775
Location of cancer	.713	.714	.119-4.297
Maximum posterior isometric lingual strength	.427	.976	.918-1.037
Maximum anterior isometric lingual strength	.801	1.008	.949-1.07
Maximum anterior lingual endurance	.067	1.05	.997-1.107
Months since surgery	.336	1.011	.989-1.033
Radiotherapy	.446	.593	.154-2.279
Surgical approach	.659	.402	.099-2.52
Site of anastomosis	.372	.550	.148-2.046
Days in ICU	.738	.968	.802-1.169
Days in hospital post-surgery	.137	.938	.862-1.021
Risk of sarcopenia (SARC-F)	.199	.318	.414-15.096
Abnormal FOIS (<7)	.046	4.05	1.025-16.007

6.3.4 Summary of Oropharyngeal Phase Results

The key results identified in Section 1 are:

1. 35% participants presented with COD on the DIGESTv2 (score >0),
2. 100% participants had at least one impaired component on MBSImP. 40 (100%) had impaired swallow initiation, 36 (90%) had pharyngeal residue, 32 (80%) had reduced anterior hyoid excursion and 70% had impaired laryngeal elevation.
3. Two (5%) participants had uncleared penetration on the PAS, two (5%) had uncleared laryngeal aspiration.
4. There was a statistically significant difference ($\chi^2(2) = 7.07$, $p < 0.029$) in aspiration (PAS 6-8) versus no aspiration (PAS 1-5) across the three surgical groups. Only participants from the transhiatal group aspirated.
5. Oral phase: 72.5% participants had abnormal amounts of oral residue on MBSImP.
6. Mean maximum isometric posterior tongue strength, anterior tongue strength and anterior tongue endurance results on the IOPI were within normal limits based on normative data (39.9 kPa, 42.9 kPa and 23.5 seconds).
7. There was a weak negative significant association between months since surgery and Bolus Transport/Lingual Motion (MBSImP Component 4) ($r_s = -.385$, $p = .014$), meaning as months improve, bolus Transport/Lingual Motion scores decrease (improve).
8. There was a moderate significant negative association between anterior tongue endurance and days in hospital post-surgery ($r_s(37) = -.405$, $p = .01$), meaning as days in hospital post-surgery increase, endurance decreases (worsens).
9. Scoring below 7 on FOIS (avoiding or modifying foods/fluids) is associated with pharyngeal dysphagia on DIGESTv2 (4.05 (95% CI 1.03-16.00), $p = .046$)

6.3.5 Results: Oesophageal Phase of Swallowing

Question 1D. What is the nature and extent of oesophageal bolus flow in adults in the long-term post oesophageal cancer surgery and is it associated with any clinical/surgical/pharyngeal dysphagia variables?

Oesophageal Clearance on Videofluoroscopy

MBSImP Component 17 results are displayed in Figure 29 below.

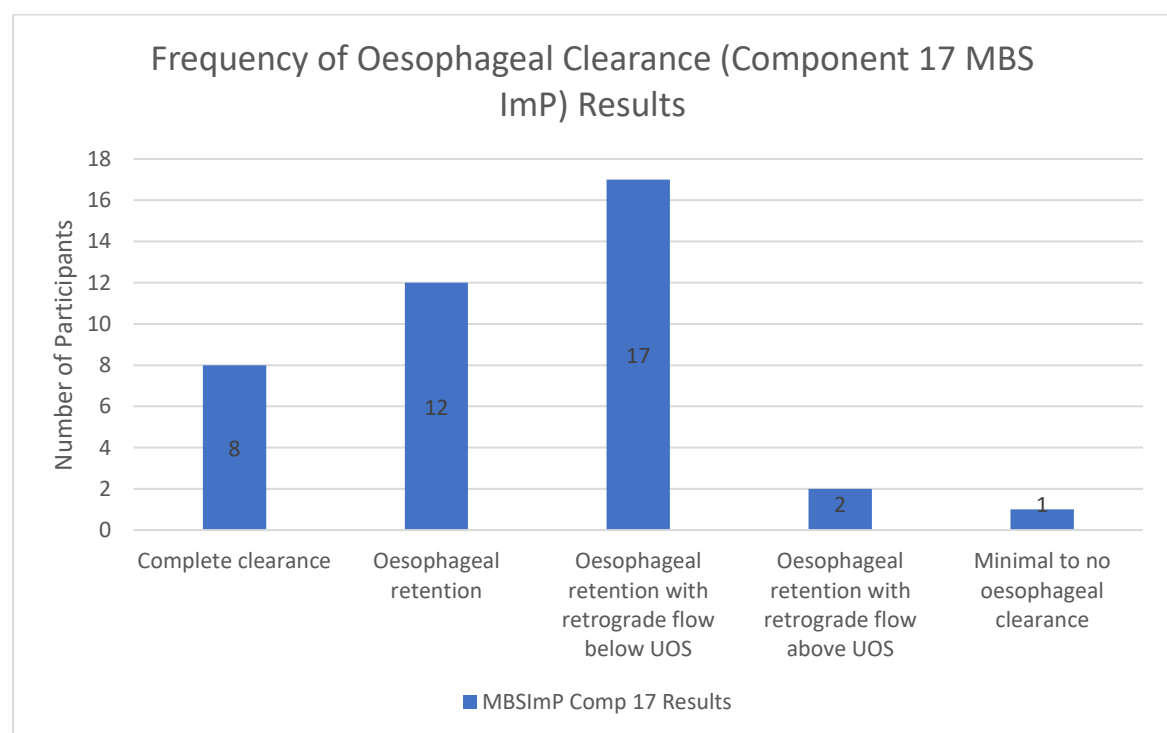


Figure 29 Frequency of results across Component 17 of MBSImP

Footnote: Definition of oesophageal retention = incomplete clearance of the bolus following the primary (and where it exists secondary) wave of peristalsis

The most frequently occurring phenomenon above, that is, retrograde flow of bolus within the oesophagus that remains below the UOS, occurred in 76.3% of IDDSI level 4 (pureed consistency) trials, 55% of IDDSI level 0 (thin water consistency) trials, and 17.9% of tablet trials.

Statistically significant weak correlations were found between oesophageal clearance and dysphagia on DIGESTv2 ($p = .003$), pharyngeal stripping (MBSImP Component 12) ($r_s(38) = .345$, p

= **.029**), tongue base retraction (MBSImP Component 15) ($r_s(38) = .331$, $p = .037$), location of cancer ($p < .001$), neoadjuvant treatment ($p = .009$) and site of anastomosis ($p = .003$)). There is also a weak negative correlation with time since surgery ($r_s(38) = -.321$, **.043**), meaning that as time since surgery increases, MBS Imp17 scores (oesophageal clearance) decrease (improve).

Table 6-16 Associations between oesophageal clearance and clinical/surgical/ dysphagia variables (Fishers Exact Test)

	MBSImP Component 17 Score Fishers Exact Test p-value
Location of Cancer	<.001
Site of anastomosis	.003
Neo-adjuvant treatment	.009
Radiotherapy received	.467
Dysphagia on DIGESTv2	.038
Risk of sarcopenia (SARC-F >1)	.801
RSI abnormal	.142

Table 6-17 Associations between oesophageal clearance and clinical/surgical/ dysphagia variables (Spearman's correlation)

	MBSImP Component 17 Score Spearman's correlation $r_s(38)$, p-value
MBSImP Component 8 Laryngeal Elevation	.187, .248
MBSImP Component 9 Anterior hyoid excursion	.218, .079
MBSImP Component 12 Pharyngeal stripping wave	.345, .029
MBSImP Component 13 Pharyngeal Contraction	.068, .678
MBSImP Component 14 UOS Opening	.284, .076
MBSImP Component 15 Tongue base	.331, .037
MBSImP Component 16 Pharyngeal residue	.135, .408
Months since surgery	-.321, .043

The bar chart below Figure 30 illustrates the breakdown of each MBSImP Component 17 score by consistency trialled (Note: two trials of Level 0 and Level 4 were consumed and the worst was recorded. One tablet was consumed). It reflects how the tablet was the most successfully cleared consistency in general, and that IDDSI Level 4 appears to result in the most oesophageal retention

overall. There was minimal difference between the presence of retrograde flow across IDDSI levels 0 and 4.

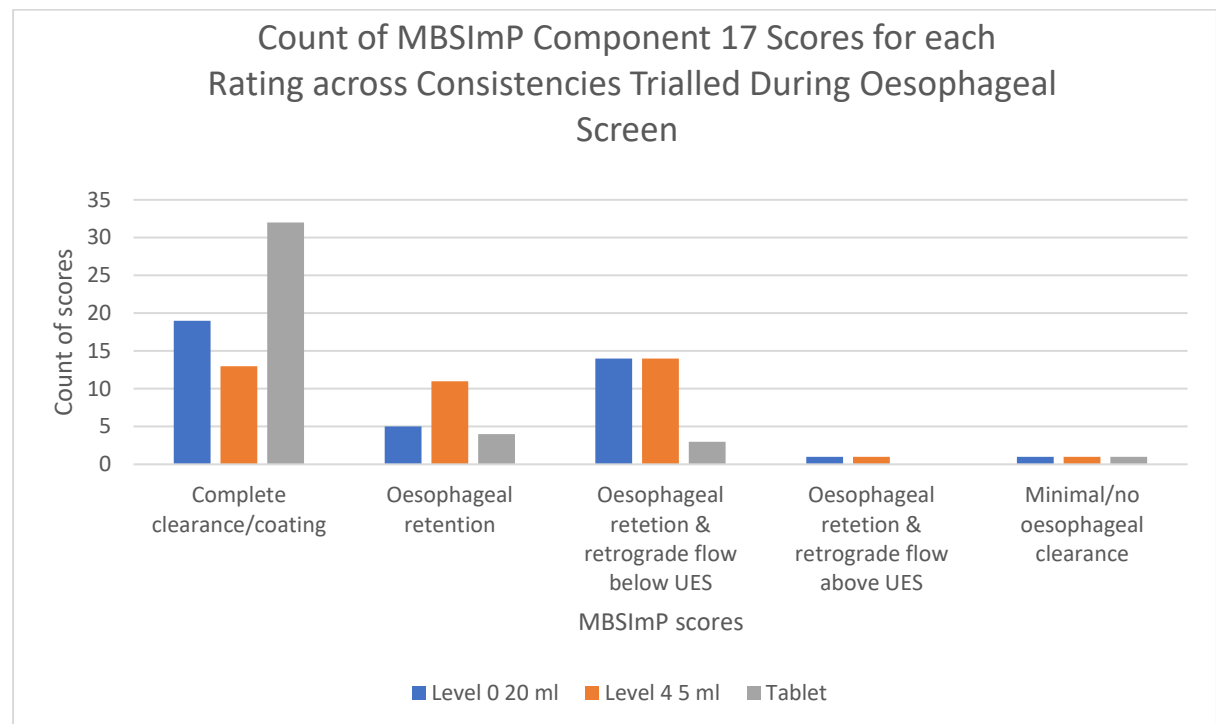


Figure 30 MBSImP Component 17 ratings across each consistencies trialled

Oesophageal transit time on videofluoroscopy

The mean OTT for IDDSI levels 0 and 4 were 26.4 seconds and 38.31 seconds, respectively. It is worth noting that OTT was capped at 60 seconds for 14/39 participants with Level 0 fluids and 22/39 participants with Level 4 fluids. Of the remaining 25 and 17 participants on Level 0 and 4 respectively, who were not capped, the mean OTT was 7.88 and 12.5 seconds, respectively.

The mean OTT for a tablet was 2.99seconds which included three participants who were capped at 60 seconds.

The below scatter charts (Figure 31) represent the distributions of OTT across consistencies and highlight the proportion of participants whose videofluoroscopies had to be capped at 60 seconds across consistencies.

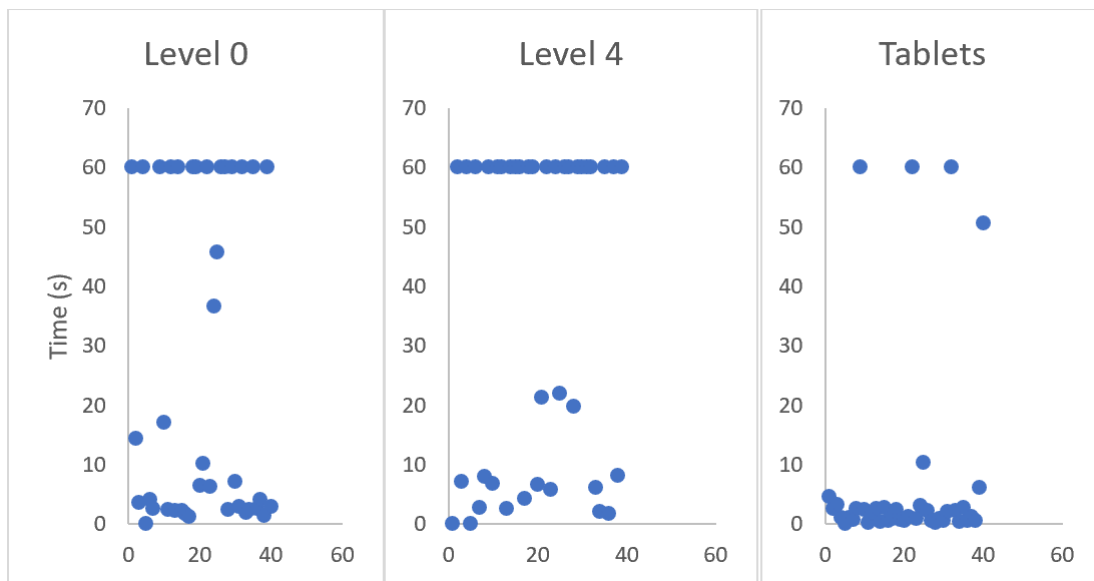


Figure 31 Breakdown of OTT across each consistency

The breakdown of OTT across surgical groups for each consistency is displayed in Figure 32 below:

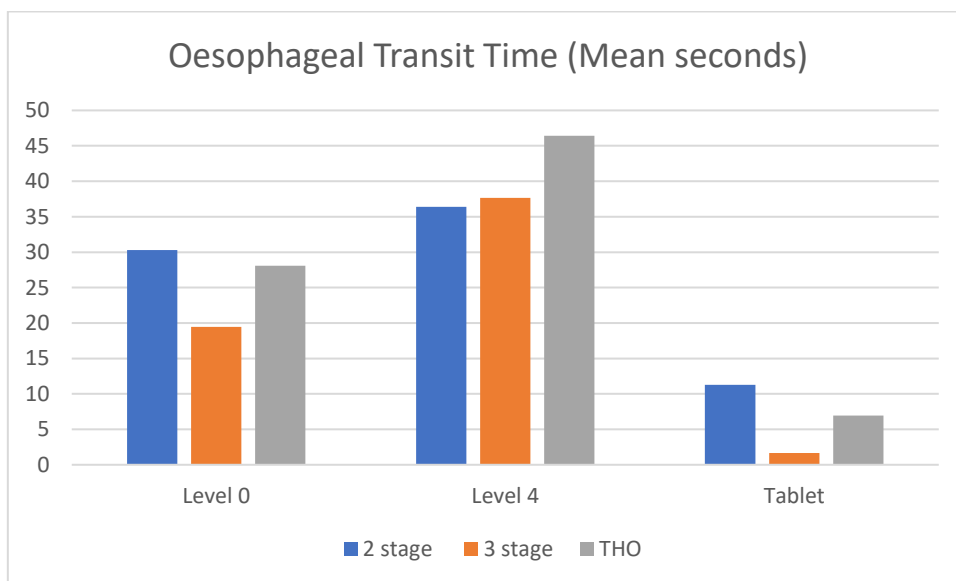


Figure 32 Breakdown of OTT across surgical groups for each consistency

Differences in oesophageal clearance results across surgical groups

There were statistically significant differences in oesophageal clearance results (MBSImP Component 17) between the different cancer locations ($\chi^2(2)=8.199$, $p = .017$), with a mean rank score of 24.56 for the oesophagogastric junction, 15.17 for the middle oesophagus, and 13.95 for the lower oesophagus. There was also a statistically significant difference in oesophageal clearance depending on the site of anastomosis ($\chi^2(1)= 4.339$, $p = .037$) with mean rank scores of 23.95 for the thoracic site of anastomosis and 16.68 for the cervical site of anastomosis.

There was no statistically significant difference in oesophageal clearance based on the type of cancer. See Table 6-18 for more information.

Table 6-18 Oesophageal clearance scores across subgroups

Kruskal Wallis (df), p value	Location of Cancer			Site of Anastomosis		Neo-adjuvant treatment			
	Mid oesoph n = 6	Lower oesoph n = 10	OG Junction n=24	Cervical n = 19	Thoracic n = 20	Neo-adjuv chemo n = 17	Neo-adjuv chemo + post op chemo n = 3	Neo-adjuv chemo and radiotherapy n =12	Surgery only n = 8
MBS Imp 17	15.17	13.95	24.56	16.68	23.95	22.71	29.00	16.92	18.00
	$\chi^2(2)=8.199$, p = .017			$\chi^2(1)= 4.339$, p = .037		$\chi^2(3)= 4.146$, p = .246			

Key: Adeno = adenocarcinoma, scc = squamous cell carcinoma, neo-adjuv = neo-adjuvant, chemo = chemotherapy

Differences in OTT across surgical / surgical subgroups

There were no statistically significant differences in OTT across surgical groups however there were statistically significant differences in OTT of level 0 fluids depending on Location of cancer ($\chi^2(2)=6.043$, $p = .049$). Mean ranks were 25.37, 16.05, and 12.92 for OG junction, lower oesophagus and mid oesophagus, respectively. There was also a statistically significant difference in OTT for level 0 fluids depending on age ($\chi^2(2)=4.997$, $p = .025$) with a mean rank of 23.69 for >65 years of age and 15.69 if not over 65 years of age. There was a statistically significant difference in OTT of tablets depending on the type of neo-adjuvant treatment received ($\chi^2(3)=11.485$, $p = .009$). Mean ranks were 33.33 for neoadjuvant and post-operative chemo, 23.38 for surgery only, 23.0 for neo-adjuvant chemotherapy, and 11.53 for chemotherapy and radiotherapy. Please see Table 6-19 for further information.

Table 6-19 Comparison of oesophageal transit times across clinical/ surgical variables

(Mean rank) Kruskal Wallis (df), p value	Location of Cancer			Age		Site of Anastomosis		Neo-adjuvant			
	Mid oesoph h n = 6	Lower oesoph h n = 10	OG Junction n=24	65 or older n = 21	<65 n = 18	Cervical n = 19	Thoracic n = 20	Chemo n = 17	Chemo + post op chemo n = 3	chemo and radiotherapy n =12	Surgery only n = 8
OTT L0	12.92	16.05	23.57	23.69	15.69	17.29	22.58	23.47	29.0	14.25	18.31
	$\chi^2(2)=6.043$, p = .049			$\chi^2(2)=4.997$, p = .025		$\chi^2(2)=2.195$, p = .138		$\chi^2(3)= 6.895$, p = .075			
OTT L4	20.92	20.9	20.23	23.05	17.68	21.79	189.33	22.18	20.17	17.0	22.31
	$\chi^2(2)=.039$, p = .981			$\chi^2(2)=2.518$, p = .113		$\chi^2(2)=.528$, p = .467		$\chi^2(3)= 1.943$, p = .584			
OTT Tablet	22.0	17.0	21.58	20.74	20.74	18.7	22.12	23.0	33.33	11.83	23.38
	$\chi^2(2)=1.203$, p = .548			$\chi^2(2)= .018$, p = .892		$\chi^2(2)=.849$, p = .357		$\chi^2(3)= 11.485$, p = .009			

Key: OTT = oesophageal transit time, oesoph = oesophagus, OG = oesophagogastric THO = transhiatal, chemo = chemotherapy

Note: no cancers were located in the cervical oesophagus.

6.3.6 Results: Clinical Context- Predictors of Disrupted Oesophageal Clearance

Question 1E: What are the predictors of disrupted oesophageal bolus flow in the long-term post oesophageal cancer surgery?

- i. Are surgical and clinical variables predictive of abnormal oesophageal clearance?

There were no statistically significant predictors of impaired oesophageal clearance as displayed in Table 6-20.

Table 6-20 Univariate regression model representing factors associated with impaired oesophageal clearance (MBSImP Component 17)

Predictor of impaired oesophageal clearance	p-value	Odds Ratio	95% CI
Age >65	.419	-	-
Location of cancer	.399	-	-
Site of anastomosis	.355		
Type of neo-adjuvant treatment	.999	-	-
Pathological Stage	.797		

6.3.7 Summary of Oesophageal Phase Results

The key results identified in Section 2 are:

1. 80% had impaired oesophageal clearance.
2. Two (5%) participants had oesophageal retention with retrograde flow of the bolus above the UOS.
3. One (2.5%) participant had no/ minimal oesophageal clearance of any consistency.
4. Statistically significant weak correlations were found between oesophageal clearance and dysphagia on DIGESTv2 ($p = .003$), pharyngeal stripping (MBSImP Component 12) ($r_s(38) = .345$, $p = .029$), tongue base retraction (MBSImP Component 15) ($r_s(38) = .331$, $p = .037$), location of cancer ($p < .001$), site of anastomosis ($p = .003$).
5. There were statistically significant differences in oesophageal clearance results (MBSImP Component 17) across the different cancer locations ($\chi^2(2) = 8.199$, $p = .017$), with worse oesophageal clearance for participants who had tumours in the oesophagogastric junction, followed by the middle oesophagus, and then the lower oesophagus.
6. There were statistically significant differences in oesophageal clearance results (MBSImP Component 17) between the site of anastomosis ($\chi^2(1) = 4.339$, $p = .037$) with worse oesophageal clearance for the thoracic site of anastomosis compared to the cervical site of anastomosis.
7. The mean OTT for IDDSI levels 0, IDDSI level 4, and tablets were 26.4 seconds, 38.31 seconds and 2.99 seconds, respectively.
8. There were statistically significant differences in mean OTT of level 0 fluids depending on location of cancer ($\chi^2(2) = 6.043$, $p = .049$), with higher OTT for the OG junction, followed by the lower oesophagus and then the mid oesophagus.

9. There were statistically significant differences in mean OTT of level 0 fluids depending on age ($\chi^2(2)=4.997$, $p = .025$) with a higher OTT for those 65 years and over compared to those who were below 65.
10. There was a statistically significant difference in mean OTT for tablets depending on the type of neo-adjuvant treatment received ($\chi^2(3)= 11.485$, $p = .009$) with highest OTT for neoadjuvant and post-operative chemotherapy, followed by surgery only, then neo-adjuvant chemotherapy, and finally chemoradiotherapy ($\chi^2(3)= 11.485$, $p = .009$).

7 Chapter 7 - Impact of COD and other Aerodigestive Symptoms on Quality of Life: Methods and Results

Results of this chapter are published in:

1. Gillman A, Kenny C, Hayes M, Walshe M, Reynolds JV, Regan J. Nature, severity, and impact of chronic oropharyngeal dysphagia following curative resection for esophageal cancer: a cross-sectional study. *Dis Esophagus*. 2024 Apr 27;37(5):doae003. doi: 10.1093/dote/doae003. PMID: 38266037; PMCID: PMC11060100.
2. Gillman A, Hayes M, Walsh I, Walshe M, Reynolds JV, Regan J., (2024): Long-term impact of aerodigestive symptoms on adults with oesophageal cancer: A qualitative study, *International Journal of Speech-Language Pathology*, DOI: 10.1080/17549507.2024.2360065

7.0 Methods

7.0.1 Ethical Approval

The ethical approval mentioned in Chapter 6 above from the SJH/Tallaght University Hospital Joint Research and Ethics Committee (JREC): Reference Submission number 315, Approval Date 24/11/2021 is relevant to this study too.

7.0.2 Study Design

Mixed methods research was implemented to benefit from the strengths of both quantitative and qualitative data that would more accurately and deeply convey the impact of oesophageal cancer related dysphagia on an individual's QoL. A mixed method design in health related research has been reported to provide a better understanding of the issue than either type of research alone

[499, 565]. Qualitative analysis can give readers a greater understanding of experiential phenomena in health care that are otherwise not captured [499].

Recruitment was conducted as part of the study mentioned in Chapter 6 above, using the same sampling method, eligibility criteria, consent, storage of data, analysis of quantitative data, and study setting. For this study, PROMs were collected from participants and an interview was conducted as per Figure 33.

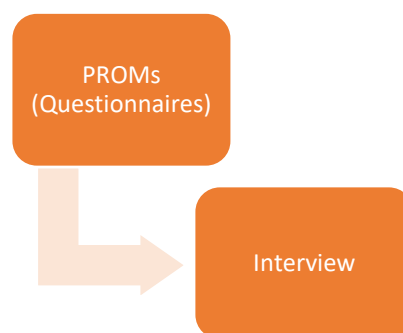


Figure 33 Protocol for collecting quality of life data

7.0.3 Study Details

This section will detail the tools used, the outcomes measured, the rationales and the data analyses used to answer the aforementioned research questions.

Patient Reported Outcome Measures (PROMs)

Regarding QoL PROMs, two tools were selected that were recommended for use by Patel et al (2017) in their systematic review, and were deduced to be robust in upper-aerodigestive oropharyngeal dysphagia (MD Anderson Dysphagia Questionnaire – MDADI) and oesophageal cancer related dysphagia (EORTC-QLQ-OES-18).

The MDADI is a 20 item questionnaire which has been validated in head and neck cancer to quantitatively reflect self-perceived swallow related QoL [525]. The Composite Score is a sum of results across the Physical, Emotional, and Functional domains (19 questions) with the mean calculated. The mean is multiplied by 20 to obtain a Total Score that falls between 20 (extremely low functioning) and 100 (high functioning) where a higher score is perceived to signify a higher QoL [525]. The final question referred to as ‘Global’ is reported separately and asks how daily routine is affected by the swallowing difficulty. A difference in Composite Scores of 10 has consistently been associated with clinically meaningful differences in swallowing function between groups [566].

The European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire – Oesophagus - 18 (EORTC-QLQ-OES-18) is a five point 18-item questionnaire that has moderate to good reliability and discriminant validity for identifying dysphagia, reflux and pain relating to swallowing in oesophageal cancer [567]. Results from the questionnaire are summed and a linear transformation was calculated to bring results to a range of 0-100 in adherence with the scoring manual on the EORTC website for EORTC-QLQ-OES-30 [568] and the supplementary version 18 [569], and as per other published research [570]. Higher scores reflect more swallow related problems impacting QoL.

Table 7-1 Patient Reported Outcomes

Outcome	Measure	Means of completion	Rationale	Research Question
Self-reported impact of chronic pharyngeal	MDADI (MD Anderson Dysphagia Inventory) [187]	Questionnaire completed by participant.	QoL research has shown	2

dysphagia in QoL			significant impact of	
Self-reported impact of chronic oesophageal dysphagia on QoL	EORTC-QLQ-OES-18 [188]	Questionnaire completed by participant	COD on QoL [362, 371]	2

QoL Interview

A semi-structured face-to-face interview took place in the VFS suite. This is not an ideal location for an interview so if other personnel were present following the VFS, such as a radiographer, the interview was relocated to a nearby office. The doctors in that office had to leave the room for this interview to take place so because of the impact on their work and due to a lack of other spaces available, it was not possible to conduct 100% of interviews there.

The main researcher conducted all interviews and commenced by asking participants if they had experienced any changes to their swallowing, voice, reflux or coughing since their oesophageal cancer surgery. Depending on the participants' response, they were then asked if and how these changes had impacted upon their QoL. Additional probing questions were asked depending on the natural flow of the conversation to gain a better understanding about how participants' QoL had been affected. Please see the Interview guide in Appendix K.

Outcomes and Data Analysis

The Impact of Aerodigestive Symptoms on QoL (qualitative analysis)

A semi-structured interview style was selected as it allows for a wide range of responses, given that no research has previously explored this area, and as it also provides some structure to guide the interview [571]. Reflexive Thematic Analysis was the type of analysis chosen as it can be used to effectively explore and understand the individual experiences of participants for qualitative health research [572] and generates patterns of experience around a central concept [573]. It enabled the analysis to go deeper than the words verbalised, to infer shared meanings that would accurately portray an element of the oesophageal cancer survivors' story. In addition, this type of analysis embraces the researcher as part of the analysis; it values the main researcher's role as the interviewer and as an experienced clinician, with social, cultural, historical and disciplinary positions that may impact upon analysing and interpretation of the data [574, 575]. Similarly, it is appreciated that the interviewer's interviewing behaviours may have impacted upon the participants' responses, for example, the main researcher purposefully used earlier participants' responses as prompts to elicit additional information from later participants, and during later interviews.

Table 7-2 Outcomes regarding the impact of aerodigestive symptoms on QoL

Outcome	Measure	Means of completion	Rationale for selecting aerodigestive symptoms	Research Question
Themes around the impact of aerodigestive symptoms on QoL	Semi-structured interview between main researcher and participant.	Reflexive Thematic Analysis [575]	Our PPI committee advised that this interview should investigate the impact of aerodigestive symptoms (due to difficulty distinguishing	2

			symptoms of dysphagia from other aerodigestive symptoms)	

Interviews were recorded on the main researcher's password protected computer and deleted following transcription. All interviews were transcribed by two researchers manually and with the assistance of Microsoft Word's transcription function. All identifiable information was removed from the transcripts. Direct quotes were extracted from the transcripts as they are key to portraying the suffering of this cohort, and these quotes were pseudonymised.

The main researcher conducted analysis initially using an inductive approach (i.e. guided by the data in the dataset) of the entire dataset, however, 'deductive' reasoning (i.e. guided by existing research) was used back and forth throughout the process as existing research has previously referred to QoL generally being impaired in oesophageal cancer survivors [575]. Braun & Clark's six phases of reflexive thematic analysis were implemented (Data Familiarisation and Writing Familiarisation, Systematic Data Coding, Generating Initial Themes from Coded and Collated Data, Developing and Reviewing Themes, Defining and Naming the Themes, Writing the Report[576]). (See Figure 35 below.) Initially, transcripts were read and re-read and codes allocated. Codes were refined over time. After open coding throughout the entire text, exploratory searches were conducted to locate any missed references. The transcript was then uploaded to NVivo, a computer-assisted qualitative data analysis software, to assist with developing a clear audit trail in order to ensure there was rigour and credibility to findings [577]. NVivo's insight function was not used as the main researcher was keen to independently connect data. NVivo was however used to write annotations and memos, establish further codes, move references into codes, and then to group codes for the early identification of larger patterns and ultimately 'themes'. Initially codes and themes were

semantic in nature and as the researcher became more familiar with the dataset, more latent themes evolved that went beyond the words spoken by participants. The essentialist method of analysis allowed the researcher to extrapolate meaning from the dataset [573]. Themes were actively generated instead of allowing them to passively emerge from the data [578]. The main researcher initially searched broadly for themes. Self-reflection and critique ensured that themes were directly from the data, and not from previously published research [579]. Themes were mapped on paper to see if broader themes that answered the research question were evident, and this revealed a very rich dataset consisting of one theme and three subthemes. In order to do the story justice, the main researcher delved back into the analysis again. The researcher returned to the data many times to ensure output was strongly justified by the data. Thematic maps assisted with visually displaying the themes for appropriate categorising, merging and deleting of themes. (See Figure 34.) Once the themes were refined, summaries and titles were developed.

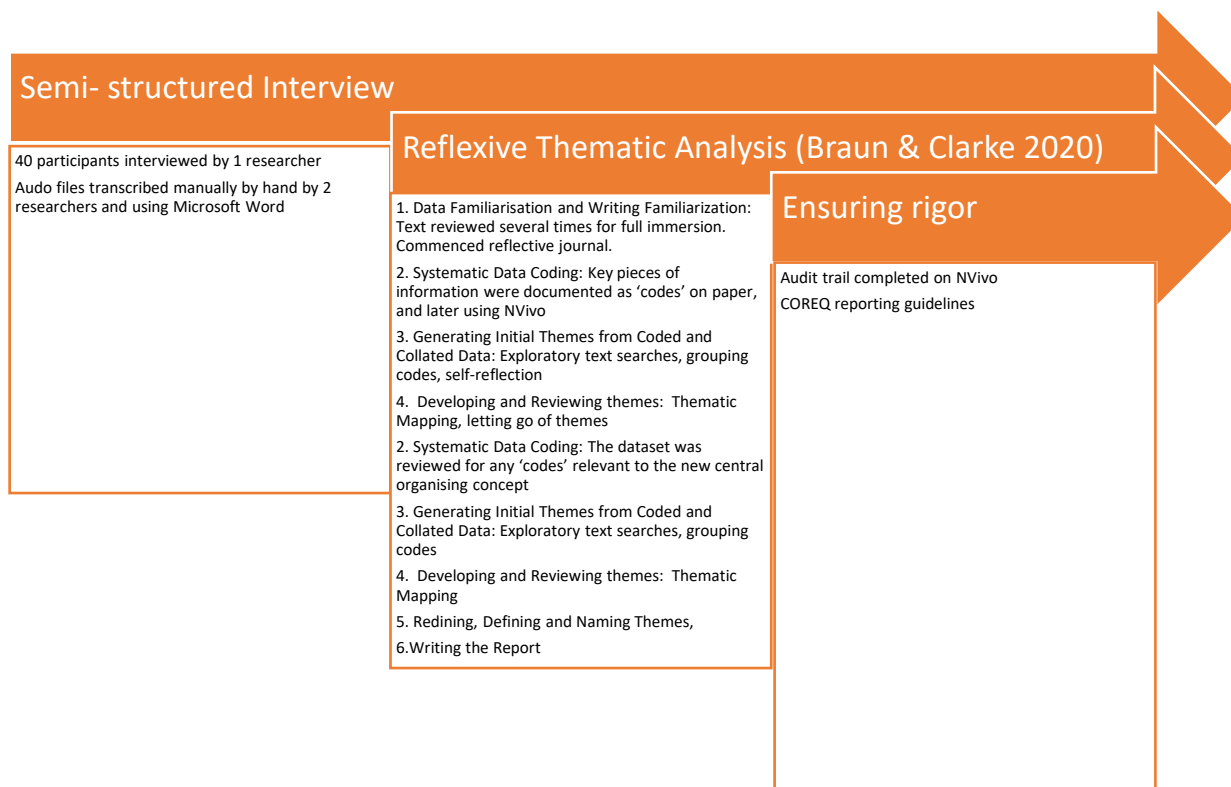


Figure 35 Analytical Process

7.0.4 Statistical Analysis

Question 2: What is the impact of dysphagia and other aerodigestive symptoms on QoL?

- i. What is the impact of oropharyngeal and oesophageal dysphagia on QoL and are there differences in QoL impact across various clinical/treatment subgroups?

Descriptive analysis was used to measure QoL results from the MDADI Composite, MDADI Global and EORTC-QLQ-OES-18. Descriptive results are provided as median (IQR and range).

Sub-group analyses were conducted using Kruskal-Wallis H test, because data was non-parametric, to identify differences in QoL across clinical and surgical groups (age, type of cancer, location of cancer, age, site of anastomosis, radiotherapy). It is worth noting that a higher MDADI Composite score (maximum 100) and MDADI Global (maximum 5) score equates to a lower impact of dysphagia on QoL, and a higher EORTC score equates to a more severe impact of dysphagia on QoL.

ii. What dysphagia, clinical and surgical variables are associated with reduced QoL?

Spearman's correlation test was completed to measure the strength and direction of association between QoL (MDADI Composite, Global and EORTC 18) and clinical/surgical/ dysphagia variables (MBSImp Total Oral and Pharyngeal scores, MBSImp Component 17 Oesophageal Clearance, maximum anterior tongue strength, maximum posterior tongue strength, mean anterior tongue endurance, months since surgery, number of days in ICU/hospital). Fisher's Exact Test was used when participants fell entirely or mostly into two categories (dysphagia on DIGESTv2, location of cancer, site of anastomosis, RLN injury, anastomotic leak). The Kruskal Wallis H test was then used to further explore an identified association between location of cancer and QoL to determine if there might be a difference depending on the various cancer locations.

iii. What is the impact of chronic aerodigestive symptoms on quality of life post curative oesophageal cancer surgery?

Reflexive Thematic Analysis was conducted [573]. The analytical approach is explained in greater detail below in Section 7.1.

This concludes the Methods for this chapter. The Results will be explored below.

7.1 Results: Impact of COD and Aerodigestive Symptoms on Quality of Life

Question 2 What is the impact of dysphagia and other aerodigestive symptoms on QoL?

7.1.1 Results: Impact of oropharyngeal and oesophageal dysphagia on QoL

- i. What is the impact of oropharyngeal and oesophageal dysphagia on HRQoL and are there differences in QoL impact across various clinical/treatment subgroups?

The median (IQR) results for patient-reported outcomes are mild in general: MDADI Global: 5(4,5) (where 5 is minimal/no impact), MDADI Composite 77.9 (60.0,92.6) (where results can range from 20 – 100 and 100 is high functioning), and EORTC-18 33.3 (24.1-48.2) (where results can range from 0 – 100 and 100 is severely impacted). Results are displayed in Table 7-4 below.

Table 7-3 Median (IQR) and Range QoL results

Quality of Life questionnaires	Median (IQR)	Range
MDADI Global (n=39)	5 (4-5)	4
MDADI Composite (n=39)	77.895 (60.0-92.6)	67.4
EORTC-QLQ-OES-18 (n=39)	33.33 (24.07-48.15)	70.37

There were no statistically significant differences across subgroups for QoL outcomes. Mean ranks results across groups are provided in Table 7-5 below.

Table 7-4 QoL results (mean ranks) and differences in QoL outcomes across clinically and surgically relevant subgroups

(Mean rank) Kruskal Wallis (df), p value	Location of Cancer			Age		Site of Anastomosis		Radiotherapy	
	Mid oesoph n = 6	Lower oesoph n = 10	EG Junction n=24	65 or older n = 21	<65 n = 18	Cervical n = 19	Thoracic n = 20	Radiotherapy n = 13	No radiotherapy n = 26
MDADI Global	17.5	22.05	19.76	20.21	19.75	19.68	20.3	19.15	20.4
	$\chi^2(2) = .753, p = .686$			$\chi^2(1) = .019, p = .889$		$\chi^2(1) = .034, p = .853$		$\chi^2(1) = .13, p = .718$	
MDADI Composite	19.83	21.05	19.59	19.12	21.03	19.55	20.43	19.92	20.04
	$\chi^2(2) = .117, p = .943$			$\chi^2(1) = .272, p = .602$		$\chi^2(1) = .057, p = .811$		$\chi^2(1) = .001, p = .976$	
EORTC-QLQ-OES-18	20.58	20.45	19.65	20.33	19.61	20.76	19.27	20.27	19.87
	$\chi^2(2) = .027, p = .871$			$\chi^2(2) = .039, p = .843$		$\chi^2(1) = .166, p = .683$		$\chi^2(2) = .011, p = .917$	

Key: scc = squamous cell carcinoma, adeno = adenocarcinoma, other = other carcinoma types, oesoph = oesophagus, OGJ = oesophagogastric junction

Please refer to Appendix J for participant level summary of QoL results.

- ii. What dysphagia, clinical and surgical variables are associated with reduced QoL?

There was a statistically significant moderate positive association between maximum anterior tongue strength and QoL results (MDADI Composite (r_s (37)= .514, $p < .001$) and MDADI Global (r_s (37) = .454, $p = .004$)), and a weak negative association on another QoL test (EORTC-QLQ-OES-18 (r_s (37)= -.377, $p = .018$)), meaning that as tongue strength increases, EORTC results (QoL) decrease (improve). There was also a moderate association between maximum posterior tongue strength and QoL results (MDADI Composite (r_s (37)= .510, $p < .001$) and MDADI Global (r_s (37)=.350, $p = .029$)). Finally, there was a weak positive association between QoL (MDADI composite) and location of cancer using Fisher's Exact Test ($p=.048$). Please see Tables 7-6 and 7-7 below for further information.

Table 7-5 Associations between QoL and various clinical, surgical and dysphagia variables (Spearman's correlation)

Spearman's correlation, p-value	MDADI Composite (n=39)	MDADI Global (n= 39)	EORTC-QLQ-OES-18 (n=39)
MBSImP Total Oral	$r_s(37) = -.181, p = .27$	$r_s(37) = -.219, p = .179,$	$r_s(37) = .177, p = .281$
MBSImP Total Pharyngeal	$r_s(37) = -.302, p = .062$	$r_s(37) = -.396, p = .013$	$r_s(37) = .298, p = .065$
MBSImP Component 17	$r_s(37) = -.062, p = .708$	$r_s(37) = -.221, p = .176$	$r_s(37) = .07, p = .671$
Mean maximum anterior tongue strength	$r_s(37) = .514, p < .001$	$r_s(37) = .454, p = .004$	$r_s(37) = -.377, p = .018$
Mean maximum posterior tongue strength	$r_s(37) = .510, p < .001$	$r_s(37) = .350, p = .029$	$r_s(37) = -.210, p = .199$
Mean anterior tongue endurance	$r_s(37) = .07, p = .672$	$r_s(37) = -.04, p = .809$	$r_s(37) = -.031, p = .852$
Months since surgery	$r_s(37) = -.008, p = .962$	$r_s(37) = .002, p = .988$	$r_s(37) = .093, p = .575$
No of days in ICU	$r_s(37) = .059, p = .722$	$r_s(37) = .043, p = .797$	$r_s(37) = -.20, p = .223$
No of days in hospital post-surgery	$r_s(37) = .143, p = .385$	$r_s(37) = .109, p = .509$	$r_s(37) = -.041, p = .805$

Table 7-6 Associations between QoL and various clinical, surgical and dysphagia variables (Fishers Exact Test)

Fisher Exact Test p-value	MDADI Composite	MDADI	EORTC-QLQ-OES-18
Dysphagia on DIGESTv2	P = .103	P = .442	P = .062
Site of anastomosis	P = .624	P = .99	P = .686
Location of cancer	p = .048	P = .562	P = .204
RLNP	P = .359	P = 1	P = .821
Anastomotic leak	P = .964	P = 1	P = .787

There was no statistically significant difference between the locations of cancer for QoL (MDADI Global ($\chi^2(2) .753 , p = .686$)).

Regarding the P = 1 values in Table 7-7, it is acknowledged that it is theoretically impossible to have a score of 1 and that SPSS reports it like this because of the small number of participants (RLNP n=1, anastomotic leak n=2). It is not possible to determine a correlation when samples include such few cases as the results will be unrealisable, however despite this, analysis was still attempted based on the fact that these were variables that were planned to be examined from the outset.

7.1.2 Results: Impact of Chronic Aerodigestive Symptoms on QoL

- ii. What is the impact of chronic aerodigestive symptoms on quality of life post curative oesophageal cancer surgery?

Results

The majority of participants experience ongoing aerodigestive symptoms throughout survivorship, which can significantly impact upon QoL. Some of the aerodigestive symptoms commonly reported include painful abdominal cramps, nausea, vomiting and diarrhoea after eating, reflux, coughing/choking when eating and drinking, poor weight maintenance, fatigue and dizziness after eating, loss of enjoyment of food.

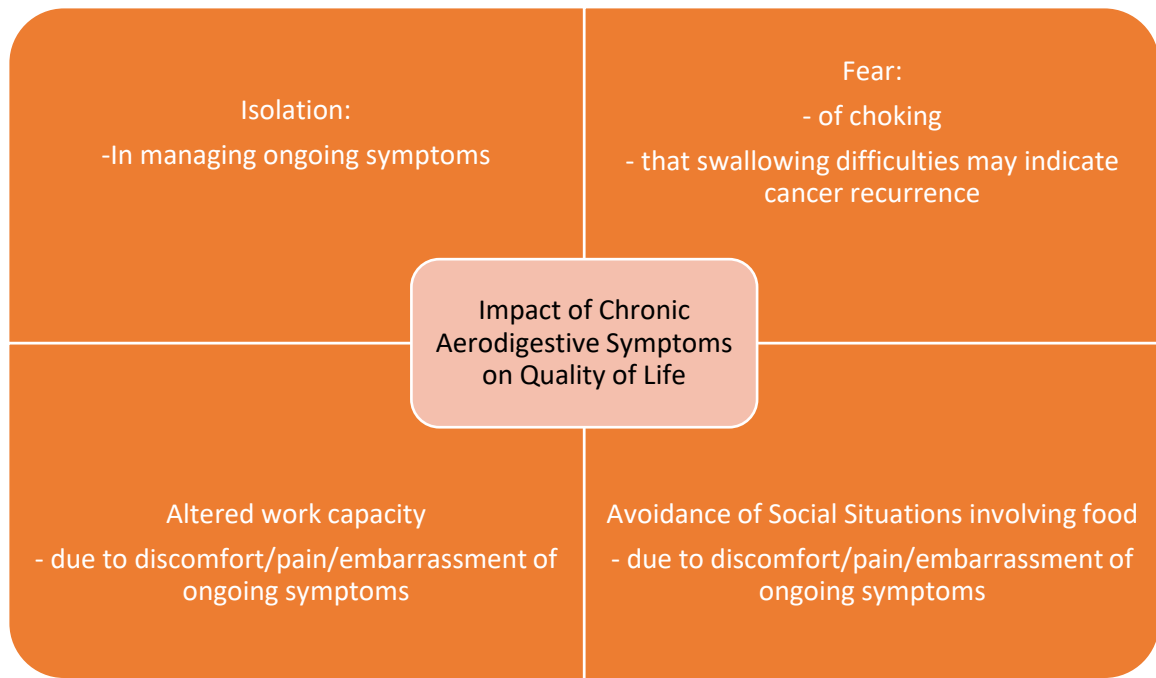


Figure 36 Four themes identified using RTA

Four main themes were identified via Reflexive Thematic Analysis as per Figure 36.

- 1) Isolation: This theme demonstrated a perspective of aloneness when navigating a life with chronic aerodigestive symptoms post oesophageal cancer surgery. Many participants commented on how they had little support to manage their pain once discharged from hospital. *"I never felt I had any real support after that. I-I felt very isolated, on my own."* (Participant 16). Some participants felt that health professionals in the community did not have the level of expertise required to manage post-oesophagectomy aerodigestive symptoms, for example, these professionals *"haven't a clue"* (Participant 1) or *"don't really understand"* (Participant 16). Furthermore, participants reported that because of the 50% survival rate, they had lost peers who they had undergone the same treatment which had resulted in a further sense of isolation in managing their symptoms. Even when they did meet other survivors, symptoms were felt to be very unique and strategies that worked for one participant may be ineffective for another. This lack of peer support, and limited health care support in the community, has resulted in this sense of perceived isolation for many survivors.

- 2) Fear: There was an apparent fear amongst participants that signs of dysphagia might be an indicator of cancer recurrence. *"Thought it was the cancer back y'see"* (Participant 7). In addition, participants often reported having experienced choking episodes and were fearful of this happening again *"I worry if it gets really bad and I'm on my own."* (Participant 39). In addition to these valid concerns, participants were also fearful of their family members discovering they had these dysphagia symptoms because they acknowledged that their family members had already worried so much about them during their cancer journey, *"Y'know you just say you're fine... when you weren't even fine, you just put on a good face."* (Participant 15). Many participants reported experiencing this sense of fear on a daily basis because of these ongoing aerodigestive symptoms.
- 3) Altered work capacity: Many participants stated that *"It'd be a significant problem going back to work"* (Participant 3) because of their aerodigestive symptoms including nausea, vomiting, fatigue, brain fog, and *"the dumping syndrome, and the burping all the time, and having to eat all the time..."* (Participant 37). *"To this day I still don't have natural movements."* (Participant 15). It was reported that participants were *"heading towards more... solitary work"* (Participant 3). Several participants reported that following their treatment they felt as though they had no option but to alter their working habits or even resign from the jobs, despite not wanting to.
- 4) Avoidance of Social Situations involving food: The impact of aerodigestive symptoms on individuals' participation in society is significant, with certain participants saying they *"tend to prefer to eat alone"* (Participant 3) including the avoidance of restaurants or attending meals in other people's houses: *"I hate going out for a meal...I just stopped going out"* (Participant 15). At celebrations such as birthdays, Christmases, or christenings, participants reported avoiding eating and choosing to *"meet up when the meal was over"* (Participant 21). As social occasions frequently include food and drinks, this has resulted in social isolation for many participants including elderly participants who

have lost relationships that were important to them for many years and young participants whose reduced social life reportedly has a substantial impact on their QoL. These four themes highlight the significant impact of chronic aerodigestive symptoms on QoL. Further information is included in the manuscript which has been accepted for publication this year in International Journal of Speech Language Pathology and is included in Appendix M.

7.1.3 Summary of Quality of Life Results

The key results identified in Section 3 are:

1. The median (IQR) QoL results for patient-reported outcomes are: MDADI Global: 5(4,5), MDADI Composite 77.9 (60.0,92.6), and EORTC-18 33.3 (24.1,48.2), revealing a mild impairment.
2. There was a statistically significant positive moderate association between maximum anterior tongue strength and QoL results on the MDADI Composite ($r_s(37) = .514, p < .001$) and MDADI Global ($r_s(37) = .454, p = .004$), and a weak negative association with EORTC-QLQ-OES-18 ($r_s(37) = -.377, p = .018$), meaning that as tongue strength increases, EORTC results decrease (improve).
3. There was also a moderate association between maximum posterior tongue strength and QoL results on the MDADI Composite ($r_s(37) = .510, p < .001$) and MDADI Global ($r_s(37) = .350, p = .029$).
4. RTA revealed four main themes highlighting the impact of aerodigestive symptoms on QoL.
 - a. Isolation: being alone in managing chronic aerodigestive symptoms because of a lack of community support and expertise.
 - b. Fear: concern that dysphagia may result in a choking episode or be a sign of cancer recurrence.

- c. Altered work capacity: pain, embarrassment, discomfort, fatigue caused by chronic aerodigestive symptoms impact the ability to return to work in the same capacity as before.
- d. Avoidance of social situations that involve food: pain, embarrassment, and discomfort caused by chronic aerodigestive symptoms restrict the ability to socialise as before.

8 Chapter 8 - Exercised Based Dysphagia Rehabilitation in Oesophageal Cancer; Systematic Review Methods and Results

The Systematic Review results are published in:

Gillman, A., Hayes, M., Sheaf, G. *et al.* Exercise-based dysphagia rehabilitation for adults with oesophageal cancer: a systematic review. *BMC Cancer* **22**, 53 (2022).

<https://doi.org/10.1186/s12885-021-09155-y>

8.0 Methods

A Systematic Review was conducted and published in BMC Cancer in 2022. The article can be found in Appendix B. The protocol for this systematic review is outlined in Appendix A. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [717] guidelines were adhered to throughout this chapter. The protocol was registered on the PROSPERO database of prospectively registered systematic reviews (reference number CRD42020172029; https://www.crd.york.ac.uk/prospERO/display_record.php?RecordID=172029).

8.0.1 Search strategy

A database search of ten electronic databases was conducted (CINAHL Complete, MEDLINE, EMBASE, Web of Science, CENTRAL, and ProQuest Dissertations and Theses, OpenGrey, PROSPERO, RIAN and SpeechBITE) using the following search terms: “oesophageal cancer”, “dysphagia/deglutition” and “rehabilitation” as well as a search of clinical trial registries (ClinicalTrials.gov, ISRCTN, WHO Trial Registry) and a manual search of reference lists, Google Scholar and conference abstracts. Below is an example of a MEDLINE search strategy.

Search strategy for MEDLINE

1. (MH "Deglutition") OR (MH "Deglutition Disorders+") OR TI (dysphagi* OR deglutition* OR swallow* OR ((feeding OR eating OR drinking) N3 disorder*)) OR AB (dysphagi* OR deglutition* OR swallow* OR ((feeding OR eating OR drinking) N3 disorder*))
2. (MH "Gastrointestinal Neoplasms+") OR TI ((esophag* OR oesophag* OR gastrointestinal OR "gastro-intestinal") N3 (cancer* OR neoplasm* OR carcinoma* OR tumor* OR tumour*)) OR AB ((esophag* OR oesophag* OR gastrointestinal OR "gastro-intestinal") N3 (cancer* OR neoplasm* OR carcinoma* OR tumor* OR tumour*))
3. (MH "Exercise+") OR (MH "Rehabilitation+") OR TI (Intervention* OR exerci* OR rehabilit* OR prehabilitat* OR "pre-habilitat*" OR treat* OR therap*) OR AB (Intervention* OR exerci* OR rehabilit* OR prehabilitat* OR "pre-habilitat*" OR treat* OR therap*)

8.0.2 Eligibility Criteria

Articles published at any time point and any language were accepted. Inclusion criteria were applied independently by two reviewers and consisted of peer-reviewed randomized control trials, quasi-experimental designs, observational studies, conference presentations, abstracts and non-systematic reviews. Expert opinions, letters to editors, commentaries, editorials and textbooks were not included. Participants had to have undergone/ be about to undergo curative intent oesophageal resection for oesophageal cancer, have a swallowing disorder, and have participated in dysphagia rehabilitation. Participants were not included if they had conditions with a known impact on swallowing (e.g. neurodegenerative disease).

Given a recent systematic review discussed in the Literature Review in Chapter 2 which had identified studies implementing compensatory strategies with oesophageal cancer patients, the focus of this systematic review was solely on exercise-based dysphagia rehabilitation. As such, a definition was coined to include intervention that was specifically exercise-based:

“an exercise which aims to create lasting functional change to the efficiency, strength, coordination and safety of an individual’s swallow by improving underlying physiological function, rather than compensating for a deficit in the moment.”

8.0.3 Outcome Measures

The following outcomes were measured:

1. Oral intake status rated on the Functional Oral Intake Scale [181].
2. Respiratory Complications: on chest x-ray or CT and as defined by the Centre for Disease Control (CDC) [581] and the Standardized Endpoints for Perioperative Medicine (StEP) collaborative network [582].
3. QoL: such as scores on the MD Anderson Dysphagia Intervention Questionnaire [583] or SWAL-QOL (Swallow Quality of Life Questionnaire) [189].

The Secondary Outcomes were:

1. Change to patient-reported dysphagia ratings on validated scales, for example, the EAT-10 (Eating Assessment Tool- 10) [176].
2. Changes to swallow physiology, efficiency or safety as visualized on Instrumental assessment (pharyngeal high-resolution impedance manometry (PHRIM), MBS Impairment Profile [216], Dynamic Imaging Grade of Swallowing Toxicity-DIGEST [531], the Penetration-Aspiration Scale (PAS) [525] on videofluoroscopy or Flexible Endoscopic Evaluation of Swallowing (FEES)).
3. Time to return to oral intake (days).
4. Length of stay in hospital (days).
5. A change in nutritional status: for example the MUST (Malnutrition Universal Screening Tool) [584].
6. Adverse events such as increased fatigue, deterioration of swallow function or patient discomfort.

8.0.4 Data Extraction and Analysis

Question 3 Is there evidence to guide oropharyngeal dysphagia rehabilitation for adults with oesophageal cancer?

Two authors of the published study, including the main researcher, extracted data independently using Covidence software. Disagreements were resolved by consensus and discussions with a third author. The TIDieR checklist was used (Template for Intervention Description and Replication)[585] to ensure complete reporting of interventions. Meta-analysis was not possible due to the limited data provided therefore it was attempted to group relevant information from the retrieved studies for descriptive analysis and discussion.

The ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) Tool [586] was used to assess the risk of bias across studies, where an overall judgement was formed relating to each study. Given that one study was particularly weak and had insufficient information to use this tool, the Downs & Black Checklist [587] was used because it can assess non-randomised studies, and as its questions are less specific in nature allowing for the inclusion of studies with weaker designs. Item 27 was scored as per prior research [588]. Higher scores reflected stronger methodological quality (ranging from 0 to 28 with 26-28 considered excellent, 20-25 considered good, 15-29 considered fair and 14 or less considered poor). The GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) was then applied to identify the certainty of this entire body of evidence as a whole [589, 590]. A grade of 'high', 'moderate', 'low', or 'very low' will be assigned to all factors. The evidence will be downgraded a level if the study lacks quality (e.g. design limitations; downgrade one level if the majority are non-randomised controlled trials), if there is an inconsistency of results; if there is imprecision, or if there is a probability of bias (e.g. downgrade one level if ROBINS-I level of bias is critical or severe as per the Cochrane guidelines [731] or if average risk of bias in the majority of the studies score <20 on Downs and Black scale as per previous research [732]).

Those factors that can increase the quality of evidence include 'large magnitude of effect', 'all plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed' and 'dose-response gradient'.

This concludes the Methods for this Chapter. The Results will be explored below.

8.1 Results

Question 3 Is there evidence to guide oropharyngeal dysphagia rehabilitation for adults with oesophageal cancer?

- i. What is the effectiveness of dysphagia rehabilitation in improving clinical outcomes (oral intake status, pneumonia and swallow) and health related QOL outcomes in adults with oesophageal cancer across time points?

A search of 10 database and 3 clinical trial registries retrieved 7938 articles. Three studies met the eligibility criteria which included 311 participants who had oesophagectomy performed in different centres in Japan. Please see the reasons for exclusion in Appendix N as per the PRISMA 2020 statement [591].

The designs of the three studies were a case control study [69] (n=26), case series [73] (n=9) and retrospective case control study [74] (n=276). Demographic data and intervention data are included in the published paper in Tables 8-1 and 8-2 below (permission granted for inclusion)

Table 8-1 Demographic characteristics of included studies

Authors, year	Study Design and Setting	N	Age	Sex	Co-morbidities	Stage of cancer	Location of cancer	Type of cancer treatment	Complications post-surgery	Dysphagia Assessment for Outcomes
Okumura et al, 2016 [69]	Case Control Study (CCS) Hospital Japan	26	CG; Mean 65.9 +/- 9.7 yrs. TG: 68 +/- 5.1 yrs.	CG: 13/1 M:F TG: 12 M	NI	TNM Classification (UICC) - I/II CG: 12 (85.7%) TG: 8 (66.7%) - III/IV CG: 2 (14.3%) TG: 4 (33.3%)	Thoracic	"Oesophagectomy" 5 participants: neoadjuvant chemotherapy	CG: RLNP (n=4) AP (n=3) AL (n=2) TG: RLNP(n=2), AP (n=3), AL (n=2)	Non-validated: 1. Functional Outcomes Assessment Measure of Swallowing (FOAMS). 2 Measured biomechanical positions on x & y axis from VFS images
Tsubosa et al, 2005 [73]	Case Series (CS) Rehab hospital, Japan	9	Mean 57.8 +/- 9 yrs	9 M	Case 1: RTC; 2: old age; 3: Stroke Remaining cases no comorbidities relevant to swallowing	NI	Thoracic	"Oesophagectomy"	RLNP (n= 5. 1 of which was bilateral resulting in severe AP)	Non-validated: VFS rating tool suggested by Logemann, 1998 [70]
Takatsu et al, 2020 [74]	Single centre retro-spective case control study	276	CG; median 68 (IQR 64-74) TG; 69 (IQR 62-73)	CG: 91/18 M:F	NI	TNM Classification (UICC) -I/II CG: 49 (45%) TG: 56 (45%) -III/IV CG: 60 (55%)	Thoracic	All: Open thoracoscopic Oesophagectomy Cervical anastomosis CG: Neoadjuvant therapies: 87 (80%)	CG: RLNP 22 (20%), Pneumonia 25 (23%), AL: 8 (7%)	1. Start of oral intake 2. Length of oral intake rehabilitation 3. Length of postoperative stay

Authors, year	Study Design and Setting	N	Age	Sex	Co- morbidities	Stage of cancer	Location of cancer	Type of cancer treatment	Complicat ions post- surgery	Dysphagia Assessment for Outcomes
	Cancer Centre Hospital Japan			TG: 142/2 5 M:F		TG: 91 (55%)		TG: Neoadjuvant therapies: 133 (80%)	TG: RLNP 34 (20%) Pneumonia 39 (23%) AL 22 (13%)	

Key: Std Dev = Standard Deviation. NI = No Information provided. RLNP = Recurrent Laryngeal Nerve Palsy. AP = Aspiration Pneumonia. VFS = Videofluoroscopy. CG = control group. TG = treatment group. JES = Japan Esophageal Society, UICC = Union for International Cancer Control. Yrs. = years. AL = Anastomotic Leak. Hx = history. RTC = radiotherapy for tongue cancer

Table 8-2 Intervention characteristics of included studies

Authors, year	Exercises with Rehabilitative Purpose	Other Exercises and/or Compensatory Strategies	Mode, Frequency, Intensity, Duration Dosage of Intervention	Timing of dysphagia rehabilitation from start of cancer treatment	Duration of rehabilitation (Mean +/-Std dev)
Okumura et al, 2016 [69]	Pursed lip breathing [71], Tongue exercises [72], Shaker “head lift” exercises [73]	Cervical range of motion exercise Shoulder stretch Jaw opening Respiratory therapy Compensatory strategies: Modified food and fluids.	SLT & nurses in the surgical ward delivered initial verbal & written instruction. Exercises x5 a day at home and upon admission to the hospital until surgery Unclear if patient-led.	Prehab: Approximately 23+/-9.2 Days preoperatively Rehab: from the time oral intake was resumed after confirming the absence of anastomotic leakage post-surgery.	Prehab: 23+/-9.2 Days pre-surgery. Rehab: 26+/-15 days post-surgery.
Tsubosa et al, 2005 [73]	Mendelsohn manoeuvre. [592] Long lasting change may have potentially occurred from super- supra glottic swallow [592-597]	Oral care Neck and shoulder exercises Oral exercises Thermal tactile stimulation Super-supraglottic swallow Effortful breath hold Compensatory strategies: Multiple swallows, chin down, Modified food and fluids.	Article states ‘Intensively’ however no definition or information provided.	Post-operative- unknown precisely when.	9.7 +/- 6.9 days post-surgery. 5/9 participants required more than 1 round of rehabilitation.

Authors, year	Exercises with Rehabilitative Purpose	Other Exercises and/or Compensatory Strategies	Mode, Frequency, Intensity, Duration Dosage of Intervention	Timing of dysphagia rehabilitation from start of cancer treatment	Duration of rehabilitation (Mean +/-Std dev)
Takatsu et al, 2020 [69]	Indirect training: Tongue exercises [72] Shaker exercise [73] Jaw opening [80] Thermal-tactile stimulation [81] Voice therapy [82]	Direct training: Education provision Training while eating jelly: Position adjustment- chin down Effortful swallows, supraglottic swallow, adjusted bolus size supervised. Food and fluid intake increased based on patient progress.	No detail provided on duration, frequency or intensity of indirect or direct training.	Modified water swallow test (MWST) completed by SLT after routine CT on POD 5 or 6. Patients with intermediate or high aspiration risk based on MWST provided with indirect and, if possible, direct rehabilitation.	Not provided

Key: Std Dev = Standard Deviation. SLT = Speech and language therapist. Prehab = Prehabilitation. Rehab = Rehabilitation

Because of the limited data provided in the studies, the heterogeneity across studies, the various times of intervention, the variety of assessment tools and outcomes measured, it was not possible to complete meta-analysis, hence descriptive analyses were conducted.

Primary Outcomes

Extent of oral intake

12/ 26 adults participated in peri-rehabilitation (prior to and following surgery) in one study [69] and scored 7 out of 7 on the Functional Outcomes Assessment Measure of Swallowing (FOAMS) Scale (7 = functional safe and efficient swallowing, 0 = profound swallow impairment) before surgery. Following surgery, the treatment group had non-significant higher FOAMS scores, with mean (+/- standard deviation) scores of 5.6 (+/1.2) and 4.7 (+/-1.4) respectively for the treatment and control groups, with a p value of 0.054. At discharge there was a statistically higher FOAMS score for the treatment group compared to the control group, 6.3 (+/- 0.8) and 5.5 (+/ 1.3), respectively (p = .049).

Respiratory complications

There were no significant differences in aspiration pneumonia rates in the one study which measured this outcome: 25% in the treatment group and 21.4% in the control group (p=0.83) [69]. This study reported a non-significant reduction in rehospitalisation for pneumonia three month post-operatively, with no admissions for the treatment group and three admissions for the control group.

Quality of Life

This was not measured in any of the studies.

Secondary Outcomes

Swallow biomechanics and symptoms on instrumental evaluation

A significant increase in maximum superior excursion of the hyoid bone was observed in the intervention group of one study (n=12/26) following prehabilitation and post-surgical rehabilitation [69] (p=.046). Non-validated measures of assessment were used.

Pharyngeal residue after the initial swallow was measured in the aforementioned study. A subgroup of participants (n=4) who had residue after prehabilitation had decreased pharyngeal residue post-surgery (p=.047).

One study reported on aspiration status in two participants, which improved from mild to normal, and severe to normal, however a validated tool was not used to measure this. [73]

Length of stay in hospital

While one study found that indirect and direct rehabilitation reduced length of stay in hospital from 22 (17-27) days to 19 (15-27.5) days (p=.001) [74], length of stay increased from 32 (+/-12) to 36 (+/- 11) days in another study (p=.022) [69].

Time to return to oral intake

One study found a significantly shorter time to return to oral intake following post-operative dysphagia treatment (n=167) compared to the control group (n=109) (11 v 8 days; p=0.009) [74]. Another study found no significant difference in time to return to oral intake (9.6 v 11 days; p=0.32) [69].

Nutrition

No nutritional measures were mentioned however one study reported no significant difference in change in weight between the dysphagia peri-rehabilitation treatment group and the control group three months after surgery, with 91.4% (+/- 5.8) and 90.6% (+/- 5.5) weight maintenance for the control and treatment groups respectively (p = 0.36) [69].

Patient reported dysphagia outcomes

Patient reported dysphagia outcomes were not reported on across the three studies.

Table 8-3 conveys the outcomes measured in this systematic review.

Table 8-3 Summary of Main Outcomes Table

Authors, year	Respiratory	Oral intake	Penetration/Aspiration	Pharyngeal residue	Biomechanical change to swallow	Nutrition	Time to return to oral intake: Days (average +/- SD)	LOHS after surgery: Days (average $\pm$ SD)	Quality Assessment	Tidier Checklist
Okumura et al, 2016 [69]	AP: CG = 3pts (21.4%) TG = 3pts (25%) p=0.83 Rehospitalisation for pneumonia within 3 months after surgery: CG =3 (21.4%), TG = 0.	FOAMS scores suggest primary mode of intake prior to and following surgery for all participants was oral means of nutrition.	Not reported h/e FOAM scores of 4,5,6 post-surgery and post- rehab suggest compensatory strategies needed, which may indicate risk of pen/asp. Number of participants with these scores not provided.	4 participants had pyriform sinus residue prior to prehabilitation; the volume decreased significantly following prehabilitation, with a p value of 0.047 Between start of rehab post-surgery and post rehab: volume of laryngeal vestibule and PS residue decreased significantly (p values of 0.031 and 0.027,)	From prior to prehab to post prehab, and from post-surgery to post-rehabilitation: the TG's maximum superior excursion of hyoid bone increased significantly during swallowing with p values of 0.03 and 0.046 respectively. No significant difference between the maximum anterior excursion of the hyoid bone or the anteroposterior diameters of the UOS	Not reported. Body weight change 3 months after surgery (% average +/- SD) was CG: 90.6% +/- 5.5 TG: 91.4% +/- 5.8 (p value= 0.36)	CG: 9.6+/-5.3 TG: 11+/- 5.5 (P = 0.32)	CG: 32.4 $\pm$ 12.2 TG: 36.1 $\pm$ 10.7 (p=0.22)	ROBINS-I: Serious Downs & Black: 13 (poor)	9
Tsubosa et al, 2005 [73]	1 pt developed 'severe' AP. Other severities of AP not mentioned.	Data provided not clear.	Data available for 2 participants only: in 1 participant mild aspiration	Limited f/u data available h/e no improvement noted in the 1 participant with	NI	NI	One participant: diet recovered to 'independence' on the 6th day.	25.3 days for 8 participants. 96 days for remaining participant.	ROBINS-I: Critical Downs & Black: 1 (poor)	5

	No post-discharge AP.		improved to normal. In 2 nd participant, severe penetration and aspiration did not improve, but severe silent aspiration improved to normal.	mild vallecular and PS residue			Otherwise, unclear when oral intake recommenced.	No further detail given.		
Takatsu et al, 2020 [69]	NI	NI	NI	NI	NI	NI	Start of oral intake significantly earlier in treatment group TG: 8 days (6-13) CG: 11 days (8-14)	CG: 22 days (17-27) TG: 19 days (15-27.5)	ROBINS-I: Serious Downs & Black: 15 (fair)	10

Key: Pen/Asp = penetration/ aspiration. QOL = Quality of Life. LOHS = Length of hospital Stay. NI = No information. RLNP = Recurrent Laryngeal nerve paralysis. AP = aspiration pneumonia. AL = Anastomotic leak. CG = control group. TG = treatment group. PS = pyriform sinus. UOS = Upper oesophageal sphincter. Pts. = participants. H/e = however. F/u = Follow up. Note: Table included from our systematic review with permission granted.

Since the publication of the aforementioned systematic review, one relevant low quality study has been published by Wu et al (2023) regarding rehabilitation exercises. This randomised controlled trial (RCT) conducted in a hospital in China did not use instrumental evaluation of swallowing [345] and contained three groups: 1) a control group (n=26), 2) a respiratory rehabilitation group (n=26) and 3) a swallowing and respiratory rehabilitation group (n=27)). One day of prehabilitation and 10 days postoperative rehabilitation were completed including active labial and lingual movements, Shaker exercise, vibratory stimulation, pharyngeal muscle ice stimulation, mastication training, sub-chin muscle exercise, vocal cord training, supraglottic swallowing, Masako exercise, and swallowing and breathing coordination in addition to respiratory training (respiratory muscle strength training, coughing, thoracic mobility training, exhalation training etc). A limitation of this study is that swallowing was only measured using patient reported outcomes on the EAT-10. Regarding our Primary Outcomes, there were no statistically significant differences in respiratory outcomes between groups ($p > 0.05$) or in swallow-related QoL (EORTC-QLQ-OES-18) between groups (p-values not provided). Only one Secondary Outcome was measured which found that there were non-significantly better EAT-10 scores for those who underwent swallowing rehabilitation and respiratory training than the other two groups ($p = .68$).

- ii. [What are the key elements of rehabilitation \(delivery, dose, intensity, timing, adverse events and fidelity\) which may inform future research of dysphagia rehabilitation in oesophageal cancer?](#)

Limited information was provided in the three studies of the systematic review regarding delivery, dose, intensity, timing, adverse events and fidelity.

Delivery, dose, intensity of intervention

One study reported that when patients were on the ward, the speech and language therapists and nurses provided initial verbal and written instructions for exercises to be completed five times a day at home and when in hospital. It is not clear if this was entirely patient led, or what adherence

was achieved [69]. One study reported that rehabilitation was performed 'intensively' without additional information provided [73] and the third study provided no detail on delivery, dose or intensity [74].

Timing of intervention

All studies conducted rehabilitation post-surgery however it is unclear precisely when. One study included prehabilitation which commenced approximately 23 +/-9.2 days pre-surgery.

Adverse events in hospital

Adverse events in hospital were not reported on in any of the three studies.

Fidelity of intervention

Fidelity was not reported in any study. Across all three studies, it was not clear which participants were given which specific exercises or if all participants completed all exercises. It is also not clear which participants adhered to instructions or what those instructions were.

Quality Assessment

When interpreting these results, it is important to consider the quality of this evidence. Please see further information at Appendix O.

The quality of these studies were limited by the use of non-validated assessment tools of dysphagia, lack of individualised rehabilitation targets based on pathophysiology observed on instrumental evaluation, not reporting eligibility criteria, lack of reporting of statistical analyses, limited information about the interventions, and small sample sizes. The ROBINS-I tool was utilised and revealed that because of the reasons above, two studies had a serious risk of bias [69, 74] and one study had a critical risk of bias. The case series study is of a particularly weak study design and 'No information' was a common response to the signalling questions meaning that there is insufficient information to make a judgement on the risk of bias. As a result the Downs and Black

checklist was utilised as the questions in this tool are less specific and can be more broadly interpreted. Two studies were of poor quality (scores of 13 and 1) [69, 73] and one was of fair quality (score of 15) [74].

Inadequate analyses were conducted in the case control study and the case series, for example, neither study reported confidence intervals, standard error of means or estimates of random variability.

In the case series, participants were discharged if they did not show overt signs of aspiration and may have had unidentified silent aspiration given a lack of an instrumental assessment. There was no follow up VFS data available for 4/9 participants. There was no definition for 'mild' and 'severe' aspiration, or 'severe' aspiration pneumonia.

Based on the ROBINS-1, the case control study[36] and retrospective case control study[69] were found to have a serious risk of bias in one domain 'Bias of Confounding', and low risk of bias or 'No information' across all other domains. These studies were graded as overall having a 'serious' risk of bias, the lowest domain score. With regard to the case series, two domains scored 'Low'; 'Bias in classification of intervention' and 'Bias due to deviations from intended interventions', however 'Bias of Confounding' was found to be at a 'critical' risk of bias. This study is considered to have an overall rating of 'critical' risk of bias. As per Downs and Black checklist, the retrospective case control study has fair quality [598] with the other two studies having low quality [36, 68]. The TIDieR checklist revealed low scores regarding completeness of reporting of the interventions (checklist score range 5-10). While the retrospective case-control study [69] scored 10/24, the case control study scored 9/24 and the case series scored 5/24.

Please see the Quality Assessment and Tidier Checklist Results in Table 8-3 above.

Regarding the study by Wu et al (2023) that was published after our systematic review, no information was provided on delivery, intensity, timing, adverse events or fidelity. The following information was provided regarding daily dose: balloon blowing 3-4 times a minute for 5 minutes, 30 repetitions of the Shaker, 50 repetitions of chewing a stick on either side of the mouth, holding a ball under the chin for five seconds repeated 15 times, two minutes of vocal cord training (yawn, hum, vowel pronunciation), five Masako exercises, Supraglottic swallow five times. No dose information was provided for the remaining swallowing and respiratory exercises.

8.1.1 Summary of Results

The key result identified from the systematic review and the additional recently published study is that:

There is a low-volume (four studies) of low-quality evidence to support exercise-based dysphagia rehabilitation in adults undergoing surgery for oesophageal cancer.

8.2 Summary of the Three Results Chapters

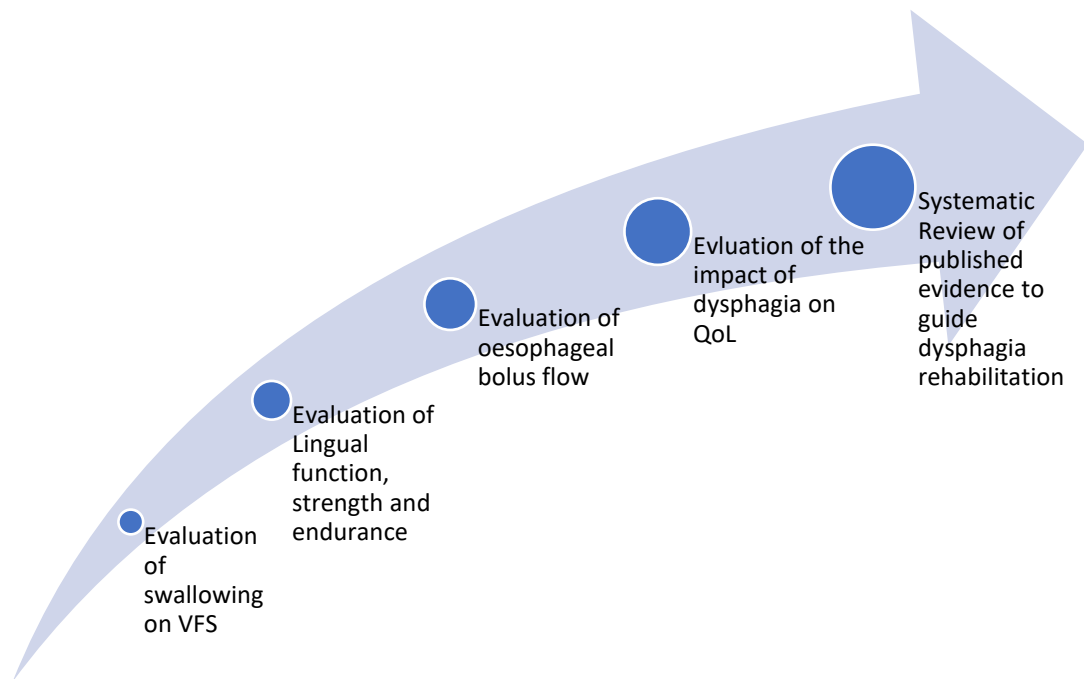


Figure 37 Steps Completed in this Research

Chapters 6, 7 and 8 formed the Methods and Results section. This section commenced by focussing on COD and swallow pathophysiology following oesophageal cancer surgery, including an in-depth exploration of lingual function, strength, and endurance and oesophageal bolus clearance. The impact of dysphagia on QoL was measured quantitatively and qualitatively. Finally, given the presence, severity and impact of dysphagia, Chapter 8 proceeded to investigate whether there was evidence in the literature to guide dysphagia rehabilitation via a systematic review. Figure 37 above conveys the overall research trajectory.

Figure 38 below summarises the statistically significant relationships between key outcomes and clinical/ surgical /dysphagia variables (see red arrows). The key results relating to each research question are summarised below in Figure 39.

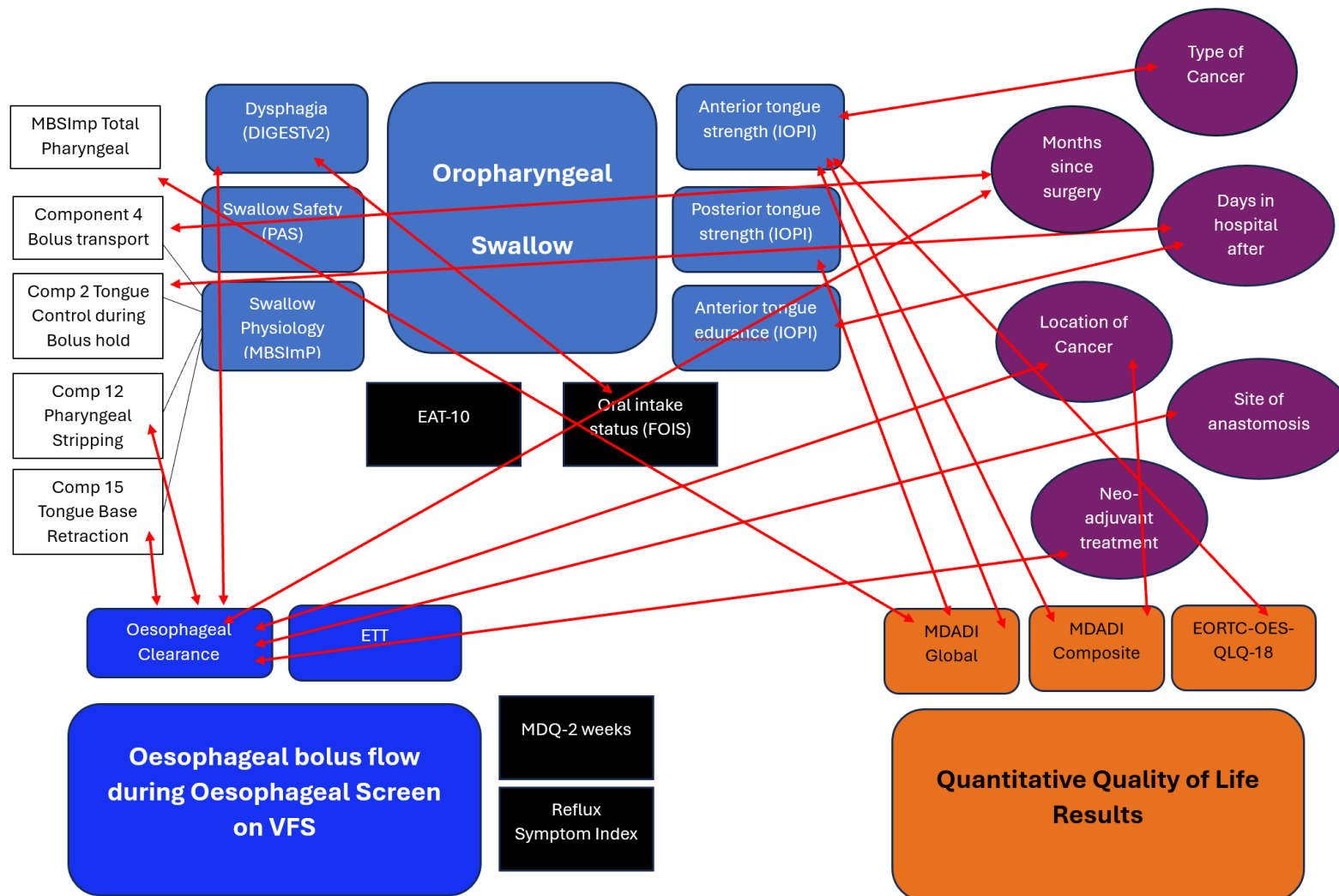


Figure 38 Statistically significant correlations between outcomes and clinical/surgical/dysphagia/QoL variables

Question 1A:
How does COD
present post-
oesophageal cancer
surgery?

- COD present in 35% of participants (DIGESTv2): 79% of whom had mild dysphagia
- Most frequently and severely impaired pathophysiological components on MBSImP: oral residue, swallow initiation, laryngeal elevation, anterior hyoid excursion, pharyngeal residue and oesophageal clearance.
- Aspiration/uncleared penetration occurred in 10% of participants. Only IDDSI level 0 (thin fluid) was aspirated.
- No statistically significant differences in dysphagia outcomes across clinical/surgical groups except for aspiration across surgical approach (only post transhiatal surgery).
- Scoring below 7 on FOIS (avoiding or modifying foods/fluids) is associated with pharyngeal dysphagia on DIGESTv2 (4.05 (95% CI 1.03-16.00), $p = .046$)

Question 1B:
What is the strength,
nature and function of
the tongue in the long-
term post-oesophageal
cancer surgery?

- Significant association between months since surgery and MBSImP Component 4 ($r_s = -.385$, $p = .014$), meaning as months improve, bolus transport/lingual motion scores decrease (improve).
- Significant association between anterior tongue endurance and days in hospital post surgery ($r_s (37) = -.405$, $p = .01$), meaning that the more time in hospital post surgery the lower the long-term anterior tongue endurance was for participants.

Question 1C:
Are there surgical/
treatment related
variables or clinical
tools that can predict
COD post-oesophageal
cancer surgery?

- The odds ratio of dysphagia (DIGESTv2) for participants who scored <7 on FOIS (i.e., abnormal) was 4.05 (95% CI 1.03-16.00), $p = .046$, meaning that participants were four times more likely to have dysphagia on the DIGESTv2 if they were modifying their diet/ avoiding foods.

Question 1D:
What is the nature and extent of long-term oesophageal bolus flow post oesophageal cancer surgery and is it associated with any clinical/surgical/pharyngeal dysphagia variables?

- 80% had impaired oesophageal clearance
- Statistically significant correlations were found between oesophageal clearance and dysphagia on DIGESTv2 ($p = .003$), pharyngeal stripping (MBSImP Component 12)($r_s.345$, $p = .029$), tongue base retraction (MBSImP Component 15) ($.331, p = .037$), location of cancer ($p < .001$), site of anastomosis ($p = .003$)).
- Statistically worse oesophageal clearance for participants who had tumours in the OGJ, followed by the middle oesophagus, and then the lower oesophagus ($\chi^2(2)=8.199$, $p = .017$), and for the thoracic site of anastomosis compared to the cervical site of anastomosis ($\chi^2(1)= 4.339$, $p = .037$).
- Statistically longer OTT of level 0 fluids for the lower oesophagus followed by the the mid oesophagus ($\chi^2(2)=6.043$, $p = .049$), and for those who were 65 years and over compared to those who were below 65 ($\chi^2(2)=4.997$, $p = .025$).
- Statistically longer OTT for tablets for participants post neoadjuvant and post-operative chemotherapy, followed by surgery only, then neo-adjuvant chemotherapy, and finally chemoradiotherapy ($\chi^2(3)= 11.485$, $p = .009$).

Question 1E:
What are the predictors of disrupted oesophageal bolus flow in the long-term post-oesophageal cancer surgery?

- No statistically significant predictors were identified.

Question 2:

What is the impact of COD and other aerodigestive symptoms on QoL min 12 months post-oesophageal cancer surgery?

- Quality of life outcome measures revealed participants were mildly impacted by dysphagia, however more in depth qualitative analysis revealed that when participants experienced suffering, there were four main themes (isolation, fear, altered work capacity, avoidance of social situations).
- QoL results were significantly associated with tongue strength results across all QoL measures, for both anterior tongue strength (MDADI Composite (r_s (37)= .514, $p < .001$) MDADI Global (r_s (37) = .454, $p = .004$), and EORTC-QLQ-OES-18 (r_s (37)= -.377, $p = .018$), and for posterior tongue strength (r_s (37)= .510, $p < .001$) and MDADI Global (r_s (37)=.350, $p = .029$).

Question 3:

Is there evidence to guide oropharyngeal dysphagia rehabilitation in adults with oesophageal cancer?

- There is a low-volume (4 studies) of low-quality evidence to support exercise-based dysphagia rehabilitation in adults undergoing surgery for oesophageal cancer.

Figure 39 Key results relating to each research question

9 Chapter 9 - Discussion

This chapter will discuss the key results from the research carried out in this thesis, potential causes of dysphagia in participants from this research, potential future directions from a clinical and research prospective, limitations of this research, and an overall conclusion.

9.0.1 Oropharyngeal phase of swallowing

Oesophageal cancer survivors are affected by long-term oropharyngeal dysphagia (COD), with 35% of participants in our study having COD and 10% presenting with uncleared laryngeal penetration/ aspiration a minimum of 12 months (mean 51 months) post curative-intent oesophageal cancer surgery. Regarding swallow pathophysiology, 73% of participants had impaired oral components, 100% had impaired pharyngeal components, and 80% presented with impaired oesophageal clearance.

The COD that was detected was mostly mild in severity, was subjectively present in 54% of participants (EAT-10), and on instrumental evaluation was present in 35% of participants when evaluated using the DIGESTv2, with all participants presenting with at least one impaired component of swallowing. The QoL results revealed that, even though the dysphagia was mostly mild and that QoL was mostly mildly impacted when analysed using quantitate analysis, the qualitative results exposed significantly diminished QoL for some people who do continue to experience chronic aerodigestive symptoms.

These data may provide reference data for these cohorts and guide considerations for assessment and management of oesophageal cancer survivors as current international clinical practice guidelines do not currently recommend referrals to swallow specialists for assessment [429, 599].

Eating patterns continue to be impacted with 43% of participants modifying or avoiding certain food consistencies because of dysphagia and other aerodigestive concerns. The avoidance or modification of foods (FOIS scores below 7) was found to be associated with pharyngeal dysphagia (DIGESTv2), and had a 4.05 times higher chance of having dysphagia compared to those who did not restrict or avoid food consistencies (score of 7 on FOIS) (OR 4.05, 95% CI 1.03 – 16.00). This information suggests that even if a patient is not reporting symptoms of dysphagia, their FOIS score may suggest that they would be appropriate for a swallow assessment referral. It is important for the multi-disciplinary team (MDT) to be educated on this.

The following impaired components were found in over half of our participants: oral residue, delayed swallow initiation, laryngeal elevation, anterior hyoid excursion, pharyngeal stripping, UOS opening, tongue base retraction, pharyngeal residue, and oesophageal clearance. The most comparable results between our study and the only other study which evaluated chronic dysphagia using FEES or VFS were delayed swallow initiation and pharyngeal residue. The results for all comparable outcomes are listed in Table 9-1 below:

Table 9-1 Comparable outcomes across results from our study and Yuen et al's study (2019)

	Our study (n=40)	Yuen et al, 2019 (n=29)	Potential reason for differences across these studies
Premature spillage/ Reduced tongue control during bolus hold	33%	7%	Different results; unclear why. Mean age in Yuen et al's study is 65.2 and our study 66.6 so this is unlikely to be a factor. Time since surgery was also similar at mean 4.3 years in Yuen et al's study and 4.25 years in ours. Sarcopenia/nutrition were not measured in Yuen et al's study.
Delayed swallow initiation	100%	90%	Similar finding.
Impaired laryngeal elevation	70%	100%	28% of participants in Yuen et al's study had a 3-field lymphadenectomy whereas none in our study did which may potentially have caused nerve damage during cervical node dissection.
Aspiration	5%	28%	Worse aspiration/ penetration in Yuen et al's study may be because of impaired laryngeal elevation detected in more participants above, or
Penetration	15%	45%	

			because participants were accepted in their study from 6 months post-surgery. They also found that a shorter time since oesophagectomy was significantly correlated with worse PAS scores. In addition, their study included 3x trials of each consistency on VFS compared to only x2 in our study which may have been more sensitive in detecting aspiration. Finally, Yuen et al's study had 17% participants with upper thoracic cancer and 79% had cervical anastomosis compared to 0% and 48% in ours, respectively, which may have potentially impacted upon pharyngeal nerve and muscle function.
Pharyngeal residue	90%	45% vallecular, 93% pyriform sinuses	Similar: as our score encompasses entire pharynx
Dysphagia	35% on DIGESTv2: 27% mild, 3% moderate, 5% severe	Mild to moderate on Videofluoroscopic dysphagia scale (VDS)	Similar findings.

Many of the frequently impaired components in our study were also commonly present in the studies referred to in Chapter 2's literature review which evaluated dysphagia in the acute period whereas none were mentioned in the literature relating to the sub-acute phase. Table 9-2 below lists the key outcomes in our study and the acute studies which also reported these findings:

Table 9-2 Key outcomes from this study and the references of studies which reported similar outcomes in the acute phase

	Our study (n=40)	Studies reporting similar impaired components in post-operative phase
Lip closure	33%	
Tongue control during bolus hold	33%	[57]
Bolus preparation	5%	
Bolus transport	18%	

Oral residue	100%	
Delayed swallow initiation	100%	
Soft palate elevation	13%	
Laryngeal elevation	70%	[36, 60, 227, 229]
Anterior hyoid excursion	80%	[71, 91, 251]
Epiglottic movement	33%	[71, 91, 229] [256]
Laryngeal vestibule closure	35%	[60, 71, 252],
Pharyngeal stripping	55%	
Pharyngeal contraction	15%	[227, 250, 252]
UOS opening	58%	
Tongue base retraction	65%	[250] [256]
Pharyngeal residue	90%	[93] [57, 91, 93, 227, 254, 256],
Aspiration	5%	[57, 60, 61, 71, 72, 74, 91, 249, 252, 254]
Penetration	15%	[68] [254]
Dysphagia	35%	75% [150], 90% [252], and 90% [73]

More in-depth exploration of lingual function, strength, and endurance abilities revealed mean results of mean maximum isometric posterior tongue strength, anterior tongue strength and anterior endurance of 40 kPa, 42 kPa and 23 seconds. A clinical cut-off that has been recommended to distinguish between normal – versus – abnormal anterior and posterior tongue strength is 40kPa in Canadian adults [600] and 33kPa in Chinese adults [601] therefore tongue strength in our study is considered normal. The mean maximum isometric tongue pressure in the anterior and posterior positions were 55.95kPa and 53.23kPa in Chinese adults[601], 44.27kPa and 41.07kPa in Belgian Caucasian adults [602] and 57.5kPa and 56.5kPa for men and women anteriorly, and 52.0kPa and 53.6kPa for men and women posteriorly, in a study from the U.S. [450]. Typically the maximum isometric anterior tongue strength in healthy adults has a higher peak strength than maximum isometric tongue posterior [448, 601, 602] which is in line with findings from this study.

The mean endurance for the anterior tongue was 13.86 seconds in Chinese adults [601], 22.39 seconds in Belgian Caucasian adults [602] and 17/15.3 seconds in middle-aged men/women from Korea and 15.7/17.9 seconds in older men/women from Korea [448], demonstrating that mean anterior tongue endurance for this study was within normal limits.

In our study, there was a trend of decreased maximum isometric tongue pressure in both positions and anterior tongue endurance with older age, which is largely in line with existing research [448, 601], however this was not statistically significant when comparing those under 65 years of age with those who were 65 or over.

In a retrospective observational study by Kokima et al (2022) decreased tongue pressure was found to be a predictor of aspiration acutely post-oesophagectomy and was associated with pneumonia [255]. This may potentially have been due to muscle atrophy from disuse or sarcopenia. The anterior maximum isometric pressure results from their study, 34.2+/- 7.3kPa, was lower than our results suggesting that patients' tongue strength improves with time, which is in line with our functional results that suggested that bolus transport tended to improve as months passed since surgery. However, no significant correlation was found between tongue strength and bolus transport in our study. Despite this, lingual rehabilitation earlier in the survivorship journey may speed up this effect.

Analyses revealed that the more time a patient spent in hospital after surgery was moderately associated with tongue endurance a minimum of 12 months after surgery. Further research would be beneficial to investigate the efficacy of lingual peri-rehabilitation in this population in a longitudinal study. No significant association was found between tongue results and sarcopenia, however, a more robust assessment of sarcopenia is warranted to determine whether there may be a link between sarcopenia and reduced lingual strength in the acute and sub-acute phases.

Based on the findings from this current study, future studies could be designed to evaluate the efficacy of exercises specifically targeting the most frequently impaired pathophysiological

impairments of the oropharyngeal swallow such as laryngeal elevation, hyoid movement, swallow initiation, oral and pharyngeal residue.

9.0.2 Oesophageal phase of swallowing

In addition to a comprehensive evaluation of oropharyngeal swallowing, this research has included analysis of components of the oesophageal phase of swallowing which can be observed during the SLT screen of the oesophagus on videofluoroscopy. Understanding normal oesophageal bolus transport patterns and oesophageal transit times is important for adequate differential diagnosis of conditions such as dysphagia, gastroesophageal reflux, oesophagitis, and achalasia [603]. Oesophageal stasis has been shown to cause candida oesophagitis and mucosa changes such as ulcers [604, 605]. If the previously mentioned oesophageal transition zone is not functioning adequately, it may result in bolus hold up at this level, or may cause proximal retrograde flow of the bolus [137, 606, 607].

In our study, 20% of participants had complete oesophageal clearance with no/trace coating of the oesophagus remaining after secondary peristalsis. On at least one consistency 30% had oesophageal retention, 43% had retrograde flow of the bolus within the oesophagus, 5% had retrograde flow from the oesophagus into the pharynx and 2.5% had no/minimal clearance of the bolus from the oesophagus.

Oesophageal screen results were similar to those found in the study published by Yuen et al (2019). (See Table 9-3). Yuen et al measured 'significant hold up in the oesophagus' but it was not clear how this was measured or defined and therefore for comparison purposes it has been assumed to be similar to our measure of 'minimal to no oesophageal clearance'. Both studies found that small numbers (3-7%) of participants had significant hold-up of IDDSI level 0 thin fluids and had retrograde flow of the bolus into the pharynx. Yuen's study had significant hold-up of IDDSI level 4 pureed consistency in 55% (n=16) of participants whereas our study only had no/minimal oesophageal clearance in 3% (n=1). However, our study found oesophageal retention

of IDSSI level 4 in 52% (n=27) participants which perhaps may be a more comparable outcome. Further research is needed to make sense of this discrepancy with clearer definitions regarding the level of 'hold up' and 'oesophageal clearance'.

Table 9-3 Comparable oesophageal screen ratings from our study and Yuen et al (2019)

	My study (n=40)	Yuen et al, 2019 [70] (n=29)	Potential reason for differences across these studies
Minimal to no oesophageal clearance/ Significant hold-up of IDSSI Level 0 Fluid	3% (n=1)	7% (n=2)	Similar finding
Minimal to no oesophageal clearance/ Significant hold-up Level 4 Fluid	3% (n=1)	55% (n=16)	As explained above, this discrepancy is likely due to differing definitions of 'hold up' and 'oesophageal clearance'.
Backflow into the pharynx	5% (n=2)	7% (n=2)	Similar finding

There are conflicting results in the literature regarding normative data for oesophageal clearance in healthy adults [143, 476, 608]. In a study by Jou et al (2009), oesophageal stasis (greater than coating) occurred in at least one semi-solid barium swallow in 63% of participants and at least one liquid swallow in 16% of participants. Oesophageal stasis (filling the lumen) occurred in at least one semi-solid swallow for 37% of participants and on at least one liquid swallow of 15% of healthy participants [143]. In another study, 93% of healthy adults had at least 80% complete liquid transit, and at least 70% had complete viscous bolus transit [609]. In our study, retention to some extent was present in 53% (n=21) of participants with thin fluids.

Reflux, any upward movement of the bolus in the oesophagus (e.g. thoracic oesophagus to aortic oesophagus), has been observed in at least one swallow in 60% (15/25) of participants, and was more frequent with liquid than semisolid trials in healthy older adults [143]. On manometry, 73% (61/83) of healthy adults had 'normal bolus transit', 8.4% (7/83 swallows) had stasis, 16.9% (14/83 swallows) had retrograde flow of liquid bolus [610]. In our study retrograde flow was more common with IDDSI Level 4 puree than thin liquid. DiMarino et al (2002) state that thin liquid should be fully cleared through the oesophagus with the first swallow and food is usually completely transferred via secondary peristalsis [611].

OTT is usually completed using scintigraphic and manometric methods. OTT, the time it takes the bolus to pass from the UOS to beyond the OGJ is reportedly approximately 4-8 seconds for solid and semi-solid food and 1-2 seconds for thin fluids in healthy people [611]. However this differs significantly from results found on videofluoroscopy by Miles and her team in 2016 where mean OTT of 20 ml fluid was 10.7 seconds, paste was 28.6 seconds, and tablets was 25.3 seconds. It is expected that OTT differs in patients with various oesophageal diseases [603] (e.g. GORD [468], achalasia [464], connective tissue disorders [612] and oesophageal cancer). Our study found that the mean OTT for 20ml thin fluids was 26.5 seconds and for 5ml pureed consistency was 38.1 seconds which is remarkably higher than previous studies.

As a result of these differences across healthy adults, it is challenging to determine what is normal versus abnormal. More research investigating normative data is warranted.

Potential reasons for the discrepancy in oesophageal bolus flow/clearance and OTT results across studies could be due to the density of barium used [613], a risk which our study aimed to eliminate by using standardised recipes, the differing mean ages across studies (e.g. mean of 38 years [609] and minimum of 45 years [143]), and the different definitions and protocols for example the varying times permitted between trials (e.g. 10 seconds/ not provided [143, 609]).

9.0.3 Quality of life

Quantitative analysis of results revealed that QoL was mildly impacted by oropharyngeal and oesophageal dysphagia symptoms. Reduced maximum isometric anterior and posterior tongue strength were consistently associated with reduced QoL across the three swallow-related QoL scales. This correlation between tongue strength and QoL warrants further investigation. Given that tongue strength results in our study appear to be on the weaker end of normal [600, 601], and that an important component of tongue function, oral residue, was impaired in a high number of our participants, this may be an area that should be targeted in rehabilitation research.

Location of cancer was found to be associated with QoL and given that location of cancer is associated with oesophageal clearance and oesophageal transit time, this warrants further investigation.

Interestingly, there was also a weak association between improved pharyngeal swallowing on MBSImP Total Pharyngeal Scores and improved QoL highlighting the impact of dysphagia on QoL.

To further explore the impact of dysphagia following oesophageal cancer surgery, a qualitative study was conducted. A key theme detected in this research was the inability to return to work at a similar capacity as before oesophageal cancer because of ongoing aerodigestive issues. This has previously been reflected in other more broad research which found that cancer survivors find it difficult to work in the same capacity as before [614] having a significantly higher likelihood of being unemployed or retiring early with 36.5% of cancer survivors never returning to work [417, 615, 616]. Patients have previously spoken about how a history of cancer can impact earning potential [422]. It is therefore important for employers to offer altered work schedules and environments to enable cancer survivors to work [422].

It appears as though there is an inconsistency between the severity of QoL results from our quantitative and qualitative analyses. Perhaps this is due to the fact that those who are severe are struggling significantly and it was their stories that were most represented in the qualitative

research. Perhaps the severe outcomes retrieved from qualitative analysis relates to the aerodigestive symptoms other than dysphagia and it is therefore recommended that further research detangles the dysphagia symptoms from the remaining aerodigestive symptoms given the difficulty that patients reportedly have in doing so. It is also possible that the positive responses on questionnaires from some participants were related to dispositional optimism, a topic that has been explored recently in this population [617], where it was revealed that higher dispositional optimism, when a personality is more predisposed to positive expectations for the future, is associated with lower all-cause mortality after oesophageal cancer surgery. It has also been shown to be associated with reduced psychological distress up to two years after oesophagectomy and it has been hypothesised that these people may have superior coping skills and social supports. This suggests that survivorship multi-disciplinary teams in the community setting, which includes psychology, might be beneficial to help those with worse psychological distress [618, 619].

9.0.4 Exercise-based dysphagia rehabilitation for adults with oesophageal cancer

The four studies identified revealed a low quantity of low quality evidence to support the use of exercise-based dysphagia rehabilitation with adults who have/had oesophageal cancer. A small number of participants had improved maximum superior hyoid excursion, reduced aspiration, improved pharyngeal residue, and improved FOAMS scores at discharge following peri-rehabilitation. The treatment group in one study had non-significantly better swallow efficiency after surgery than the control group suggesting that prehabilitation may be somewhat protective of a deterioration to swallow function[69]. Another study found better self-reported dysphagia scores (EAT-10) for those who underwent swallowing rehabilitation and respiratory training [345]. Inadequate information was provided across the studies regarding key elements of rehabilitation that could guide future research and clinical practice such as delivery, dose, intensity, timing, adverse events and fidelity. No studies mentioned the long-term efficacy of dysphagia rehabilitation in the community after discharge from the acute setting. The quality of this body of

work is low because of the use of non-validated assessment tools of dysphagia, lack of instrumental assessments, not individualising therapy based on outcomes, poor reporting of methods and statistical analyses, weak study designs and small sample sizes.

9.1 Potential causes of dysphagia following oesophageal cancer surgery

As explored in Chapter 2, surgery for oesophageal cancer is associated with complications in between 50-60% of patients [51, 52]. Post-surgical complications that may contribute to oropharyngeal swallowing deficits may be caused by chemotherapy [209], radiotherapy inducing oesophageal inflammation, ulcers, fibrosis, strictures or stenosis [146, 206, 270], anastomotic scarring [36], anastomotic leaks [119], endotracheal tube trauma, adhesion of the gastric tube to the trachea [251, 620], altered anatomy (i.e. gastric pull-up and reduced size of neo-oesophagus) impacting upon oesophageal peristalsis and inducing reflux [117, 119], mechanical denervation and inflammation of key nerve pathways involved in swallowing such as the vagus nerve, ansa cervicalis or the pharyngeal plexus [206, 251, 620-626], age [256, 298], sarcopenia, and cachexia [256]. In addition, it has been hypothesised that scarring of the sternohyoid and sternothyroid muscles might antagonistically work against laryngeal elevation [60]. Potential arytenoid and vocal fold oedema from endotracheal tube trauma [61] may impact on swallow safety. An operation time of more than five hours and vocal cord paralysis were identified as risk factors for subglottic aspiration with a high probability of occurrence (42.3%) if either risk factor was present [61]. It has been suggested that the mechanisms most likely to impact upon pharyngeal swallowing in this population when they are impaired are insufficient vocal fold closure and impaired laryngeal sensation [627]. Finally, excessive surgical stress in the cervicothoracic region potentially could impact upon laryngeal elevation and may occur due to 3FLD as Yasuda et al (2013) found that participants experienced significantly higher laryngeal penetration/aspiration in 70% of the 3FLD group (n=10) compared to 20% of the 2FLD group (n=10) [60].

9.2 Potential causes of dysphagia in this thesis' research participants

This section will discuss some of the potential causes of COD specific to our research participants. It is worth noting that this research focusses only on survivors of oesophageal cancer surgery, which was completed with curative intent, who are a minimum of 12 years post treatment. It does not include people who may have received local modality treatments for superficial cancers or those receiving palliative treatment. Recruitment took place from the National Oesophageal Cancer Centre of Ireland which provides a follow up outpatient MDT service to patients, for example it may result in patients receiving multiple oesophageal dilatations when needed which can continue for years post treatment therefore it is possible that the overall severity of dysphagia was reduced as a result.

9.2.1 Oropharyngeal Phase

The factors causing COD following oesophageal cancer surgery are many. The direct cause of dysphagia in our study remains unclear however the following section will consider the key potential causes based on our results.

Clinical/surgical factors

Regarding site of anastomosis, there were no significant differences in dysphagia, aspiration or QoL outcomes depending on the site of anastomosis (cervical -v- thoracic). Interestingly however, there was a significant difference in aspiration rates across surgical approach with aspiration only present in transhiatal participants. The cause of this is unknown given that a transhiatal approach has the same site of anastomosis as the 3-stage approach while being less invasive, given it excludes a thoracotomy. Nonetheless only two participants aspirated so further research would need to explore this association further. Interestingly, although non-significant, the transhiatal group also scored worse than 2- and 3-stage cohorts for dysphagia observed on VFS, dysphagia self-reported by participants, and functional oral intake scores. Perhaps the inferior performance

is due to the fact that patients who are respiratory compromised may be selected for a transhiatal resection and therefore their respiratory status may have contributed to these observations [628]. Age may also be a contributing factor given that the transhiatal group were significantly older than the other groups, however, no significant correlation was identified across outcomes for age (greater than or less than 65) through statistical analysis. There were significant differences between the surgical approach groups for cancer type, cancer location and neo-adjuvant treatments so these variables may also be relevant. Months since surgery was longest for the transhiatal participants so this is not considered a likely cause.

Our study did not find a significant association between dysphagia and RLNP which is similar to one existing study [150] but contrary to another [256]. Having said that, only one participant in our study had RLNP so a larger sample is required to further explore this topic. Table 2-3 of the literature review demonstrated the variation of RLNP presence across studies and one potential reason for this is the discrepancy in how RLNP is measured and reported across research groups [629].

All participants who aspirated / penetrated (n=7) did so on IDDSI level 0 fluids, and all had delayed swallow initiation suggesting that airway protection may be compromised by a timing and/or coordination issue. A timing or coordination issue may be due to reduced sensation following nerve/surgical damage or ageing, although no statistically significant differences were detected. All participants who aspirated had reduced tongue base to pharyngeal wall retraction and pharyngeal residue, which could potentially indicate overall reduced base of tongue strength, reduced pharyngeal stripping (as observed in 4/7 on VFS), or could be secondary to inadequate timing or duration of UOS opening (as detected in 5/7 on VFS). Interestingly, high residue volumes were also evident in the valleculae (45%) and pyriform sinuses (93%) in the long-term study by Yuen et al (2019). Thus, pharyngeal high resolution manometry analysis would be beneficial to better understand the exact location of breakdown.

In Langmore et al's observational study in 1998 which included 189 older adults across various settings, neither dysphagia nor the aspiration of food or fluids were deemed to be high predictors of developing aspiration pneumonia. Rather, predictive variables included oral care, decayed teeth, tube feeding, dependence for feeding, number of medications, smoking, and multiple co-morbidities therefore the small percentage of penetrators and aspirators in this study is not of high concern.

Regarding lingual results, there were no statistically significant correlations between tongue strength/ endurance and oral residue. The other lingual parameters, tongue control during bolus hold and bolus transport/ lingual motion were mostly functioning normally. The cause of a collection of oral residue (i.e. more than trace) occurring in a high number of participants (27/40) is therefore unclear. Perhaps there is reduced sensation in the oral cavity for an unknown reason, or perhaps if the person is subconsciously or consciously aware of upcoming difficulties in a later phase of swallowing, there may be altered behaviour in the oral phase. Only 4 of the 27 participants with oral residue did not also have impaired oesophageal clearance so further research investigating an association between these variables and a potential cause is warranted.

Sarcopenia was not detected in participants in our study using a screen, the SARC-F, however a more robust measure of assessment is required such as CT. Nonetheless, mastication was intact in all but two participants which may suggest that geniohyoid muscle function is not impaired at this timepoint, and geniohyoid muscle size has previously been found to be correlated with both sarcopenia and dysphagia [259].

Combined inter-relationship

As briefly touched on previously, the inter-relationship between the oesophagus and pharynx must not be overlooked. Allen et al (2012), identified that 63% of patients admitted to an ENT clinic with dysphagia had oesophageal abnormalities and that half of those had symptoms of oropharyngeal dysphagia as a result [387]. A wealth of research has proven that there is an

intricate two-way connection between the oesophagus and the oropharynx [147, 630-632]. In particular, studies have demonstrated the impact of oesophageal conditions such as oesophageal obstructions, GORD and achalasia on the oropharyngeal swallow such as delayed initiation of the pharyngeal swallow, pharyngeal residue, and increased number of swallows per bolus [440, 528, 633-636], with researchers hypothesising that the oesophagus has the ability to modulate the motor pattern of the oropharyngeal swallow [227].

UOS functioning has been found to be impaired in patients with oesophageal issues. One study found that UOS resting pressure can be hypotonic/impaired in individuals with GORD [283, 637], and even though achalasia is believed to affect smooth muscle, the UOS residual pressure has been found to be hypertonic in people with achalasia, which may potentially be a secondary compensatory attempt to protect against aspiration of refluxed material [638]. A hypertonic UOS may result in diminished UOS opening and subsequent increased residue in the pyriform sinuses post-swallow, which was found in 90% of participants in our study. A study found that participants with reduced relaxation of the UOS during swallowing tend to do an effortful swallow, most likely as a compensatory behaviour [638]. In that study, velopharyngeal contraction was short, premature, and hypertonic along with hypertonic epiglottic deflection. It is therefore plausible that impaired oesophageal clearance in 80% of participants in our study may impact upon their UOS function and even on their pharyngeal contraction during swallowing in a compensatory attempt to minimise the risk of retrograde flow into the pharynx and laryngeal vestibule, and to push the bolus into the neo-oesophagus, respectively.

It is not inconceivable that a UOS with restricted relaxation may even tether the hyoid impacting upon overall swallow safety and efficiency, which may explain reduced laryngeal elevation in 70% of participants, and reduced epiglottic deflection in 80% of participants. Research exploring UOS function using pharyngeal high resolution manometry would be beneficial to investigate this further.

Interestingly, Martin et al (2001) [227], reported how oesophageal cancer participants in their study presenting with minimal obstructions in the oesophagus, due to very small tumours, still presented with pharyngeal dysphagia on VFS prior to receiving any cancer treatment. Hence the authors conjectured that there are 'normal oesophagogastric reflexive mechanisms responding to cancer related oesophageal alterations, which in turn modulate the oropharynx'. Given how other studies have shown that reflex mechanisms which originate in the oesophagus modulate oropharyngeal and UOS function [639, 640], it is possible that abnormal neural pathways of the oesophagus in patients with oesophageal cancer may, therefore, potentially modulate the neural movements within the pharynx and the oesophagus. This theory is strengthened by the fact that research on human cadavers has shown that there are continuous longitudinal muscle fibres between the upper oesophagus and the pharynx [641]. When using balloon distension oesophageal manometry, Koh et al (2004) [248], also demonstrated the presence of hypertensive peristalsis (mean pressures above 100mmHg in response to balloon dilatation) in the cervical oesophagus in 80% of clinically symptomatic oesophageal cancer patients [248] which may also theoretically impact upon the UOS and pharynx. Perhaps alterations in the oral phase may even be explained by this theory given related findings in other studies such as in Triadafilopoulos et al.'s study which found disturbed lingual peristalsis in 62% of patients with oesophageal motor dysfunction and nonobstructive dysphagia [642].

9.2.2 Oesophageal phase

In our study, there is an association between oesophageal clearance and pharyngeal dysphagia, and oesophageal clearance and pharyngeal stripping. This is in line with other research which has found oropharyngeal swallow pathophysiology on instrumental assessment (FEES, HRM and VFS) in adults with oesophageal issues such as achalasia and GORD [635, 643]. It is plausible that perhaps the removal of the oesophagus impacts peristaltic wave motions in the oesophagus and peristaltic waves in the pharynx. There is also an association between tongue base retraction and oesophageal clearance so perhaps inadequate 'thrust' from the pharynx impacts the ability to

clear the oesophagus [467, 468]. This may be further compounded by the previously discussed hypothetical 'reduced muscle strength' of the oesophagus in a shorter remnant [119] and warrants further investigation.

Location of cancer is significantly associated with oesophageal clearance and when a sub-group analysis was conducted, it was identified that the OGJ location had the worst oesophageal clearance of the bolus. It is not clear why this might be the case, however, theoretically it is conceivable that if reduced oesophageal peristalsis exists following surgery, then a longer oesophagus would be less effective at clearing the bolus than a shorter oesophagus because the bolus has to travel further before successfully exiting the oesophagus, and typically a longer oesophageal remnant exists following OG junction cancer compared to more proximal cancers. Similarly the site of anastomosis, specifically the thoracic anastomosis, has worse oesophageal clearance/ more reflux when compared to a cervical anastomosis, which relates to other research that found more reflux following thoracic anastomosis compared to cervical anastomosis [644].

There is an association between oesophageal clearance improving as months go by meaning that participants experience less issues with oesophageal retention and retrograde flow of bolus the more time that passes after surgery, which can give hope to patients experiencing debilitating symptoms.

Miles et al (2016) also found a statistically significant difference in OTT of 20ml fluid for age which was not replicated in another study [645], however our study did find a statistically significant difference in OTT of 20ml thin fluids for age, with OTT being longer for participants who were 65 years and older compared to those who were younger than 65 years. Unsurprisingly, OTT was significantly longer depending on the location of the cancer, specifically for the OGJ location. This may simply be because the distance to travel is longer if a more distal part of the oesophagus was removed. This is also in line with the theory suggested previously that a longer oesophagus with reduced peristalsis is less effective at clearing the bolus than a shorter oesophagus with reduced

peristalsis given there is a longer distance for the bolus to travel before it is fully cleared. The mean OTTs of tablets in our study was only 2.99 seconds and there was a statistically significant difference in this score depending on the type of neo-adjuvant treatment received with higher duration detected for those who received neo-adjuvant and post-operative chemotherapy.

Further research investigating the intricate inter-relationship between the neo-oesophagus and pharyngeal swallow in this population is warranted to better understand the impact of the reduced or absent oesophagus on pharyngeal swallow function.

9.3 Additional Potential Factors impacting oral intake and appetite

Consequences of a swallowing difficulty in oesophageal cancer include malnutrition, weight loss and tube-feeding reliance [168-171], with significantly impaired QoL reported up to 15 years post-surgery [246]. As we approach the conclusion of this research, it is worth remembering that there are factors other than dysphagia which can also lead to these aforementioned consequences. These factors, some of these which were previously mentioned in the Literature Review in Chapter 2, can significantly impact upon oral intake such as altered taste [114], decreased appetite [111, 112], early satiety [120], dumping syndrome [116], pyloric dysfunction [117], altered gut bacteria [646, 647], nausea and vomiting [114], refeeding syndrome [118] malabsorption [123], panic and/or anxiety at mealtimes [648, 649], avoidance of social situations involving food or drink [648] [650], and loss of enjoyment of eating and drinking [649]. These are outlined in Figure 40.

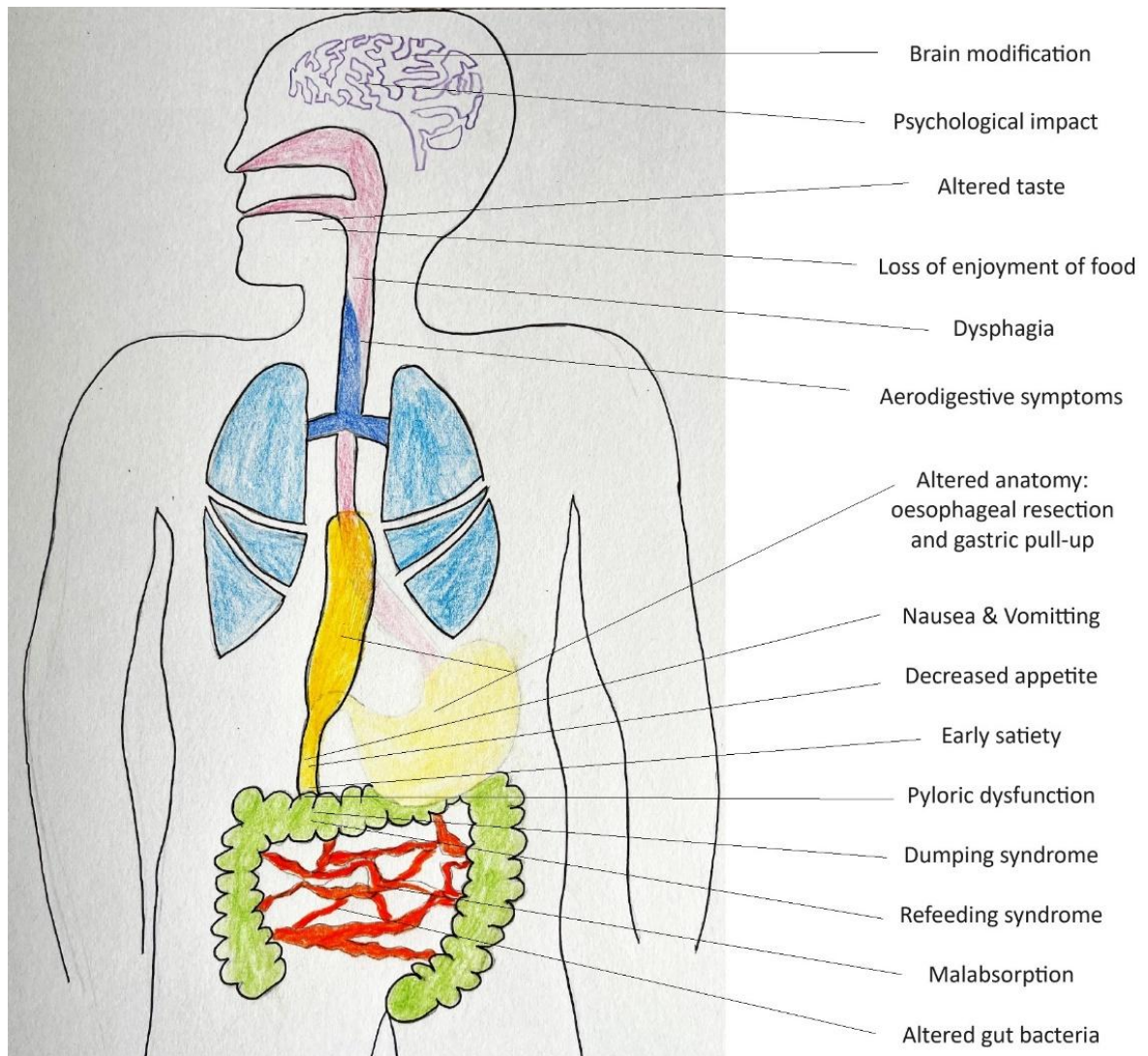


Figure 40 Multiple factors which may be impacting upon oral intake

9.4 Future Direction

9.4.1 Future Direction of Research

Future research could evaluate the efficacy of dysphagia rehabilitation targeting the most severely and frequently impaired pathophysiological components of oropharyngeal swallowing identified in this study which were oral residue, pharyngeal residue, tongue base retraction, pharyngeal stripping, hyoid excursion, laryngeal elevation, UOS opening, swallow initiation and oesophageal clearance. As discussed above, the potential causes are numerous. Figure 41 displays the complex relationship between potential causes and deficits, and importantly, the deficit type, which would guide the form of swallow rehabilitation.

Given a shift in understanding within the dysphagia community in the last decade or so, it is now better understood that weakness-induced dysphagia is usually most likely to occur in cases of lower motor neuron impairment, sarcopenia and occasionally upper motor neuron impairment, for which strengthening exercises may be most appropriate [441]. Otherwise, it appears as though other approaches such as a focus on swallow skill training may be a more appropriate direction for improving dysphagia. In order to treat an area of impairment, it is always important to consider the biomechanical breakdown and the true cause of this [441], and to be aware of contraindications of selected treatments [441].

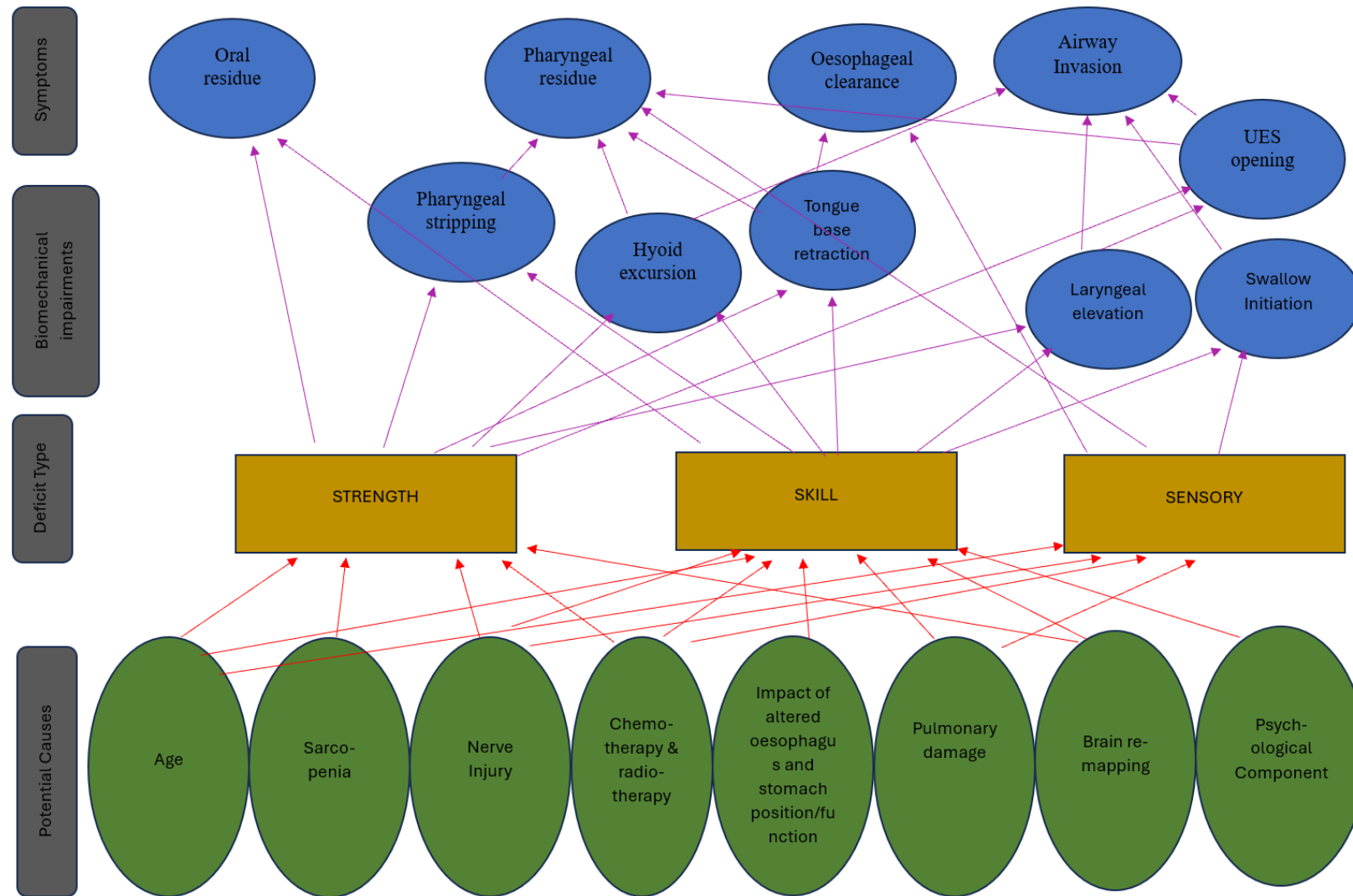


Figure 41 Most severely and frequently impaired symptoms and biomechanical impairments, their potential causes and deficit type

A proposal for the next step of research could be a three arm longitudinal randomised control trial which includes individualised peri-operative rehabilitation (prehabilitation and post surgical-rehabilitation) targeting the most likely areas of impairment which are also the most frequently and severely impaired components in COD. These are also the impairments which have been mentioned in the acute literature (as discussed previously in Chapter 2) except for penetration and aspiration which occurred less frequently in the long-term. Instrumental evaluation would include VFS, FEES and HRM, as FEES would provide visualisation of vocal fold movement during non-swallow related tasks and HRM would provide quantitative information relating to intraluminal pharyngeal pressures during swallowing [651].

It is suggested that this future study would measure sarcopenia using CT prior to surgery and post-operatively. Should sarcopenia be present, strength training focussing on the following would be beneficial in group 1:

- Tongue strength training may be warranted given findings in other research, including systematic reviews, which found that tongue strength correlates with sarcopenia [452], and that peri-operative rehabilitation of swallowing including tongue strengthening in oesophageal cancer may improve swallowing [297], and may reduce the risk of aspiration [255]. Tongue pressure significantly decreases in cancer patients undergoing treatment from the day before surgery to post operative day 4 when they are receiving no oral intake (e.g. upper GI cancers) compared to cancer patients who receive oral intake (e.g. genitourinary and lung cancer).
- Improved geniohyoid strength to assist with hyolaryngeal excursion can be targeted using jaw opening exercises, which is important as a systematic review with meta-analysis has shown an association between geniohyoid cross-sectional area and postoperative pneumonia and dysphagia after oesophagectomy [297]. Geniohyoid cross-sectional area has been shown to be associated with tongue pressure and jaw opening strength [652].

- Improved base of tongue to posterior pharyngeal wall contraction to start the propulsion of the bolus that will travel through the oesophagus could be targeted aiming to reduce pharyngeal residue [653] and improve oesophageal clearance [654].
- Improved anterior and superior hyolaryngeal movement could be targeted to improve epiglottic deflection, minimising vallecular residue, improving airway protection, and improving UOS opening [655].
- Improved pharyngeal contraction and stripping may be an appropriate focus to reduce pharyngeal residue. The Effortful Swallow has been found to have mixed efficacy in the literature, for example, increased pharyngeal pressures and decreased UOS pressure (i.e. improve UOS opening) were identified in healthy older adults thereby reducing residue [656, 657] yet worse pyriform sinus residue and less pharyngeal shortening were found in another study with healthy older adults [658]. A systematic review compared Effortful Swallow results to normal swallows and found further contradictions in the literature for example it found reduced anterior hyoid excursion and increased hyoid excursion, reduced laryngeal elevation and higher hyoid elevation, shorter UES opening and longer UES opening [633]. As a result this exercise should only be used in individuals where it is deemed appropriate (e.g. if no anterior hyoid excursion impairment is present given that theoretically the antagonistic posterior digastric belly and stylohyoid will likely be strengthened during the Effortful Swallow which may worsen anterior hyoid movement). This is in line with research which found that pharyngeal pressure increased and submental activity significantly decreased during the Effortful Swallow [659].

If sarcopenia is not present, a focus on skill training to rehabilitate swallowing would be implemented as part of group two, with a third control group receiving standard care. Should the participants in Group 2 present with the following symptoms/impaired biomechanics, the therapy could be conducted as follows:

- Oral residue: Aim to target clearance of oral residue by increasing tongue skill.

- Pharyngeal residue: targets could include tongue base retraction as it may result in lower pharyngeal residue [660] (note the tongue-hold exercise may be contraindicated in those with decreased hyoid excursion and/or reduced pharyngeal motility [661, 662]), pharyngeal stripping (through cortical modulation using feedback via pharyngeal HRM [663]), vallecular residue (hyoid excursion exercise, tongue hold exercise), hyolaryngeal elevation (Mendelsohn manoeuvre appears to improve timing measures (e.g. duration of hyoid movement and UOS opening appear to have a greater impact on durations of swallowing movements rather than structural movements[655])).
- Improved approximation of the base of tongue and posterior pharyngeal wall at the correct moment: (targeting cortical modulation using feedback on pharyngeal HRM [663]) as oesophageal clearance may improve with improved propulsion from oropharyngeal and hypopharyngeal areas [654].
- Swallow initiation: sensory training for example neuromuscular electrical stimulation has reportedly improved swallowing initiation in stroke [664]. Similarly, pharyngeal electrical stimulation is showing promising evidence for improving sensation as it may be targeting corticobulbar excitability and reorganising of the motor cortex which may potentially compensate for nerve injuries or brain remapping that could have occurred [665].

A longitudinal study which can identify patients at risk of dysphagia/aspiration post-operatively and chronically is recommended to minimise post-surgical decline and long-term QoL [402]. This finding is supported by a study which showed a non-significant trend of improved swallowing abilities (FOIS) in a group of patients who received prehabilitative dysphagia training (n=14) prior to surgery compared to the control group who received no rehabilitation pre-surgery (n=12) (p=0.054)[66]. Collecting VFS and other data pre-operatively, acutely and chronically post-operatively will provide a better understanding of the changes that occur to swallowing due to treatment.

Our systematic review suggested that it is important for future RCTs to measure tumour histology, tumour location, surgical approach, anastomosis site, co-morbidities, sex, age, ethnic group, inclusion and exclusion criteria, rehabilitation dosage and frequency, adherence, extent of oral intake, incidence rates of aspiration pneumonia, swallow-related QoL, instrumental measures of swallowing including aspiration, patient reported dysphagia outcomes, time to return to oral intake, length of time in hospital, nutrition, and adverse events. The development of a core outcomes set would be valuable to provide comparable data across studies.

Future research should also focus more explicitly on specific areas of impairment. Our research explored tongue pressures and oesophageal clearance in more depth, however, future studies could investigate other elements in detail for example, hyoid displacement. A study by Kim et al used kinematic analysis to measure maximum superior and anterior hyoid displacement, maximal rotation of the epiglottitis and pharyngeal delay time acutely post oesophagectomy [249]. Their research found that pharyngeal delay time was the main factor relevant to aspiration and given this was still present in all long-term survivors in our study, more in depth analysis of this is warranted at the longer time-point.

Further consideration could be given to whether there may be differences between the nature, severity and impact of dysphagia post-oesophagectomy for males and females, potentially due to anatomical size or for other reasons, as has been evident in people who have had laryngectomy surgery [666].

Further studies could also attempt to quantitatively measure long-term oesophageal clearance in oesophageal cancer through the use of HRM. Research has previously measured ineffective oesophageal clearance where peristaltic contractions of amplitude < 30mmHg are unable to propel oesophageal contents, and found that > 30% of these contractions or nonperistaltic contractions in the distal oesophagus when swallowing may be associated with dysphagia [464].

Learning from our MDT colleagues as precedence for dysphagia rehabilitation

High quality research in physiotherapy has demonstrated the benefits gained from exercise-based interventions in oesophageal cancer. A systematic review by Bolger et al (2019) [431] found that a preoperative exercise programme led to a reduction in perioperative morbidity, most notably pulmonary complications, in people with oesophagogastric malignancies. This systematic review included the ReStOre (Rehabilitative Strategies Following Oesophageal Cancer) research conducted by our TCD and SJH colleagues. O'Neill et al (2018) implemented a randomised controlled trial which incorporated a 12 week multi-disciplinary rehabilitation programme consisting of physical exercise, dietary counselling and education in patients more than one year post oesophagectomy [414]. Clinically meaningful and statistically significant improvements to functional performance and HRQoL were reported. It is hoped that dysphagia interventions can be trialled in future research and ultimately improve nutrition, survival rates and QoL throughout survivorship.

Figure 42 reflects how along with physiotherapy and nutritional rehabilitation, dysphagia management plays a vital role in reducing post-operative complications and increasing long-term QoL in this increasing group of survivors, thanks to advances in cancer treatment and improved peri-treatment multi-disciplinary management.

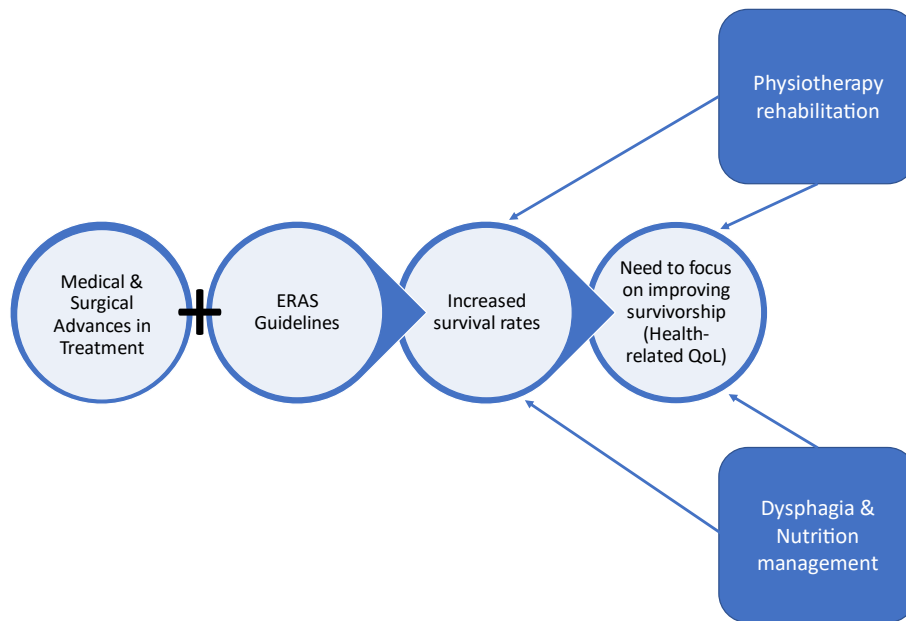


Figure 42 A model of how multi-disciplinary management improves survival rates and QoL post-oesophageal cancer

In a narrative review by Guinan et al (2017) [667] it was discussed how theoretically hospital costs may be reduced through physical prehabilitation, given that published studies found reduced length of stay in hospital post oesophagectomy/ intra-cavity surgery [668, 669]. Therefore it is plausible that dysphagia prehabilitation may potentially reduce hospital costs if nutritional status can be improved thereby minimising length of hospital stay. This is an outcome that should be measured in future research.

A focus on caregivers is beyond the scope of this thesis, however, it is an important topic and investigation into the impact on their QoL is warranted.

9.4.2 Future Direction of Clinical Practice

Swallowing rehabilitation could become a key component of ERAS [484], as it may lead to earlier oral feeding, shorter length of stay in hospital, and potentially less postoperative pneumonia that occurs from aspiration [286].

Speech and language therapists along with other MDT members such as dentists and nurses play a key role in promoting oral hygiene awareness. Sato et al (2016) found that approximately 29–39% of patients undergoing oesophagectomy presented with poor oral hygiene and periodontitis. Given that oral bacteria is a major cause of postoperative pneumonia following oesophageal surgeries [670], a focus on maintaining oral hygiene prior to and post oesophagectomy surgery may reduce the incidence of pneumonia [410] in this cohort. Oral hygiene in long-term survivors does not appear to have been studied yet. The number and quality of dentition has been found to be associated with impaired mastication and oral intake in head and neck cancer patients which can impact upon nutrition status [671], and therefore warrants further research in people with oesophageal cancer. Patients should be educated on the importance of having well-fitting dentures and providing adequate oral care. Mastication and oral health could be assessed by clinicians and researchers using tools such as the Test of Masticating and Swallowing Solids (TOMASS) [195] and the Oral Health Assessment Tool [672].

Improvements in surgical techniques and interventions are continuously reducing rates of complications and improving survival rates. Enhanced Recovery After Surgery (ERAS) guidelines published in 2019 strongly recommend multidisciplinary care using a standardised pathway [101]. The ERAS protocol reported that patients with dysphagia may have a moderate risk of post-operative complications if they have dysphagia or a high risk if they have severe dysphagia [400]. The Irish National Oesophageal Cancer Clinical Guidelines (No 19) recommend considering a referral to speech and language therapists post-surgery [26] as SLTs are a vital part of the team when patients are experiencing oropharyngeal dysphagia. Our research has shown that some survivors continue to present with dysphagia for many years, with a detrimental impact on QoL, therefore, it is essential that further funding is sourced for dysphagia services to be available for patients who need it in the community throughout survivorship.

Our research and others have identified the importance of educating the health care professionals in the community as well as the public, for example, through interventional manuals for medical staff and brochures for patients' family members and friends [297].

There is a need for improved primary care services throughout survivorship such as the primary care survivorship clinic at John Hopkins which was valued by 17 patients who were interviewed. One of the reasons that this service was considered to be of high quality was the expertise of the staff regarding their needs, something that participants in our study identified as lacking in the general community [673].

Finally it is important that intervention and support are tailored for individuals throughout survivorship to maximize gains [674].

9.5 Limitations of this Research

Given the time limit of a full-time PhD, it was not deemed possible to do a long-term longitudinal study for this project. As a result, this study was limited to a cross-sectional study meaning that it was not possible to compare the nature, severity or impact of COD at various timepoints. A longitudinal study is warranted to measure participants' swallowing at various timepoints from before surgery and throughout survivorship. Additionally, this study was an observational design therefore causality cannot confidently be implied [675].

Although this sample size is reflective of similar exploratory cross-sectional observation studies [354, 497, 498], it was still relatively small with subgroup analyses consisting of even smaller sample sizes. Further research of a larger sample size would be beneficial. Participants who chose to participate may have had concerns about their swallowing therefore it is possible that this study reflects a higher proportion of dysphagic participants than the typical oesophagectomy cohort in the community. Consecutive admission sampling may remediate this in future research. Although eligibility criteria excluded participants with premorbid dysphagia, participants' swallowing was

not evaluated at any time prior to their surgery so it is not possible to rule out premorbid dysphagia. All participants were recruited from one single site therefore the results do not reflect other surgical approaches such as minimally invasive and hybrid/robotic approaches. A multi-site study would be beneficial in future research.

Despite the interaction with a PPI committee, a PPI framework was not used. This would have avoided potential pitfalls as recent PPI research in oesophageal cancer, by Schandl et al (2022), found that the framework was important to comprehensively and thoroughly facilitate the process of collaborating with a PPI group in research [676].

A limitation of this research is that only two bolus trials of each consistency were assessed on videofluoroscopy. Ideally, more trials would have been provided to participants however following discussions with the Upper Gastrointestinal Consultant and PPI representatives, a decision was made for the protocol to be limited to just the two trials because of early satiety, regurgitation and abdominal discomfort in this cohort as well as to reduce the exposure to ionizing radiation during videofluoroscopy. There is currently wide variation in international research regarding the number of trials being provided with some studies using one bolus [516, 677], two [217], three [678], four [679], five [680], and six boluses [218, 681]. More recently, it has become clear that greater trials are required to detect aspiration [682]. For example, when determining sensitivity in detecting aspiration on FEES, Baijens et al (2014) implemented ten swallow trials and found that there was a risk of under-identifying aspiration in people with oncological and neurological impairments with only three or four trials, particularly with thin fluids during FEES evaluation [683]. In hindsight it would have been preferential to provide 5 to 6 uncompensated IDDSI Level 0 liquid trials as used by Hutcheson et al (2022) [217] when validating the DIGESTv2 and four sets of thickened/solid trials as used by Steele et al when developing reference values in healthy adults [679].

During the oesophageal screen, participants were not asked to “swallow only once”. Other researchers have prompted participants to try to not take a second swallow [529] or otherwise considered a second swallow to be an inability to clear the oesophagus and they have therefore graded a second swallow as 4: minimal/no clearance on MBSImP Component 17 [608]. By not doing this in our study, it may have resulted in underestimating oesophageal clearance compared to others. In addition, the oesophagus reportedly ‘collapses’ approximately one minute after swallowing in healthy adults [684]. Other researchers have reviewed images several minutes later to evaluate whether residual is present as this may indicate the presence of neuromuscular dysmotility or obstructions warranting investigation [685]. Therefore, it may be a limitation of this study that the oesophagus was not reviewed more than a minute after swallowing.

Because this research is in its infancy, no dysphagia assessment tools have been validated in people with oesophageal cancer therefore this research used a variety of assessment tools which were not validated for its intended use. It was attempted to select tools that were validated with other populations that may be considered relevant to people with oesophageal cancer.

This research used the DIGESTv2 to measure pharyngeal dysphagia, however, it is understood that this tool only measures swallow safety and efficiency. The MBSImP was therefore utilised to measure pathophysiology in order to develop a broader understanding of swallow function/dysfunction. The PAS was used to grade penetration and aspiration however it is also considered in the grading of the DIGESTv2 so it is important to acknowledge when interpreting our results that it is used twice in the overall results. Kinematic analysis, such as frame by frame calculation of hyoid movement or the pharyngeal constrictor ratio [686-688] on VFS, may have provided rich data on changes and differences that occurred during swallow physiology however this was beyond the scope of this thesis. Further research employing kinematic analysis would be valuable. OTT was capped at 60 seconds to minimise radiation exposure which means that OTT may have been underestimated in our participants. This should be considered when interpreting

findings. Our research did not measure posterior tongue endurance as this is not typically assessed in the literature. Only one other published study was found that has evaluated this measure [602] but this would have been an interesting outcome to identify in case it had diagnostic ability in identifying sarcopenia or tongue base retraction in our participants as a tongue pressure assessment is an easily administered assessment in a clinical setting.

It must be considered when interpreting the QoL results, that although the MDADI was originally designed to measure the impact of oropharyngeal dysphagia on QoL in people with head and neck cancer [187], it has been queried in the literature whether it is in fact more of a patient-reported outcome measure of swallowing than a QoL tool given that some of the questions are specific to swallow impairment [689]. The SWAL-QOL appears to be the most appropriate alternative tool because of its robust psychometric properties for evaluating the impact of dysphagia on QoL [690], however, due to its length and the time required to complete it, it was not a viable tool for this study which already included other questionnaires and assessment tools during one time-restricted session. In the interest of time, given the large number of questionnaires provided to participants, a decision was made to omit the recommended core EORTC questionnaire which looks broadly at QoL in oesophageal cancer, the EORTC-QLQ-OES-30, and focus on the questionnaire that was relevant to dysphagia symptoms alone, EORTC-QLQ-OES-18 [567]. Because of a shortage of clinical rooms in the hospital, interviews were often conducted in a videofluoroscopy suite. It must be considered that an interview location, in particular a medicalised environment, can impact upon the responses from an interviewee [691].

This study did not evaluate sarcopenia using Computed Tomography which would have been a more robust measure [692] than using a questionnaire screen, the SARC-F. An additional limitation of this research is that the Reflux Symptom Index has poor/moderate sensitivity (48.2% [693] – 79.1%[694]) in identifying laryngopharyngeal reflux symptoms. The Reflux Symptom Score (RSS) may have been a more appropriate tool as it includes more GORD symptoms and has reported

sensitivity of 92.8% [693] or the RSS-12 which is a shorter, reliable and validated version for use with outpatients however it has not yet been validated in English [695].

Our systematic review was limited by the inclusion of all study types and not just RCTs which can impact upon confidence in interpreting findings. This was due to the lack of eligible studies for inclusion. The review was conducted rigorously in an attempt to minimise any chance of bias. In addition, a meta-analysis was not conducted due to the heterogenous methods and outcomes measured in the included studies. Finally, an online translation tool was used with a professional Japanese interpreter which means that some information may have been misunderstood impacting upon the authors' perception of bias in one of the studies.

9.6 Conclusion

In conclusion, this research identified a high incidence of COD after oesophageal cancer surgery. This is the first research to illustrate the most frequently and severely impaired physiological components of swallowing a minimum of 12 months after oesophageal cancer in the survivorship literature.

In the majority of participants, dysphagia was normal or mildly impaired, with all participants having pathophysiology to some extent. There are many potential causes of this which will be explored below.

There was a high incidence of **oral residue** however given that anterior tongue strength and endurance and posterior tongue strength were within normal limits, weakness is unlikely to be the cause. It may occur due to reduced **sensation** or reduced **skill**.

Pharyngeal residue may be due to **1) reduced pharyngeal stripping**, as identified on VFS, which may be consequential to neurological damage caused by surgery, or ageing, or because of the neural inter-relationship that appears to exist between the pharynx and oesophagus. (It would be beneficial to measure pharyngeal pressures on pharyngeal HRM); **2) Reduced hyoid excursion**

(which would need to be re-evaluated with kinematic analysis), and may be caused by reduced strength or skill (timing/coordination) of submental muscles (geniohyoid, mylohyoid and anterior digastric belly) secondary to ageing or by being tethered to the UOS (and whose cross-sectional area could be assessed using ultrasonography [643] and whose activity could be measured using surface electromyography [696]). **3) Tongue base retraction** towards the posterior pharyngeal wall could be caused by ageing or by altered pressures between the pharynx and oesophagus (whose strength could be measured using pharyngeal HRM and whose ability to clear the bolus could be measured using HRM that includes impedance), and **4) Inadequate distension/timing of UOS opening** (which could be evaluated using HRM) could potentially be caused by reduced laryngeal elevation which may be secondary to reduced strength or skill (timing/coordination) of suprahyoid muscles due to ageing or hypertension caused by the absent lower oesophagus, or by altered nerve function following surgery/brain remapping resulting in inadequate relaxation of the cricopharyngeus muscle.

Delayed swallow initiation may be due to **ageing**, or **altered sensation** at the meso- and hypopharynx associated with nerve damage post-surgery/ radiation treatment, or by **anticipation** of issues that may occur during the oesophageal phase or because of the **inter-relationship** between the oesophagus and pharynx.

Oesophageal clearance may be impacted by the **loss of a segment** of the oesophagus post-surgery impacting upon its neural function including peristalsis and sensation, the **repositioned pulled-up stomach** and altered pressures in the upper gastrointestinal tract, or **tongue base retraction** failing to get the adequate thrust of the bolus from the pharynx.

Airway protection was relatively intact in our participants, however, the **surgical approach** used may be associated with chronic aspiration and warrants further investigation in a larger sample.

HRQoL continues to be impacted by oropharyngeal dysphagia for many years after surgery. Although the impact was mild in the majority of participants, for those who continued to struggle

with aerodigestive symptoms, their QoL was significantly impacted, with many feeling isolation as they tried to manage symptoms in the community because of generalist practitioners' limited knowledge and understanding of their symptoms. Their ability to socialise and work as before were hindered by experiencing pain and embarrassment due to their symptoms. Fear of choking and fear that their symptoms signify cancer recurrence were ever present at mealtimes.

Now more than ever, as this group of survivors thankfully continues to grow, management of swallowing disorders in oesophageal cancer is needed in the community to reduce symptoms and their burden. Access to specialists is necessary, and education of community health professionals and the public would benefit these survivors.

So far, only minimal low quality evidence has been published investigating the efficacy of dysphagia rehabilitation in oesophageal cancer. Further research is warranted to explore peri-operative dysphagia rehabilitation and improve QoL.

This research highlights the importance of speech and language therapists becoming a member of the multidisciplinary oesophageal cancer team.

10 Appendices

10.0 Appendix A Protocol for the Systematic Review

Exercise-Based Dysphagia Rehabilitation for Adults with Oesophageal Cancer: a Protocol for a Systematic Review

Gillman A., Walshe M., Sheaf G., Hayes M., Reynolds J.V., Regan J.

Abstract:

Background: Dysphagia is the most common presenting symptom of oesophageal cancer. In addition, specific cancer treatments including surgery and radiation therapy can impact on this symptom. Associated complications include malnutrition, weight loss, tube-feeding reliance, aspiration pneumonia and reduced health-related quality of life. This systematic review aims to i) examine the impact of exercise-based dysphagia rehabilitation on clinical and quality of life outcomes in this population at any time point and ii) to identify key rehabilitation components that may inform future research of dysphagia rehabilitation in oesophageal cancer.

Methods: 10 databases and 3 clinical trial registries will be searched from inception with no language restriction. All peer reviewed published and non-published studies will be considered, including RCTs, control studies, cross-sectional studies, case series, published abstracts, conference presentations and grey literature. Conference proceedings of relevant annual congresses will be hand-searched. The main outcomes are changes in respiratory function, oral intake status, patient-reported dysphagia ratings, swallow-related quality of life, penetration or aspiration of food or fluids, change in timing or efficiency of swallowing, time taken to return to oral intake, nutritional status, and hospital length of stay. Information will be recorded on delivery, intensity, fidelity, adverse events and adherence to intervention. Two independent authors will assess articles for eligibility, data extraction and quality assessment.

Discussion: No systematic review has focused on exercise-based dysphagia rehabilitation in oesophageal cancer. Findings will guide future research and clinical practice.

Keywords: Dysphagia, esophageal cancer, curative treatment, swallow rehabilitation, swallow exercises.

Introduction

Oesophageal cancer has an overall poor survival compared with many other malignancies. Recent reports indicate an approximate 5-year survival of between 15-25% [697-699]. In patients however, that can be treated with curative intent, the 5-year survival is currently approximately 50 per cent [700]. Consequently, survivorship has increased and there is an emerging focus on recovery and maintenance of health-related quality of life (QOL) [374, 701].

For curative therapy, this usually involves surgery alone, either open or minimally invasive oesophagectomy (MIE). For locally advanced but curable disease, preoperative chemotherapy or a combination of chemotherapy and radiation therapy is increasingly a standard of care [25].

Dysphagia, meaning difficulty swallowing, is a central symptom for the majority of patients with oesophageal cancer, and the commonest presenting symptom [620, 702]. Prevalence of dysphagia is high in this population, with reports of dysphagia in 93% of patients with squamous cell carcinoma of the oesophagus, and in 79% of patients with adenocarcinoma of the oesophagus [703]. Complications of a swallowing difficulty in oesophageal cancer include malnutrition, weight loss, muscle weakness and wasting (sarcopenia), and tube-feeding reliance [168-171].

In the context of dysphagia, oropharyngeal dysphagia is rarely studied. However, it may exist following surgery and radiation therapy, as well as prior to cancer treatment [623]. Pre-treatment, individuals with oesophageal cancer often report odynophagia (pain when swallowing), the sensation of retrosternal sticking of solid foods, regurgitation of undigested food, coughing when swallowing, and heartburn [623]. An important observation albeit in a small study of 10 patients by Martin et al, [623], was that 9 out of 10 patients had mild oral-preparatory dysphagia and 100% of participants had at least mild oral and mild pharyngeal dysphagia prior to oesophageal cancer surgery. The characteristics most observed on videofluoroscopy were impaired tongue movement, oral residue, hesitancy initiating the tongue stripping wave, impaired bolus formation, premature posterior spillage of the bolus from the oral cavity, delay in pharyngeal swallow initiation and post-swallow pharyngeal residue. Videofluoroscopic evaluation of swallowing also revealed altered hyoid trajectories in relation to the timing of its superior-most and anterior-most positions [623]. Post-surgery videofluoroscopy studies have revealed that new-onset pharyngeal biomechanical impairments include reduced tongue pressure, reduced base of tongue to posterior pharyngeal wall closure, delayed initiation of the pharyngeal swallow, reduced hyo-laryngeal elevation and excursion, reduced pharyngeal contraction, vocal fold immobility and

reduced maximum opening of the UOS during swallowing, resulting in symptoms such as overt and silent aspiration, and pharyngeal residue [249, 253, 620, 622, 623, 626].

Research studies for other diseases, including gastro-oesophageal reflux disease, and achalasia have highlighted the intricate connection between the oesophagus and the oropharynx [440, 528, 643]. Interestingly, Martin et al, [623] proposed that oropharyngeal modulation may be impacted by oesophagopharyngeal reflexes responding to cancer-related oesophageal alterations, given that their results revealed oropharyngeal changes to swallowing prior to treatment even in patients who had only a very mild obstruction. When using balloon distension oesophageal manometry, Koh et al (2004), demonstrated hypertensive peristalsis in the cervical oesophagus in 80% of clinically symptomatic patients [248]. Abnormal neural pathways of the cervical oesophagus in patients with oesophageal cancer may, therefore, potentially modulate the neural movements within the pharynx and the oesophagus.

The surgery for oesophageal cancer is associated with complications in between 50-60% of patients [51, 52]. Complications that may contribute to oropharyngeal swallowing deficits include anastomotic leaks, anastomotic scarring or inflammation, radiation-induced inflammation, fibrosis and strictures, endotracheal tube trauma, adhesion of the gastric tube to the trachea, and mechanical denervation and inflammation of key nerve pathways such as the vagus nerve, Ansa Cervicalis or the pharyngeal plexus [620-626]. A study by Mafune et al (2019), has reported RLN paralysis in 65.6% of patients, as observed on laryngoscopy in 21 patients on post-operative day 1 (POD1) [150]. Operation time greater than or equal to 6 hours and vocal cord paralysis were found to be risk factors for subglottic aspiration with a high probability of occurrence (42.3%) if either risk factor was present [61]. The most likely mechanism impairments are insufficient vocal fold closure and impaired laryngeal sensation [627].

The most closely associated complication of surgery for oesophageal cancer is postoperative pulmonary complications (PPCs), in particular pneumonia, which occurs in approximately 25% of patients and is the most common cause of death [64, 65]. The presence of dysphagia postoperatively is an independent risk factor of pneumonia [340]. Berry et al (2010), [340] found that 12% of patients had evidence of aspiration, hence approaches that minimise aspiration and aspiration pneumonia are clinically of great relevance to achieving optimum outcomes for these patients. Improving swallowing would be expected to reduce aspiration, reduce pneumonia and PPCs, and may impact on sarcopenia and malnutrition, treatment-related morbidity, hospital length of stay and readmissions [257, 258, 340, 341].

Health-Related QOL Complications of Dysphagia in Oesophageal Cancer

The impact of a swallowing difficulty on the health-related QOL of a person with oesophageal cancer can also be devastating, leading to anxiety during meals and limiting participation in family mealtimes and social occasions [380]. Health-related QOL was found to be significantly impaired 10 years after both open oesophagectomy and MIE across many domains including dysphagia, reflux, eating difficulties, oesophageal pain, trouble swallowing saliva, choking, dry mouth and taste problems, with eating difficulties being one of the most outstanding problems [373, 374]. Survivors have reported persistent swallowing difficulties 5 and 10 years after treatment, demonstrating that this is a chronic issue in need of addressing [374].

Medical Management of Dysphagia in Oesophageal Cancer

As symptoms often present at a late-stage, cancer may not be diagnosed until palliative intervention is the only option [704]. Medical treatments that may relieve symptoms of dysphagia include stents (such as self-expanding metal stents (SEMS), anti-reflux stents and Nito-S stents), dilatation, intraluminal brachytherapy, or thermal and chemical ablative techniques (including laser, ethanol injection and photodynamic therapy) [233].

These medical treatments often focus on treating the symptoms of dysphagia, as opposed to targeting the underlying causes of the dysphagia pathophysiology that occur prior to surgery and/or chemo-radiation, the extent of which remains largely unknown to this day [623]. These interventions can also be costly [705], and may result in adverse events, for example, oral feeding following stent insertion can result in migration of the stent [706] and endoscopic dilatation carries a risk of perforation of the oesophagus [707].

Multidisciplinary Rehabilitation in Oesophageal Cancer

Multi-disciplinary management of oesophageal cancer is strongly recommended to maximise recovery, including the improvement of clinical and QOL outcomes [25, 101, 708-710]. In addition to medical and surgical interventions, rehabilitation can be provided to patients prior to, during or following oesophageal cancer treatment. Cancer prehabilitation involves the delivery of rehabilitation between diagnosis and acute treatment to reduce post-operative morbidity and improve functional recovery, and it has been found to improve clinical outcomes in oesophageal cancer [431]. Bolger et al (2019) [431] completed a systematic review on prehabilitation and rehabilitation in oesophagogastric malignancies and found that a preoperative exercise

programme led to a reduction in perioperative morbidity, most notably pulmonary complications. These findings are significant given that a proportion of patients do not progress to curative treatment because of physiological and nutritional deterioration [432].

Enhanced Recovery After Surgery (ERAS) aims to reduce the high perioperative morbidity rates associated with complex surgeries including oesophagectomy [125]. This multidisciplinary approach seeks to improve quality of care and maximise the efficiency of surgical recovery [101, 126]. A systematic review and meta-analysis of ERAS in oesophageal cancer surgery revealed that this approach results in a reduction in overall non-surgical and pulmonary complications [127]. There was also a reduction in length of hospital stay with no consequential impact on readmission rates. The ERAS guidelines, in 2019 [101], strongly recommend multidisciplinary care using a standardized pathway in the perioperative care of patients undergoing oesophagectomy. It is discussed that, although research in this area is in its infancy, small studies suggest that prehabilitation, including nutritional intervention, medical optimisation and psychological intervention, appears to have a positive impact on patients' return to baseline functioning, even more so than post-surgical rehabilitation.

Identifying patients with dysphagia may assist in limiting post-surgical complications, as the ERAS society outlines that a patient may have a moderate risk of complications if they have dysphagia and/or unintentional weight loss of 5-9%, or a high risk if they have severe dysphagia (tolerating puree/fluids only), unintentional weight loss >10% or a body mass index of < 18 kg/m² [101].

The ERAS society [101] recommends early introduction of nutrition given the high risk of malnutrition in this population, however, they stipulate that at the time of publication, it was not yet clear at what point it is safest to commence oral intake post-surgery. Surgeons are often reluctant to commence oral intake directly following surgery due to fears of increased anastomotic leakage and aspiration pneumonia [711], advising total parenteral nutrition, nasoduodenal/nasojejunal tube feeding or jejunostomy tube feeding after an oesophagectomy to optimise patients' nutritional status [712].

A Cochrane review of 37 RCTs (N = 5711) found that avoiding nasogastric tube was associated with reduced pneumonia, a quicker return of bowel function and a reduced hospital length of stay.⁷⁷ [713].

Recent research has revealed that patients who received early oral feeding, following a MIE surgery, utilising ERAS approaches, had reduced hospital stays with no associated increase in morbidity [125, 711]. Centres, which have progressed through their MIE learning curve, resulting in stable and acceptable postoperative complication rates, may find that a direct start of oral feeding after a MIE-IL (Ivor Lewis) results in a significantly shorter time to functional recovery, a significant reduction in 30-day post-operative complications, and shorter length of hospital stay, compared to standard care (nil-by-mouth for 5 days) as was observed in Fransen et al's cohort study in 2020, which included 296 participants [711].

Dysphagia Rehabilitation in Oesophageal Cancer

Dysphagia rehabilitation improves swallow function and reduces aspiration pneumonia in stroke and older adults [714-716]. Multidisciplinary management of dysphagia has been proven as more effective at improving diagnosis and treatment of dysphagia in stroke and head and neck cancer populations compared to disciplines working in silo [717-719]. However, there is limited research exploring swallowing rehabilitation in oesophageal cancer. In one recent systematic review, Kaneoka et al (2018)[257] found four studies that evaluated dysphagia intervention in this population. Three of these four studies investigated the chin tuck postural strategy. This strategy compensates for a swallow deficit during the act of swallowing, as opposed to rehabilitative exercises, which aim to induce long-term improvements to swallow function. Only one included study evaluated dysphagia rehabilitation in this review [69].

It is widely known that patients with head and neck cancer suffer significant short-term and long-term dysphagia, impacting upon their QOL and activities of daily living [388], and that swallow rehabilitation in head and neck cancer has improved QOL and dysphagia outcomes such as severity of aspiration and pharyngeal efficiency [389-395].

Given the clinical and QOL complications of dysphagia in this growing oesophageal cancer population, justification for a detailed systematic review of the literature is strong; one which focuses specifically on rehabilitation exercises that aim to induce long-lasting improvements in the physiological function of swallowing in individuals with oesophageal cancer. This review is important given the current dearth of knowledge about the efficacy of swallow rehabilitation in this population. It is currently not known how and why swallow rehabilitation may improve swallowing, and if there are any contraindications for its use with patients with oesophageal cancer. The current focus remains on compensatory strategies. The review will need a clear definition of 'rehabilitative exercises' to ensure that the results retrieved are not compounded by

compensatory strategies. This systematic review should consist of a broader search of the literature than has previously been completed, including all published and non-published studies that can be retrieved in any language, to ensure literature saturation. Systematic review findings may guide clinical decision-making regarding dysphagia rehabilitation, and inform future research in this area.

Study Aims:

1. To determine the effectiveness of dysphagia rehabilitation in improving clinical outcomes (swallow, pneumonia, tube-feeding related) and health-related QOL outcomes in adults with oesophageal cancer.
2. To identify key elements of rehabilitation (delivery, dose, intensity, timing, adverse events and fidelity) which may inform future research of dysphagia rehabilitation in oesophageal cancer.

Methods

This protocol was created using guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [720]. The protocol has been registered on the PROSPERO database of prospectively registered systematic reviews (reference number CRD42020172029).

Study Designs

Due to the limited research in this area, all published and non-published peer-reviewed randomized control trials (RCTs), quasi-experimental designs, observational studies (i.e. cohort studies, case-control studies, cross-sectional studies, and case series), conference presentations, abstracts and non-systematic reviews will be included. Grey literature will be searched to locate relevant non-published studies. Expert opinions, letters to editor, commentaries, editorials, and textbooks will be excluded.

Search Strategy

Six electronic databases (CINAHL Complete, Medline, EMBASE, Web of Science, Cochrane and ProQuest Dissertations and Theses) will be searched for eligible studies. One author will design and run a systematic search across all databases using the following MESH and keyword search terms: “oesophageal cancer”, “dysphagia/deglutition” and “rehabilitation”, using

synonyms and related terms in the titles and abstracts, and controlled vocabulary, and then combined as appropriate. Four remaining databases (Open Grey, PROSPERO, RIAN and Speech Bite) will be searched using the term '(o)esophageal cancer' . All literature published since inception of databases will be considered, to include as many relevant studies as possible. Publications from any country of origin, written in any language, are eligible. Clinical trial registries (ClinicalTrials.gov, ISRCTN, WHO Trial Registry) will be searched by the first author (AG). Reference lists of relevant studies and a manual search on Google Scholar will be completed by the first author to ensure that a thorough search of the literature is completed. In addition, the first author will complete a manual search of relevant conference proceedings of the annual congresses of the Dysphagia Research Society, the European Society of Swallowing Disorders, the European Society for Diseases of the Oesophagus and the International Society for Diseases of the Oesophagus from inception.

Study Selection

Search results will be exported into the systematic review management software, Covidence (www.covidence.org) and duplicates will be removed. Two researchers will double-screen titles and abstracts of publications to identify full-text articles. Two authors will review the full-text articles for eligibility. Disagreements will be resolved through discussion. A third author will be consulted should conflicts not be resolved. Study authors will be contacted for further information or if a full text is not retrievable through library or online means.

The reference manager software, EndNote (www.endnote.com), will be used to manage references.

Eligibility Criteria

Participants/Population

Inclusion criteria for participants will encompass adults (≥ 18 years old) undergoing curative intent resection (oesophagectomy) and/or neoadjuvant therapy for oesophageal cancer, who have a swallowing disorder of any severity, and who are participating in rehabilitative intervention to improve their swallowing disorders. An oesophagectomy is defined as a type of surgery whereby part of or all of the oesophagus is removed, any method, either open or minimally invasive, will be included. Participants of any gender and ethnicity with any stage and type of cancer at any location in the oesophagus will be included. There will be no restriction on settings. Participants will be excluded if they present with other conditions known to impact on swallowing (for example the presence/history of stroke, neurodegenerative disease or head and

neck cancer) or if palliative treatment is being provided. Participants with gastric cancer will be excluded.

Interventions

Articles for inclusion will be those studies investigating dysphagia rehabilitation in oesophageal cancer. Rehabilitation will be delivered to participants by trained personnel initially. All intensities and durations of rehabilitation will be included.

A dysphagia rehabilitative exercise is defined, for the purpose of this systematic review, as an exercise which aims to create lasting functional change to the efficiency, strength, coordination and safety of an individual's swallow by improving underlying physiological function, rather than compensating for a deficit in the moment. This includes strength-based exercises, skill-based exercises and sensory-rehabilitative exercises. The main goal of strength training is the enlargement of the muscle fibres (hypertrophy) [721]. Skill-based training aims to modulate the cortex resulting in adaptive swallowing practices, such as increased precision and timing of swallowing [722]. The intent of sensory-based rehabilitation is to produce long-term changes in the organisation of sensory and motor areas of the cerebral cortex, as sensory input has been proven to alter the excitability of the motor cortex (cross-system plasticity) [723].

Types of rehabilitation interventions included in the review may be individual swallowing exercises to target a swallow pathophysiology such as the Mendelsohn Manoeuvre [724], respiratory muscle training such as EMST (Expiratory Muscle Strength Training) [725], lingual strength training [726], swallow skill training using biofeedback such as sEMG (surface Electromyography), the McNeill Dysphagia Therapy Program [727], sensory-motor interventions such as thermal-tactile stimulation [728], electrotherapeutic interventions such as NMES (Neuro-Muscular Electrical Stimulation) [729] and non-invasive brain stimulation such as tDCS (transcranial Direct Current Stimulation) [730]. All variations of rehabilitation interventions are included as long as the exercises meet our definition of a rehabilitative exercise. Studies employing staff and/or caregivers' training as the only intervention practice will be excluded.

With respect to our review, dysphagia rehabilitation is not considered to include compensatory interventions which are defined as: strategies implemented at the time of swallowing that aim to temporarily compensate for the swallow dysfunction or compromised airway, for example food/fluid texture and volume modification, head and neck postures, environmental/utensil/pacing modifications etc. will be excluded. Studies will be excluded if their only focus is compensatory intervention. Studies which contain both rehabilitative exercises and compensatory strategies will be included.

Dysphagia rehabilitation may take place prior to, during or at any time-point following participants' surgical or neo-adjuvant treatment for oesophageal cancer.

Comparison

Any comparison groups in the included studies will receive:

- No intervention
- Usual care that does not include rehabilitative exercises, for example compensatory strategies (as defined above).
- A placebo group (for example if patients are receiving a sham intervention such as with Expiratory Muscle Strength Training when they breathe into a device with no resistance).

Outcome Measures

Four primary outcome measures will be examined:

1. Incidence of respiratory complications including pneumonia indicated by the presence of new/worsening chest x-ray or computed tomography (CT) results.
2. Incidence of PPCs and pneumonia. The definition of pneumonia established by the Center for Disease Control (CDC) will be utilized ("new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which include the new onset of fever, purulent sputum, leucocytosis, and decline in oxygenation" [78]), as well as the PPC definition as per the Standardized Endpoints for Perioperative Medicine (StEP) collaborative network [82]:

Signs/Symptoms/Laboratory:

ONE of [fever $>38.0^{\circ}\text{C}$, WBC $<4\times 10^9$ or $>12\times 10^9 \text{ L}^{-1}$, altered mental status in >70 year old with no other recognised cause] and TWO of [new onset purulent sputum/change in character of sputum/increased respiratory secretions or increased suctioning OR worsening cough/dyspnoea/tachypnoea OR rales or bronchial breath sounds OR worsening gas exchange]

▪ *Imaging:*

Two or more serial chest imaging results with either [new and persistent OR progressive and persistent] changes of [infiltrate OR consolidation OR cavitation]

▪ *OR one of:*

- Organism seen on Gram stain of lung tissue or pleural fluid, or identification of pathogenic organism from fluid or tissue from affected site (see outcome 3)
- Abscess or other evidence of infection on gross anatomical or histopathologic examination
- Imaging test evidence of abscess or other infection which if equivocal is supported by clinical correlation, specifically, physician documentation of antimicrobial treatment for lung infection

3. Change in oral intake status, for example, feeding-tube reliance rated on the Functional Oral Intake Scale [181].
4. Change to patient-reported dysphagia ratings on validated scales, for example, the EAT-10 (Eating Assessment Tool- 10) [176].
5. Change to swallow-related QOL scores on validated scales such as the MD Anderson Dysphagia Intervention Questionnaire [583] or SWAL-QOL (Swallow Quality of Life Questionnaire) [189].

Secondary Outcomes:

1. Change in incidence, frequency or volume of laryngeal penetration/aspiration, and safety of swallowing, as determined by instrumental swallow evaluation (Videofluoroscopy or Fiber-Endoscopic Evaluation of Swallowing (FEES)), and a validated tool (such as the Penetration-Aspiration Scale (PAS) [525] or Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) [531]).
2. Change in pharyngeal pressures as determined by Pharyngeal High Resolution Impedance Manometry (PHRIM).
3. Change in timing of swallowing as determined by instrumental swallow evaluation and using a validated scale (such as the MBS Impairment Profile or DIGEST).
4. Change in efficiency/residue of swallowing as determined by instrumental swallow evaluation and using a validated scale (for example the MBS Impairment Profile [216] or DIGEST or PHRIM).
5. Time taken in days to return to oral intake.
6. Change to nutritional status such as a validated tool for measuring weight loss, malnutrition, sarcopenia, cachexia, dehydration such as the MUST (Malnutrition Universal Screening Tool) [584].
7. Hospital length-of-stay in days.

8. Adverse events such as increased fatigue, deterioration of swallow function or patient discomfort.
9. Adherence with intervention, which may, for example, be measured by self-monitoring diaries or questionnaires, or withdrawal from the intervention.
10. Secretion severity as measured by FEES on a validated tool such as The Secretion Severity Rating Scale [731].

All pre-intervention, peri-intervention or post-intervention (including long-term) outcome measurements will be recorded.

Data Extraction

Data will be extracted independently by two authors through a data extraction form specifically designed for the purpose of this study. If a study presents with any missing data, study authors will be contacted to resolve any uncertainties. Disagreements will be resolved by consensus and consultation with a third author. Four main domains will be explored: participant characteristics; study characteristics; intervention characteristics; and outcomes of interest. Data regarding key intervention components such as delivery, intensity, timing, fidelity and adherence will be collected using the TIDIER checklist [585]. Once extracted, data will be merged into tabular form on a Microsoft Excel spreadsheet.

The specific data to be extracted are listed below:

- Study characteristics: title, authors, year of publication, journal, study design, setting and country, number of participants, time before or after surgery.
- Participant characteristics: age, sex, type of cancer, stage of cancer, location of cancer, type of cancer treatment (e.g. type of surgery, chemo-radiation etc.), thoracic access, surgical complications.
- Intervention characteristics: type of exercise, timing of rehabilitation (i.e. pre -v- peri -v- post cancer treatment), mode of delivery, duration, frequency, intensity, dose, fidelity, adverse events, adherence, measure of adherence.
- Outcomes of interest: efficiency/ pharyngeal residue scores, penetration/aspiration scores, reported dysphagia symptoms, chest status, nutrition status, means of oral intake/modified textures, time to return to oral intake, QOL ratings.

Data Analysis

If extracted results are available and from similar sources, a meta-analysis of primary and secondary outcomes will be completed. Results will be analysed using Review Manager software (Rev Man 5.4) with a fixed effect model and assessed for heterogeneity in forest plots and using the Chi squared test. If there is substantial heterogeneity, we will display the results of included studies in a forest plot while suppressing the summary estimate, where studies may be sorted by study design feature or their risk of bias [732]. Due to the limited literature surrounding dysphagia rehabilitation in oesophageal cancer, it is possible that there may be insufficient data available to complete a meta-analysis. In this situation, subgroups will be analysed to look for differences between groups, for example, to determine if there are improvements in outcomes listed above for those participants who completed each exercise across all eligible studies. Narrative description of the data will be conducted, and the data will be presented in tables, grouped by intervention type.

Assessment of Methodological Quality

The ROB 2 (Risk of Bias 2) Cochrane tool will be used for data analysis if only randomized controlled trials are included [732]. It is anticipated that a variety of non-randomised studies will be included in this systematic review, and therefore, a Risk of Bias tool such as the ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) tool will be appropriate to assess quality of the included studies [586]. Bias is defined as a tendency for study results to differ systematically from the results expected from a randomized trial, conducted on the same participant group that had no flaws in its conduct. The bias domains for consideration are:

- Bias due to confounding
- Bias in deletion of participants into the study
- Bias in classification of intervention
- Bias due to deviations from intended interventions
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in selection of the reported result

The confounding domains relevant to all eligible studies will be considered. The co-interventions that could differ between interventions and impact the study outcomes will also be considered. The signalling questions will then be answered across each of the domains listed

above for each relevant outcome, with the following response options: (1) Yes, (2) Probably Yes, (3) Probably No, (4) No, (5) No information. Free text will also be collected to support answers where necessary. These responses will support the judgement for the 'risk of bias' at each domain-level. Based on these decisions, an overall judgement about risk of bias will be made regarding the entire study. The overall risk of bias will be 'Low', 'Moderate', 'Serious', 'Critical', or 'No information' if there is insufficient information to make a judgement on the risk of bias.

Should insufficient information be available in any of the studies to determine the risk of bias across these domains (for example if the answer to most of the signalling questions is 'No information'), the Downs & Black tool [587] will be considered as an adjunct tool given its suitability for assessing the quality of randomised and non-randomised studies, and as its questions are less specific than the ROBINS-I questions. This checklist consists of 27 questions, which assess the quality of various components of the studies:

1. Study quality (10 items) – the overall quality of the study
2. External validity (3 items) – the ability to generalize findings of the study
3. Study bias (7 items) – to assess bias in the intervention and outcome measure(s)
4. Confounding and selection bias (6 items) – to determine bias from sampling or group assignment and
5. Power of the study (1 item) – to determine if findings are due to chance.

The GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) will be conducted to determine the certainty of the systematic review as a body of evidence as this will assist clinicians with the development of health care recommendations [589]. A grade of 'high', 'moderate', 'low', or 'very low' will be assigned to all factors. The evidence will be downgraded a level if the study lacks quality (e.g. design limitations; downgrade one level if the majority are non-randomised controlled trials), if there is an inconsistency of results; if there is imprecision, or if there is a probability of bias (e.g. downgrade one level if ROBINS-I level of bias is critical or severe as per the Cochrane guidelines [733] or if average risk of bias in the majority of the studies score <20 on Downs and Black scale as per previous research [734]).

Those factors that can increase the quality of evidence include 'large magnitude of effect', 'all plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed' and 'dose-response gradient'.

‘Summary of Findings’ Table

The review will include a summary of findings table [733], highlighting key information such as results for the interventions relating to key outcomes, the number of participants for each outcome, description of the exercises implemented, any reported adverse effects for each exercise, and the level of bias for that outcome as per the Quality Assessment.

Discussion

Oropharyngeal dysphagia is common in individuals with oesophageal cancer, and is often the first symptom to present. It is further impacted by surgery and neo-adjuvant therapy. As mortality rates decrease globally, survivors are now living with symptoms for many years following oesophagectomy. A study by Yuen et al in 2019 [70], revealed that 29 survivors who were an average of 3.5 years post oesophagectomy, and who had no history of swallowing impairment, continued to present with a mild to moderate pharyngeal dysphagia on videofluoroscopy.

Despite the significant impact of dysphagia throughout the oesophageal cancer journey both from a clinical perspective and on an individual’s QOL, little is known about rehabilitation to optimise swallowing. To date, most clinical trials investigating dysphagia rehabilitation in cancer have involved head and neck cancer populations. No systematic review has attempted to summarise the evidence for dysphagia rehabilitation in oesophageal cancer with a specific focus on exercises that will induce long-lasting functional change.

A broad searching systematic review of the literature will be conducted to ensure that all relevant published and non-published studies are retrieved. It is anticipated that results from this systematic review will reveal valuable information regarding the impact of rehabilitation on clinical and QOL outcomes, as well as providing insight into key components such as adherence, adverse outcomes, delivery, intensity and timing. Results of the proposed systematic review will inform clinical practice and future research in this area.

Exercise-Based Dysphagia Rehabilitation for Adults with Oesophageal Cancer: a Systematic Review

Gillman A., Walshe M., Sheaf G., Hayes M., Reynolds J.V., Regan J.

Keywords: Oesophageal cancer – Curative treatment – Dysphagia - Swallowing rehabilitation – Swallow exercises

Abstract

Background: Dysphagia is prevalent in oesophageal cancer with significant clinical and psychosocial complications. The purpose of this study was i) to examine the impact of exercise-based dysphagia rehabilitation on clinical and quality of life outcomes in this population and ii) to identify key rehabilitation components that may inform future research in this area.

Methods: Randomised control trials (RCT), non-RCTs, cohort studies and case series were included. 10 databases (CINAHL Complete, MEDLINE, EMBASE, Web of Science, CENTRAL, and ProQuest Dissertations and Theses, OpenGrey, PROSPERO, RIAN and SpeechBITE), 3 clinical trial registries, and relevant conference abstracts were searched in November 2020. Two independent authors assessed articles for eligibility before completing data extraction, quality assessment using ROBINS-I and Downs and Black Checklist, followed by descriptive data analysis. The primary outcomes included oral intake, respiratory status and quality of life. All comparable outcomes were combined and discussed throughout the manuscript as primary and secondary outcomes.

Results: Three single centre non-randomised control studies involving 311 participants were included. A meta-analysis could not be completed due to study heterogeneity. SLT-led post-operative dysphagia intervention led to significantly earlier start to oral intake and reduced length of post-operative hospital stay. No studies found a reduction in aspiration pneumonia rates, and no studies included patient reported or quality of life outcomes. Of the reported secondary outcomes, swallow prehabilitation resulted in significantly improved swallow efficiency following

oesophageal surgery compared to the control group, and rehabilitation following surgery resulted in significantly reduced vallecular and pyriform sinus residue. The three studies were found to have 'serious' to 'critical' risk of bias.

Conclusions: This systematic review highlights a low-volume of low-quality evidence to support exercise-based dysphagia rehabilitation in adults undergoing surgery for oesophageal cancer. As dysphagia is a common symptom impacting quality of life throughout survivorship, findings will guide future research to determine if swallowing rehabilitation should be included in enhanced recovery after surgery (ERAS) programmes. This review is limited by the inclusion of non-randomised control trials and the reliance on Japanese interpretation which may have resulted in bias. The reviewed studies were all of weak design with limited data reported.

Background

Oesophageal cancer has an overall poor survival compared with many other malignancies. Recent reports indicate an approximate 5-year survival of between 15-25% [6, 697, 698]. However, 5-year survival has increased to approximately 50% amongst those who can be treated with curative intent [700]. Consequently, there is an emerging focus on enhanced recovery after surgery (ERAS) pathways to optimize clinical and health related quality of life outcomes amongst survivors (QOL) [374, 701]. For curative therapy, treatment usually involves surgery alone, either open or minimally invasive oesophagectomy (MIE). For locally advanced but curable disease, preoperative chemotherapy or a combination of chemotherapy and radiation therapy is increasingly a standard of care [25].

Dysphagia is a central symptom for the majority of patients with oesophageal cancer and the commonest presenting symptom [620, 702]. Prevalence of dysphagia is high in this population, with reports of dysphagia in 93% of patients with squamous cell carcinoma of the oesophagus, and in 79% of patients with adenocarcinoma of the oesophagus [703]. Most published research that reports on dysphagia in this population combines symptoms of dysphagia, without

distinguishing between the different phases (for example oropharyngeal versus oesophageal dysphagia), therefore, it is not clear how prevalent each type of dysphagia is in isolation. Complications of a swallowing difficulty in oesophageal cancer include malnutrition, weight loss, muscle weakness and wasting (sarcopenia), and tube-feeding reliance [168-171].

There is little known about the prevalence and severity of oropharyngeal dysphagia in oesophageal cancer. Research that has been conducted to date has been limited and consists mostly of retrospective cohort studies. Despite this, early studies have shown that oropharyngeal dysphagia may exist following surgery and radiation therapy, as well as prior to any cancer treatment [623]. An important observation, albeit in a small study of 10 participants by Martin et al [623], was that 9 out of 10 patients had mild oral-preparatory dysphagia and 100% of participants had at least mild oral and mild pharyngeal dysphagia prior to oesophageal cancer surgery. The characteristics most observed on videofluoroscopy (VFS) were impaired tongue movement, oral residue, hesitancy initiating the tongue stripping wave, impaired bolus formation, premature posterior spillage of the bolus from the oral cavity, delay in pharyngeal swallow initiation and post-swallow pharyngeal residue. VFS evaluation of swallowing also revealed altered hyoid trajectories in relation to the timing of its superior-most and anterior-most positions [623]. Post-surgery VFS studies have revealed that new-onset pharyngeal biomechanical impairments include reduced tongue pressure, reduced base of tongue to posterior pharyngeal wall approximation, delayed initiation of the pharyngeal swallow, reduced hyo-laryngeal elevation and excursion, reduced pharyngeal contraction, vocal fold immobility, and reduced maximum opening of the UOS during swallowing, resulting in symptoms such as overt and silent aspiration, and pharyngeal residue [249, 253, 620, 622, 623, 626].

Surgery for oesophageal cancer is associated with complications in between 50-60% of patients [51, 52]. Complications that may contribute to oropharyngeal swallowing deficits include

anastomotic leaks, anastomotic scarring or inflammation, radiation-induced inflammation, fibrosis and strictures, endotracheal tube trauma, adhesion of the gastric tube to the trachea, and mechanical denervation and inflammation of key nerve pathways such as the vagus nerve, Ansa Cervicalis or the pharyngeal plexus [620-626]. A study by Mafune et al (2019) reported RLN paralysis in 65.6% of patients, as observed on laryngoscopy in 21 patients on post-operative day 1 [150]. Operation time greater than or equal to 6 hours and vocal cord paralysis were found to be risk factors for subglottic aspiration with a high probability of occurrence (42.3%) if either risk factor was present [61]. The most likely mechanism impairments are insufficient vocal fold closure and impaired laryngeal sensation [627].

The most closely associated complication of surgery for oesophageal cancer is postoperative pulmonary complications (PPCs), in particular pneumonia, which occurs in approximately 25% of patients and is the most common cause of death [64, 65]. The presence of dysphagia postoperatively is an independent risk factor of pneumonia [340]. Berry et al (2010) [340] found that 12% of patients had evidence of aspiration, hence approaches that minimise aspiration and aspiration pneumonia are clinically of great relevance to achieving optimum outcomes for these patients. Improving swallowing would be expected to reduce aspiration, reduce pneumonia and PPCs, and may impact on sarcopenia and malnutrition, treatment-related morbidity, hospital length of stay and readmissions [257, 258, 340, 341].

Health-Related QOL Complications of Dysphagia in Oesophageal Cancer

The impact of a swallowing difficulty on the health-related QOL of a person with oesophageal cancer can also be devastating, leading to anxiety during meals and limiting participation in family mealtimes and social occasions [380]. Health-related QOL was found to be significantly impaired 10 years after both open oesophagectomy and MIE across many domains including dysphagia, reflux, eating difficulties, oesophageal pain, trouble swallowing saliva, choking, dry mouth and taste problems, with eating difficulties being one of the most outstanding problems [373, 374]. A

study by Yuen et al (2019) [70] revealed that 29 survivors who were an average of 3.5 years post oesophagectomy, and who had no history of swallowing impairment, continued to present with a mild to moderate pharyngeal dysphagia on videofluoroscopy. Survivors have reported persistent swallowing difficulties 5 and 10 years after treatment, demonstrating that this is a chronic issue in need of addressing [374].

Dysphagia Rehabilitation in Oesophageal Cancer

There is limited research exploring swallowing rehabilitation in oesophageal cancer. In one recent systematic review, Kaneoka et al (2018), [257] found four studies that evaluated dysphagia intervention in this population. Three of these four studies investigated the chin tuck postural strategy. This strategy compensates for a deficit during the act of swallowing, as opposed to rehabilitative exercises, which aim to induce long-term improvements to swallow function. Only one included study evaluated dysphagia rehabilitation in their review [69].

It is widely known that patients with head and neck cancer suffer significant short-term and long-term dysphagia, impacting upon their QOL and activities of daily living [388], and that swallow rehabilitation in head and neck cancer has improved QOL and dysphagia outcomes such as severity of aspiration and pharyngeal efficiency [389-395]. It is currently not known if and how swallow rehabilitation may improve swallowing, and if there are any contraindications for its use with patients with oesophageal cancer. Systematic review findings may guide clinical decision-making regarding dysphagia rehabilitation and inform future research in this area.

Study Aims:

3. To determine the effectiveness of dysphagia rehabilitation in improving clinical outcomes (oral intake status, pneumonia and swallow) and health related QOL outcomes in adults with oesophageal cancer across time points.

4. To identify key elements of rehabilitation (delivery, dose, intensity, timing, adverse events and fidelity) which may inform future research of dysphagia rehabilitation in oesophageal cancer.

Methods

Registration

The guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [720] were adhered to. The protocol was registered on the PROSPERO database of prospectively registered systematic reviews (reference number CRD42020172029; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=172029).

Search Strategy

Six electronic databases (CINAHL Complete, MEDLINE, EMBASE, Web of Science, CENTRAL, and ProQuest Dissertations and Theses) were searched for eligible studies. One author (GS) designed and ran a systematic search across all six databases for the concepts “oesophageal cancer”, “dysphagia/deglutition” and “rehabilitation”, using controlled vocabulary and synonyms and related terms in the titles and abstracts, and then combined as appropriate. Four remaining databases (OpenGrey, PROSPERO, RIAN and SpeechBITE) were searched by the first author (AG) using the term ‘(o)esophageal cancer’. All literature published since inception up until November 2020 was considered to ensure that a thorough search of the literature was completed. Publications from any country of origin and written in any language were deemed eligible, and were translated using online professional tools and a professional interpreter. Clinical trial registries (ClinicalTrials.gov, ISRCTN, WHO Trial Registry) were searched by the first author (AG). Reference lists of relevant studies and a manual search on Google Scholar were also completed by the first author (AG) to ensure literature saturation. In addition, the first author (AG) completed a manual search of relevant conference proceedings of the annual congresses of the Dysphagia

Research Society, the European Society for Swallowing Disorders, the European Society for Diseases of the Oesophagus, and the International Society for Diseases of the Oesophagus from inception. Reference checks and citation tracking were conducted to ensure all relevant articles were retrieved for analysis. The reference manager software, EndNote, was used to manage references.

Study Selection

Inclusion and exclusion criteria were applied independently to the articles by 2 reviewers (AG, MH). All published and non-published peer-reviewed randomized control trials (RCTs), quasi-experimental designs, observational studies, conference presentations, abstracts and non-systematic reviews were included in the search criteria due to the limited number of publications in this area of research to date. Grey literature was searched to locate relevant non-published studies. The first author (AG) attempted to obtain further information on relevant studies reported in conference abstracts. Expert opinions, letters to editor, commentaries, editorials, and textbooks were excluded. Full texts were retrieved, and inclusion and exclusion criteria were re-applied independently to the articles by 2 reviewers (AG, MH).

Eligibility Criteria

Participants

Inclusion criteria for participants encompassed adults (≥ 18 years old) undergoing curative intent resection (oesophagectomy) and/ or neoadjuvant therapy for oesophageal cancer, who had a swallowing disorder of any severity, and who participated in rehabilitative intervention to improve their swallowing disorders. An oesophagectomy is defined as a type of surgery whereby part of or all of the oesophagus is removed. Both methods of surgery (open or minimally invasive) were included. Participants of any gender and ethnicity with any stage and type of cancer at any location in the oesophagus were included. There was no restriction on settings. Participants were excluded if they presented with other conditions known to impact on swallowing (for example the

presence/history of stroke, neurodegenerative disease, head and neck cancer) or if palliative treatment was being provided. Participants with gastric cancer were excluded.

Interventions

Articles for inclusion were studies that investigated dysphagia rehabilitation in oesophageal cancer. All intensities and durations of rehabilitation were included. A clear definition of dysphagia rehabilitation exercises was created to ensure that results retrieved were not compounded by compensatory strategies. A dysphagia rehabilitative exercise was defined, for the purpose of this systematic review, as *an exercise which aims to create lasting functional change to the efficiency, strength, coordination and safety of an individual's swallow by improving underlying physiological function, rather than compensating for a deficit in the moment*. This includes strength-based exercises, skill-based exercises and sensory-rehabilitative exercises. The main goal of strength training is the enlargement of the muscle fibres (hypertrophy) [721]. Skill-based training aims to modulate the cortex resulting in adaptive swallowing practices, such as increased precision and timing of swallowing [722]. The intent of sensory-based rehabilitation is to produce long-term changes in the organisation of sensory and motor areas of the cerebral cortex, as sensory input has been proven to alter the excitability of the motor cortex (cross-system plasticity) [723].

With respect to our review, dysphagia rehabilitation did not include compensatory interventions, which were defined as *strategies implemented at the time of swallowing that aim to temporarily compensate for the swallow dysfunction or compromised airway*, for example food/fluid texture and volume modification, head and neck postures, environmental/utensil/pacing modifications etc. Studies were excluded if their only focus was compensatory intervention. Studies that contained both rehabilitative exercises and compensatory strategies were included.

Dysphagia rehabilitation was considered for inclusion if it was prior to, during or at any time-point following participants' surgical or neo-adjuvant treatment for oesophageal cancer.

Comparison

Groups were considered for comparison of outcome measures if they received:

- No intervention
- Usual care that did not include rehabilitative exercises, for example compensatory strategies (as defined above).
- A placebo or control group (for example if patients received a sham intervention such as with Expiratory Muscle Strength Training when they breathe into a device with no resistance).
- The same or different dysphagia rehabilitation programs.

Outcome Measures

A comprehensive list and definition for all outcomes was prepared in line with the PRISMA 2020 statement 10a [591]. Oral intake was considered to be the main outcome given its significant relevance to both clinicians and patients.

The three primary outcome measures for examination were:

4. Oral intake: Change in oral intake status, for example, feeding-tube reliance rated on the Functional Oral Intake Scale [181].
5. Respiratory Complications: Incidence of respiratory complications including pneumonia indicated by the presence of new/worsening chest x-ray or computed tomography (CT) results and defined by the Centre for Disease Control (CDC) [581] and the Standardized Endpoints for Perioperative Medicine (StEP) collaborative network [582].
6. Quality of Life: Change to swallow-related QOL scores on validated scales such as the MD Anderson Dysphagia Intervention Questionnaire [583] or SWAL-QOL (Swallow Quality of Life Questionnaire) [189].

The Secondary Outcomes were:

7. Change to patient-reported dysphagia ratings on validated scales, for example, the EAT-10 (Eating Assessment Tool- 10) [176].
8. Instrumental measures of swallowing including change in pharyngeal pressures as determined by pharyngeal high-resolution impedance manometry (PHRIM), change in timing of swallowing as determined by instrumental swallow evaluation and using a validated scale (such as the MBS Impairment Profile or the Dynamic Imaging Grade of Swallowing Toxicity-DIGEST), change in incidence, frequency or volume of laryngeal penetration/aspiration, and safety of swallowing, as determined by instrumental swallow evaluation (VFS or Fiber-Endoscopic Evaluation of Swallowing (FEES)), and a validated tool (such as the Penetration-Aspiration Scale (PAS) [525] or Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) [531]), change in efficiency/residue of swallowing as determined by instrumental swallow evaluation and using a validated scale (for example the MBS Impairment Profile [216] or DIGEST or PHRIM).
9. Time taken in days to return to oral intake.
10. Hospital length-of-stay in days.
11. Nutrition: Change to nutritional status such as using a validated tool for measuring weight loss, malnutrition, sarcopenia, cachexia, dehydration for example the MUST (Malnutrition Universal Screening Tool) [584]
12. Adverse events such as increased fatigue, deterioration of swallow function or patient discomfort.

All pre-intervention, peri-intervention and post-intervention (including long-term) outcomes measurements were recorded.

Data Extraction

Data was extracted independently by two authors (AG, MH) through a data extraction form specifically designed for the purpose of this study. If a study presented with any missing or unclear

data, study authors were contacted in an attempt to resolve uncertainties. Disagreements were resolved by consensus and consultation with a third review author (JR). Four main domains were explored: participant characteristics; study characteristics; intervention characteristics; and outcomes of interest. Data regarding key intervention components such as delivery, intensity, timing, fidelity and adherence were collected using the TIDieR checklist (Template for Intervention Description and Replication)[585]. This instrument contains 12 items that describe a trial's completeness of reporting of interventions. Yamato et al (2018) [735], developed a TIDieR Summary Score for this tool, where elements are scored '0' if something is not reported, '1' if partially reported, and '2' if adequately reported. Once data were extracted, they were merged into tabular forms on a Microsoft Excel spreadsheet.

Data Analysis

The authors intended to tabulate all information relevant to each outcome. The authors aimed to stratify data by patient characteristics such as tumour site, tumour type, surgical approach, site of anastomosis, partial resection, and total oesophagectomy in order to conduct thorough meta-analyses. If meta-analyses were not possible, the authors planned to conduct descriptive synthesis of the data, focusing on all primary and secondary outcomes. Information would be aggregated in a spreadsheet under appropriate outcome headings. Comparable outcomes would then be combined for discussion and included in tables.

Assessment of Methodological Quality

Risk of bias assessment of the selected studies was completed independently by two authors using the ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) Tool [586]. An overall judgement about risk of bias was made regarding the entire study. The case series study is of a particularly weak study design and 'No information' was a common response to the signalling questions meaning that there is insufficient information to make a judgement on the risk of bias. As a result, the Downs & Black Checklist [587] was selected as an adjunct quality assessment tool

given its suitability for assessing quality of randomised and non-randomised studies, and given that its questions are less specific in nature and allow more information to be elicited from studies of weaker designs. In this review, the scoring of item 27, that refers to the power of the study, has been modified as per previous research [588]. Total scores range from 0 to 28, with higher scores indicating a stronger methodological quality study. Hooper et al (2008) suggest score ranges that correspond to levels of quality: Excellent (26-28), Good (20-25), Fair (15-19), and Poor (≤ 14) [598].

The GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) was conducted to determine the certainty of the systematic review as a body of evidence, as this may assist clinicians with the development of health care recommendations [589, 590].

Results

Study Selection

Figure 1 presents the final study selection flowchart based on the systematic search. A total of 7938 articles were retrieved from the 10 databases and 3 Clinical Trial registries. Twenty-one full text articles were reviewed [AG & MH], eighteen of which were excluded mostly due to study design (such as review articles and observational studies). In line with the PRISMA 2020 statement, 16b [591], a list of the excluded full text articles, and reasons for their exclusion, can be reviewed in the Appendices. Three studies were included based on the inclusion and exclusion criteria outlined above. Included studies varied in methodological design (case control study, case series, retrospective case control study). A meta-analysis could not be completed due to the limited data in the studies and the heterogeneity across studies in terms of the participant characteristics, rehabilitation exercises implemented, the timing of the interventions, the measuring tools and the outcomes measures.

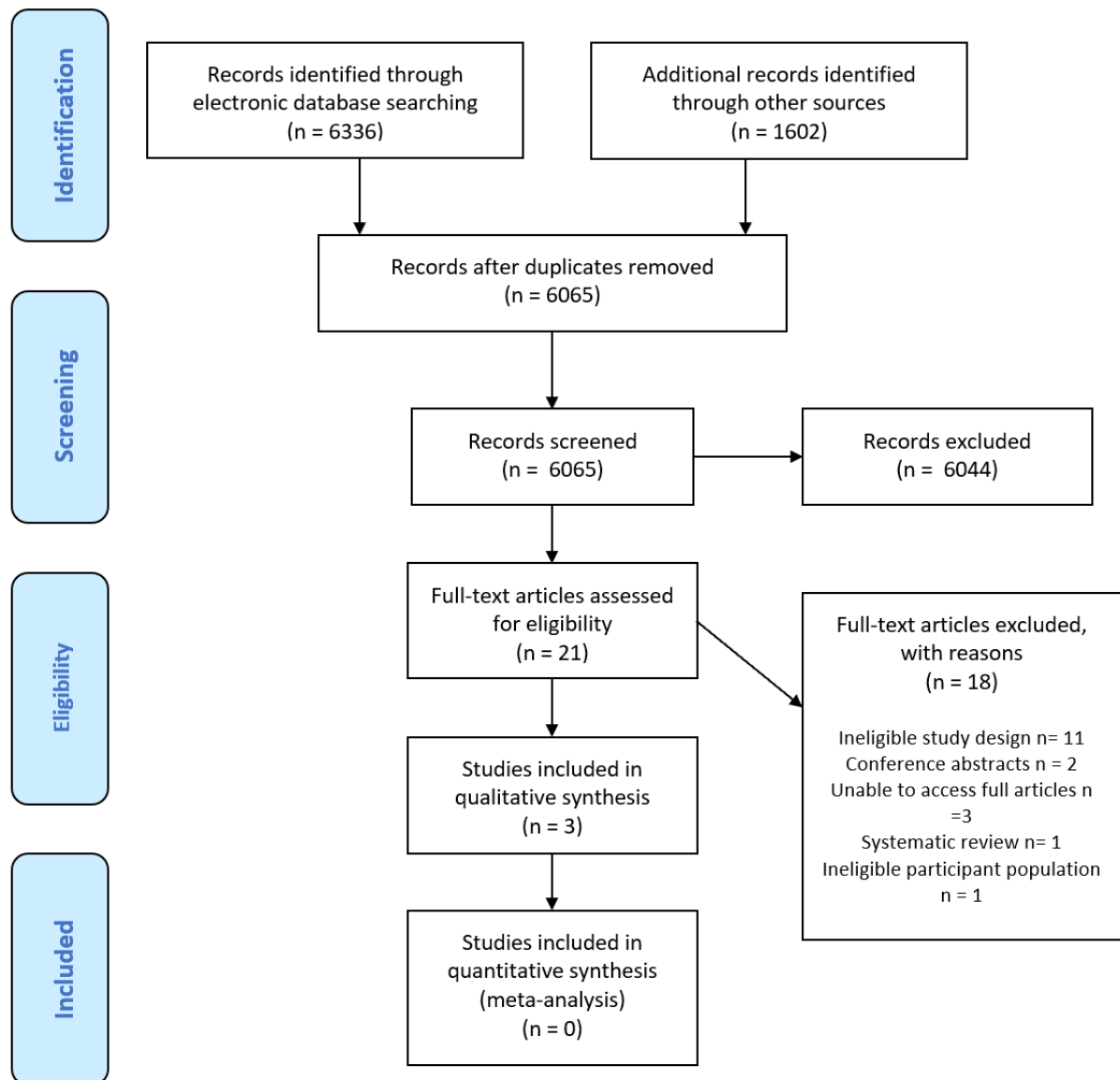


Fig. 1 PRISMA 2009 Flow Diagram

Baseline Characteristics

Three studies with a combined total of 311 participants who underwent oesophagectomy with thoracoscopy met inclusion criteria [36, 68, 69]. All three studies evaluated the impact of exercise-based dysphagia interventions on swallow related outcomes in adults with oesophageal cancer. Participants were enrolled over a minimum 15-year period up to December 2018. Each of these studies were completed in single centre settings in Japan. The authors were from different research teams at different hospitals. They focused on the short-term effects of peri-operative exercise-based dysphagia intervention on swallow-related outcomes. The case control study

contained a control group, which comprised historically collected data from 14 participants who attended hospital from January 2012 to March 2013. The treatment group included 12 participants who attended hospital between April 2013 and September 2014 while a swallowing rehabilitation program was in place. There were 9 participants in the case series. In the third retrospective case control study, 167 participants who received dysphagia rehabilitation were compared to 109 patients who had previously received standard care. Demographic characteristics from the three included studies are outlined in Table 1 below.

Authors, year	Study Design	Study Setting	N	Age	Sex	Co-morbidities	Stage of cancer	Location of cancer	Type of cancer treatment	Complications post-surgery	Dysphagia Assessment for Outcomes
Okumura et al, 2016 [69]	Case Control Study (CCS)	Toyoma University Hospital, Japan	26	CG; Mean 65.9 +/- 9.7 yrs. TG: 68+/-5.1 yrs.	CG: 13/1 M:F TG: 12 M	NI	TNM Classification (JES) -I/II CG: 11 (78.6%) TG: 5 (41.7%) -III/IV CG: 3 (21.4%) TG: 7 (58.3%) TNM Classification (UICC) - I/II CG:12 (85.7%) TG: 8 (66.7%) -III/IV CG: 2 (14.3%) TG: 4 (33.3%)	Thoracic	"Oesophagectomy" 5 participants: neoadjuvant chemotherapy	CG: RLNP (n=4) AP (n=3) AL (n=2) TG: RLNP(n=2), AP (n=3) AL (n=2)	Non-validated: 1. Functional Outcomes Assessment Measure of Swallowing (FOAMS) Scale. 2 Measured relevant biomechanical positions and volumes on x-axis and y-axis plots from VFSS images
Tsubosa et al, 2005 [73]	Case Series (CS)	Shizuoka Cancer Hospital Rehabilitation Dept., Japan	9	Mean 57.8 +/- 9 yrs	9 M	Cases 1: Hx of RTC; 2: old age; 3: Hx of stroke and abnormal shape of epiglottis; and 4: abnormal shape of epiglottis.	NI	Thoracic	"Oesophagectomy"	RLNP (n= 5. 1 of which was bilateral resulting in severe AP)	Non-validated: VFSS rating tool suggested by Logemann, 1998 [70]

						The remaining 5 cases had no relevant co-morbidities that may affect swallowing					
Takatsu et al, 2020 [69]	Single centre retro-spective case control study	Aichi Cancer Centre Hospital, Japan	276	CG; median 68 (IQR 64-74) TG; 69 (IQR 62-73)	CG: 91/18 M:F TG: 142/25 M:F	NI	TNM Classification (UICC) -I/II CG: 49 (45%) TG: 56 (45%) -III/IV CG: 60 (55%) TG: 91 (55%)	Thoracic	CG: Neoadjuvant therapies: 87 (80%) Thoracoscopic oesophagectomy Open Oesophagectomy Cervical anastomosis TG: Neoadjuvant therapies: 133 (80%) Thoracoscopic	CG: RLNP 22 (20%) Pneumonia 25 (23%) AL: 8 (7%) TG: RLNP 34 (20%) Pneumonia 39 (23%) AL 22 (13%)	4. Start of oral intake 5. Length of oral intake rehabilitation 6. Length of postoperative stay

									oesophagecto my Open oesophagecto my Cervical anastomosis		

Key: Std Dev = Standard Deviation. NI = No Information provided. RLNP = Recurrent Laryngeal Nerve Palsy. AP = Aspiration Pneumonia. VFSS = Videofluoroscopy. CG = control group. TG = treatment group. JES = Japan Esophageal Society, UICC = Union for International Cancer Control. Yrs. = years. AL = Anastomotic Leak. Hx = history. RTC – radiotherapy for tongue cancer.

Participant characteristics

Two-hundred and sixty-seven of 311 (86%) participants across studies were male. Within treatment groups, the average age ($\pm$ standard deviation) was 68 ($\pm$ 5.1) years in the case control study and 57.8 ($\pm$ 9) in the case series, whereas median age was 69 years in the retrospective case control study. In the control groups [36, 69], 114/122 participants were male with an average and median age of 65.9 ($\pm$ 9.7) years [36] and 68 years respectively [69]. Within the three studies, there were unmatched participant characteristics such as the severity of dysphagia experienced, co-morbidities, and the types, locations and stages of oesophageal cancer, surgical approach, site of anastomosis, partial resection, and total oesophagectomy. Four participants in the case series had medical histories which the study's authors reported may have pre-disposed them to dysphagia, including history of radiotherapy for tongue cancer, 'old age', history of cerebral infarct and altered epiglottis shape respectively. Therefore, outcome results for these participants are not included in this review as per our exclusion criteria.

Intervention Characteristics

Intervention characteristics from the included studies are outlined in Table 2. None of the studies provided rationales for selection of the rehabilitation exercises based on swallow pathophysiology of this clinical population. Furthermore, no studies reported information to adequately address the second aim of this review, that is, regarding the mode, frequency, intensity, duration and dose of intervention.

Please see Table 2 for more information on intervention characteristics of the included studies.

Table 2 Intervention characteristics of included studies

Authors, year	Exercises with Rehabilitative Purpose	Other Exercises and/or Compensatory Strategies	Mode, Frequency, Intensity, Duration Dosage of Intervention	Timing of dysphagia rehabilitation in relation to start of cancer treatment	Duration of rehabilitation (Mean +/-Std dev)
Okumura et al, 2016 [69]	Pursed lip breathing [71], Tongue exercises [72], Shaker "head lift" exercises [73]	Cervical range of motion exercise Shoulder stretch Jaw opening Respiratory therapy Compensatory strategies: Modified food and fluids.	SLT & nurses in the surgical ward delivered initial verbal & written instruction. See Appendix 3 for instructions. Exercises x5 a day at home and upon admission to the hospital, up until the day before surgery. Unclear if patient-led thereafter.	Prehab: Approximately 23+/-9.2 Days preoperatively Rehab: from the time oral intake was resumed after confirming the absence of anastomotic leakage post-surgery.	Prehab: 23+/-9.2 Days pre-surgery. Rehab: 26+/-15 days post-surgery.
Tsubosa et al, 2005 [73]	Mendelsohn manoeuvre. [592] Long lasting change may have also potentially occurred from the super-supraglottic swallow [592-597]	Oral care Neck and shoulder exercises Oral exercises Thermal tactile stimulation Super-supraglottic swallow Effortful breath hold Compensatory strategies: Multiple swallows, chin down, Modified food and fluids.	Article states 'Intensively' however no definition or information provided. See Appendix 4 for information on exercises.	Post-operative- unknown precisely when.	9.7 +/- 6.9 days post-surgery. 5/9 participants required more than 1 round of rehabilitation.

Takatsu et al, 2020 [69]	Indirect training: Tongue exercises [72] Shaker exercise [73] Jaw opening [80] Thermal-tactile stimulation [81] Voice therapy [82]	Direct training: Education provision Training while eating jelly: Position adjustment- chin down Effortful swallows, supraglottic swallow, adjusted bolus size supervised. Food and fluid intake increased based on patient progress.	No detail provided on duration, frequency or intensity of indirect or direct training.	Modified water swallow test (MWST) completed by SLT after routine CT on POD 5 or 6. Patients with intermediate or high aspiration risk based on MWST provided with indirect and, if possible, direct rehabilitation.	Not provided

Key: Std Dev = Standard Deviation. SLT = Speech and language therapist. Prehab = Prehabilitation. Rehab = Rehabilitation

Rehabilitation Results

Quantitative analysis of data in the three articles was not possible given the heterogeneity of studies (analysis conducted, interventions used, outcomes measured) and the small number of participants. Very few outcomes were reported by more than one study. Given the lack of core outcome sets for this type of research, and the few existing studies, there was insufficient and inadequate data that could be pooled together to conduct quantitative meta-analysis. Therefore, descriptive synthesis of the data was conducted focusing on the primary and secondary outcomes. All information provided was initially aggregated in a spreadsheet under an appropriate outcome heading. Comparable outcomes were combined for discussion and included in tables. All outcome results are discussed below. The key results are outlined in Table 3. Results are presented across outcome categories below.

Primary Outcomes

Extent of oral intake

In one study [36], participants underwent dysphagia prehabilitation prior to surgery, as well as dysphagia rehabilitation following surgery. Both the treatment and control groups scored 7 out of 7 on the Functional Outcomes Assessment Measure of Swallowing (FOAMS) Scale prior to prehabilitation and following prehabilitation, indicating efficient and functional swallowing. The FOAMS score following surgery and prior to rehabilitation was higher for the treatment group than the control group, with average (+/- standard deviation) scores of 5.6 (+/-1.2) and 4.7 (+/-1.4) respectively, with a p value of 0.054, where 7 indicates functional, safe and efficient swallowing, and 0 indicates a profound swallow impairment necessitating only non-oral means of nutrition.

FOAMS scores at discharge were significantly worse than prior to prehabilitation for the control and treatment groups with average (+/- standard deviation) scores of 5.5 (+/- 1.3) and 6.3 (+/- 0.8) respectively (p value ≤ 0.01 for both groups). Perioperative swallow rehabilitation resulted in significantly higher swallow function scores for the treatment group discharge compared to the control group (p value = 0.049).

Respiratory Complications

One study evaluated respiratory complications and found no significant difference in aspiration pneumonia rates between a dysphagia rehabilitation treatment group (25%) and a control group (21.4%) (p=0.83) [36]. In this same study, there was a non-significant reduction in rehospitalisation for pneumonia within three months of surgery in the treatment group (n=0) compared to controls (n=3). Of note, a clear definition of aspiration pneumonia was not provided in this study [36].

None of the studies reported on QOL outcomes.

Secondary Outcomes:

Instrumental Measures of Swallowing

One of three included studies evaluated swallow biomechanics using VFS in the treatment group only [36]. Within this treatment group, the VFS examination took place pre-prehabilitation, pre-operatively and an average of 11 days (SD 5.5) post-esophagectomy. A significant increase in maximum superior excursion of the hyoid bone during swallowing was observed with intervention ($p=0.046$), whereas anterior hyoid movement and anterior-posterior diameters of upper oesophageal sphincter (UOS) opening did not change. Of note, the methods used to measure hyoid excursion and UOS opening during VFS were not validated [36].

One study evaluated a change in pharyngeal residue with dysphagia intervention [36]. In this study, residue was rated based on the VFS evaluation by measuring volume (height x weight) of pharyngeal residue after the initial swallow [36]. Based on VFS, a significant decrease in pharyngeal residue was found following prehabilitation in a subgroup of patients with pyriform residue at baseline ($p=0.047$) ($n=4$). In another study [68], no improvement was noted in one participant with residue in the valleculae and pyriform sinuses although a validated rating scale was not used.

Change in aspiration status was only reported on two participants in one study [68]. In these two cases, “mild” aspiration improved to “normal”, and “severe” silent aspiration improved to “normal”. A validated rating scale to measure aspiration was not used.

Length of Hospital Stay

Two studies evaluated effects of dysphagia intervention on post-operative length of hospital stay (PLOHS) and they had conflicting results [36, 69]. While a more recent post-operative dysphagia intervention combining indirect and direct rehabilitation significantly shortened PLOHS from 22 (17-27) to 19 days (15-27.5) ($p=0.001$) [69], PLOHS was increased from 32 (+/-12) to 36 (+/- 11) days in a smaller, combined pre- and post-operative rehabilitation study, although this increase was not significant ($p=0.22$) [36] (Table 3).

Time to return to oral intake

Two of three studies measured time to return to oral intake with conflicting results. One small study found no reduction in return to oral intake with rehabilitation (9.6 v 11 days; $p=0.32$) [36], whereas a more recent, larger study found a significantly shorter return to oral intake in the dysphagia treatment group compared to the control group (11 v 8 days; $p=0.009$) [69].

Nutrition

One study found no significant difference in weight change between dysphagia rehabilitation treatment (91.4% $\pm$ 5.8) and control (90.6% $\pm$ 5.5) groups three months post-surgery ($p=0.36$) [36]. No other nutritional measures were used across the included studies.

None of the studies noted patient-reported dysphagia outcomes or adverse events in hospital.

The Key Findings are outlined in Table 3 below.

Table 3: Summary of Key Findings Table

Authors, year	Respiratory	Oral intake	Penetration / Aspiration	Pharyngeal residue	Biomechanical change to swallow	Nutrition	Time to return to oral intake: Days (average +/- SD)	LOHS after surgery: Days (average ± SD)	Quality Assessment	Tidier Checklist
Okumura et al, 2016 [69]	AP: CG = 3pts (21.4%) TG = 3pts (25%) p=0.83 Rehospitalisation for pneumonia within 3 months after surgery: CG =3 (21.4%), TG = 0.	FOAMS scores suggest primary mode of intake prior to and following surgery for all participants was oral means of nutrition.	Not reported h/e FOAM scores of 4,5,6 post-surgery and post- rehab suggest compensatory strategies needed, which may indicate risk of pen/asp. Number of participants with these scores not provided.	4 participants had pyriform sinus residue prior to prehabilitation ; the volume decreased significantly following prehabilitation , with a p value of 0.047 Between start of rehab post-surgery and post rehab: volume of laryngeal vestibule and PS residue decreased significantly (p values of 0.031	From prior to prehab to post prehab, and from post-surgery to post-rehabilitation: the TG's maximum superior excursion of hyoid bone increased significantly during swallowing with p values of 0.03 and 0.046 respectively. No significant difference between the maximum anterior	Not reported. Body weight change 3 months after surgery (% average +/- SD) was CG: 90.6% +/- 5.5 TG: 91.4% +/- 5.8 (p value= 0.36)	CG: 9.6+/-5.3 TG: 11+/- 5.5 (P = 0.32)	CG: 32.4 ± 12.2 TG: 36.1 ± 10.7 (p=0.22)	ROBINS-I: Serious Downs & Black: 13 (poor)	9

				and 0.027, respectively)	excursion of the hyoid bone or the anteroposterior diameters of the UES					
Tsubosa et al, 2005 [73]	1 participant developed 'severe' AP. Other severities of AP not mentioned. No post-discharge AP.	Data provided not clear.	Data available for n=2 only: 1 had mild aspiration improved to normal. 2 nd had severe penetration and aspiration did not improve, but severe silent aspiration improved to normal.	Limited f/u data available h/e no improvement noted in the 1 participant with mild vallecular and PS residue	NI	NI	One participant: diet recovered to 'independence' on the 6th day. Otherwise, unclear when oral intake recommenced.	25.3 days for 8 participants . 96 days for remaining participant. No further detail given.	ROBINS-I: Critical Downs & Black: 1 (poor)	5
Takatsu et al, 2020 [69]	NI	NI	NI	NI	NI	NI	Start of oral intake significantly earlier in treatment group TG: 8 days (6-13) CG: 11 days (8-14)	CG: 22 days (17-27) TG: 19 days (15-27.5)	ROBINS-I: Serious Downs & Black: 15 (fair)	10

Key: Pen/Asp = penetration/ aspiration. QOL = Quality of Life. LOSH = Length of stay in hospital. NI = No information. RLNP = Recurrent Laryngeal nerve paralysis. AP = aspiration pneumonia. AL = Anastomatic leak. CG = control group. TG = treatment group. PS = pyriform sinus. UES = Upper oesophageal sphincter. Pts. = participants. H/e = however. F/u = Follow up

Quality Assessment

The quality of all three studies was limited by numerous factors such as measuring outcomes using non-standardised rating tools, not documenting inclusion and exclusion criteria, implementing rehabilitation exercises without clear rationale based on swallow pathophysiology, and not considering or accounting for the impact of other treatments that participants may have been receiving at the same time. Inadequate analyses were conducted in the case control study and the case series, for example, neither study reported confidence intervals, standard error of means or estimates of random variability.

The case series was particularly weak. Participants were discharged if they did not show overt signs of aspiration with a whole meal of porridge and fluids; an instrumental assessment was not completed meaning that participants may have been discharged with subclinical aspiration, and there was no report of any further monitoring of their respiratory statuses. As a result of not conducting a VFS at the end of rehabilitation, there was no follow up data available for 4/9 participants. Only those who required a further round of rehabilitation had one additional VFS prior to starting the second round of rehabilitation. There was also a lack of clarity regarding definitions such as 'mild aspiration' and 'severe aspiration'. Finally, authors of the case series reported that 8 participants did not achieve 'severe' aspiration pneumonia, however, other severities of pneumonia are not reported on, nor the method for measuring this outcome.

Based on the ROBINS-1, the case control study[36] and retrospective case control study[69] were found to have a serious risk of bias in one domain 'Bias of Confounding', and low risk of bias or 'No information' across all other domains. As the lowest domain score is considered to be the overall risk of bias for the study, these studies were deemed to have a 'serious' risk of bias. With regard to the case series, two domains scored 'Low'; 'Bias in classification of intervention' and 'Bias due to deviations from intended interventions', however 'Bias of Confounding' was found to be at a 'critical' risk of bias. Therefore, this study is given an overall rating of a 'critical' risk of bias.

According to the Downs and Black checklist, the retrospective case control study was deemed to be fair quality [598] and the other two studies were low quality [36, 68] (please refer to Appendices 5 and 6 for more information on the ROBINS-I and the Downs and Black Checklists respectively). The TIDieR checklist demonstrated relatively low scores regarding completeness of reporting of the interventions (checklist score range 5-10). While the retrospective case-control study [69] scored 10/24, the case control study scored 9/24 and the case series scored 5/24.

Discussion

Main Findings

This systematic review found only three eligible studies, including a total of 311 participants, which examined the effects of exercise-based dysphagia rehabilitation in adults with oesophageal cancer. It was not possible to complete a meta-analysis because of the lack of comparable data that could be pooled together. These studies provided limited evidence to support dysphagia rehabilitation in this clinical population. The limited evidence was restricted to clinical and functional outcomes including time to oral intake and length of hospital stay. None of the included studies investigated the impact of dysphagia intervention on quality of life or patient reported outcome measures, and there was very limited data on changes to swallow biomechanics and aspiration status. Furthermore, no data was obtained relating to the second aim of this study, for example, delivery, dose, intensity, timing, adverse events and fidelity which may have assisted with directing future research of dysphagia rehabilitation in oesophageal cancer. Finally, included studies focused on prehabilitation and post-surgical rehabilitation before hospital discharge, whereas no studies were found which evaluated the long-term benefit of dysphagia intervention post discharge in the community. While identification of these gaps in the evidence base is of concern, these issues can be addressed within future research in this area.

VFS results in the case series confirmed the presence of oral and pharyngeal dysphagia in participants who received an oesophagectomy and otherwise had no relevant medical history [68]. A small number of cases were followed up (n=2) following post-surgical rehabilitation and authors reported improved laryngeal elevation, reduced aspiration and reduced silent aspiration across these participants. Perioperative rehabilitation in the case series [36] resulted in significantly better swallow function scores for the treatment group compared to the control group at the time of discharge, indicating that swallow function is improved by perioperative dysphagia rehabilitation. Interestingly, the treatment group was found to have better swallow efficiency following surgery than the control group indicating that exercises conducted during prehabilitation may help to minimise the impact of surgery on swallowing. Further high-quality research investigating the benefits of prehabilitation is warranted. Despite these gains, the case control study did not find significant improvements to respiratory status, time to return to oral intake or hospital length of stay following surgery.

The authors of the case series suggested that there is a high risk of severe aspiration in participants with bilateral RLN paralysis, but not with unilateral palsy. The retrospective case study found that 20.3% of participants experienced RLN paralysis as diagnosed by head and neck surgeons via fiberoscopy. 66.7% of these patients were found to have moderate or low risk of aspiration on videofluoroscopy at least day 5 days post-operatively.

The impact of presbyphagia, meaning normal healthy age-related swallow changes, must be taken into account when considering the swallowing presentation of this cohort as signs of presbyphagia do not constitute a swallowing impairment and must not be considered as oropharyngeal manifestations in people with oesophageal cancer. For example, 39% of healthy adults with a mean age of 73 presented with pharyngeal residue on FEES, in a study by de Lima et al in 2018 [736], however, 15% of oesophageal cancer participants in the case control study [69]

experienced a significant increase in residue following oesophagectomy compared to pre-surgery ($p = 0.003$ and $p = 0.0031$ for laryngeal and pyriform sinus residue respectively). Any potential impact of age related swallow changes may be relevant when considering the two main cancer types; in particular individuals with adenocarcinoma, as the global incidence rate of oesophageal cancer is highest in adults over 70 years of age [12], with incidence of oesophageal adenocarcinoma in the US peaking at 80-84 years for men and 85 years + for women [14]. The global median age of squamous cell carcinoma has been reported to occur at 67.5 years [13]. It is noted that the mean age across the three included studies is approximately 65 years, with no details provided on the types of cancer that participants presented with.

Existing Research

Despite the significant impact of dysphagia throughout the oesophageal cancer journey, both from a clinical perspective and on an individual's QOL, little is known about the benefit of dysphagia rehabilitation to optimise oropharyngeal swallowing in this population. A previous systematic review completed by Kaneoka et al (2018) [257] focused on four questions, one of which examined the efficacy of rehabilitative interventions for oropharyngeal dysphagia in oesophageal cancer. Their search, which was conducted in August 2017, was limited to 5 databases and only included studies which used VFS or FEES, and which contained more than 5 participants. Three of the 4 studies included in their review focused on compensatory strategies to temporarily optimise swallowing, and 1 focused on rehabilitative exercises. Consequently, their review differs from our systematic review, which consisted of a broad literature search of 10 databases, 3 clinical trial registries and proceedings from 4 conferences to ensure literature saturation and included studies that did or did not use instrumental assessment. We focused specifically on exercise-based dysphagia rehabilitation by developing a definition that would differentiate rehabilitative exercises from compensatory strategies to focus only on long-lasting

functional change. Our results retrieved an additional case series and retrospective case control study.

Multi-disciplinary management of oesophageal cancer is strongly recommended to maximise recovery, including the improvement of clinical and QOL outcomes [25, 101, 708-710]. In addition to medical and surgical interventions, rehabilitation can be provided to patients prior to, during or following oesophageal cancer treatment. Cancer prehabilitation involves the delivery of rehabilitation between diagnosis and acute treatment to reduce post-operative morbidity and improve functional recovery, and it has been found to improve clinical outcomes in oesophageal cancer [431]. Bolger et al (2019) [431] completed a systematic review on prehabilitation and rehabilitation in oesophagogastric malignancies and found that a preoperative exercise programme led to a reduction in perioperative morbidity, most notably pulmonary complications. These findings are significant given that a proportion of patients do not progress to curative treatment because of physiological and nutritional deterioration [432].

Recent advances in dysphagia research include the development of validated rating scales, improved understanding of optimum intervention dosages, the development of new interventions guided by underlying swallow pathophysiology and better awareness of adherence promotion and goal-oriented treatment. As a result of this and improved research quality, the evidence base for dysphagia rehabilitation is emerging across clinical populations including head and neck cancer [37-44] where a need for further high quality research appears to be under way in a proposed randomised control trial by Martino et al [737]. There is a strong rationale for exercise-based dysphagia rehabilitation in oesophageal cancer to optimise clinical and quality of life outcomes. However, robust research is required to identify the nature of this intervention to guide clinical practice.

Study Limitations

This systematic review has a number of limitations that warrant consideration. Firstly, given the relatively new field of dysphagia rehabilitation, all study designs were eligible for inclusion in this review. As a result, included studies presented with weak study designs and limited data. The inclusion of non RCT studies in a systematic review may impact upon confidence in interpreting findings, because of potential biases, which the authors have attempted to minimise through implementing a rigorous, methodological approach when conducting this review. A meta-analysis was not possible due to the heterogeneity of these non-randomised control trials, particularly in terms of evaluation methods, outcome data, timing and type of intervention. Further information regarding the differences between the studies is listed in Tables 1 and 2, and expanded upon under Quality Assessment. The study authors all utilised non-validated outcomes meaning that the results outlined may be unreliable. The lack of information on the intensity, frequency and duration of intervention was alarming, and as a result, it was not possible to address the second aim of this review. In addition to this, the case series did not define its exercises. Consequently, it was not possible to confirm with certainty which exercises met our definition of rehabilitative exercises. Many of the outcomes anticipated by authors of this review were not reported on in either study including quality of life measures, self-reported dysphagia outcomes, and adverse events. The most recent study included in this review, the retrospective case control study [69], was of the highest methodological quality which is promising. Nonetheless, non-blinding of raters and limited information on co-morbidities and intervention dosage limited the rigour of this study. As a result, the quality of this body of evidence as a whole is deemed to be of 'low quality', as per the GRADE approach [66][589]. This may of course change when more evidence of higher quality is published.

Secondly, this systematic review included articles in any language. Dutch, Japanese and German articles were excluded at the title/abstract screening stage using online translation tools and with assistance from a professional Japanese interpreter. The case series full article was professionally

translated from Japanese characters to English. As a result of using Japanese interpreters and online translation tools, some information may have been misunderstood, which potentially could have contributed towards the Reporting Bias perceived in the case series. Finally, this systematic review excluded letters to editors which may potentially have included useful information about trials, however, none were retrieved during the screening. Despite these limitations, an important purpose of systematic reviews is to demonstrate when evidence is lacking in a particular area to guide future research [738] as observed in previous studies [739] According to the Cochrane Collaboration, although a minimum of two studies is required to complete a meta-analysis, there is no minimum number necessary to complete a systematic review, as long as relevant studies have been retrieved [740-743].

Implications for Policy, Practice and Future Research (using EPICOT) [744].

This review highlights the need for randomised controlled trials to evaluate the effectiveness of dysphagia rehabilitation in improving swallowing function and safety in adults with a diagnosis of oesophageal cancer. Important outcomes to be measured include extent of oral intake, incidence rates of aspiration pneumonia, swallow-related quality of life, instrumental measures of swallowing including aspiration, patient reported dysphagia outcomes, time to return to oral intake, length of time in hospital, nutrition, and adverse events. Research leading to the development of core outcomes sets to be used across studies would help to provide comparable data for the assessment of efficacy. Clear data should be provided on participant characteristics including tumour histology, tumour location, surgical approach, partial/total oesophagectomy, anastomosis site, co-morbidities, sex, age, ethnic group, and inclusion or exclusion criteria. The importance of rehabilitation dosage and frequency, adherence promotion, biofeedback and goal-oriented treatment is recognised in dysphagia research and should all be integrated into intervention design. Adverse events should also be commented on given their relevance for both

clinicians, patients and the potential for adverse events to decrease patient adherence to rehabilitation programmes.

Conclusion

Despite the prevalence and impact of dysphagia in oesophageal cancer, no systematic review has previously attempted to summarise the evidence for exercise-based dysphagia rehabilitation in patients receiving curative treatment for oesophageal cancer. This systematic review included three studies and no meta-analysis was possible due to study heterogeneity. It revealed that there is very limited low-quality evidence that dysphagia rehabilitation may result in functional swallowing improvements, faster return to oral intake and reduced length of hospital stay. However, no evidence regarding reduction in aspiration rates or aspiration pneumonia and no patient reported outcomes were found. As survivorship for this population is increasing, the findings from this review will guide the design of future high-quality research in this area.

10.2 Appendix C Published Study on the Nature, Severity and Impact of Chronic Oropharyngeal Dysphagia following Curative Resection for Oesophageal Cancer

Title: Nature, Severity, and Impact of Chronic Oropharyngeal Dysphagia following Curative Resection for Esophageal Cancer: A Cross-Sectional Study

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Introduction

Esophageal cancer (EC) is the seventh most common cancer worldwide and is responsible for approximately 1 in every 20 cancer deaths[1, 2]. 5-year survival rates are low at approximately 20-25% overall, rising to approximately 50% for patients with locally advanced disease who can be treated with curative intent, and up to 90% for patients diagnosed with Stage I cancer[2, 3, 7]. Many factors have improved survival trends, including the centralisation of esophageal cancer surgeries, the use of trimodality therapy and pre- or perioperative chemotherapy, the development of enhanced recovery after surgery (ERAS) protocols, and increased early diagnosis through surveillance of Barrett's esophagus cohorts[9-11].

With improved prospects of survivorship, there is an increased clinical and research focus on health-related quality of life (HR-QL), in particular in patients who have undergone surgery[363, 745, 746]. The nutritional consequences, and the impact on muscle mass and conditioning, have dominated reported research, however the impact of surgery on swallowing function has been rarely studied[150]. It is known notwithstanding that symptoms of dysphagia can be present years following surgery, and that dysphagia may be an independent predictor of HR-QL in survivorship[52, 70, 362, 747]. In this context however, few studies have explored the nature and severity of oropharyngeal dysphagia throughout survivorship, and studied it systematically. Accordingly, further investigation is necessary to gain a more comprehensive understanding of

the nature and severity of chronic oropharyngeal dysphagia (COD) through survivorship, as well as its psycho-social impact on patients. In addition, the prediction of COD could potentially assist with surgical decision-making and appropriate referrals for swallow assessments and support.

In this cross-sectional prospective observational study we aimed to define the nature and severity of COD at a minimum of 12 months post EC resection, and its impact on aspiration risk and QL, and to determine risk factors relating to operative approaches.

Methods

The STROBE Statement guidelines[748] were adhered to (See Appendix). Forty participants (10 females, 30 males) were recruited from the National Center for Esophageal Cancer in Ireland via purposive sampling. Ethical approval was granted by the Tallaght University Hospital Research Ethics Committee. Eligible participants had undergone a transthoracic (2 or 3-stage en bloc) resection or transhiatal resection at least 12 months prior. A 3 stage approach included an abdominal and neck exploration for mid and upper-esophageal cancers (mostly squamous cell carcinomas), with a 2 stage approach including an abdominal exploration for most lower third and junctional tumors (typically adenocarcinoma)[749]. 1 field and 2-field lymphadenectomies were completed. Exclusion criteria included a history of oropharyngeal dysphagia, neurological impairment, head and neck cancer, recurrent esophageal disease, severe COPD, and cognitive impairment. The first author accessed a dataset established in the data collection site which contained details of all patients who had undergone esophageal resection at the National Center of Esophageal Cancer. Using this information along with data collected from the hospital information system, the first author selected eligible participants, to whom a participant information leaflet and cover letter were posted, followed by a phone call 7 days later. Eligible participants from anywhere in Ireland were selected in chronological order from the database. The intention was to recruit roughly the same number of participants who underwent cervical and thoracic anastomoses. It was not known whether any of these participants had

ongoing swallowing difficulties. Those who wished to participate in this prospective study, and who met the inclusion criteria outlined above, were provided with an appointment time for the next available assessment. Informed verbal and written consent were obtained. The same protocol was used for all participants.

A Patient and Public Involvement group, including two esophageal cancer survivors (>5 years post-surgery), assisted with the selection of appropriate outcomes and assessment tools. Data collection took place from November 2021 to August 2022. Each participant underwent a standardised videofluoroscopy (VFSS) exam and completed swallowing related questionnaires. See the outcomes measured and tools utilised in Table 1.

Table 1: Outcomes and tools

	Outcome measured	Source
Swallow safety, efficiency, pathophysiology	Presence of pharyngeal dysphagia	Dynamic Imaging Grade of Swallowing Toxicity v2 (DIGEST v2)[217].
	Presence and depth of laryngeal penetration/aspiration, response to airway invasion	Penetration-Aspiration Scale (PAS)[525]
	Nature of oropharyngeal swallow impairment	Modified Barium Swallow Impairment Profile (MBSImp) [216]
Oral Intake Status	Functional Oral Intake	Functional Oral Intake Scale (FOIS)[181]
Patient reported dysphagia	Self-reported functional impact of swallowing	EAT-10[176]

Reported QL Impact	Self-reported impact of oropharyngeal dysphagia on QoL	MD Anderson Dysphagia Inventory (MDADI)[583]
Clinical Information	Age, sex, type of cancer, location of cancer, stage of cancer	Medical files
Surgical Information	Surgical approach, site of anastomosis, date of surgery, type of neoadjuvant treatment, length of stay in ICU, months since surgery	Surgical files

Videofluoroscopies were conducted by the first named author (AG; an experienced speech and language therapist) and a radiographer using continuous fluoroscopy, and recorded on TIMS DICOM (Foresight Imaging LLC) whilst captured at 25 frames per second, a commonly used frame rate in Europe[750] due to the 50Hz power standard. Consistencies were prepared according to the International Dysphagia Diet Standardisation Initiative (IDDSI) framework[513] and using standardised recipes including 20% weight to volume (w/v) concentration of barium contrast (Maxibar™ 98.45% w/v)[751] [512]. Participants were initially seated upright with head and neck in a neutral position to gain a lateral view of the lips and anterior oral cavity, the soft palate superiorly, the cervical spine posteriorly, and the proximal cervical esophagus inferiorly. Barium trials consisted of IDDSI Level 0 water presented by cup (2 x 5ml, 2x 10ml, 2 x uncontrolled volume sequential sips), IDDSI Level 4 water by spoon (2 x 5ml bolus), and half a Level 7 cracker (Carr's Table Water Crackers) with 3mls of level 4 barium on top. Participants were repositioned to an anteroposterior viewing plane, which showed the inferior pharynx superiorly and cervical esophagus (if still intact) inferiorly. During trials, the radiographer tracked the bolus inferiorly towards the gastric cardia/body (if still intact). Barium trials included level 0 water by cup (2x

20ml), Level 4 water by spoon (2 x 5ml), and 1 x 13mm barium tablet. Further information on the protocol is included in Supplemental Table 1. Inter-rater agreement, completed by two experienced MBSImP certified clinicians who were blinded to participant information and results, was completed on 25% of the VFSS ratings and measured using a two-way random model assessment on SPSS[532]. Airway protection was determined using PAS (Penetration-Aspiration Scale), an 8-point ordinal scale. The worst score for each consistency was recorded[525]. Results were grouped into safe (1), penetrating (2-5), and aspirating (6-8) categories. Presence and severity of pharyngeal dysphagia were rated using the Dynamic Imaging Grade of Swallowing Toxicity v2 (DIGESTv2) protocol; an ordinal scale (0 =no pharyngeal dysphagia, 4 =life threatening pharyngeal dysphagia[217]). For the purpose of this study, *pharyngeal dysphagia* refers to a diagnosis of dysphagia on the DIGESTv2 only (i.e. an abnormal score). The DIGESTv2 captures only two, albeit important, markers; swallow safety and swallow efficiency. Additional swallow pathophysiological findings were rated using the MBS Impairment profile (MBSImP). The MBSImP includes physiologic measures of oral, pharyngeal and esophageal function during swallowing, rated on ordinal scales from 0-2, 0-3 or 0-4 (where 0 is normal), with the highest score representing the Overall Impression Score[216]. For this study, the term ‘chronic’ refers to ongoing dysphagia a minimum of 12 months post surgery.

EAT-10 is a patient-reported self-administered tool that is validated with a wide array of swallowing disorders[176, 752-754]. Scores ≥ 3 indicate difficulty swallowing[176, 755] (range: 0-40, where 40 =severe impairment). The FOIS indicates a feeding tube requirement (1-3), modified/avoided food/fluid consistencies (4-6), or no food/fluid restrictions (7)[181]. The MDADI is a self-administered questionnaire containing 19 items with adequate validity and reliability in identifying the impact of dysphagia in head and neck cancer patients[583]. (Normalised score of 20 =extremely low functioning, 100 =high functioning /QL[566]).

Statistical Analysis

SPSS Version 24 (SPSS, Inc, Chicago, IL, USA) was used for data analysis. Subgroup analyses examined differences in dysphagia, aspiration and QL results (DIGESTv2, PAS, MBSImP, EAT-10, FOIS, MDADI) for various subgroups (surgical approach, site of anastomosis, age, cancer location, cancer type, radiotherapy). A dichotomous variable (aspirators/non-aspirators) was used given the small number of aspirators (n=2). A mean rank Kruskal-Wallis H-test was utilised as the non-parametric equivalent of one-way ANOVA when distributions of each group did not have the same shape, and as an alternative to the Mann Whitney U when independent variables contained more than 2 categories. Fisher Helton Exact Test was used as the sample size was small and non-parametric[560]. For aim 3, regression analysis assessed for predictors (age, months since surgery, cancer type, cancer stage, surgical approach, site of anastomosis, radiotherapy, days in ICU, self-reported dysphagia (EAT-10), oral intake status (FOIS)) of COD (DIGESTv2). Univariate binary logistic regression analyses were completed because the independent variables were dichotomous.

One participant did not complete the questionnaires and these missing data were excluded.

Results

40 patients (30M/10F) were recruited, with a mean (range) age of 66 (43-84) years, with 23 (57.5%) adenocarcinoma, 12 (30%) squamous cell cancer, 3 (7.5%) high grade dysplasia, and 2 (5%) intramucosal carcinoma. 24 (60%) tumors were at the esophagogastric junction, 10 (25%) in the lower esophagus, and 6 (15%) in the mid esophagus. 21 participants (52.5%) had undergone a radical 2 stage en bloc esophagectomy, 10 (25%) a radical 3 stage en bloc resection, and 9 (22.5%) a transhiatal resection, all with gastric conduit reconstruction. The mean (range) time since surgery was 52 months (13-125). Inter-rater agreement on videofluoroscopy ratings was good-to-excellent: 82.2% (i.e. ICC 2,2 =.822) on the MBSImP (98.8% of responses were within one point difference or less), and 93.75% and 94.9% on PAS and DIGESTv2 scores, respectively.

Nature, severity, and impact of chronic oropharyngeal dysphagia: 14 (35%) participants presented with dysphagia on the DIGESTv2 (score >0), 11 (27%) had mild dysphagia, (score =1), 1 (3%) had moderate dysphagia (score =2) and 2 (5%) had severe dysphagia (score =3). All participants had at least one impaired component on MBSImP; 40 (100%) had impaired swallow initiation, 36 (90%) had pharyngeal residue, 32 (80%) had reduced anterior hyoid excursion and impaired esophageal clearance. The frequency of impairment across components is shown in Figure 1. Bars are highlighted when frequency is $\geq 70\%$ to visually convey the six most frequently impaired components (oral residue, swallow initiation, laryngeal elevation, anterior hyoid excursion, pharyngeal residue, and esophageal clearance). The components whose median (interquartile range (IQR)) results were impaired (>0) include oral residue 2(0,2), swallow initiation 2(2,3), laryngeal elevation 1(0,1), anterior hyoid excursion 1(1,1), pharyngeal stripping 1(1,1), upper esophageal segment opening 1(1,1), tongue base retraction 1(1,2), pharyngeal residue 2(1,2), and oesophageal clearance 1.5(1,2). The median scores for each MBSImP Component are presented in Fig 2.

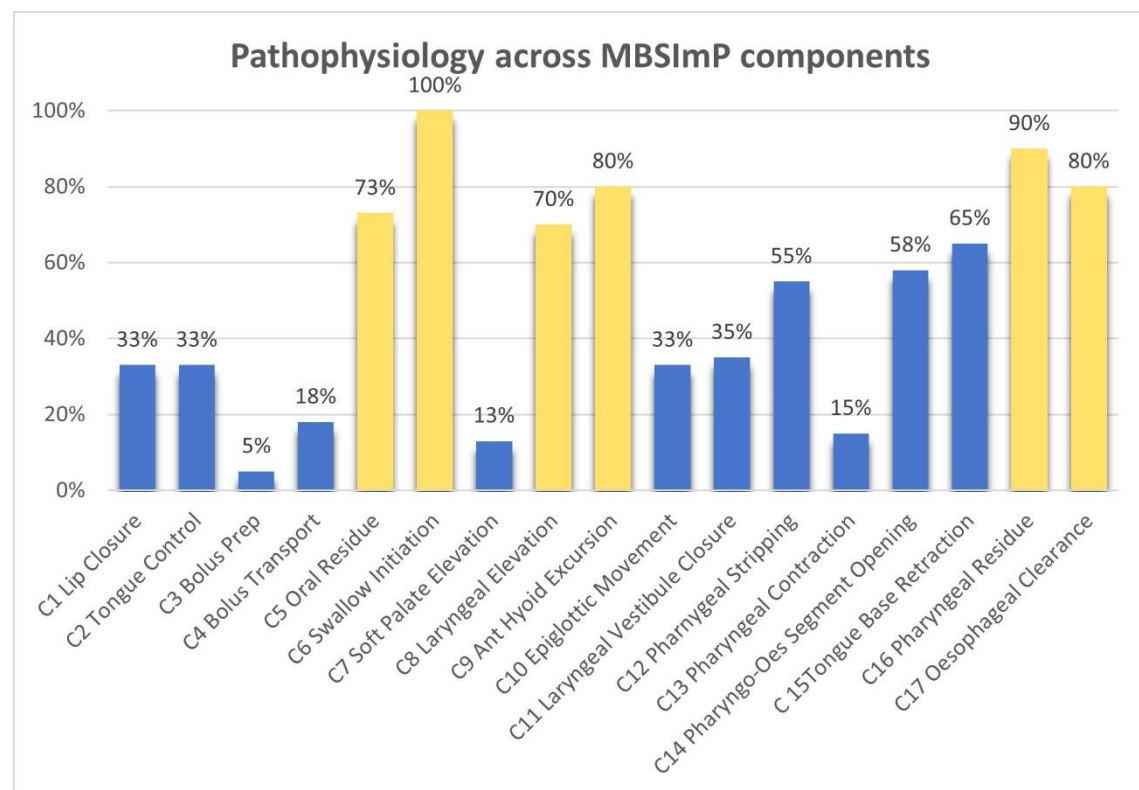


Fig 1 Percentage of Participants with Impairments on 17 MBSImp Components

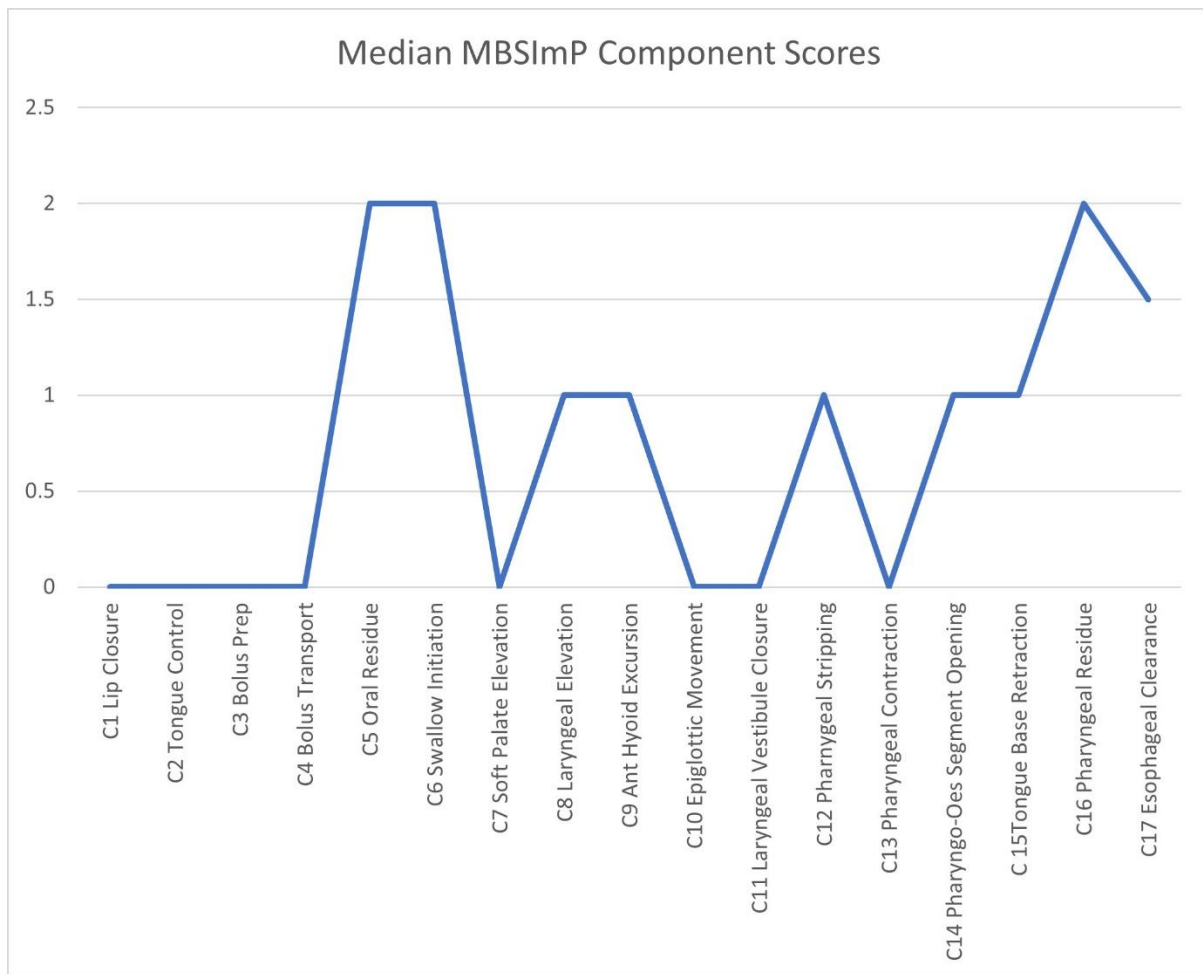


Fig 2 The median scores for MBSImp Components

The median (IQR) scores for dysphagia, aspiration and swallow physiology are: DIGESTv2: 0 (0,1), PAS: 1(1,1), MBSImp Total Oral Score: 4(3,6) and Total Pharyngeal Score: 7(3.25,9). 21 (54%) participants scored >3 on the EAT10 which indicates abnormal swallowing [176]. The median (IQR) results for patient-reported outcomes are: FOIS: 7(6,7), EAT-10: 3(0,14), MDADI Global: 5(4,5) and MDADI Composite 77.9 (60.0,92.6). 17 (43%) participants scored <7 on the FOIS indicating either avoidance (30%) or modification of certain/all food consistencies (13%). Table 2 provides descriptive results (mean, SD, range, median, and IQR) for the entire cohort regarding dysphagia and aspiration outcomes, swallow pathophysiology, and patient-reported outcomes

(relating to oral intake status, dysphagia, and QL). Individual participant level breakdown of each of these scores is shown in supplemental table 2.

Table 2: Dysphagia, aspiration and QL results across the entire cohort.

	Mean +/- Std Dev Scores	Median/IQR	Range
DIGESTv2 (n=40)	.49+/- .79	.00/ 0-1	0-3
PAS (n=40)	1.54 +/- 1.502	1/1-1	1-8
MBSImP Total Oral (n=40)	4.82 +/- 2.293	4/3.0-6.0	1-10
MBSImP Total Pharyngeal (n=40)	6.36 +/- 3.004	7/3.25-9.0	1-11
FOIS (n=40)	6.49 +/- .683	7/6-7	5-7
EAT-10 (n=39)	7.79 +/- 9.163	3/0-14	0-30
MDADI Global (n=39)	4.21 +/- 1.105	5/4-5	1-5
MDADI Composite (n=39)	76.302 +/- 18.9564	77.895/60.0-92.6	32.6-100

With respect to aspiration, 2 (5%) participants had uncleared penetration on the PAS, 2 (5%) had uncleared laryngeal aspiration, 4 (10%) effectively cleared laryngeal penetration, and 32 (80%) did not have laryngeal penetration or aspiration. A visual of a participant aspirating a sip of thin fluid is displayed in Figure 3.

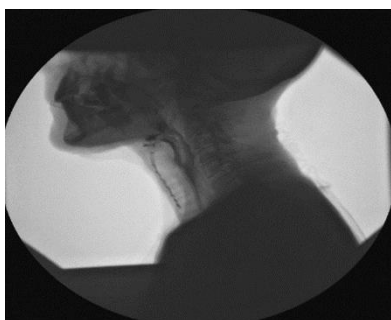


Fig 3 Aspiration observed on videofluoroscopy

The background information across thoracic and cervical (2 stage and 3 stage) groups is outlined in Table 3.

Table 3 Comparison of background information, surgical information, and dysphagia, aspiration and QL results across surgical groups.

	2 stage n=21 (52.5%)	3 stage n=10 (25%)	Transhiatal n=9 (22.5%)	$\chi^2(2), p$
Age: Mean rank (mean)	19.88 (65.1)	16.85 (62.8)	26 (71.7)	3.037 .219
Sex	3 females 18 males	4 females 6 males	3 females 6 males	2.749 .253
Cancer Type	Adenocarcinoma =18 scc =2 Intramucosal =1	Adenocarcinoma =2 scc =8	Adenocarcinoma =3 scc =2 High Grade Dysplasia =3 Intramucosal =1	13.73 .001
Recurrent nerve palsy	0	1	0	ns

Location of cancer in esophagus	Middle:0 Lower:3 EGJ:18	Middle :5 Lower:2 EGJ:3	Middle: 1 Lower:5 EGJ:3	13.053 .001
Months since surgery Mean Rank (Mean)	 12 (44)	 28.9 (79)	 31 (76)	 23.552 <0.001
No penetration or aspiration n(%) Mean Rank	 17(80%) 20.31	 8(80%) 20.5	 7(78%) 29.94	 2.033 .367
Penetration n(%) Mean Rank	 4(19%) 19.69	 2(20%) 19.5	 0 23.5	 .039 .981
Aspiration n(%) Mean Rank	 0 21.5	 0 21.5	 2(22.2%) 17.06	 7.070 0.029
Dysphagia Present n(%) Mean Rank	 6(28.5%) 21.79	 4(40%) 19.5	 4(44.4%) 18.61	 .823 .663
FOIS<7	7(33.3%)	3(30%)	7(77.8%)	5.796

n(%)	22.33	23	13.44	.055
Mean Rank				
EAT-10<3	10(47.6%)	5(50%)	6(66.7%)	.754
n(%)	20.75	20.75	17.5	.686
Mean Rank				

Key: scc = squamous cell carcinoma, EGJ = esophagogastric junction

Oropharyngeal dysphagia, aspiration and dysphagia-related QL results across cervical and thoracic subgroups: Comparing cervical and thoracic anastomotic cohorts (Table 4), the median (IQR) results for dysphagia (DIGESTv2), penetration/aspiration (PAS), oral and pharyngeal pathophysiological impairments (MBSImP Total Oral and MBSImP Total Pharyngeal Scores), oral intake status (FOIS), self-reported dysphagia (EAT-10), and QL (MDADI) are the following: DIGESTv2 : .00 (.0,1) -v- .29 (.0,1) ($p = .246$), PAS: 1(1,1) -v- 1(1,1) ($p=.816$), MBSImP Total Oral Scores: 4(3,5) -v- 5(3.5,7) ($p=.098$), MBSImP Total Pharyngeal Scores: 7(5,8) -v- 7(3,10) ($p=.935$), FOIS: 6(6,7) -v- 7(6,7) ($p=.251$), EAT-10: 5(.0, 17) -v- 2.5(.1, 12) ($p=.648$), MDADI Global: 5(4,5) -v- 5 (4,5) ($p=.853$) and MDADI Composite: 73.7(55.8, 93.7) -v- 81.6(67.1, 91.6) ($p=.811$).

Table 4 Median (IQR) and mean rank dysphagia, aspiration and QL results across the cervical and thoracic subgroups.

<u>Median (IQR)</u> <u>Mean rank, p-value</u>	Site of Anastomosis	
	Cervical (n = 19)	Thoracic (n=20)
DIGESTv2	.00, (.0,1)	.29, (.0,1)
	$\chi^2(1)= 1.349, p = .246$	
PAS	1, (1,1)	1, (1,1)
	$\chi^2(1)= .054, p = .816$	
MBSImP Total Oral	4, (3,5)	5, (3.5,7)
	$\chi^2(1)= 2.731, p = .098$	
MBSImp Total Pharyngeal	7, (5,8)	7, (3,10)
	$\chi^2(1)= .007, p = .935$	

FOIS	6, (6,7)	7, (6,7)
	$\chi^2(1)= 1.318$, $p = .251$	
EAT-10	5, (.0,17)	2.5, (.0, 12)
	$\chi^2(1)=.208$, $p = .648$	
MDADI Global	5, (4,5)	5, (4,5)
	$\chi^2(1)=.034$, $p = .853$	
MDADI Composite	73.737, (55.789,93.684)	81.579, (67.105,91.579)
	$\chi^2(1)=.057$, $p = .811$	

There were no significant differences across subgroups (type of cancer, location of cancer, age, site of anastomosis, or neo-adjuvant treatment) for any dysphagia, aspiration or QL outcomes (Supplemental Table 3). However, as aspiration was only evident in patients who had undergone a transhiatal resection, a subgroup analysis was conducted across the three surgical groups to further explore whether the surgical approach might have been relevant. Results revealed a statistically significant difference ($\chi^2(2)= 7.07$, $p<0.029$). None from the transhiatal group penetrated but 4 (19%) patients who had a 2 stage resection, and 2 (20%) who had a 3 stage resection, showed penetration ($\chi^2(2)=.039$, $p=.981$). 4 (44.4%) patients who had undergone a transhiatal resection had dysphagia on the DIGEST compared to 6 (28.5%) 2 stage and 4 (40%) 3 stage resection patients ($\chi^2(2)=.823$, $p =.663$). 7 (77.7%) in the transhiatal cohort scored below 7 on the FOIS, compared with 3 (33.3%) 2 stage and 3 (30%) 3 stage ($\chi^2(2)= 5.796$, $p=.055$). For EAT-10, 6 (66.7%) in the transhiatal cohort had abnormal swallowing compared with 10 (47.6%) 2 stage and 5 (50%) 3 stage ($\chi^2(2)= .754$, $p =0.686$).

Clinical and surgical variables associated with pharyngeal dysphagia: FOIS scores were associated with pharyngeal dysphagia in this population ($p= .047$) based on DIGESTv2 results. The odds ratio of dysphagia (on DIGESTv2) for participants who scored <7 on FOIS (i.e., abnormal) was 4.05 (95% CI 1.03-16.00). The remaining variables (age, type and stage of cancer, months since

surgery, radiotherapy, surgical approach, site of anastomosis, days in ICU, and EAT-10) were not found to be predictors of pharyngeal dysphagia as illustrated in Table 5.

Table 5 Univariate regression model representing factors associated with pharyngeal dysphagia (DIGESTv2).

Predictor of Pharyngeal Dysphagia	p-value	Odds Ratio	95% CI
Age >65	.666	-	-
Type of cancer	.966	-	-
Stage of cancer	.880	-	-
Months since surgery	.336	-	-
Radiotherapy	.446	-	-
Surgical approach	.659	-	-
Site of anastomosis	.372	-	-
Days in ICU	.738	-	-
EAT-10	.064	-	-
Abnormal FOIS (<7)	.046	4.05	1.025- 16.007

Discussion

Long-term oropharyngeal dysphagia (COD) affects esophageal cancer survivors, with 35% of participants in our study presenting with COD and 10% experiencing uncleared laryngeal penetration/aspiration a minimum of 12 months (mean 51 months) following curative-intent esophageal cancer surgery. With respect to swallow physiology, 73% of participants presented with impaired oral components, 100% had impaired pharyngeal components, and 80% had impaired esophageal clearance. In addition, 43% of participants continued to modify or avoid certain food consistencies because of dysphagia and other aero-digestive issues, with a consequent adverse impact on HR-QOL. These data may be important in providing reference data

for these cohorts, and also to guide support considerations to esophageal cancer survivors as current international clinical practice guidelines do not recommend referrals to swallow specialists for assessment[429, 599].

The factors underpinning prolonged oropharyngeal dysphagia following esophageal cancer surgery are unclear. There were no significant differences in dysphagia, aspiration or QL outcomes depending on the site of anastomosis (cervical -v- thoracic). Of the surgical approaches, a transhiatal approach was the only operation associated with aspiration, and although non-significant, the transhiatal group was also poorer than 2- and 3-stage cohorts for dysphagia observed on VFSS, dysphagia reported by participants, and functional oral intake. Nevertheless, given that only 2 participants aspirated, a larger study would be required to determine if the surgical approach is relevant. In addition, the cervical anastomosis in a transhiatal resection is no different to that of a 3-stage resection, so it is possible that the age profile of these patients, with the transhiatal group significantly older, may be relevant, notwithstanding, age per se ($> vs < 65y$) did not significantly impact on this finding. Months since surgery was longest for the transhiatal participants so this is unlikely to be a cause. Patients who are deemed to be at a higher operative risk based on respiratory factors are typically selected for a transhiatal resection so it is therefore possible that their respiratory status contributed to these observations[628]. There were also statistically significant differences across surgical groups for the cancer type, location of cancer, and neo-adjuvant treatments received so any of these factors may likewise be relevant.

In terms of implications on eating patterns, FOIS scores below 7 (i.e., modifying/ avoiding certain food textures) were associated with pharyngeal dysphagia (based on DIGESTv2), and had a 4.05 times higher chance of having dysphagia compared to those who scored 7 (did not restrict/avoid food consistencies) (OR 4.05, 95% CI 1.03 – 16.00). This is important for the multi-disciplinary team (MDT) to be aware of because even if a patient is not reporting symptoms of dysphagia, their FOIS score may suggest that they would be appropriate for a swallow assessment

referral. The FOIS is not a dysphagia screening tool and was initially developed to evaluate oral intake/tube-feeding status, therefore, further research could explore the validity and reliability of existing MDT dysphagia screening tools to prevent missed opportunities for swallow assessment referrals.

If these data have clinical importance and relevance, how is it predicted, prevented, and treated? We recently conducted a systematic review which highlighted a paucity of evidence on dysphagia rehabilitation exercises both prior to and following esophageal cancer surgery[413]. Future studies could evaluate the efficacy of exercises specifically targeting the most frequently impaired pathophysiological impairments and symptoms of dysphagia detected in this current study including oral and pharyngeal residue, reduced laryngeal elevation, reduced hyoid movement, and delayed swallow initiation. Oral and pharyngeal residue may potentially be caused by reduced lingual and pharyngeal strength[320] secondary to sarcopenia, a known cause of dysphagia acutely post-esophagectomy [254], and therefore exercises targeting sarcopenic dysphagia may be beneficial to treat chronic symptoms. Research investigating the intricate inter-relationship between the neo-esophagus and pharyngeal swallow in this population is also warranted as some researchers have suggested that the esophagus has the ability to modulate the motor pattern of the oropharyngeal swallow[227], which could explain atypical behaviours seen in this study such as delayed swallow initiation. Reduced hyo-laryngeal movement could potentially be a consequence of esophageal shortening and stomach pull-up. Previous research identified how chronic hypertensive peristalsis exists in the upper esophagus following esophageal cancer surgery[248] and how upper esophageal sphincter relaxation is impacted by esophagogastric issues such as gastro-esophageal reflux and achalasia[638, 756], in what is hypothesised to be a protective mechanism against aspiration. It is therefore plausible that the upper esophageal sphincter may be hypertensive following esophageal resection to compensate for the absent lower esophageal sphincter, thereby tethering hyo-laryngeal movement and altering swallow physiology throughout the pharyngeal phase. It may be advantageous to consider

further interventions such as a free flap to improve hyolaryngeal function or behavioural strategies that relax the upper esophageal sphincter.

This study's limitations include the use of assessment tools that have not yet been validated with esophageal cancer patients. This was unavoidable as this research is in its infancy. The DIGESTv2 was the only tool used to diagnose dysphagia in this study. We recognise that this tool only evaluates airway protection and swallow efficiency (residue) as part of this diagnosis. The MBSImP allowed for greater exploration of pathophysiological function across all phases of swallowing. PAS was used to rate airway protection, however this measurement has been considered twice given that it is also a component of DIGESTv2. The FOIS was used to determine the participant's status of oral intake and although it was subsequently found to have an association with dysphagia, which may suggest that it could be used to prompt the MDT to refer a patient for a dysphagia assessment, it would be beneficial for future researchers to explore the reliability and validity of existing MDT screens for oropharyngeal dysphagia with this population. This study moreover included a relatively small sample size, particularly in the subgroup analyses. Furthermore, those who chose to participate may have had heightened concerns about their swallowing so results may not reflect the wider esophageal cancer survivor population. Limitations may be remediated in future research through consecutive admission sampling and multi-site recruitment.

In conclusion, in unselected survivors we report a high incidence of COD after esophageal cancer surgery and the most frequently impaired physiological components, providing novel data to the EC survivorship literature. For most, airway protection appears to be relatively intact, however the surgical approach used, may be associated with chronic aspiration. The FOIS is associated with pharyngeal dysphagia and could be a valuable prompt for the wider MDT to improve referrals for oropharyngeal swallow assessment. Further research is warranted to explore peri-rehabilitative dysphagia interventions and improve quality of life. Finally, the study suggests

an expanded role and value of the speech and language therapist within the ideal modern multidisciplinary esophageal cancer team.

10.3 Appendix D Ethics Form

APPLICATION FORM

For the Ethical Review of
Health-Related Research Studies, which are not Clinical Trials of Medicinal Products For Human
Use
as defined in S.I. 190/2004

DO NOT COMPLETE THIS APPLICATION FORM
IF YOUR STUDY IS A CLINICAL TRIAL OF A MEDICINAL PRODUCT

THIS APPLICATION FORM HAS BEEN ADAPTED FROM THE STANDARD APPLICATION FORM TO
COMPLY WITH THE DATA PROTECTION ACT (2018) AND THE DATA PROTECTION ACT (HEALTH
RESEARCH) REGULATIONS 2018: APPLICATIONS SUBMITTED ON OR AFTER 8TH AUGUST 2018
WILL ONLY BE ACCEPTED USING THIS VERSION OF THE FORM

REVISIONS ARE HIGHLIGHTED IN YELLOW

Title of Study: The nature, severity and impact of oro-pharyngeal and oesophageal dysphagia
in patients with oesophageal cancer from diagnosis through to survivorship

Application Version No: 1

Application Date: 20th February 2020

For Official Use Only – Date Stamp of Receipt by REC:

Table of Contents	Mandatory/Optional
SECTION A: GENERAL INFORMATION	MANDATORY*
SECTION B: STUDY DESCRIPTORS	MANDATORY*
SECTION C: STUDY PARTICIPANTS	MANDATORY*
SECTION D: RESEARCH PROCEDURES	MANDATORY*
SECTION E: DATA PROTECTION	MANDATORY*
SECTION F: HUMAN BIOLOGICAL MATERIAL	(OPTIONAL)
SECTION G: RADIATION	(OPTIONAL)
SECTION H: MEDICAL DEVICES	(OPTIONAL)
SECTION I: MEDICINAL PRODUCTS / COSMETICS / FOOD AND FOODSTUFFS	(OPTIONAL)
SECTION J: INDEMNITY AND INSURANCE	MANDATORY*
SECTION K: COST AND RESOURCE IMPLICATIONS, FUNDING AND PAYMENTS	MANDATORY*
SECTION L: ADDITIONAL ETHICAL ISSUES	(OPTIONAL)

This Application Form is divided into Sections.

*Sections A, B, C, D, E, J and K are **Mandatory**.

(Sections F, G, H, I and L are optional. Please delete Sections F, G, H, I and L if these sections do not apply to the application being submitted for review.)

IMPORTANT NOTE: Please refer to **Section I** within the form before any attempt to complete the Standard Application Form. **Section I** is designed to assist applicants in ascertaining if their research study is in fact a clinical trial of a medicinal product.

IMPORTANT NOTE: This application form permits the applicant to delete individual questions within each section depending on their response to the preceding questions. Please respond to each question carefully and refer to the accompanying *Guidance Manual* for more in-depth advice prior to deleting any question.

PLEASE ENSURE TO REFER TO THE ACCOMPANYING GUIDANCE MANUAL

WHEN COMPLETING THIS APPLICATION FORM.

SECTION A: GENERAL INFORMATION

SECTION A IS MANDATORY

A1. What is the title of the research study?

The nature, severity and impact of oro-pharyngeal and oesophageal dysphagia in patients with oesophageal cancer: from diagnosis through to survivorship.

A2. Is this a single site or multi-site study?

For single site studies: Answer questions A3 (a) and (b) and delete questions A3 (c), (d) and (e)

A3(a). Where will this single site study will take place?

A3(b). Who is the principal investigator with overall responsibility for the conduct of this single site study?

Title:

Name: Anna Gillman

Qualifications: BComm, MSc

Position: PhD Student

Dept: Department of Clinical Speech & Language Studies

Organisation: Trinity College Dublin

Address: 7-9 South Leinster Street, Dublin

Tel: 0874131127

E-mail: gillmana@tcd.ie

A4. Who are the co-investigators for this study?

Title:

Name: Julie Regan

Qualifications: BSc, MSc, PhD

Position: Assistant Professor

Dept: Department of Clinical Speech & Language Studies

Organisation: Trinity College Dublin

Address: 7-9 South Leinster Street, Dublin

Tel: 01- 8961492

E-mail: juregan@tcd.ie

Name of site (if applicable): St James's Hospital

Role in Research e.g. statistical / data / laboratory analysis: Supervisor, Research design, data analysis.

A4. Who are the co-investigators for this study?

Name of site (if applicable): St James's Hospital

Title:

Name: John Reynolds

Qualifications: MA, MB, BCh, MCh, FRCSI

Position: Specialty Upper GI Consultant, Professor and Head of Dept, Surgery, Trinity College Dublin
Dept: Upper Gastrointestinal Cancer
Organisation: Saint James Hospital
Address: James' Street, Dublin 8
Tel: 01- 4103595
E-mail: reynoldsjv@stjames.ie
Role in Research e.g. statistical / data / laboratory analysis: Supervisor. Patient recruitment. Research design and analysis.

A4. Who are the co-investigators for this study?

Name of site (if applicable): St James's Hospital

Title: *Name:* Claire Donohoe

Position: Specialty Upper GI Consultant

Dept: Upper Gastrointestinal Cancer

Organisation: Saint James Hospital

Address: James' Street, Dublin 8

Tel: 01- 4103595

E-mail: reynoldsec@stjames.ie

Role in Research e.g. statistical / data / laboratory analysis: Patient recruitment. Research design and analysis.

A4. Who are the co-investigators for this study?

Name of site (if applicable): St James's Hospital

Title: *Name:* Michelle Hayes

Position: Speech and Language Therapist, St James Hospital. PhD Student, Trinity College Dublin.

Dept: Speech and Language Therapy

Organisation: Saint James Hospital

Address: James' Street, Dublin 8

Tel: 0864089092

E-mail: mhayes6@tcd.ie

Role in Research e.g. statistical / data / laboratory analysis: Patient recruitment. Data collection and analysis.

A5. Who is the lead contact person i.e. the person to receive correspondence in relation to this application or be contacted with queries about this application.

Name: Anna Gillman

Position: Student

Organisation: Trinity College Dublin

Address for Correspondence: 7-9 South Leinster Street, Dublin

Tel (work): NA

Tel (mob.): 0874131127

E-mail: gillmana@tcd.ie

A6(a). Is this study being undertaken as part of an academic qualification?

If No, delete A6(b) and (c).

A6(b) If Yes, complete the following:

Student Name(s): Anna Gillman

Academic Course: PhD Clinical Speech and Language Studies

Academic Institution: Trinity College Dublin

A6(c) Academic Supervisor(s):

Title:

Name: Julie Regan

Qualifications: BSc, MSc, PhD

Position: Assistant Professor

Dept: Department of Clinical Speech & Language Studies

Organisation: Trinity College Dublin

Address: 7-9 South Leinster Street, Dublin

Tel: 01- 8961492

E-mail: juregan@tcd.ie

A6(c) Academic Supervisor(s):

Title:

Name: Margaret Walshe

Qualifications: BSc, MSc, PhD

Position: Associate Professor

Dept: Department of Clinical Speech & Language Studies

Organisation: Trinity College Dublin

Address: 7-9 South Leinster Street, Dublin

Tel: 01- 8962382

E-mail: walshema@tcd.ie

A6(c) Academic Supervisor(s):

Title:

Name: John Reynolds

Qualifications: MA, MB, BCh, MCh, FRCSI

Position: Specialty Upper GI Consultant, Professor and Head of Dept, Surgery, Trinity College Dublin

Dept: Upper Gastrointestinal Cancer

Organisation: Saint James Hospital,

Address: James' Street, Dublin 8

Tel: 01- 4103595

E-mail: reynoldsjv@stjames.ie

A7. Has an application been submitted to any other research ethics committee in relation to this study?

SECTION B: STUDY DESCRIPTORS

SECTION B IS MANDATORY

B1. What is the anticipated start date of this study?

B2. What is the anticipated duration of this study? State the anticipated duration in months or, if more than 12 months, in years.

B3. Provide a brief lay (plain English) description of the study. The description should be in the format of an abstract using the following headings: study background, research

aim(s), study design, study setting, participants (including selection and recruitment), data collection and processing, data analysis). Ensure the language used in your answer is at a level suitable for use in a research participant information leaflet. This section should not exceed 500 words.

Study Background:

Patients with oesophageal cancer experience dysphagia (swallowing difficulties) pre-oesophagectomy (surgery to remove part or all of the food pipe), during their chemotherapy /radiation therapy, and following oesophagectomy. Dysphagia can result in malnutrition, weight loss, tube feeding reliance, aspiration pneumonia (a lung infection caused by inhalation of food/liquid) and reduced quality of life. Further research is required to better understand the nature and cause of this swallowing impairment, as well as the psycho-social impact that it has on patients.

Study Design:

The proposed design is a cross-sectional prospective study.

Setting:

St James's Hospital.

Recruitment:

Patient and Public Involvement: Oesophageal cancer survivors attending an upcoming Oesophageal Cancer Fund event will be invited to assist with tasks such as improving patient information leaflets. In January, 2020, Anna Gillman and Julie Regan met with Noelle Ryan, the CEO of the Oesophageal Cancer Fund regarding patient/public involvement. There has not yet been any recruitment of oesophageal cancer participants for this study.

Patients will be recruited at three different time points during their cancer journey:

- 1) maximum 10 days post diagnosis,
- 2) maximum 14 days following neo-adjuvant therapy and before surgery
- 3) 12 months after oesophagectomy.

Study Aims and Method:

Patients will be recruited from St James's Hospital Clinical Research Facility. All eligible patients will be invited to participate through a gatekeeper, who is not involved in the research study, or by receiving a letter in the post with a Patient Information Leaflet. All patients who have provided written consent will be invited to participate in the study, which has two main aims.

- 1) To determine the nature, severity and impact of oro-pharyngeal and oesophageal dysphagia in patients with oesophageal cancer from diagnosis through to survivorship.

Background information will be collected at time points 1, 2 and 3 regarding participants' medical history and current swallowing abilities. Information regarding current swallow function will be ascertained from a swallow x-ray (Videofluoroscopy assessment). The Mayo Dysphagia Questionnaire will be administered to investigate self-reported swallowing difficulties and the MD Anderson Dysphagia Inventory (MDADI) to explore swallow-related quality of life. Patients may be sent the questionnaires prior to their appointment to give them adequate time to consider their responses before discussing their answers with the researcher.

2) To establish the diagnostic accuracy of clinical signs of dysphagia at the bedside (such as tongue strength, voice quality, malnutrition, cachexia and sarcopenia, self reported swallow outcomes) in predicting aspiration, aspiration pneumonia, tube reliance and quality of life from diagnosis through to survivorship.

Data will be collected at Time point 3 (post oesophagectomy surgery) regarding participants' surgical outcomes, height and weight, and participants' swallowing abilities during a bedside clinical assessment. In addition, data will be collected on self-reported swallow outcomes (EAT-10 questionnaire), observed swallowing (the 3 ounce swallow test), reflux (Reflux Symptom Index), voice function (GRBAS scale), tongue strength (IOPI assessment), sarcopenia risk (SARC-F questionnaire), nutritional status (MUST screen) and presence of cachexia (Weight Loss Grading Scale). Patients will be asked open-ended questions about their experience of living with dysphagia and/or dysphonia, and about the support they received from health care professionals for this. Patients may be sent the questionnaires prior to their appointment to give them adequate time to consider their responses before discussing their answers with the researcher.

Data analysis:

All data will be collected in an Excel database.

Statistical analysis will be completed within SPSS.

Descriptive and inferential analysis will be conducted. Thematic analysis may be conducted on answers to the open questions.

Question 1:

Based on exploratory analysis, the nature and severity findings from the videofluoroscopy will be analysed. Differences between subgroups will be tested.

Question 2:

An ROC curve will be established as a plot of test sensitivity as the y coordinate and its 1-specificity of False positive rate (FPR) as the x coordinate to evaluate the performance of diagnostic tests.

B4. Provide brief information on the study background. Ensure the rationale for undertaking the research is clear. This section should not exceed 500 words and five references.

Oesophageal cancer has one of the lowest 5-year survival rates (21.5%), and is the 5th most common mortality-causing cancer for men in Ireland (1). Oesophageal cancer can significantly impact a person's oro-pharyngeal swallow function pre-surgery and post-surgery (2), with dysphagia being the predominant symptom in advanced oesophageal carcinoma.

If an individual cannot consume adequate volumes of nutrition, they may experience weight loss, malnutrition, sarcopenia, cachexia and have an increased risk of post-operative complications (3).

Furthermore, the presence of dysphagia has been reported to increase the risk of aspiration pneumonia and mortality following oesophagectomy. Pneumonia is a common cause of death after oesophagectomy. Pneumonia is a major complication in acutely post surgical patients with a mortality rates at 12.8% (Linden P A, Towe C W, Watson T J et al. Mortality after esophagectomy: analysis of individual complications and their association with mortality. *J Gastrointest Surg* 2020; 24(9): 1948–54.),

A systematic review published in 2018 (4) identified 12 studies which investigated swallowing abnormalities in oesophageal cancer. Only two studies looked at dysphagia in pre-oesophagectomy patients. They revealed that there are swallowing impairments prior to oesophagectomy surgery but further research is warranted to develop a greater insight into the type and severity of these deficits (2, 5). This current lack of knowledge makes it impossible to attempt pre-habilitation at this point. The remaining studies attempted to demonstrate pathological patterns post oesophagectomy, however, given the small sample sizes and inconsistent findings, their study was limited. Only one small study implemented rehabilitation interventions, highlighting the need for future trials examining health-related outcomes post oesophagectomy to determine the potential benefits of rehabilitation.

The proposed study is aiming to identify the nature and severity of swallowing impairments secondary to oesophageal cancer, and its cancer treatment, as well as the impact that this has on individuals with oesophageal cancer. A secondary aim of this study is to establish the diagnostic accuracy of clinical signs of dysphagia at the bedside in predicting pneumonia, aspiration pneumonia, tube reliance and quality of life from diagnosis through to survivorship.

Once this has been determined, the intention of a future study is to develop a prehabilitation program for patients who are due to undergo an oesophagectomy, which will target their biomechanical impairments of swallowing in the hope that it will limit the severity of post oesophagectomy dysphagia. It is hoped that this would improve many of the devastating consequences of oesophageal cancer and its treatment, such as high rates of pneumonia and mortality, malnutrition, cachexia and sarcopenia, hospital length of stay and readmissions.

1. Cancer in Ireland 1994-2014: Annual Report of the National Cancer Registry. NCRI. Cork, Ireland; 2017. Retrieved March 19th, 2019 from https://www.ncri.ie/sites/ncri/files/pubs/NCRReport_2016.pdf
2. Martin, RE, Letsos P, Taves DH, Inculet RI, Johnston H, Preiksaitis HG. Oropharyngeal Dysphagia in Esophageal Cancer Before and After Transhiatal Esophagectomy. *Dysphagia*. 2001; 16 (1) 23-31.
3. Shiozu H., Higashijima M, Koga T. Association of sarcopenia with swallowing problems, related to nutrition and activities of daily living of elderly individuals. *Journal of physical therapy science*. 2015;27(2), 393–396.

4. Kaneoka A, Yang S, Inokuchi H, Ueha R, Yamashita H, Nito T, Seto T, Haga N. Presentation of oropharyngeal dysphagia and rehabilitative intervention following esophagectomy: a systematic review. *Dis Esophagus*. 2018; 1;31(8).
5. Okumura T, Shimada Y, Watanabe T, Nakamichi N, Nagata T, Tsukada K. Functional outcome assessment of swallowing (FOAMS) scoring and videofluoroscopic evaluation of perioperative swallowing rehabilitation in radical esophagectomy. *Surg Today* 2016; 46: 543–51.

B5. List the study aim(s) and objective(s).

The aim of this study is to determine the nature, severity and impact of oro-pharyngeal and oesophageal dysphagia in patients with oesophageal cancer from diagnosis through to survivorship.

A second aim of this study is to establish the diagnostic accuracy of clinical signs of dysphagia at the bedside in predicting aspiration, aspiration pneumonia, tube reliance and quality of life from diagnosis through to survivorship.

This study is a cross-sectional study which sources patients at various timepoints throughout their cancer journey from diagnosis through to survivorship. It does not follow patients through that journey. Each participant will be recruited at one time point, they will participate in the swallow assessment and complete the questionnaires as outlined in the ethics form. In addition to one direct contact with participants, the researchers will then collect data from the medical notes, surgical notes and medical imaging notes relating to that patient's medical admission for example regarding their surgical procedure, their levels of nutrition, and any signs of pulmonary complications. This data will be collected within a week of the direct contact with the participant. The data from the direct contact the patient notes will be used as outcome data for both the first and second aims of the study. Recruitment will take place for a maximum of 24 months.

B6. List the study outcomes (s).

The outcome measures are listed below:

Outcome	Measure
Swallow safety and efficiency	DIGEST (Dynamic Imaging Grade of Swallowing Toxicity) safety and efficiency rating tool (Hutcheson et al 2017)
Swallow physiology	MBS (Modified Barium Swallow) Impairment Profile (Harris et al, 2008)
Clinical swallow	EAT-10 (Belafsky et al 2008) Mayo Dysphagia Questionnaire – 2 week version (Taft et al 2016-update this reference with correct one 10.14309/00000434-200609001-01063) GRBAS (Nemr et al 2020) 3ounce water test (DePippo et al 1992)

	Reflux Symptom Index (Thejas et al 2021)
Pneumonia	Uniform Pneumonia Score (Weijs et al 2016)
Nutritional status	MUST (Malnutrition Universal Screening Tool) (Boléo-Tomé et al 2011) Weight Loss Grading Scale (Martin et al 2015) SARC-F (Strength, Assistance in Walking, Rise from Chair, Climb Stairs, Falls) sarcopenia questionnaire (Borges et al 2020, Malmstom & Morley 2013) IOPI (Iowa Oral Performance Instrument) tongue strength measurement (White et al 2009, Lazarus et al 2000)
Tube Reliance	FOIS (Functional Oral Intake Scale) (Crary et al, 2005)
Patient's swallow related quality of life	MDADI (MD Anderson Dysphagia Inventory) (Chen et al 2001) EORTC-QLQ-OES-18 (Blazeby et al 2003) Open Ended Questions: 1) How have your voice/swallowing difficulties impacted your life? 2) How adequate was the support and advice you received from health care professionals regarding your voice/swallowing difficulties before surgery and after surgery?

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B7. Provide information on the study design and the rationale for that design.

This is a prospective observational study using convenience sampling to recruit participants.

A cross-sectional study design has been selected to gather data around the nature, severity and impact of dysphagia in patients with oesophageal cancer at various key time points: 1) time of diagnosis, 2) following chemo-radiation therapy 3) at least 12 months post oesophagectomy.

The researchers have met with the CEO of the Oesophageal Cancer Fund who has organised for the main researcher to provide details about this study at two key events, giving oesophageal cancer survivors the opportunity to be involved in this project.

B8. For experimental studies, provide information on the study intervention(s).

Answer

B8. List where the study will take place i.e. where:

- **the participants will be recruited;**
- **the participants will undertake the research;**
- **the data will be collected;**
- **the data will be stored;**
- **the data will be analysed.**

Participants will be recruited from St James's Hospital Clinical Research Facility.

Participants will be invited to participate in this research in person by a gatekeeper at each time point (at time of diagnosis, post chemoradiation and prior to surgery, at least 12 months post surgery). The gatekeeper at each timepoint will be the Clinical nurse specialists in the outpatient clinic, who are based at St James's Hospital, and who are not involved in this research project.

The data will be collected during one session onsite in an office and in the radiology department (videofluoroscopy suite) at St James' Hospital

The data will be analysed in SJH's speech and language therapy department, and in the main researcher's office in Trinity College Dublin.

The data will be stored in the St James's Hospital medical records and on the main researcher's password protected computer.

All patients undergoing neo-adjuvant therapy will receive this at St James' Hospital.

B8. Who is the target population for the study?

Patients who have been diagnosed with first time oesophageal cancer and whose plans for treatment with curative intent include(d) transhiatal or transthoracic resections.

B10 (a) Please justify the proposed sample size and provide details of its calculation (including minimum clinically important difference).

Based on the sample sizes of other cross-sectional studies in previous research and based on the timeframe of a PhD, a sample of 80 participants is our target.

A power analysis was completed based on published literature as per below:

Nutritional status, food intake, and dysphagia in long-term survivors with head and neck cancer treated with chemoradiotherapy: a cross sectional study. Van den Berg MG, Rutten H, Rasmussen- Conrad EL, Knuijst S, Takess RP, van Herpen CM, Wanten GJ, Kaanders JH, Merks MA. Head Neck. 2014 Jan; 36(1):60-5. Doi:10.1002/hed.23265. Epub 2013 Apr 4. <https://www.ncbi.nlm.nih.gov/pubmed/23559543>

Thirty-two patients with stage III-IV head and neck cancer treated by chemoradiotherapy were invited to evaluate nutritional status (malnutrition, relative weight loss), food intake (food modification; quality), and dysphagia

Garcia-Peris P, Paron L, Velasco C, et al. Long-term prevalence of oropharyngeal dysphagia in head and neck cancer patients: impact on quality of life. Clin Nutr 2007; 26(6):710-717. Doi: 10.1016/j.clnu.2007.08.006

Retrospective cross-sectional study of 87 head and neck cancer patients treated with surgery and radiotherapy or chemoradiotherapy.

A Cross-Sectional, Quantitative Videofluoroscopic Analysis of Swallowing Physiology and Function in Individuals with Amyotrophic Lateral Sclerosis Ashley A. Waito, Emily K. Plowman, Carly E.A. Barlon, Melanie Peladeau-Pigeon, Lauren Tabor-Gray, Kelby Magennis, Raele Robison, Catriona M. Steele

19 adults with a diagnosis of ALS underwent a videofluoroscopic swallowing study in a cross-sectional study.

B10 (b) Where sample size calculation is impossible (e.g. it is a pilot study and previous studies cannot be used to provide the required estimates) then please explain why the sample size to be used has been chosen.

Given the time limitations of this study, the research team will consider every patient for inclusion in the study, as opposed to calculating a specific sample size.

B11 How many research participants are to be recruited in total?

It is hoped that this study will be able to recruit 80 patients; 20 participants at the first two timepoints and 40 at the third timepoint as outlined below in B12a.

B12 (a) How many research participants are to be recruited in each study group (where applicable)? Please complete the following table (where applicable).

Name of Study Group:	Name of Study Group:	Name of Study Group:
Timepoint 1 (Max 10 days post diagnosis)	Timepoint 2 (Max 14 days post neoadjuvant therapy)	Timepoint 3 (At least 12 months post oesophagectomy)
Number of Participants in this Study Group:	Number of Participants in this Study Group:	Number of Participants in this Study Group:
20	20	40

B12 (b) Please provide details on the method of randomisation (where applicable).

N/A

B13 How many research participants are to be recruited at each study site (where applicable)? Please complete the following table.

Site:	Number of Research Participants at this site:
ST JAMES'S HOSPITAL	80

B7. List the data set that will be created and tools used to collect the data.

Background Information (Collected at Time Points 1,2,3)

Name: electronic records

Age: electronic records

Sex: electronic records

Date of Birth: electronic records

Type of oesophageal cancer: electronic records

T-factor of cancer: electronic records

N-Factor of cancer: electronic records

Stage of cancer: electronic records

Location of cancer: electronic records

Presence of swallowing difficulty: as reported by patient

Recent chest infection: as reported by patient

Recent antibiotics for chest related concerns: as reported by patient

Recent admission to hospital for chest related concerns: as reported by patient

Medical history of hiatus hernia, GORD, oesophageal motility disorder: electronic record

Post-Surgical Information (Collected at Time Point 3)

Surgical approach: electronic records

Surgical duration: electronic records

Surgical complications: electronic records

Field of lymphadenectomy: electronic records

Extubation day: electronic records

Presence of Anastomotic leak: radiology report

Location of Anastomotic leak: radiology report

Days between surgery completion and initiation of oral intake: electronic records

Length of ICU stay: electronic records

Hospital length of stay: electronic records

Voice Assessment (GRBAS score): audio recording

Nutrition (Collected at Time Point 3)

Current consistency of food and fluids: patient report

When patient starting modifying consistencies and how food and fluids are modified: patient report

Tube reliance (FOIS score): electronic rating, patient report

When patient started modifying oral intake: patient report

Current and previous (3-6 months ago and 12 months ago) height and weight measurements: A weighing scale and height measurement chart, and patient report

Nutritional rating (MUST nutrition screen): patient report and electronic records

Cachexia (Weight Loss Grading Scale): patient report and electronic records

Sarcopenia: SARC-F questionnaire

Tongue strength: IOPI assessment

Pneumonia (Collected at Time Point 3)

Pneumonia: Uniform Pneumonia Score and CDC Pneumonia Criteria via electronic records

Blood results: specifically leucocyte count and C Reactive Protein level via laboratory results on electronic records

Sputum results: laboratory results on electronic records

Pulmonary radiography findings and where consolidation is noted: electronic records and radiology report

Fever: electronic records

Swallow: Clinical Assessment (Collected at Time Point 3)

Clinical signs of dysphagia at bedside: self-reported outcome (EAT-10 and Mayo Dysphagia Questionnaire, 3 Ounce Water Swallow Test, Reflux Symptom Index)

Swallow: Instrumental Assessment (Collected at Time Points 1,2,3)

Swallow safety: DIGEST Safety rating tool (videofluoroscopy assessment)

Swallow efficiency: DIGEST efficiency rating tool (videofluoroscopy assessment)

Swallow physiology: MBS Impairment Profile (videofluoroscopy assessment)

Oesophageal screen for fluid and tablet (videofluoroscopy)

Quality of Life:

Patient's swallow related quality of life: MDADI questionnaire, EORTC-QLQ-OES-18 and Open questions: 'how have your swallowing/voice difficulties impacted your life?' 2) 'How adequate was the support and advice you received from health care professionals regarding your voice / swallowing difficulties before surgery and after surgery?

B9 Provide information on the statistical approach to be used in the analysis of your results (if appropriate) / source of any statistical advice.

Descriptive and inferential analysis will be conducted. Thematic analysis may be conducted on answers to the open questions.

Question 1:

Based on exploratory analysis, the nature and severity findings from the videofluoroscopy will be analysed against various outcome measurements.

First, the distribution of data will be examined to establish the need for parametric/ non-parametric testing. If non-parametric, statistical analysis will be completed utilizing the Friedman test (nonparametric repeated-measures analysis of variance) to compare differences in severity and nature of swallowing. The Wilcoxon signed- rank test for repeated measures will be used for statistical analysis of ordinal data when comparing two groups (i.e. different types of surgery completed), and Fisher's exact test will be used for categorical data comparisons between two conditions.

Question 2:

An ROC curve will be established as a plot of test sensitivity as the y coordinate and its 1-specificity of False positive rate (FPR) as the x coordinate to evaluate the performance of diagnostic tests.

SPSS Version 24 (SPSS, Inc, Chicago, IL, USA) will be used for data analysis. Significance will be determined a priori as $p < 0.05$. If necessary, researchers can liaise with CSTAR (University College Dublin statistics) for statistical support.

SECTION C: STUDY PARTICIPANTS

SECTION C IS MANDATORY

C1: Selection and Recruitment

C1.1. What are the inclusion criteria? Justify where necessary.

	Time Point 1	Time Point 2	Time Point 3

Inclusion Criteria	First time diagnosis of oesophageal cancer	First time diagnosis of oesophageal cancer	First time diagnosis of oesophageal cancer
	Curative plan includes transhiatal or transthoracic resection	Curative plan includes transhiatal or transthoracic resection	Curative plan included transhiatal or transthoracic resection
	Diagnosis received within maximum 10 days	Maximum 14 days post neoadjuvant therapy	Discharged from hospital. Oesophagectomy completed at least 12 months prior
	All stages of oesophageal cancer	All stages of oesophageal cancer	All stages of oesophageal cancer
	Medical approval to participate	Medical approval to participate	Medical approval to participate
	Willingness to participate in assessment	Willingness to participate in assessment	Willingness to participate in assessment
	Adequate language comprehension and cognitive abilities to participate	Adequate language comprehension and cognitive abilities to participate	Adequate language comprehension and cognitive abilities to participate

C1.2. What are the exclusion criteria? Justify where necessary.

Exclusion Criteria	Current presence of tracheostomy tube	Current presence of tracheostomy tube	Current presence of tracheostomy tube
	History of neurological impairment	History of neurological impairment	History of neurological impairment
	History of oral or pharyngeal dysphagia	History of oral or pharyngeal dysphagia	History of oral or pharyngeal dysphagia
	History of head and neck cancer	History of head and neck cancer	History of head and neck cancer
	Evidence of metastatic or recurrent disease	Evidence of metastatic or recurrent disease	Evidence of metastatic or recurrent disease
	Formal diagnosis of Chronic Obstructive Pulmonary Disease	Formal diagnosis of Chronic Obstructive Pulmonary Disease	Formal diagnosis of Chronic Obstructive Pulmonary Disease

	Pregnant women	Pregnant women	Pregnant women
	Palliative treatment	Palliative treatment	Palliative treatment
	Inadequate cognition or language abilities to consent to or adhere to programme	Inadequate cognition or language abilities to consent to or adhere to programme	Inadequate cognition or language abilities to consent to or adhere to programme

C1.3. How will potential research participants be identified by or to the researchers?

Ensure that you specify any source(s) that will be used e.g. databases, healthcare records.

The gatekeepers, the clinical nurse specialists the outpatient clinic, will identify patients at time points 1,2, 3 who are eligible for the study. These patients will already be attending appointments with the upper GI surgeon and if they are appropriate candidates, the gatekeepers will provide them with written information about the study.

The main researcher will then contact each patient by phone 7 days later to ascertain consent to participate.

C1.4. Who will identify potential research participants?

The clinical nurse specialists in the outpatient clinic, who are based at St James's Hospital, and are not involved in this research project.

Under the Health Research Regulations 2018,

- Health professionals **providing care to a patient** may access **that patient's** healthcare record in order to identify if the patient is suitable for inclusion in health research without the patient's explicit consent;
- Health professionals or other persons **not connected with the care of a patient** may not access that patient's healthcare record in order to identify if the patient is suitable for inclusion in health research without the patient's explicit consent.

C1.5. What sampling method(s) will be used?

- **Simple random sampling** ☐ No
- **Stratified sampling** ☐ No
- **Systematic sampling** ☐ No
- **Convenience sampling** ☐ Yes
- **Cluster sampling** ☐ No

C1.6. How will the research participants be recruited?

7 days after patients receive the invitation letter, they will be contacted by the main researcher by phone to ascertain whether they wish to participate in the study or not. Patients who wish to participate will be provided with an appointment time. At this appointment, the

main researcher will provide detailed verbal and written information prior to gaining full written consent.

C1.7. Who will recruit the research participants?

The main researcher, Anna Gillman

C1.8 Will any participants recruited to this research study be simultaneously involved in any other research project?

C2: CONSENT

C2.1 (a) Will informed consent be obtained?

Under the Data Protection Act (Health Research Regulations) 2018, explicit consent **is required** to process personal data for research purposes except if a consent declaration has been made by the Health Research Consent Declaration Committee.

C2.1 (b) If no, please justify. You must provide a full and detailed explanation as to why informed consent will not be obtained.

Answer

C2.1 (c) If yes, please outline the consent process in full. (How will consent be obtained, when, by whom and from whom etc.)

The gatekeeper will provide appropriate patients with an information leaflet. They see patients at time points 1, 2 and 3 as outpatients. The main researcher will contact the patient 7 days later to ascertain if the patient has any questions and/or if they wish to consent to participate in the study.

The main researcher will verbally provide information detailing:

- the study's purpose
- data collection methods
- the nature of commitment required from participants

Patients who wish to participate will be provided with an appointment time. At this appointment, the main researcher will provide verbal and written information outlining

- the study's purpose
- data collection methods
- the nature of commitment required from participants
- the data management plans

- secure storage plans
- the participant's rights to access, edit and withdraw their data
- the participant's right to decline to participate without any repercussions
- the participant's right to withdraw from the study at any time
- the main researcher's contact details should the participant have any questions or wish to withdraw from the study

Full verbal and written consent will be obtained from participants who wish to participate.

C2.2 (a) Will participants be informed of their right to refuse to participate and their right to withdraw from this research study? ☒ Yes

C2.2 (b) If no, please justify.

Answer

C2.3 (a) Will there be a time interval between giving information and seeking consent? ☒ Yes

C2.3 (b) If yes, please elaborate.

Patients will not be contacted for at least 7 days to ensure they have had time to review and process all of the information in the Patient Information Leaflet, and to provide adequate time to liaise with family, friends or their GP to discuss their potential participation in the study.

C2.3 (c) If no, please justify and explain why an instantaneous decision is reasonable having regard to the rights of the prospective research participants and the risks of the study.

Answer

C3: CAPACITY – ADULT PARTICIPANTS (AGED 18 OR OVER)

C3.1 (a) Will all adult research participants have the capacity to give informed consent? ☒ Yes

C4: Capacity – Child Participants (Aged 17 or Under)

C4.1 (a) Will any research participants be under the age of 18 i.e. Children? ☐ No

C5.1 Please confirm if persons from any of the following groups will participate in this study. This is a quick checklist to assist research ethics committee members

and to identify whether study participants include persons from vulnerable groups and to establish what special arrangements, if any, have been made to deal with issues of consent. It is recognised that not all groups in this listing will automatically be vulnerable or lacking in capacity. Please refer to the HSE's National Consent Policy, particularly Part 3, Section 5.

Committees are particularly interested to know if persons in any of these groups are being targeted for inclusion, as per the inclusion criteria.

(a) Healthy Volunteers

(b) Patients

- Unconscious patients
- Current psychiatric in-patients
- Patients in an emergency medical setting

(c) Relatives / Carers of patients

(d) Persons in dependent or unequal relationships

- Students
- Employees / staff members
- Persons in residential care
- Persons highly dependent on medical care

(e) Intellectually impaired persons

(f) Persons with a life-limiting condition

(Please refer to guidance manual for definition)

(g) Persons with an acquired brain injury

C5.2 If yes to any of the above, please comment on the vulnerability of the research participants, and outline the special arrangements in recognition of this vulnerability (if any).

C5.3 Please comment on whether women of child-bearing potential, breastfeeding mothers, or pregnant women will be included or excluded in this research study.

Pregnant women will be excluded given the exposure to radiation.

SECTION D: research PROCEDURES

SECTION D IS MANDATORY

D1 (a) What activities, procedures or interventions (if any) are research participants asked to undergo or engage in for the purposes of this research study?

Nutrition:

Nutrition screen (MUST) [Timepoint 3 only]

Cachexia questions (WLGS) [Timepoint 3 only]

Sarcopenia questionnaire (SARC-F) [Timepoint 3 only]

Instrumental swallow assessment:

Videofluoroscopy assessment [Timepoints 1, 2, 3]

Clinical swallow assessment:

3 ounce water swallow test [Timepoint 3 only]

Self-reported outcomes (EAT-10) [Timepoint 3 only]

Self-reported oesophageal swallow questionnaire (Mayo Dysphagia Questionnaire) [Timepoints 1, 2, 3]

Tongue strength test (IOPI) [Timepoint 3 only]

Voice assessment (GRBAS) [Timepoint 3 only]

Reflux Symptom Index [Timepoint 3 only]

Quality of life assessment:

MDADI [Timepoints 1, 2, 3]

EORTC-QLQ-OES-18 [Timepoints 1, 2, 3]

Open questions [Timepoint 3 only]

D1 (b) What other activities (if any) are taking place for the purposes of this research study e.g. chart review, sample analysis etc?

Review of medical and surgical notes

Review of radiology reports

Review of laboratory results (blood and sputum)

D2. Please provide details below of any potential harm that may result from any of the activities, procedures, interventions or other activities listed above.

The primary documented risk of videofluoroscopy is exposure to radiation. However, the radiation dose during videofluoroscopy is much lower than that of a routine chest CT, and more than 40 annual videofluoroscopy would be needed to exceed the annual radiation exposure dose

limit (Kim HM¹, Choi KH, Kim TW. Patients' Radiation dose during videofluoroscopic swallowing studies according to underlying characteristics. *Dysphagia*. 2013 Jun;28(2):153-8.).

The X-ray beam intensity incident on a patient is expressed as air Kerma (K_{air}) measured in mGy. KAP is directly related to the patient's carcinogenic risk. The total KAP (Kerma Area Product) used in an average examination may be taken to be approximately 1.0 Gy-cm². A typical PA chest X-ray is 0.1 Gy-cm² and an anterior-posterior abdomen xray is 2.5Gy-cm² (Bonilha, H.S., Huda, W., Wilmskoetter, J. et al. *Dysphagia* (2019) 34: 922.)

Measures will be put in place to limit the radiation exposure, for example, the videofluoroscopy will take place for the shortest amount of time possible.

The secondary risk inherent in VFS is aspiration; however the procedures will be completed at a medical facility with radiographers in close conjunction with trained speech and language therapists who all have experience in performing videofluoroscopic swallowing studies in impaired populations.

Finally, consumption of barium powder can result in constipation. The volume of barium consumed will be minimal compared to a barium swallow, therefore, it is expected that, at worst, patients would experience very mild constipation as a result.

D3. What is the potential benefit that may occur as a result of this study?

This study will contribute information on the nature, severity and impact of oesophageal cancer and its treatment on swallowing at different time-points. The diagnostic accuracy aspect of this project will assist clinicians to identify those who are at high risk and who should be prioritised for instrumental evaluation/intervention.

It may inform future research as part of this main researcher's PhD.

D4 (a) Will the study involve the withholding of treatment?

☒ No

D4 (b) Will there be any harms that could result from withholding treatment? ☒ No

D4 (c) If yes, please elaborate.

Answer

D5 (a) How will the health of participants be monitored during the study, and who will be responsible for this?

It is not foreseen that there will be any adverse effects. The patient will have only one encounter with the research team. During this time, the researcher will be able to refer the patient to the medical team or the emergency department should the patient present with any urgent health issues.

Patients with oesophageal cancer would typically be referred for a videofluoroscopy by the medical team if they present with symptoms suggestive of potential aspiration, for example,

aspiration pneumonia, subtle or inconsistent signs of laryngeal penetration or aspiration while swallowing or shortly afterwards (change to respiration rate, eye tearing, cyanosis, reddening of the skin etc.)

If the videofluoroscopy reveals unexpected anatomical or physiological abnormalities, the researcher (speech and language therapist) will organise for a radiologist to review the images.

If dysphagia is identified, the researcher will discuss the case with Professor Reynolds and the Speech and Language Therapy dept at St James's Hospital to establish if a referral for further management is appropriate.

If patients demonstrate psychological distress during data collection, the patient will be referred to the St James's Hospital psychology department.

The videofluoroscopy proposed for this project is a condensed version of a typically conducted videofluoroscopy in order to ascertain the most pertinent information, and to limit each participant's time. Each patient will consume only twelve single/sequential sips of normal water (with barium), nine mouthfuls of water (with barium) that is thickened to a consistency where it can only be consumed by a spoon instead of a cup, a Carr cracker (with barium on top), and a tablet made of barium. A typical videofluoroscopy would involve patients consuming a variety of volumes and consistencies depending on what is deemed appropriate by the speech and language therapist based on their current level of function.

The speech and language therapist typically completes the report and provides handover to the treating medical team. A radiologist may be consulted for diagnosis of pathology and will complete an additional report.

D5 (b) How will the health of participants be monitored after the study, and who will be responsible for this?

It is not foreseen that there will be any adverse effects. The patient's treating oncology or upper gastro-intestinal surgical team will continue to monitor this patient after the study.

D6 (a) Will the interventions provided during the study be available if needed after the termination of the study? Non-applicable

D6 (b) If yes, please state the intervention you are referring to and state who will bear the cost of provision of this intervention?

Answer

D7. Please comment on how individual results will be managed.

The main researcher will provide feedback to the patient after the videofluoroscopy if any abnormality is noted or if the participant requests the results from the researchers.

If dysphagia is identified on the videofluorocopy, the researcher will discuss the case with Professor Reynolds and the Speech and Language Therapy Department at St James's Hospital to establish if a referral for further management is appropriate.

If an unforeseen abnormality is incidentally discovered that is outside of the researcher/speech and language therapist's field of expertise, then the patient's oncology team will be consulted.

Background information will be recorded on a laptop. Results from the nutrition screen, cachexia questions, sarcopenia questionnaire, EAT-10 questionnaire, Mayo Questionnaire, MDADI questionnaire, IOPI test and 3 ounce water test will be recorded on a laptop and stored in a password protected excel dataset. The Voice assessment audio-recording will be recorded on an iPad and stored on a password protected computer/iPad. The scores will be stored in a password protected excel dataset. The videofluoroscopy will be stored on St James's Hospital computer system, and will be analysed by a member of the research team. Results will be logged in the password protected excel dataset on One Drive.

If appropriate, further analysis of the data will be completed to better understand the nature, severity and impact of dysphagia in this population or to better understand the predictive value of clinical or Quality of Life presentations.

D8. Please comment on how aggregated study results will be made available.

Anonymised data will be published in peer reviewed journals, posters, oral presentations, and as a submission of a final thesis to Trinity College Dublin.

D9. Will the research participant's general practitioner be informed that the research participant is taking part in the study (if appropriate)? Any report that has clinical significance will be placed in the patient's medical file..

D10. Will the research participant's hospital consultant be informed that the research participant is taking part in the study (if appropriate)? Yes

SECTION E: data protection

SECTION E IS MANDATORY

E1: data processing – consent

E1.1 (a). Will explicit consent be sought for the processing of data?
Yes

Under the Data Protection Act (Health Research Regulations) 2018, explicit consent **is required** to process personal data for research purposes except if a consent declaration has been made by the Health Research Consent Declaration Committee.

- Identifiable and pseudonymised data (e.g. linked by code) is classified as personal data by GDPR and **is subject to this requirement**.
- Fully (irrevocably) anonymised data is not classified as personal data and is not subject to this requirement. However, consent **is required** to process personal data to make the data fully (irrevocably) anonymised and **is subject to this requirement**.

An **explicit** consent statement should:

- specifically refer to the particular data set that is to be processed;
- specifically refer to the precise purpose of processing (including any automated decision-making);
- identify any risks and/or implications that might arise for the data subject as a result of the data processing;
- provide any other relevant and specific information that might influence the decision of a data subject to give or not give their consent.

E1.1 (b). If no, please elaborate.

Answer

E2: data processing – PERSONNEL

E2.1. Who will control (i.e. determine the purpose for which and the way in which the data will be processed) and be responsible for the data (i.e. the data controllers)?

Trinity College Dublin

E2.2. Who will hold or process the data (i.e. the data processors)?

Include anyone who will collect, store or analyse the data. An individual can be both a data controller and processor simultaneously (and may need to be listed in E2.1 and E2.2).

The research team: Anna Gillman, Professor Regan, Professor Reynolds, Professor Walshe, Michelle Hayes and Claire Donohoe

E2.3. What training in data protection law and practice have the data controller(s) and data processor(s) completed?

Under the Data Protection Act (Health Research Regulations) 2018, data controllers must ensure that anyone involved in carrying out research project has completed training in data protection law and practice.

Anna Gillman completed the following courses in January 2020: Online module at Trinity College Dublin: CPDDPITSDM-A-Y-201718 Data Protection, IT Security and Data Management

Research Module: CA7000-A-YEAR12-201920 Research Integrity and Impact in an Open Scholarship Era Module

Julie Regan & Margaret Walshe- online GDPR training is an annual requirement for TCD academic staff

John Reynolds & Claire Donohoe- online GDPR training is an annual requirement for TCD academic staff

Michelle Hayes – online GDPR training is an annual requirement for SJH staff

E2.4 (a). Is it intended to share any of the collected data (including pseudonymised data) with anyone else (i.e. anyone not listed in E2.1 and E2.2)? ☐ No

E2.4 (b). If yes, with whom will the data be shared and what is the purpose of such sharing?

Answer

E2.5. If the data is pseudonymised (coded), who will retain the 'key' to re-identify the data?

The main researcher, Anna Gillman. A key will be retained so that participants can be linked back to their data, however, on completion of the study, this data will no longer be retained.

E3: data processing – CONTENT

E3.1 What specific data will be collected?

Include all variables that will be collected particularly demographic details. If appropriate, attach a case report form or other document(s) detailing the variables that will be collected (e.g. questionnaire).

Instrumental Swallow Assessment:

- Modified Barium Swallow Impairment Profile: swallow ratings on videofluoroscopy will be recorded for all components of the profile from 1-17 (between 3 and 5 possible answers for each component), for each volume of each consistency trialled.
- *DIGEST Rating Scale: the following information will be recorded from the videofluoroscopy: 1) Occurrence of penetration/aspiration/neither, 2) if it occurred, did it occur just once, intermittently or chronically, 3) at what level did the penetration/aspiration occur, 4) what was the volume of the penetrated/aspirated material (trace, gross, neither trace nor gross), 4) was it silent or overt penetration/aspiration, 5) was the penetrated/aspiration material cleared or not, 6) what percentage of the bolus remained in the pharynx*

Clinical Swallow Assessment:

- *Self-reported swallowing outcome measures: EAT-10 questionnaire (10 questions – 5 possible answers per question) and MAYO Dysphagia Questionnaire (10 questions with ratings of between 0 and 5, and two free text questions regarding frequency of occurrence), Reflux Symptom Index (9 questions with ratings between 0-5)*
- *Patient's reported difficulty swallowing, current food and fluid consistencies, the duration of these difficulties*
- Tongue strength: IOPI assessment measures the maximum pressure that the tongue can push against an air-filled bulb. Displayed as kilopascals kPa
- Voice Assessment Score (GRBAS – rating between 1 and 4 based on audibly perceived Roughness, Breathiness, Asthenia and Strain when talking)

Chest Status:

- Presence of pneumonia: Uniform Pneumonia Score and CDC Pneumonia Criteria (reported in electronic records): Blood results (electronic records), Sputum results (electronic records), Pulmonary radiography findings (electronic records), Fever (electronic records),

Nutrition:

- Tube reliance: FOIS score (7 potential answers per question – data regarding oral intake/non-oral intake will be collected from electronic records)
- Cachexia: Current height and weight measurements (A weighing scale and measurement chart will be used to collect the data), Patient change in weight (as reported by patient)
- Sarcopenia (SARC-F questionnaire: 5 questions with options from 0 to 6)
- Malnutrition Risk (MUST: calculated from data from medical file: current weight, weight loss, if acutely unwell)

Quality of Life Rating:

- *Swallow-related Quality of Life rating: MDADI (M.D. Anderson Dysphagia Inventory): 20 questions to answer (5 possible answers per question)*
- *Swallow -related Quality of Life in individuals with Oesophageal Cancer (EORTC-QLQ-OES-18)*
- *'Free responses' will be audio-recorded and transcribed for Open ended questions: 1) how have your voice/swallowing difficulties impacted your life? 2) How adequate was the support and advice you received from health care professionals regarding your voice/swallowing difficulties before surgery and after surgery?*

Background and Surgical Information

- Name (patient report)
- Age (electronic records)
- DOB (electronic records)
- Sex (electronic records)
- Type of cancer (electronic records)
- Stage of cancer (electronic records)
- Location of cancer (electronic records)
- Medical history of hiatus hernia, GORD, oesophageal motility disorder (electronic record)
- Hospital length of stay (electronic record)
- Surgical approach (electronic record)
- Field of lymphadenectomy (electronic record)
- Operation duration (electronic record)
- Operation complications (Clavian Dindo Scale from electronic record e.g. bleeding)
- Extubation day (electronic record)
- Anastomatic leak (radiology report)
- Location of anastomatic leak (radiology report)
- Days between surgery and initiation of oral intake (electronic records)
- Length of stay in ICU
- Reported presence of swallowing difficulty
- Current food and fluid consistencies
- If modifying food/fluid, when did this commence, and what modifications

E3.2 What measures will be taken to limit the data collected to what is necessary to achieve the aim of the research only?

Under the Data Protection Act 2018, *collected data must be 'adequate, relevant and not excessive in relation to the purposes for which they are processed' (data minimisation).*

The entire research team will review the dataset and rule out any data points that are not necessary to achieve the aims of the study.

The protocol outlining the data required for the study will be strictly followed

E3.3 What will be the level of identification of the collected data?

- Fully identifiable (e.g. name, date of birth, address)? ☐ No
- Pseudonymised (e.g. coded)? ☒ Yes

- Fully (irrevocably) anonymised? ☐ No

E3.4 (a) Will the collected data undergo further processing after collection? ☐ Yes

E3.4 (b) If yes, what type of processing will be undertaken?

- Pseudonymisation (coding data should be classified as pseudonymisation)? ☐ Yes
- Full (irrevocable) anonymisation? ☐ No
- Other? ☐ No

E3.4 (c) If other, please elaborate.

E4: data processing – METHOD

E4.1 Who will collect the data?

Anna Gillman, Professor Julie Regan, Michelle Hayes

E4.2 Where will the data be collected?

St James's Hospital

E4.3 (a) What media of data will be collected?

- Written (paper)? ☐ Yes
- Written (electronic)? ☐ Yes
- Audio recordings? ☐ Yes
- Photographs? ☐ No
- Video recordings? ☐ Yes
- Other? ☐ No

E4.3 (b) If other, please elaborate.

E4.4 (a) Will any of the data collected consist of audio recordings / video recordings? ☐ Yes

E4.4 (b) If yes, will participants be given the opportunity to review and amend transcripts of the tapes?

Yes. At the end of the data collection session, participants will be offered the opportunity to review and amend transcripts of the tapes once they are completed.

E4.5 (a) Will any of the data collected consist of photographs / video recordings? ☐ No

E4.5 (b) If yes, please elaborate.

e5: ACCESS TO HEALTHCARE RECORDS

E5.1 (a) Does the study involve access to healthcare records (hard copy / electronic)? ☐ Yes

If NO, please delete the remaining questions in Section E5.

E5.1 (b) If yes, please elaborate.

The main researcher will access data relating to the patient's medical history, surgical history, current medical status, temperature, blood results, sputum results, radiology results.

E5.2 Who or what legal entity is the data controller in respect of the healthcare records?

St James's Hospital and Trinity College Dublin

e5.3 Who will access these healthcare records?

Anna Gillman and the research team; Professor Julie Regan, Professor Reynolds, Professor Walshe, Michelle Hayes, Ms Donohoe

E5.4 Will explicit consent be sought from patients for research team members to access their healthcare records? ☒ Yes

If YES, please delete the remaining question in Section E5.

Under the Data Protection Act (Health Research Regulations) 2018, explicit consent **is required** to access healthcare records for research purposes except if a consent declaration has been made by the Health Research Consent Declaration Committee.

E5.5 What measures have been put in place by the data controller which may make access to healthcare records permissible without consent?

Under the Data Protection Act (Health Research Regulations) 2018, the *only measures that permit access to healthcare records for research purposes are:*

- *If the Health Research Consent Declaration Committee makes a consent declaration on behalf of the data subjects, or*
- *If the data is already fully (irrevocably) anonymised.*

This data will not be accessed without consent.

E6: data processing – STORAGE

E6.1 Where will the collected data be stored?

St James's Hospital Medical records

Password encrypted Microsoft files on main researcher's password protected computer and on One Drive.

Locked in office at Trinity College Dublin

E6.2 (a) Will data that is collected leave the site(s) of storage at any stage?

☒ Yes

E6.2 (b) If yes, please elaborate.

Only when being transferred between St James's Hospital and Trinity College Dublin

E7: data processing – ANALYSIS

E7.1 Who will analyse the data?

Anna Gillman

E7.2 Where will the data be analysed?

St James's Hospital Speech and language therapy department and at Trinity College Dublin

E8: data processing – DISPOSAL

e8.1 (a) After data analysis has taken place, will data be destroyed, archived or anonymised?

- Destroyed? ☐ No
- Archived? ☒ Yes
- Anonymised? ☐ No

Archived for 7 years and then destroyed.

e8.1 (b) If destroyed, how, when and by whom will it be destroyed?

The data will be destroyed 7 years after collection. If the main researcher, Anna Gillman, has completed her PhD by then, the data will be stored by Anna's supervisor, Professor Julie Regan at Trinity College Dublin, who will delete and shred all soft and hard copy information after 7 years.

Electronic records will be erased using software applications designed to remove all data from the storage device. A record will be kept stating what records were destroyed when, by whom, and how.

e8.1 (c) If archived, for how long, for what purpose, and where will it be archived?

It will be archived in the Dept of Clinical Speech and Language Studies at Trinity College Dublin for 7 years, after which it will be shredded and discarded.

e8.1 (d) If anonymised, how, when and by whom will it be anonymised?

N/A

E9: data processing – RISK ASSESSMENT & MANAGEMENT

E9.1 What measures (including technical and organisational) will be in place to ensure the protection and security of the collected data?

Include any specific measures that maintain the confidentiality of the collected data.

The data will be pseudonymised and stored in encrypted Microsoft files on a password protected computer, on One Drive, and in a locked office at Trinity College Dublin.

E9.2 What controls will be in place to prevent unauthorised consultation, alteration, disclosure or erasure of the collected data?

Codes to alphanumeric keys will only be accessible by the main researcher.

Pre-pseudonymised data will be accessible only by the main researcher.

Files containing personal data will be password protected and these passwords will only be available to the main researcher.

None of the data (contact details, consent forms, pseudonymised key, audio files, video files, written reflections, transcripts, answers) will be shared between the main researcher and other investigators on the team

All data will only be available via encrypted, password protected computers in locked offices, or on a shared One Drive account.

E9.3 What controls will be in place to log whether and by whom the collected data has been consulted, altered, disclosed or erased?

A log with the date, time, reason for accessing personal data, signature and action taken, will be stored in a locked office or on a One Drive account.

E9.4 (a) Is there any aspect of the proposed research that indicates a high risk (either in terms of likelihood or severity) to the rights and freedoms of the data subject (e.g. a data breach)? ☒ No

E9.4 (b) If yes, complete the following data protection impact assessment.

<i>Risk Identified</i>	<i>Consequence</i>	<i>Risk Level (Low / Medium / High)</i>	<i>Risk Management</i>
<i>Example: Data collection site (OPD clinic) distant from data storage site (Research Office) – 10 minute walk but within the hospital grounds</i>	<i>Example: Loss of data in transit</i>	<i>Example: Medium risk</i>	<i>Examples: - Data carried in bag sealed prior to departure from collection site and only unsealed upon arrival at storage site - Data is brought directly from collection site to storage site</i>

E9.5 Describe how data subjects will be informed of what data will be collected (and why) and how they can exercise their data subject rights (i.e. transparency).

Participants will be informed of what data will be collected, and the rationale for that collection, in the following ways:

- Accessible Patient Information Leaflet
- Verbal explanation by phone and in person with the main researcher.

The Patient Information Leaflet will also detail how participants can exercise all of their rights as outlined in the GDPR and Health Research Regulations. Contact details will be included on all of the documents supplied.

Participants can exercise their rights in the following ways:

- Right of access: by making a verbal request to the main researcher for radiology videos and audio recordings
- Right to rectification and erasure: where inaccurate data may have been collected, participants can request that the error be corrected or that the data is completely removed by making a verbal request to the main researcher. The main researcher can document that this has occurred.
- Right to data portability: participants can make a verbal request for any information collected about them should they wish to use it for an additional purpose or their own personal use.

E9.6 Describe the measures that will be in place to ensure compliance with data subject rights.

The main researcher has completed GDPR training, and will regularly monitor compliance.

SECTION F: HUMAN BIOLOGICAL MATERIAL

f1: Bodily Tissue / Bodily Fluid Samples - general

F1 Does this study involve human biological material? ☒ No

If the answer is No, please delete Section F

section G: radiation

G1: radiation – general

G1.1 (a) Does this study/trial involve exposure to radiation? ☒ Yes

If answer is No, please delete remaining questions in Section G

G1.1 (b) If yes, please specify:

i) **Exposure to radioactive materials** ☒ No

- ii) Therapeutic ionising radiation ☐ No
- iii) Diagnostic ionising radiation ☐ Yes
- iv) Other ☐ No Details: Answer

G1.2 (a) Does this study / trial involve ADDITIONAL radiation exposure other than normally received as part of standard care? ☐ Yes

G1.2 (b) If yes, please elaborate.

Participants at time points 1 2, 3 will undergo one additional videofluoroscopy than would more than likely not have been conducted otherwise.

I received email confirmation from Dr Ciaran Johnston which states:

'With regard to your study starting next year, I can confirm to the Research Ethics Committee that the additional radiation exposure for one videofluoroscopy is negligible in the context of a patient with a diagnosis of oesophageal cancer who will ultimately have multiple CTs, PET CTs and possibly radiation therapy as part of their clinical pathway.

Ciaran Johnston

cjohnston@stjames.ie

Tel: 4284947

G1.3 Please specify if this study is due to take place at a: -

- i) Radiation Oncology Unit ☐ No
- ii) Diagnostic Imaging Facility ☐ Yes
- iii) Clinical Laboratory ☐ No
- iv) Academic Research Centre ☐ No
- v) Other ☐ No Details: Answer

G1.4 Has each study site/institution in the Republic of Ireland been licensed by the Radiation Protection Society of Ireland? ☐ Yes

G2: radiotherapy trials

G2.1 Does the study/trial involve exposure of patients to radiotherapy?

If answer is No, please delete remaining questions in Subsection G2

G3: RADIONUCLIDES

Please complete the tables below for each radionuclide to be administered

G3.1 (a) Will any of the study/trial participants be patients?

Details of patients to be studied				
Number (whole study)	Age range	Sex	Clinical condition	Total effective or target tissue dose per individual
[TA]	[TA]	[TA]	[TYPE ANSWER=TA]	[TA]

G3.1 (b) Will any of the study/trial participants be healthy volunteers?

Details of healthy volunteers to be studied			
Number (whole study)	Age range	Sex	Total effective dose per individual
[TA]	[TA]	[TA]	[TYPE ANSWER=TA]

G3.2 Dose and Risk Assessment

G3.2 (a) What is the total research protocol dose from the exposure (if any)?

Answer

G3.2 (b) What component of this is the additional dose over and above standard practice? What are the risks associated with this dose?

Answer

G3.2 (c) DECLARATION BY MEDICAL PHYSICIST (for Section G3 Radionuclides)

I am satisfied that the information in sub-section G3.1 and the assessment in sub-section G3.2 provide a reasonable estimate of the ionising radiation exposure planned in this research and the associated risks

Signature: _____ **Date:** _____

Please Print Name: _____

G4: CLINICAL ASSESSMENT

G4.1 Will the exposure exceed the exposure that might be received as part of normal care? *Less exposure than a typical videofluoroscopy, however, more exposure than if they were not going to receive a videofluoroscopy. The protocol will be kept as short as possible to minimise radiation exposure. ALARA principle will be adhered to.*

G4.2 Assessment of additional exposure

G4.2 (a) Please explain how the planned exposure compares with normal practice and assess whether it is appropriate, using language comprehensible to a lay person. Consideration should be given to the specific objectives of the exposure, the characteristics of participants, the potential diagnostic or therapeutic benefits to the participant, the potential benefits to society, the risk to the participant and the availability of alternative techniques involving less, or no, ionising radiation.

Patients who consent to participate in this study have oesophageal cancer and are scheduled to or will have recently had an oesophagectomy (surgery to partially or completely remove the oesophagus).

All participants in this study will undergo a videofluoroscopy assessment (swallow x-ray) if they provide consent.

When this information is published, it will enable the multi-disciplinary team to understand what swallowing difficulties their patients may be experiencing. The team can make appropriate, safe and more comfortable recommendations for these patients to help them to receive adequate nutrition and hydration. This may prevent loss of weight, muscle mass, discomfort or pneumonia. These studies also enable researchers to develop appropriate swallow treatments and recommendations.

Patients are exposed to radiation, however, this is much lower than that of a routine chest CT scan. More than 40 videofluoroscopies would be needed to exceed the annual radiation exposure dose limit. Measures will be put in place to limit this exposure for example if a patient is swallowing for more than 15 seconds during when the researcher (speech and language therapist) is assessing their oesophagus, the recording will be paused for 15 seconds to see if the residue is gone, instead of recording for the entire 30 seconds. If it is not gone, the recording will be paused for another 15 seconds.

G4.2 (b) If pregnant or breastfeeding mothers are to be studied give reasons and details of special radiation protection measures to be taken.

NA

G4.3 DECLARATION BY RADIATION ONCOLOGIST

I am satisfied that the exposure to ionising radiation planned in this research study (as defined in sub-section G2 and/or G3) is reasonable and that the risks are adequately described in the participant information sheet for the study.

Signature: _____ **Date:** _____

Please Print Name: _____

SECTION H: MEDICAL DEVICES

H1 (a) Is the focus of this study/trial to investigate/evaluate a medical device? ☒ No

If answer is No, please delete remaining questions in Section H.

SECTION I: MEDICINAL PRODUCTS / COSMETICS / FOOD AND FOODSTUFFS

I1: NON-INTERVENTIONAL TRIALS OF MEDICINAL PRODUCTS

I1.1 (a) Does this study involve a medicinal product? ☒ No

I2: COSMETICS

I2.1 (a) Does this study involve a cosmetic? ☒ No

I3: FOOD AND FOOD SUPPLEMENTS

I3.1 (a) Does this study involve food or food supplements? ☒ Yes

I3.2 (b) If yes, please elaborate:

Patients will consume 3x 5ml, 3x 10ml, 6 x 20ml sips of regular water containing barium (Level 0 IDDSI thickness), 3 x 5ml, 6 x10ml (Level 4 IDDSI thickness), Carr cracker with the level 4 barium water spread on top, and a barium tablet.

SECTION j: INDEMNITY and insurance

SECTION J IS MANDATORY

J1 Please confirm and provide evidence that appropriate insurance/indemnity is in place for this research study at each site.

The Research Site is St James Hospital which is covered by state claims agency.

J2 Please confirm and provide evidence that appropriate insurance/indemnity is in place for this research study for each investigator.

The main researcher is a Trinity College Dublin postgraduate student therefore insurance is covered by Trinity College.

Professor Reynolds is a staff member at St James Hospital.

Professors Regan and Walshe are staff members at Trinity College Dublin.

Michelle Hayes and Ms Donohue are staff members at St James' Hospital. Michelle is also a TCD postgraduate student.

J3.1 Please give the name and address of the organisation / or individual legally responsible for this research study?

Trinity College Dublin, College Green, Dublin 2

St James's Hospital, James' Street, Ushers, Dublin 8

J3.2 Where an organisation is legally responsible, please specify if this organisation is:

A pharmaceutical company ☐ No

A medical device company ☐ No

A university ☐ Yes

A registered charity ☐ No

Other ☐ Yes If yes, please specify: a hospital

J3.3 Please confirm and provide evidence of any specific additional insurance / indemnity arrangements which have been put in place, if any, by this organisation / or individual for this research study?

N/A

SECTION K: COST AND RESOURCE IMPLICATIONS, funding and payments

SECTION K IS MANDATORY

k1: COST AND RESOURCE IMPLICATIONS

K1.1 Please provide details of all cost / resource implications related to this study (e.g. staff time, office use, telephone / printing costs etc.)

Staff time: the clinical nurse specialists' time when they provide the patient with the information leaflet, the radiographer's time during the videofluoroscopy procedures, the radiologist's time when/if the videofluoroscopy images require review.

Office use: use of an office space to meet with patients for assessment and feedback purposes.

Cost of barium powder, barium tablets, cups, syringes, plastic spoons, napkins.

Videofluoroscopy suite: use of this suite for approximately 30 minutes per week

k2: funding

K2.1 (a) Is funding in place to conduct this study?

No

K2.1 (b) If no, has funding been sought to conduct this study? From where? Please elaborate.

Funding for PhD student fees via Trinity College Dublin Provost Award. No other funding has been sought for this study.

K2.1 (c) If yes, please state the source of funding (industry, grant or other), the name of the funder, the amount of funding and duration of funding.

Source of funding (industry, grant or other):
Answer
Name of Funder:
Answer
Amount of Funding:
Answer
Duration of Funding
Answer

K2.1(d) Please provide additional details in relation to management of funds.

Answer

K2.1(e) Is the study funded by a 'for profit' organisation?

K2.2 (a) Do any conflicts of interest exist in relation to funding or potential funding?

K2.2 (b) If yes, please elaborate.

Answer

k3: payments to investigators

K3.1 (a) Will any payments (monetary or otherwise) be made to investigators?

K3.1 (b) If yes, please provide details of payments (including amount).

k4: payments to PARTICIPANTS

K4.1 (a) Will any payments / reimbursements (monetary or otherwise) be made to participants?

K4.1 (b) If yes, please provide details of payments / reimbursements (including amount).

Answer

SECTION I: additional ethical ISSUES

L1 (a) Does this project raise any additional ethical issues?

If answer is No, please delete remaining questions in Section L.

L1 (b) If yes, please identify any particular additional ethical issues that this project raises and discuss how you have addressed them.

Answer

10.4 Appendix E Research Ethics Committee Letter of Approval



**Tallaght
University
Hospital**
Ospidéal
Ollscoile
Thamhlachta
An Academic Partner of Trinity College Dublin



Research Office

Project ID: 0371

Approval Date: 24 November 2021

Submission Number: 415

Submission Title: The nature, severity and impact of oro-pharyngeal and oesophageal dysphagia in patients with oesophageal cancer from diagnosis through to survivorship

Submission Date: 01.Oct.2021

Dear Ms Gillman,

On behalf of the Chair and members of the SJH/TUH Joint Research Ethics Committee I wish to inform you that the amendment to the above named study has received **FULL APPROVAL**. Your study can now proceed.

The following documents were reviewed and approved:

Document Type	File Name	Date	Version
Amended Documents	Two proposed changes to ethics	01.Oct.2021	1

Please note that ethical approval for this study is only active under the following conditions:

1. Applicants must submit an annual report for ongoing projects.
2. Applicants must submit an end of study declaration/end of study report upon completion of the study.
3. All adverse events must be reported to the JREC.
4. All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Ms Chita Murray

Research Ethics & Clinical Trials Manager,

10.5 Appendix F STROBE Statement for reporting quantitative data

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) If applicable, describe analytical methods taking account of sampling strategy
		(e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed

		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.



PARTICIPANT INFORMATION LEAFLET

The nature, severity and impact of dysphagia (swallowing difficulties) in patients with oesophageal cancer: from diagnosis through to survivorship

Principal Investigator(s) and Co-investigator(s): Anna Gillman, Professor Julie Regan, Professor John Reynolds, Professor Margaret Walshe, Ms Claire Donohue, Michelle Hayes

You are being invited to take part in a research study that will be carried out in St James's Hospital. Before you decide whether or not you wish to take part, please read the information provided in this leaflet carefully. Take time to ask questions – don't feel rushed or under pressure to make a quick decision. You should understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. You may wish to discuss it with your family, friends or GP.

PART 1 – THE STUDY

Why is this study being done?

People with oesophageal cancer often report difficulty with swallowing, as well as changes to their voice, cough and reflux. These difficulties can happen before diagnosis, during chemotherapy and/or radiation therapy, and after an oesophagectomy surgery. Not being able to swallow properly can lead to weight loss, reduced quality of life, and it can even cause malnutrition, dehydration and pneumonia. This study aims to improve our understanding of the types of swallowing difficulties that patients experience, and how all these changes impact their lives. These findings will help us to develop better treatment programmes for people with oesophageal cancer.

Why am I being asked to take part?

Patients who had treatment for oesophageal cancer more than 12 months ago are being asked to take part so that researchers can learn about how the swallow works at this later timepoint in the

cancer journey. Even if you never had swallowing difficulties or you only experienced very mild changes to your swallow, the information that we record from your swallow assessment will help us to better understand the swallow. We also want to look at the impact that any swallowing difficulties have had on your day-to-day life. All of this will enable researchers and clinicians to better understand what we can do to help other people with oesophageal cancer in the future.

Do I have to take part? What happens if I say no? Can I withdraw?

Please know that

- participation is **voluntary**, you do not have to take part in this study.
- a decision not to consent will not affect your current or future medical care. It will have **no adverse consequences**;
- You can withdraw from the study at any time, even if the study has already started, by contacting the main researcher. You do not have to give a reason to opt out.
- Should you withdraw, data collected up to the point of withdrawal will be retained and will continue to be processed.
- If you wish to withdraw, please contact Anna Gillman (on 087 413 1127 or gillmana@tcd.ie) who will be able to organise this for you.
- You may also contact the Data Protection Officer at St James' Hospital on 01 4103021/ 4162463 or at dataprotection@stjames.ie, or at Trinity College Dublin on 01 8961892 or at dataprotection@tcd.ie.

How will the study be carried out?

The study will take place at St James's Hospital during the years 2021 and 2022.

It is expected that approximately 80 patients will participate in this study. Approximately 20 patients will be selected after they have been diagnosed, 20 patients will be selected before their oesophagectomy surgery, and 40 patients will be selected who are more than 12 months after surgery.

Participants will attend a 60 minute session with a researcher in St James's Hospital. You will be asked basic questions about your swallowing abilities and difficulties. After the initial discussion, the swallow assessment will take place in the Radiology department, and this lasts approximately 20 minutes. A videofluoroscopy is the name of a moving x-ray that is used to observe what is happening inside your mouth and throat while you are swallowing. You will be asked to swallow sips of water, followed by sips of thickened water, half a cracker and a tablet (non-medicated). The food, tablet, and water will contain barium powder to make them appear white. This is what allows them to be seen on the x-ray.

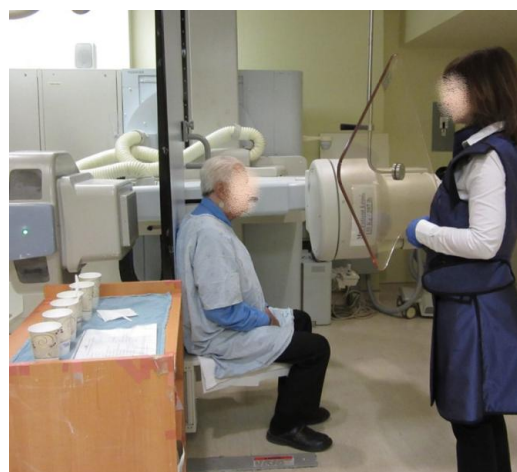
Videofluoroscopies are often used to assess any patients who have suspected swallowing difficulties. They are typically performed by a speech and language therapist and a radiographer. The speech and language therapist can then make recommendations to the patient and the medical team about how to improve the patient's swallow.

The researcher will be able to explain the results to you if you wish. You may also request that a copy of the report be included in your medical file.

What will happen to me if I agree to take part?

1. Once you have received this package, a researcher will speak to you by phone or in person within the next 10 days to discuss what happens next.
2. You will be invited to attend an appointment with the researcher in Radiology at St James' Hospital.
3. The session will include a discussion about your swallowing abilities over recent months. You will be asked to complete short questionnaires about whether your swallowing has changed or not, and if so, how this affects you.
4. A radiographer and the researcher will conduct the videofluoroscopy (the moving x-ray of your swallow). When you are ready, the x-ray procedure will start. The radiation exposure is minimised because it will be turned off between swallows. You can take a break as needed. This process will last approximately 15 minutes. If, at any point you do not feel comfortable, you do not need to continue.

You do not need to fast before the x-ray.



Are there any benefits to me or others if I take part in the study?

- The researcher can explain to you how your swallow appears on the x-ray, and whether any issues were observed. You can request that a copy of the results be placed in your medical file if you wish.
- If a swallowing difficulty is identified that may be improved through swallowing therapy, you will be referred onwards appropriately for this.

Are there any risks to me or others if I take part in the study?

- Radiation: The videofluoroscopy procedure does cause exposure to radiation. However, the radiation dose during the videofluoroscopy is much lower than that of a routine chest CT, and it would take more than 40 annual videofluoroscopies to exceed the annual radiation exposure dose limit.
- Barium: Small amounts of barium powder are mixed into the food, drink and tablet capsules so that they can be seen on the x-ray. If large amounts of barium are consumed, this can occasionally result in a little constipation but there are no other known risks associated with swallowing barium.
- Some people with swallowing difficulties aspirate, meaning that food or drink may be entering their lungs when swallowing. Aspirating can lead to pneumonia. If you are aspirating in your day-to-day life, then this may also happen during the videofluoroscopy. This assessment will be conducted with trained clinicians who do regular videofluoroscopies with patients. The clinicians will limit the risk of this occurring during the exam, however, if you are a person who aspirates, then it is important to find out this information. The clinicians can make recommendations to your medical team that may help to prevent this from happening anymore.

What will happen if something goes wrong when I'm taking part in the study?

The swallowing procedure is quick and performed by highly trained clinicians.

As mentioned above, if you are aspirating in general when eating/drinking (i.e. food or drink are entering your lungs), this may be observed during the procedure. Your medical team will then be informed so that a plan can be made to reduce the risk of this happening in your day-to-day life.

Should any unlikely and unforeseen issues arise while you are in the session with the researcher, you will be referred to an appropriate specialist or be brought to the Emergency Department.

Will I be told the outcome of the study? Will I be told the results of any tests or investigations performed as part of this study that relate to me?

The researcher can explain the results of the videofluoroscopy to you during the session. You can request that a copy of the results be placed in your medical file if you wish.

Anonymous results of the project may be published in peer reviewed journals or presented at international conferences, but you may be assured of total privacy. Your identity will not be made public without your prior consent. Information with your name on it (e.g. consent forms) will be separated from your results (pseudonymised). These will be given a code number and that code number will be used from that point onwards. The consent forms and codes will be securely stored in a locked filing cabinet or on password protected computers. Coded data and signed consent forms will be stored for 7 years. After this, they will be shredded, securely discarded and files deleted from the computers.

PART 2 – DATA PROTECTION

What information about me (personal data) will be used as part of this study? Will my medical records be accessed?

Personal information about you will be taken from your hospital medical records, the questionnaires you complete, and from your conversation with the researcher. This information is collected to see whether there are patterns between the types of swallowing difficulties that people with oesophageal cancer have and certain aspects of their personal data. For example, whether there is a correlation between the location or severity of cancer and the types of swallowing difficulties experienced.

What will happen to my personal data?

Your personal data will only be processed to analyse whether there are patterns between these data and the types of swallowing difficulties that are experienced. It will not be processed in a way that may cause any damage or distress to you. The personal data will be kept in a pseudonymised format at Trinity College Dublin for 7 years, after which it will be shredded and disposed of in a secure manner.

Who will access and use my personal data as part of this study?

Your personal data will only be accessible to the main researchers of this study: Anna Gillman, Professor Regan, Professor Walshe, Professor Reynolds, Ms Donohue and Michelle Hayes.

Will my personal data be kept confidential? How will my data be kept safe?

Data will be stored on the St James' Hospital computer system, the main researcher's password protected computer and in a locked office at Trinity College Dublin.

No presentations or publications will reveal any personal data of participants that could be identifiable.

What is the lawful basis to use my personal data?

The **lawful basis** for the using participant's personal data.

- Article 9 of GDPR:
(h): Processing is necessary for the purposes of preventive or occupational medicine, for the assessment of the working capacity of the employee, medical diagnosis, the provision of health or social care or treatment of the management of health or social care systems and services on the basis of Union or Member State law of pursuant to contract with a health professional and subject to the conditions and safeguards referred to in paragraph 3.

The legal basis for processing personal data in under Article 6(1)(e), this is research in the public interest.

The legal basis for processing sensitive personal data is under Article 9(2)(j), this is processing data for scientific purposes.

What are my rights?

All participants have the following rights regarding their **data**.

- Right to access data held
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability
- Right to object to profiling

For further information, please contact the joint data controllers at St James Hospital or Trinity College Dublin (01 4103021/4162463 and dataprotection@stjames.ie or dataprotection@tcd.ie respectively).

PART 3 – COSTS, FUNDING & APPROVAL

Will it cost me anything if I agree to take part?

There are no financial costs to participating in this research.

Who is funding this study? Will the results study be used for commercial purposes?

No funding has been sourced for this study. Researchers are not being paid to recruit patients to the study.

The results will not be disclosed for commercial purposes.

Has this study been approved by a research ethics committee?

St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee gave ethical approval to this research on 11th August 2021.

No one carrying out research has a link to the committee or the institution behind the committee. The main researcher will provide an annual report to the Research Ethics Committee, as well as a final report once the study is completed. The main researcher will inform the Research Ethics Committee of any adverse events, or any changes to the study protocol or documentation.

PART 4 – FUTURE RESEARCH

Will my personal data and/or biological material be used in future studies?

The data may be used by the researchers of this project in future studies to better understand the nature, severity and impact of swallowing difficulties in patients with oesophageal cancer.

PART 5 – FURTHER INFORMATION

Where can I get further information?

- If you wish to receive further information, please contact the principal investigator, Anna Gillman, on 0874131127 or at gillmana@tcd.ie
- The data processors are :
 - Anna Gillman PhD student 0874131127 gillmana@tcd.ie
 - Professor Julie Regan 1 896 1492 juregan@tcd.ie
 - Professor John Reynolds reynoldsjv@stjames.ie
 - Professor Margaret Walshe walshema@tcd.ie
 - Michelle Hayes mhayes6@tcd.ie
 - Ms Claire Donohue
- The Data Protection Officer at St James' Hospital is available on 01 4103021/4162463 or at dataprotection@stjames.ie. The Data Protection Officer at Trinity College Dublin is available on 01-8961892 or at dataprotection@tcd.ie

What happens if I wish to make a complaint?

If you wish to make a complaint at any time, please contact the principal researcher Anna Gillman (0874131127 or gillmana@tcd.ie) or Professor Regan (01 896 1492 or juregan@tcd.ie).

Will I be contacted again?

We will not contact you again once the study has been completed, however, you are welcome to contact us for results of the study once it has been published.

I consent to participating in this study as outlined above including an interview, questionnaires and a videofluoroscopy.

Patient signature: _____

Patient name: _____

Date: _____

10.7 Appendix H Scoring Document (including Questionnaires)

Name	
Participant No	
Consultant	
Next Apt	
DOB	
Age	
Allergies	
MRN	

To discuss with participant:

- Purpose of this study
- Data collection (risks, tasks, protocol etc)
- Data storage plans
- Withdrawal process
- Gain written consent

Complete Y/N	
Complete Y/N	
Complete Y/N	
Complete Y/N	
Complete Y/N	

VFS :

Screen for position and vocal fold location

Lateral:

- 2 x 5ml cup Level 0 'swallow all in one go when I tell you'
- 2 x 10 ml cup level 0 'swallow all in one go when I tell you'
- uncontrolled volume sips Level 0 from 100 ml cup. X2.
- 2 x 5ml spoons puree
- 1 biscuit with puree 'chew as you normally would and swallow when you're ready'

Complete Y/N	

Complete Y/N	

Complete Y/N	

Complete Y/N	

Complete Y/N	

Anterior-Posterior (screen for 15s on and off, stop at 60s)

- 2 x 20ml cup thin 'swallow all in one go when I tell you'
- 2 5ml spoon puree 'swallow all in one go when I tell you'
- 1 tablet with normal water

Complete Y/N	

Complete Y/N	

Complete Y/N	

Date of Surgery	
What neoadjuvant treatment received?	
Presence and description of swallowing difficulty	
Has the sound of your voice changed at all? If so, how	

Are you coughing more than you used to?		
Have you seen a gastroenterologist for any oesophageal or stomach issues previously? Or an SLT for dysphagia?		
Do you eat normal food and drinks or do you need to modify the textures?		
	If modifying food, when did this start?	
	What modifications?	
	If modifying fluid, when did this start?	
	What modifications?	
Pt reported current weight		
Pt reported current height		
	Recollection of weight 12 months ago?	
	Recollection of weight 3-6 months ago?	
	Unplanned weight loss?	
	Had patient intentions to lose weight?	
	If so how much	
Had any chest infections since you left hospital?		
	If so, when?	
	Needed antibiotics? When?	
Readmissions to hospital for any reason?		
FOIS – Current score (Ratings below)		

Level 1	Nothing by mouth	Level 5	Total oral diet with multiple consistencies but requiring special preparation or compensations.
Level 2	Tube dependent with minimal attempts of food or liquid	Level 6	Total oral diet with multiple consistencies without special preparation but with specific food limitations
Level 3	Tube dependent with consistent oral intake of food or liquid	Level 7	Total oral diet with no restrictions
Level 4	Total oral diet of a single consistency		

Questionnaires 1: EORTC, RSI, MDADI,

Complete Y/N

IOPI

Participant No	Posterior Peak (kPa)	Anterior Peak (kPa)	Target 50% (kPa)	Endurance (Anterior)(s)

1. "I will place the bulb in your mouth between your tongue and the roof of your mouth at the back, like in this picture. Please press the bulb as hard as possible for 2 s when I tell you to. Please do not frown too much or use your teeth."
2. "Next, I will move it forwards. Now, press it as hard as you can for 2 seconds"
3. Set bulb to 50% ie target
4. "This time squeeze the bulb so that the green light stays lit for as long as you can. I will record the time".

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.

		Not at all	A little	Quite a bit	Very Much
1	Could you eat solid food?	1	2	3	4
2	Could you eat liquidised or soft food?	1	2	3	4
3	Could you drink liquids?	1	2	3	4
4	Have you had trouble with swallowing your saliva?	1	2	3	4
5	Have you choked when swallowing?	1	2	3	4
6	Have you had trouble enjoying your meals?	1	2	3	4
7	Have you felt full too quickly?	1	2	3	4
8	Have you had trouble with eating?	1	2	3	4
9	Have you had trouble with eating in front of other people?	1	2	3	4
10	Have you had a dry mouth?	1	2	3	4
11	Have you had problems with your sense of taste?	1	2	3	4
12	Have you had trouble with coughing?	1	2	3	4
13	Have you had trouble with talking?	1	2	3	4
14	Have you had trouble with acid indigestion or heartburn?	1	2	3	4
15	Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
16	Have you had pain when you eat?	1	2	3	4
17	Have you had pain in your chest?	1	2	3	4
18	Have you had pain in your stomach?	1	2	3	4

Reflux Symptom Index (RSI)

Within the last month, how did the following problems affect you? Please give a score from 0 –5: (where 0 = No problem, 5= Severe Problem)	0	1	2	3	4	5
1) Hoarseness or a problem with your voice						
2) Clearing your throat						
3) Excess throat mucous or postnasal drip						
4) Difficulty swallowing food, liquids, or pills						
5) Coughing after you eat or after lying down						
6) Breathing difficulties or choking episodes						
7) Troublesome or annoying cough						
8) Sensation of something sticking in your throat or a lump in your throat						
9) Heartburn, chest pain, indigestion, or stomach acid coming up						

The MD Anderson Dysphagia Inventory

The questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.

The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you.

Please read each statement and circle the response which best reflects your experience in the past week

My swallowing ability limits my day-to-day activities.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E2. I am embarrassed by my eating habits.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F1. People have difficulty cooking for me.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P2. Swallowing is more difficult at the end of the day.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E7. I do not feel self-conscious when I eat.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E4. I am upset by my swallowing problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P6. Swallowing takes great effort.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E5. I do not go out because of my swallowing problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F5. My swallowing difficulty has caused me to lose income.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P7. It takes me longer to eat because of my swallowing problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P3. People ask me, "Why can't you eat that?"

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E3. Other people are irritated by my eating problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P8. I cough when I try to drink liquids.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F3 My swallowing problems limit my social and personal life.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F2. I feel free to go out to eat with my friends, neighbours, and relatives.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P5. I limit my food intake because of my swallowing difficulty.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P1. I cannot maintain my weight because of my swallowing problems.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E6. I have low self-esteem because of my swallowing problems.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P4. I feel that I am swallowing a huge amount of food.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F4. I feel excluded because of my eating habits.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

Global Score (Q1)		
Composite score (weighted average of remaining 19)		
	Emotional subscale average:	
	Functional subscale average:	
	Physical subscale average:	

MDADI Scores: (Global (Q1), Physical, Emotional, Functional). There are 2 summary scores intended to reflect the overall perfection of swallowing abilities: Made up of: 1) Global score = first question only. 2) Composite (total) score = remaining 19 items (not Q1) as a weighted average of the physical, emotional and functional subscale questions. Subscale scores (emotional, functional and physical reflect specific domains of individual's perceived swallowing abilities).

Mayo Questionnaire: Brief Esophageal Dysphagia Questionnaire

We would like to ask about your dysphagia symptoms over the past 2 weeks (14 days) and two experiences over the last 12 months. Please think about your symptom experiences and choose the best answer.

Over the past 14 days, on average, how often have you had the following? If your response falls between two categories, please make your best guess. If you are unable to eat the type of food in the question, please check "Cannot eat this."

Symptom Frequency		0	1	2	3	4	5
	<i>Cannot Eat This</i>	<i>Rarely/ Never</i>	<i>Once or twice a month</i>	<i>1-2 times per week</i>	<i>3-5 times per week</i>	<i>Daily or almost daily</i>	<i>Several times per day</i>
Trouble eating solid food (meat, bread, vegetables)							
Trouble eating soft foods (yogurt, jello, pudding)							
Trouble swallowing liquids							
Pain while swallowing							
Coughing or choking while swallowing foods or liquids							
Total Score							

Over the past 14 days, on average, how would you rate your discomfort or pain during swallowing? If you are unable to eat the type of food, please check "Cannot eat this."

Symptom Severity		0	1	2	3	4	5
	<i>Cannot Eat This</i>	<i>None</i>	<i>Very Mild</i>	<i>Mild</i>	<i>Moderate</i>	<i>Moderately Severe</i>	<i>Severe</i>
Eating solid food (meat, bread, vegetables)							
Eating soft food (yogurt, jello, pudding)							
Drinking Liquids							
Total Score							

Approximately how many times in the **past 12 months** have you:

Had food stuck in your throat or esophagus for a period lasting longer than 30 minutes?

Had to visit the emergency room because of food stuck in your throat or esophagus?

Scoring:

Total Score is calculated by summing the numeric value (0-5) for all items checked on the questionnaire. **Items where “Cannot Eat This” are checked are scored as 5.**

Total scores range from 0 to 40.

Symptom Frequency subscale contains the first 5 items, scored from 0 to 5.

Items where “Cannot Eat This” are checked are scored as 5.

Symptom Frequency scores range from 0 to 25.

Symptom Severity subscale contains the next 3 items, scored from 0 to 5.

Items where “Cannot Eat This” are checked are scored as 5.

Symptom Severity scores range from 0 to 15.

The last 2 open-ended items on the scale are meant to be qualifiers based on the following guidelines. These items **are not included** in the BEDQ scoring.

- For all patients, if at least 1 ER visit for food impaction is present, more thorough evaluation is warranted.
- For patients who have yet to receive an esophageal diagnosis, one or more self-limited food impactions warrants endoscopic evaluation.
- For patients who have a known esophageal disorder such as EoE or achalasia, or an esophageal stricture, greater than two self-limited food impactions over 6 months would necessitate further evaluation and consideration of intervention.

SARC-F questions

SARC-F		Score
How much difficulty do you have in lifting and carrying 10 pounds (4-5kg)?	(None= 0, Some = 1, A lot of unable = 2)	
How much difficulty do you have walking across a room?	(None= 0, Some = 1, A lot of unable = 2)	
How much difficulty do you have transferring from a chair or bed	(None= 0, Some = 1, A lot of unable = 2)	
How much difficulty do you have climbing a flight of 10 stairs?	(None= 0, Some = 1, A lot of unable = 2)	
How many times have you fallen in the past year?	(None= 0, Some = 1, A lot of unable = 2)	
	TOTAL SCORE	

EAT-10

Circle the appropriate response.

To what extent are the following scenarios problematic for you?

	To what extent are the following scenarios problematic for you?	0 = No problem 4 = Severe problem				
1	My swallowing problem has caused me to lose weight	0	1	2	3	4
2	My swallowing problem interferes with my ability to go out for meals.	0	1	2	3	4
3	Swallowing liquids takes extra effort.	0	1	2	3	4
4	Swallowing solids takes extra effort.	0	1	2	3	4
5	Swallowing pills takes extra effort.	0	1	2	3	4
6	Swallowing is painful.	0	1	2	3	4
7	The pleasure of eating is affected by my swallowing.	0	1	2	3	4
8	When I swallow, food sticks in my throat.	0	1	2	3	4
9	I cough when I eat.	0	1	2	3	4
10	Swallowing is stressful.	0	1	2	3	4
	TOTAL EAT					

An elevated EAT-10 score indicates a higher self-perception of dysphagia

Scores of 3 or more are abnormal.

Clinical instrument to document the initial dysphagia severity (and monitor treatment responses)

10.8 Appendix I Pathological Staging

Overall Pathological Staging of Oesophageal Cancer: The American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification system for oesophageal and esophagogastric junction cancer [757]

Stage group	pT	pN	pM	Grade	Location
<i>Squamous cell carcinoma</i>					
0	Tis	N0	M0	N/A	Any
IA	T1a	N0	M0	G1, X	Any
IB	T1b	N0	M0	G1–3, X	Any
	T1a	N0	M0	G2–3	Any
	T2	N0	M0	G1	Any
	T2	N0	M0	G2–3, X	Any
IIA	T3	N0	M0	Any	Lower
	T3	N0	M0	G1	Upper/middle
	T3	N0	M0	G2–3	Upper/middle
IIB	T3	N0	M0	GX	Any
	T3	N0	M0	Any	X
IIIA	T1	N1	M0	Any	Any
	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
	T4a	N0–1	M0	Any	Any
IIIB	T3	N1	M0	Any	Any
	T2–3	N2	M0	Any	Any
	T4a	N2	M0	Any	Any
IVA	T4b	N0–2	M0	Any	Any
	T1–4	N3	M0	Any	Any
IVB	T1–4	N0–3	M1	Any	Any
<i>Adenocarcinoma</i>					
0	Tis	N0	M0	N/A	
IA	T1a	N0	M0	G1, X	
	T1a	N0	M0	G2	
IB	T1b	N0	M0	G1–2, X	
	T1	N0	M0	G3	
IC	T2	N0	M0	G1–2	
IIA	T2	N0	M0	G3, X	
IIB	T1	N1	M0	Any	

	T3	N0	M0	Any
IIIA	T1	N2	M0	Any
	T2	N1	M0	Any
	T4a	N0–1	M0	Any
IIIB	T3	N1	M0	Any
	T2–3	N2	M0	Any
	T4a	N2	M0	Any
IVA	T4b	N0–2	M0	Any
	T1–4	N3	M0	Any
	T1–4	N0–3	M1	Any

N/A = not applicable; X = not defined

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia,* defined as malignant cells confined by the basement membrane
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Unresectable tumor invading other adjacent structures, such as the aorta, vertebral body, and trachea

*High-grade dysplasia includes all noninvasive neoplastic epithelial lesions formerly called carcinoma in situ; that term is no longer used for columnar mucosae anywhere in the gastrointestinal tract.

Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes

Distant metastasis (M)	

M0	No distant metastasis
M1	Distant metastasis

Histologic grade (G)	
GX	Grade cannot be assessed—stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated or undifferentiated*
*If undifferentiated with glandular component, stage as G3 adenocarcinoma; if undifferentiated with squamous cell component, or tumor remains undifferentiated after further testing, group as G3 squamous cell carcinoma.	

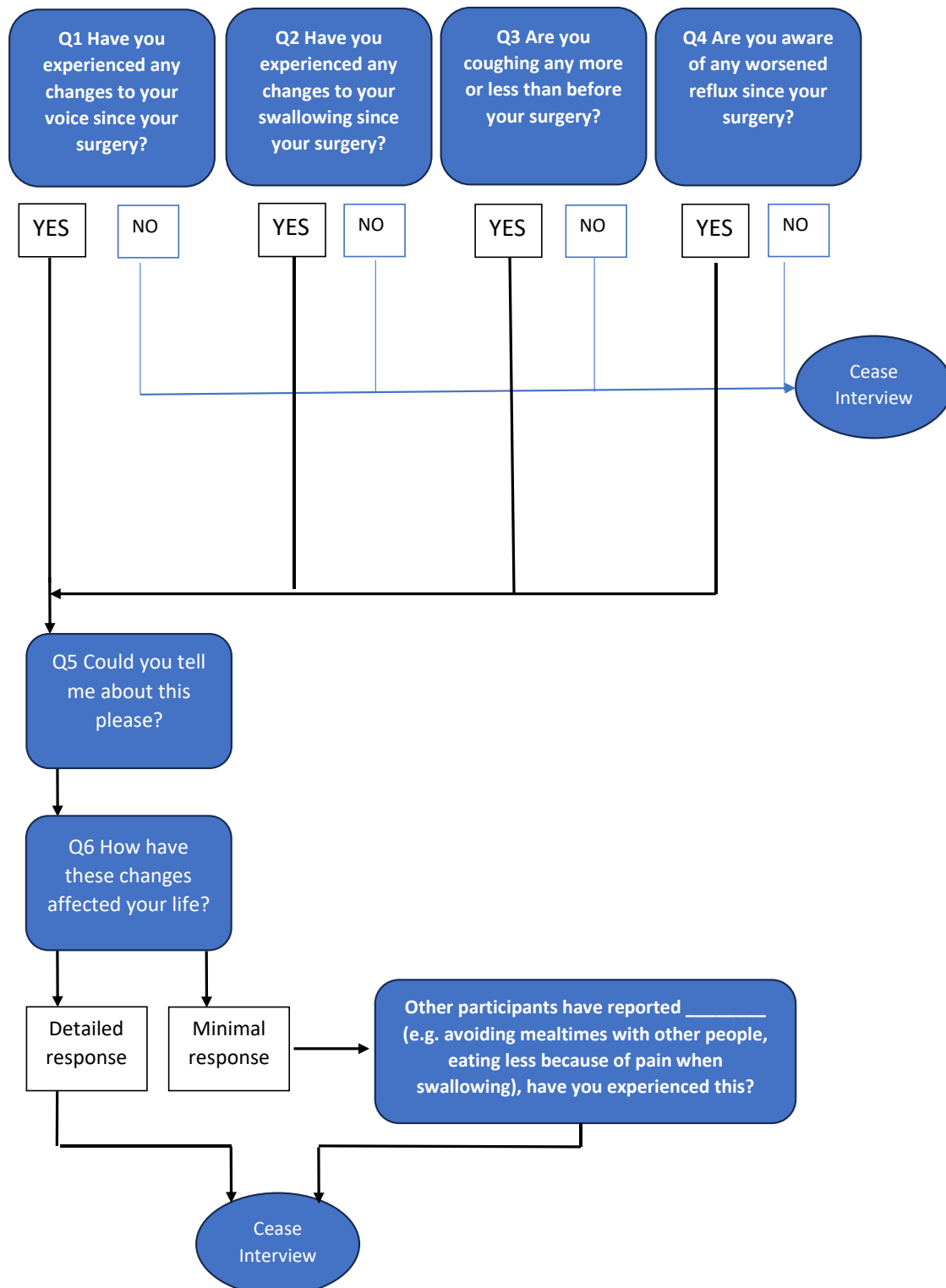
Squamous cell carcinoma location	
X	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azygos vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including gastroesophageal junction

10.9 Appendix J Participant Level Summary of Dysphagia, Aspiration and QoL Results

Part No	Age	Sex	Surg Approach	Months since surgery	Worst PAS	Worst DIGEST	MBSImP Total Oral	MBSImP Total Pharyngeal	FOIS	EAT-10	MDADI Global	MDADI Comp
1	59	M	2 stage	13	1	0	3	10	6	28	1	37.9
2	74	F	2 stage	13	3	1	5	10	6	0	5	74.7
3	58	M	2 stage	16	1	0	7	11	7	12	4	65.3
4	61	M	2 stage	13	1	0	5	8	6	2	5	93.7
5	62	M	2 stage	19	1	0	8	10	4			
6	72	M	2 stage	16	1	0	4	6	7	0	5	91.6
7	54	M	2 stage	17	1	0	4	4	7	6	3	85.3
8	64	M	2 stage	20	1	1	10	10	7	1	5	91.6
9	46	M	2 stage	14	1	1	10	8	7	0	4	77.9
10	71	M	2 stage	22	2	1	10	11	6	8	4	72.6
11	71	M	3 stage	36	1	0	2	8	7	0	5	92.6
12	83	M	Transhiatal	53	1	1	5	8	6	11	5	74.7
13	43	F	3 stage	51	1	0	4	7	7	3	4	71.6
14	63	M	3 stage	38	1	0	3	7	7	0	5	93.7
15	63	F	3 stage	67	2	0	6	3	6	19	4	55.8
16	59	M	Transhiatal	69	1	0	3	3	6	17	4	50.5
17	52	M	3 stage	69	1	0	4	9	7	0	5	89.5
18	71	F	Transhiatal	70	1	0	7	5	6	8	5	83.2
19	66	M	Transhiatal	59	1	0	5	6	6	18	3	48.4
20	69	M	2 stage	44	1	0	5	3	7	7	4	72.6
21	60	F	2 stage	38	1	1	9	10	5	14	4	60.0
22	73	M	2 stage	30	3	1	3	7	6	12	5	77.9
23	74	M	2 stage	50	1	0	3	1	7	1	5	85.3
24	61	M	2 stage	36	2	0	3	7	7	28	3	49.5
25	73	M	2 stage	31	1	0	4	3	7	2	3	60.0
26	63	M	2 stage	53	1	0	4	4	7	14	5	85.3
27	72	M	2 stage	55	1	0	7	1	7	0	5	92.6
28	51	M	2 stage	37	1	0	3	3	7	3	5	95.8
29	77	M	3 stage	63	1	1	5	8	5	5	4	70.5
30	79	F	2 stage	41	1	0	6	1	7	0	5	100.0
31	58	F	3 stage	125	1	0	2	3	7	0	5	95.8
32	72	M	2 stage	59	1	0	4	6	7	0	5	90.5
33	63	M	Transhiatal	67	1	1	4	6	7	1	5	96.8
34	71	M	Transhiatal	89	1	0	3	5	6	2	5	93.7
35	83	M	Transhiatal	84	1	0	4	2	7	0	5	100.0
36	72	M	3 stage	108	1	2	9	10	7	11	3	60.0
37	65	F	Transhiatal	84	8	3	3	9	6	14	4	65.3
38	60	M	3 stage	85	2	1	1	7	7	0	5	98.9
39	69	F	3 stage	109	1	1	5	10	5	30	2	42.1
40	84	F	Transhiatal	106	7	3	4	8	5	27	1	32.6

10.10 Appendix K Interview Guide

Appendix A Interview Guide



10.11 Appendix L COREQ Guidelines for reporting qualitative data

Table 1 Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

No	Item	Guide questions/description
Domain 1: Research team and reflexivity		
Personal Characteristics		
1.	Interviewer/facilitator	Which author/s conducted the interview or focus group?
2.	Credentials	What were the researcher's credentials? <i>E.g. PhD, MD</i>
3.	Occupation	What was their occupation at the time of the study?
4.	Gender	Was the researcher male or female?
5.	Experience and training	What experience or training did the researcher have?
Relationship with participants		
6.	Relationship established	Was a relationship established prior to study commencement?
7.	Participant knowledge of the interviewer	What did the participants know about the researcher? <i>e.g. personal goals, reasons for doing the research</i>
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? <i>e.g. Bias, assumptions, reasons and interests in the research topic</i>
Domain 2: study design		
Theoretical framework		
9.	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? <i>e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis</i>
Participant selection		
10.	Sampling	How were participants selected? <i>e.g. purposive, convenience, consecutive, snowball</i>
11.	Method of approach	How were participants approached? <i>e.g. face-to-face, telephone, mail, email</i>
12.	Sample size	How many participants were in the study?
13.	Non-participation	How many people refused to participate or dropped out? Reasons?
Setting		
14.	Setting of data collection	Where was the data collected? <i>e.g. home, clinic, workplace</i>
15.	Presence of non-participants	Was anyone else present besides the participants and researchers?
16.	Description of sample	What are the important characteristics of the sample? <i>e.g. demographic data, date</i>
Data collection		
17.	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?
18.	Repeat interviews	Were repeat interviews carried out? If yes, how many?
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?
20.	Field notes	Were field notes made during and/or after the interview or focus group?
21.	Duration	What was the duration of the interviews or focus group?
22.	Data saturation	Was data saturation discussed?
23.	Transcripts returned	Were transcripts returned to participants for comment and/or correction?
Domain 3: analysis and findings		
Data analysis		
24.	Number of data coders	How many data coders coded the data?
25.	Description of the coding tree	Did authors provide a description of the coding tree?
26.	Derivation of themes	Were themes identified in advance or derived from the data?
27.	Software	What software, if applicable, was used to manage the data?
28.	Participant checking	Did participants provide feedback on the findings?
Reporting		
29.	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? <i>e.g. participant number</i>
30.	Data and findings consistent	Was there consistency between the data presented and the findings?
31.	Clarity of major themes	Were major themes clearly presented in the findings?
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?

Title: Long-term Impact of Aerodigestive Symptoms on Adults with Oesophageal Cancer: a Qualitative Study

Running head: Oesophageal Cancer Aerodigestive Symptoms

Authors: Anna Gillman MSc, Michelle Hayes MSc, Prof Irene Walsh PhD, Prof Margaret Walshe PhD, Prof John V Reynolds MA, Prof Julie Regan PhD

**Long-term Impact of Aerodigestive Symptoms on Adults with Oesophageal Cancer:
a Qualitative Study**

Abstract

Purpose: The impact of long-term aerodigestive symptoms following oesophageal cancer surgery is still not well understood. This study aimed to qualitatively understand the long-term impact of aerodigestive symptoms on quality of life in adults post-oesophagectomy.

Method: Participants who received curative transhiatal/ transthoracic surgery for oesophageal cancer in Ireland's National Oesophageal Cancer Centre were invited to attend semi-structured interviews. Surgery had to be completed at least 12 months prior. Reflexive thematic analysis was conducted.

Result: Forty participants were interviewed individually face-to-face. Four key themes were identified; 1) Isolation; reflecting the reported solitude experienced by oesophageal cancer survivors when attempting to manage their ongoing aerodigestive symptoms, 2) Fear; fear of choking and fear that dysphagia symptoms may indicate recurrence of oesophageal cancer, 3) Altered work capacity; caused by ongoing aerodigestive symptoms, and 4) Avoidance of social situations involving food; due to the pain, discomfort and embarrassment caused by these symptoms.

Conclusion: Oesophageal cancer treatment can be lifesaving, however, such medical interventions can result in distressing physiological aerodigestive symptoms throughout

survivorship, which can significantly impact quality of life. Our findings indicate a need for greater community support to manage aerodigestive symptoms and reduce the impact these have on quality of life.

Key words: Oesophageal cancer, survivorship, chronic aerodigestive symptoms, quality of life.

Global survival rates for oesophageal cancer are improving, with significant increases in countries like Ireland, Denmark, and Norway between 1995 and 2014 [2] [758]. Some countries now achieve 5-year survival rates of approximately 50% following treatment with curative intent [7]. While numerous studies have investigated post-operative complications in the acute period following oesophagectomy [67, 407, 759], limited research exists on the nature of long-term symptoms and their burden [760].

Most cancer treatments result in late physiological and psychosocial complications [424, 761-763]. Oesophageal cancer is particularly invasive, involving partial or complete removal of the oesophagus and, in most cases, stomach repositioning [764, 765]. Consequently, survivors may experience daily symptoms for years following oesophageal resection and neoadjuvant chemo(radio)therapy.

In a recent study of 876 participants, 66.9% reported persistent symptoms more than one year after surgery [417]. Aerodigestive symptoms, such as swallowing difficulties, reflux, weight maintenance, pain, appetite loss, and diarrhoea, and psychological symptoms such as anxiety, have been reported for many years post oesophagectomy [332, 417, 764, 766, 767]. Further research has shown that only 13.8% of oesophagectomy survivors were able to return to employment at a similar intensity as before their diagnosis [417].

Our research team recently published a study (n=40) which found that 35% of participants presented with chronic pharyngeal dysphagia on videofluoroscopy using the

Dynamic Imaging Grade of Swallowing Toxicity v2 a mean of 52 months post surgery, with ongoing aspiration/ uncleared penetration in 10% of participants [768]. A study published by Sugase and colleagues, which did not evaluate COD, did however report that patients experienced significantly more pneumonia a median of 37 months post oesophagectomy if they had been acutely dysphagic on videofluoroscopy compared to the non-dysphagia group [256].

Speech-language pathologists are considered a vital member of the oesophageal cancer multi-disciplinary team in the acute phase post-surgery [72, 101] [26]. Although research is limited to date [413], there is also some early evidence to show that speech-language pathologists have an important role in the long-term management of dysphagia through implementing compensatory strategies [93, 250, 396] and rehabilitation exercises with this community based cohort [69, 73, 74, 484].

Given the growing number of survivors and the significant burden of symptoms, health-related quality of life, that is, patients' perceived physical and mental health over time, deserves to be a central focus of research. There is an argument that health-related quality of life is just as important an outcome as survival if not more so [769]. Fortunately, recent years have witnessed a gradual increase in research evaluating long-term health-related quality of life in this cohort, primarily employing questionnaires and, to a lesser extent, interviews and focus groups [552, 770-772].

In our previously mentioned study [768] and from our research team's clinical experience, it appears as though quality of life of some patients is minimally impacted by ongoing symptoms of dysphagia however others are severely affected for many years. To further explore the perspective of survivors, our research team wished to more deeply evaluate this topic using qualitative analysis.

We formed a Patient and Public Involvement Committee, which included two oesophagectomy survivors who were both more than five years post surgery, to assist with various aspects of this research. The committee highlighted however, that oesophageal cancer survivors find it challenging to distinguish symptoms of dysphagia from symptoms of the entire aerodigestive tract including coughing, voice changes, reflux, digestive issues etc. This aligns with other research that has compiled closely related cancer symptoms into clusters [489, 490]. Consequently, we decided that the focus of our research should more broadly reflect the impact of aerodigestive symptoms on quality of life to ensure that the research question was pertinent to this population group.

In addition, there is agreement in the cancer community that there is a greater need for research to focus on quality of life throughout survivorship and not just on the first couple of years [424, 425]. Therefore, our study aimed to qualitatively analyse how aerodigestive symptoms related to oesophageal cancer surgery affect quality of life throughout survivorship in anyone who was over 12 months post-surgery.

Methods

Study Design and Participants

This qualitative study is part of a larger mixed-methods study investigating the nature, severity, and impact of long-term dysphagia (swallowing difficulties) after curative oesophageal resection. Our research team in Ireland aimed to delve deeper into the patients' experience through the use of interviews.

Ethical approval was granted by the St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee (Project ID: 0371). This study was conducted in accordance with the principles outlined in the Helsinki Declaration.

Purposive sampling was used to recruit participants who had received oesophageal cancer surgery at Ireland's National Oesophageal Cancer Centre. This recruitment method enables the selection of participants experiencing a particular healthcare related phenomenon [499].

Inclusion criteria consisted of adults who were minimum 12 months post curative transhiatal or transthoracic oesophageal surgery completed with curative intent for first time oesophageal cancer. Exclusion criteria comprised history of neurological impairment, head and neck cancer, oral/pharyngeal dysphagia, recurrent or metastatic disease, severe Chronic Obstructive Pulmonary Disease, or if receiving palliative treatment.

A letter and participant information leaflet were posted in consecutive order to the homes of patients who met the criteria. The main researcher phoned seven days later to provide information and gain verbal consent.

Seventy-eight participants were contacted about the overall study and forty wished to participate. 38 participants declined because of the following reasons: 1) living too far from the test centre 2) did not want to attend a hospital during the Covid-19 pandemic 3) sick 4) caring for a sick relative or 5) not interested in participating in research. All participants also took part in the aforementioned published study which evaluated oropharyngeal dysphagia using videofluoroscopy [768]. All participants provided written informed consent.

Table 1*Participant Details*

Participant Number	Sex	Age Bracket	Months post-surgery	Surgical approach
1	Male	50-60	13	2 stage
2	Female	70-80	13	2 stage
3	Male	50-60	16	2 stage
4	Male	60-70	13	2 stage
5	Male	60-70	19	2 stage
6	Male	70-80	16	2 stage
7	Male	50-60	17	2 stage
8	Male	60-70	20	2 stage
9	Male	40-50	14	2 stage
10	Male	70-80	22	2 stage
11	Male	70-80	36	3 stage
12	Male	80-90	53	Transhiatal
13	Female	40-50	51	3 stage
14	Male	60-70	38	3 stage
15	Female	60-70	67	3 stage
16	Male	50-60	69	Transhiatal
17	Male	50-60	69	3 stage
18	Female	70-80	70	Transhiatal
19	Male	60-70	59	Transhiatal
20	Male	60-70	44	2 stage
21	Female	60-70	38	2 stage
22	Male	70-80	30	2 stage
23	Male	70-80	50	2 stage
24	Male	60-70	36	2 stage
25	Male	70-80	31	2 stage
26	Male	60-70	53	2 stage
28	Male	70-80	55	2 stage
28	Male	50-60	37	2 stage
29	Male	70-80	63	3 stage
30	Female	70-80	41	2 stage
31	Female	50-60	125	3 stage
32	Male	70-80	59	2 stage
33	Male	60-70	67	Transhiatal
34	Male	70-80	89	Transhiatal
35	Male	80-90	84	Transhiatal
36	Male	70-80	108	3 stage
37	Female	60-70	84	Transhiatal
38	Male	60-70	85	3 stage
39	Female	60-70	109	3 stage
40	Female	80-90	106	Transhiatal

Note: Surgical approach refers to the various procedure types conducted at this study's surgical centre: a 2-stage en-bloc resection (Ivor Lewis approach) a 3-stage en-bloc resection (McKeown approach) and a transhiatal procedure.

Data Collection

Individual face-to-face interviews were conducted by the first author, a speech-language pathologist with experience conducting interviews, in a clinical setting between November 2020 and August 2021. The interviews were audio-recorded. Semi-structured interviews were selected as they are considered suitable for exploring illness related experiences [773].

Initially, the interviewer asked participants if they had experienced any changes to their digestion, swallowing, voice or coughing since their cancer surgery, and if so, whether it had affected their quality of life. For those whose quality of life was impacted, an open question was employed (e.g. Could you please explain how your quality of life has been affected by this?), with the intention of casting a wide net of responses given the current limited understanding around the impact of aerodigestive symptoms. Additional probing questions were asked depending on the natural flow of the conversation to further explore participants' emotions and beliefs. Interviews were a maximum of 26 minutes and were conducted in English.

Data Analysis

Audio files were transcribed by two researchers manually and via the transcription function in Microsoft Word. Audio files were deleted after transcription to ensure anonymity, and any identifiable information was deleted from the transcripts.

Reflexive Thematic Analysis was selected as the analytical approach as it allows for an in-depth exploration of individual participant experiences in qualitative health research [572]. In addition, reflexive thematic analysis was selected as it embraces the researcher as part of the analysis; valuing the interviewer and coder as an experienced

clinician, with social, cultural, historical and disciplinary positions and subjective interpretations [574, 575, 774].

With this type of thematic analysis, the researchers' subjectivity, as well as their reflexive engagement with the data, is considered to benefit the analytical process, playing an active role in the production of themes [575, 775]. As such, it was decided that just one person, the lead researcher, would complete the analysis as per other published studies [776-779]. Braun & Clark emphasise how there should be no expectation that codes and themes will be interpreted by two researchers in the same way nor should there be attempts to gain consensus among coders to try to increase reliability, as this type of analysis is deemed to be enriched by its subjective nature [776, 780].

Braun and Clark's six phases of reflexive thematic analysis were implemented as per Figure 1 [575] to identify and understand the patterns of meaning across the transcripts [575]. The steps of reflexive thematic analysis are not rigid and can blend together or become recursive depending on the direction that the researcher's analysis takes [575]. The researcher noted ideas and potential themes during the interview and when reviewing transcripts. These key pieces of information were documented as "codes".

NVivo, a computer-assisted qualitative data analysis software, was employed to maintain an audit trail and ensure the rigour and credibility of findings [577]. Once the transcribed texts were uploaded into the software, the researcher could easily and quickly embed notes such as annotations and memos into the files, while indexes of codes were simultaneously formed to provide an overview which could then be reformed into categories or merged for the early identification of themes.

An inductive approach to analyses was utilised which means that the codes and themes were derived directly from the data and were not linked to any specific question

asked or to the researcher's previously conceived assumptions about potential themes [579] [572]. Certain codes became more meaningful depending on the frequency with which they were discussed across interviews as well as the level of impact that participants reported they had.

Themes were then actively identified by the main researcher rather than emerging passively from the data meaning that the researcher reviewed the transcripts with all of these key codes in mind to determine which best represented the participants as a group [572, 578].

Initially themes were semantic in nature, meaning they were more overt, for example, being unable to return to work in the same capacity as before cancer was a theme explicitly voiced by many participants. As the researcher became more familiar with the dataset, more latent themes evolved that were underlying or not as apparent initially, for example, how there was a sense of isolation amongst participants who tried to manage their symptoms alone because of the lack of specialist support in the community or because of the reduced survival rate among their peers. Thematic maps aided in visually displaying the themes for categorising, merging and deleting [576].

Self-reflection and critique are recommended by Clarke & Braun to ensure that themes are directly driven from the data [579]. Reflexivity, understanding one's own biases and the impact this has on the analysis process, was continuously employed throughout data collection and analysis [572]. The main researcher kept a reflective journal and, after each interview and review of the transcripts, would reflect upon the questions asked and the interpretations made. The reflective process was key for assisting the main researcher to be more active in the analysis, enabling the explicit and active consideration of choices which could otherwise have been subconscious [41]. Although this type of analysis values

the researcher's experience and perspective in identification of the key themes, it was important that the researcher ensured that each code was developed from the data and not from the researcher so that the final product was true to the participants' story. On multiple occasions throughout the process, the coder discussed the identification of themes with a senior author who has significant experience using reflexive thematic analysis.

Following extensive immersion in the data, four themes ultimately became apparent. The authors initially attempted to embed all of these themes under one umbrella however it was evident that the themes were better represented if independent from each other. Once the themes were refined, summaries and titles were developed. Braun and Clarke recommend the use of 'catchy' names derived from quotes or relating to a specific focus of the data [572].

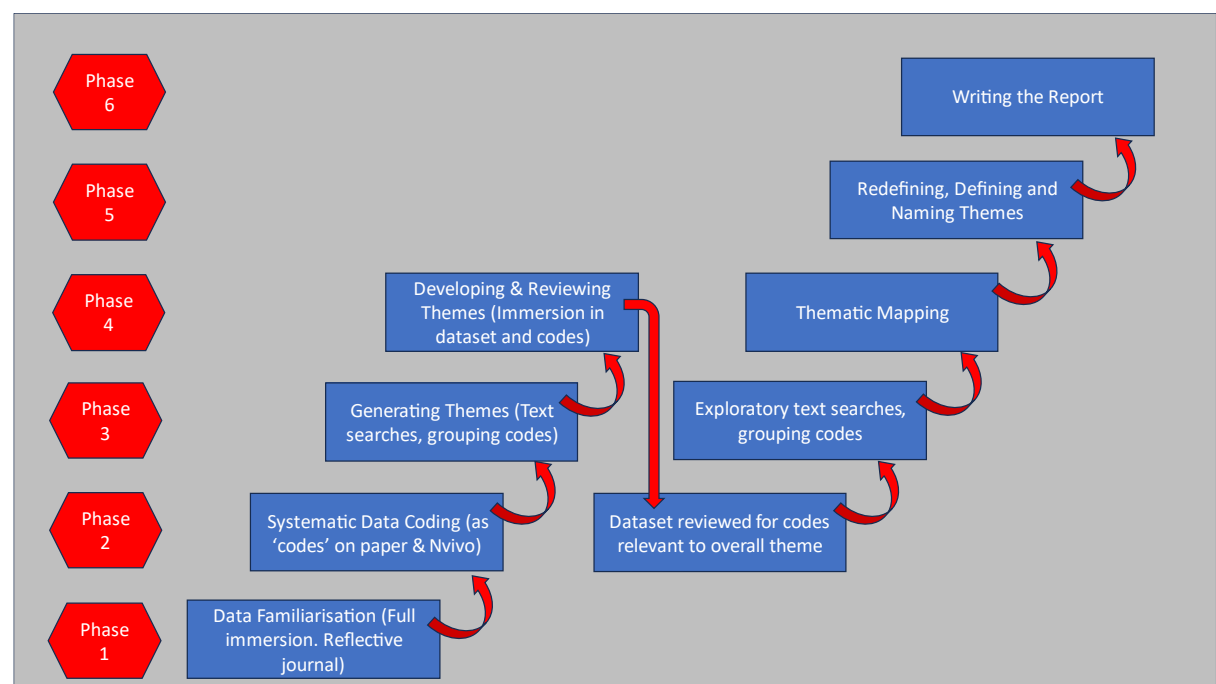


Figure 1: Analytical Process

The Consolidated Criteria for Reporting Qualitative research (COREQ) reporting guidelines [580] were followed to ensure explicit and transparent reporting and methodological rigor (See Supplementary Material 1).

Results

From November 2020 to August 2021, forty participants (30 male, 10 female) were recruited who had a mean age of 66.03 +/- 9.58 years (Range 41: 43-84) and were a mean of 51.73 +/- 30.296 months (Range 112: 13 – 125 months) post-surgery. The surgical approaches included thoracic anastomoses (52.5% 2 stage approach) and cervical anastomoses (25% 3 stage approach, 22.5% transhiatal approach).

Some participants acknowledged that their quality of life was not affected by the oesophageal cancer surgery, however, the majority of participants reported that quality of life continues to be burdened by long-term aerodigestive symptoms. The most commonly reported symptoms are listed in Table 2:

Table 2

Most commonly reported aerodigestive symptoms

Reported Aerodigestive Symptoms (Participant number)
Painful abdominal cramps (1, 3, 4, 7, 8, 13, 16, 17, 18, 19, 21, 22, 24, 25, 39, 40)
Severe reflux (1, 3, 4, 5, 9, 12, 13, 16, 17, 18, 20, 21, 23, 24, 25, 30, 32, 34, 38, 39, 40)
Coughing and/or choking when eating (13, 15, 16, 17, 19, 21, 22, 24, 28, 39, 40)
Frequent coughing (23, 32, 37)
Nausea, vomiting, diarrhoea (2, 7, 15, 16, 17, 18, 19, 20, 32)
Dizziness/fainting (hypoglycaemia-related) (6, 7, 16, 17)
Voice changes (17, 24, 29, 30, 33, 34, 36)
Loss of enjoyment of food (6, 8, 39)
Weight loss/maintenance issues (19, 39, 40)

Fatigue and poor concentration (6, 16, 17, 38)

Unable to swallow solid food because of a recurrent stricture (narrowing) in the remaining esophagus (12, 13, 17, 19, 33,39)

Reflexive thematic analysis can provide a rich description of themes from a large data set or an in-depth account of one theme from the data and this research aimed to do the former [572].

Theme A: Isolation

The most prominent theme that become apparent from the dataset was a sense of *isolation* experienced by oesophageal cancer survivors living with ongoing aerodigestive symptoms. The quotation “*I’m just very much alone with this...I’m totally alone*” (Participant 39) encapsulates this central perspective of aloneness, with participants reportedly feeling isolated while attempting to navigate this new life of long-term aerodigestive symptoms and reduced quality of life.

There was a perception that “*There’s nothing really in terms of support*” (Participant 39) for managing their aerodigestive symptoms beyond the first 6 months: “*I never felt I had any real support after that. I-I felt very isolated, on my own.*” (Participant 16)

Some participants reported having insufficient information, inadequate follow-up, and “*no (healthcare) numbers to ring*” (Participant 38). It was believed by some that healthcare teams primarily focus on cancer survival, neglecting quality of life: “*They’re gastric surgeons. I absolutely see from their point of view everything is fine because that’s how it appears. It’s not part of their remit to focus on quality of life.*” (Participant 39)

Several survivors seemed to believe that general practitioners and community health professionals lacked expertise in managing their symptoms. For example, it was reported that these professionals “*haven’t a clue*” (Participant 1) or “*don’t really understand*” (Participant 16), unfortunately resulting in one man getting “*some horse pills out in Spain*” (Participant 3) to manage his pain. A common thread throughout the dataset was how participants typically felt that they had to find their own way to cope: “*You have to kinda, learn to kinda deal with it yourself*” (Participant 12).

Support from other survivors was reportedly hindered by symptom presentations feeling unique (e.g., “*You can’t compare yourself to someone else.*” (Participant 1) and “*What somebody experiences isn’t necessarily what you’re going to experience.*” (Participant 2)) as well as by the low survival rate among peers: “*It’s hard... there’s two guys...used to have conversations with them and eh two of them went belly up...didn’t make it.*” (Participant 1)

Finally, reflux, one of the most frequently reported symptoms, which can cause severe pain especially if patients lie down, reportedly impacts upon relationships: “*I sleep separately from my wife a lot of the time now ... I mean I would wake her up four times a night.*” (Participant 3)

These experiences and examples provided by participants convey how this sense of isolation is a prominent theme caused by aerodigestive symptoms.

Theme B: Fear

This theme around *fear*, was a recurring issue caused by aerodigestive symptoms. Participants reported a fear of choking when eating/drinking: “*I worry if it gets really bad and I’m on my own.*” (Participant 39). “*At the back of your mind, ... you’re thinking,*

y'know, if I swallowed a little bit too much..." (Participant 10). *"It could just go wrong."* (Participant 9)

There was also a fear that swallowing difficulties could signify cancer recurrence given that dysphagia was the initial symptom of oesophageal cancer for the majority of participants. Additional concern was reported that their family members would also be afraid that the cancer was back if they observed their dysphagia. One participant was *"sneaking and throwing food into the fire"* (Participant 7) because he *"thought it was the cancer back y'see...but I didn't want to tell me family"* (Participant 7), *"Y'know you just say you're fine... when you weren't even fine, you just put on a good face."* (Participant 15).

Theme C: Altered Work Capacity

It was felt by some that *"It'd be a significant problem going back to work"* (Participant 3) because of aerodigestive problems such as fatigue and poor concentration that occur following eating, as well as embarrassment around more overt symptoms. Debilitating pain, for up to 24 hours following eating, and the need for privacy to release gas reportedly impact participants' ability to work

Similarly, dumping syndrome, when food travels too quickly from the stomach into the small bowel, causes nausea, vomiting, cramps, and diarrhoea. Regular access to a private toilet was problematic as one participant stated, *"it was still just diarrhoea coming out of me for a long long, a long, long time...to this day I still don't have natural movements."* (Participant 15). Another participant bought a car to dash home from work throughout the day to access a private toilet. Many participants reported that being able to

work from home during the Covid-19 pandemic was a blessing in disguise: “*I don’t think I’ll be going back to open plan ever.*” (Participant 3).

Overall, it was felt by many that oesophagectomy survivors just simply cannot expect to manage the working lives they had before: “*I think you’re heading towards more... solitary work*” (Participant 3). Several participants commented on how they had to resign, retire, sell their businesses, or alter their working habits. Most patients who were not working wanted to return to work a long time ago but couldn’t because of “*the dumping syndrome, and the burping all the time, and having to eat all the time...*” (Participant 37) illustrating the extensive impact that aerodigestive symptoms have on some survivors’ ability to work.

Theme D: Avoidance of Social Situations Involving Food

This theme reflects the significant impact of aerodigestive symptoms on social activities, of which food and drink are often an integral part. For some, social interactions are now seemingly entirely avoided because of the “*severe pain*” (Participant 3) and “*bend-over-cramps*” (Participant 7) or because of the embarrassment of their symptoms such as belching, passing wind, vomiting, choking or having to “*hoik up food*” (Participant 40). Many participants “*tend to prefer to eat alone*” (Participant 3) and reportedly no longer go out for meals or to other people’s houses: “*I hate going out for a meal...I just stopped going out*” (Participant 15). This has resulted in lost connections and relationships, with participant 40, an 84-year-old lady, explaining how she no longer meets her friend for a cup of tea every Tuesday as she had done for 40 years prior.

Avoiding or feeling uncomfortable at special occasions was frequently referred to. Some individuals said they would “*meet up when the meal was over*” (Participant 21) or

they “*wouldn’t sit at the table with everybody else*”. Some would “*ignore*” (Participant 9) their food or “*find a different time to eat*” (Participant 24).

Previous negative experiences involving food/ drink often resulted in these avoidance behaviours: “*One of my grandchildren was christened and we went out and I was so hungry ...and I missed the whole meal, I sat out just spluttering and spluttering...couldn’t get rid of it, and even when I came in I was still coughing and coughing so y’know, felt embarrassed.*” (Participant 15). “*Once I started the eating, I got this choking in me. I had to run, that ruined it.*” (Participant 12)

An unfortunate consequence of aerodigestive symptoms is that eating and drinking have ceased to become an enjoyable experience with participants reporting “*Food becomes like taking an antibiotic.*” (Participant 37) and “*I’m eating because I have to.*” (Participant 36).

Discussion

It is now widely understood that cancer care is more than just anti-cancer treatment, and that it must consider supportive care needs, including the impact on quality of life from diagnosis throughout survivorship [430]. The understanding of the specific impact of aerodigestive symptoms following oesophageal cancer surgery is limited.

This is the first qualitative study, to our knowledge, which has specifically investigated the impact of long-term aerodigestive symptoms on quality of life amongst adults with oesophageal cancer throughout survivorship. Interviews were conducted with 40 participants who were mean 52 months post curative oesophageal resection for oesophageal cancer.

Impact of Long-term Aerodigestive Symptoms on Quality of Life

Reflexive thematic analysis revealed that long-term aerodigestive symptoms significantly impact quality of life throughout survivorship for many survivors. Four main themes were identified. The first is that some participants continue to feel isolated because of their aerodigestive symptoms. Many participants commented on how the general public and generalist health care professionals in the community do not understand the aerodigestive symptoms that they experience, resulting in a sense of limited support, and a need to figure it out by themselves. Similar to findings from other cancer research, it is clear that there are ongoing unmet needs as a result of current service delivery models. [437].

Some participants are fearful of the symptoms they experience such as choking, or worrying that when they experience dysphagia it might be a symptom of cancer recurrence. Many participants reported withdrawal from society and reluctantly having to alter their work behaviours or resign from their jobs because of the discomfort, pain, and embarrassment of their symptoms.

The findings from this study are in line with other recently published studies evaluating quality of life in oesophageal cancer patients [246, 417]. The severity of ongoing aerodigestive symptoms and the duration for which these continue is largely unknown, therefore, further research is warranted.

Value of this Research

Support options for cancer patients who navigate survivorship can bring about positive outcomes such as improved mood [781, 782]. Examples might include long-term access to allied health services, education resources, peer or professionally led support programmes, peer mentors, self-care programmes, counselling, and carer education (IOMC [783]. These services are typically more established in oncology services which receive

higher funding such as breast cancer compared to cancers that are considered underfunded, relative to disease burden, such as lung cancer, colorectal cancer and oesophageal cancer [784]. The information gathered from our study is vital to demonstrate that there is a need to develop services which will support patients with oesophageal cancer to manage long-term aerodigestive symptoms following surgery.

From our experience as researchers and clinicians, there appear to be few community-based services globally that follow oesophageal cancer survivors throughout survivorship resulting in patients being seen by generalist clinicians. There is a need to upskill clinicians working in the community and/or increase access to relevant specialists such as oncologists, speech-language pathologists, psychologists and dietitians. Long-term specialist, supportive, follow-up health care is necessary for patients with oesophageal cancer given the high numbers of participants whose quality of life continues to be impacted [785, 786].

To enhance service delivery options, it is recommended that health care follow-up for oesophageal cancer survivors be treated in a manner similar to those with long-term and complex diseases [787]. There is a need for multidisciplinary practice in long-term follow up clinics for cancer patients [430], for example, multidisciplinary rehabilitation focusing on returning to work is important as many cancer survivors are more likely to resign from their work or have reduced work abilities [616, 788]. There is also a need for increased funding into other support approaches such as self-care programmes, support groups, peer mentoring, and education resources.

This study investigated the impact of aerodigestive tract symptoms as a whole rather than dysphagia or other symptoms in isolation. This study and our PPI committee have highlighted how dysphagia clinicians cannot expect patients to be able to verbally

distinguish symptoms of dysphagia from the other symptoms of the aerodigestive tract. This emphasises the importance of speech-language pathologists and other members of the allied health team working in an interdisciplinary fashion [789].

Study Limitations

A limitation of this study is the type of sampling used which may have resulted in higher participation rates of people with ongoing aerodigestive symptoms. Many oesophageal cancer survivors do not continue to live with long-term aerodigestive symptoms, and this study does not reflect their perspective. In addition, all participants were from one site and therefore had experienced similar surgical approaches. Furthermore, it was not possible to explore all themes that arose, thus only the key concepts, as perceived by the main researcher using reflexive thematic analysis, were detailed.

It may be felt that a limitation of this study was the use of only one coder, however, this type of thematic analysis embraces researchers' unique experiences and perspectives that are brought to the analytical process and interpretation of the data as part of the overall finding, and it is not expected that two researchers would produce the same result.

Although researching the impact of aerodigestive symptoms as a whole can be considered a strength of this research because it ensured that no relevant symptoms and experiences were missed, it can also be considered a limitation. The reason for this is that it is challenging for swallowing specialists to understand the true impact of dysphagia in isolation or for gastroenterologists to understand the true impact of reflux. This however reflects the reality of working with this client group where clinicians need to tease out the relevant information and further probe/ assess as required.

By working as part of an interdisciplinary team, where professionals overlap in their roles and can ask broad questions related to each other's fields, it ensures that all relevant

symptoms and information will be captured in a holistic manner. Each specialist can then apply their own specialist expertise in line with a unified patient-centred goal that ultimately aims to increase quality of life [790-792].

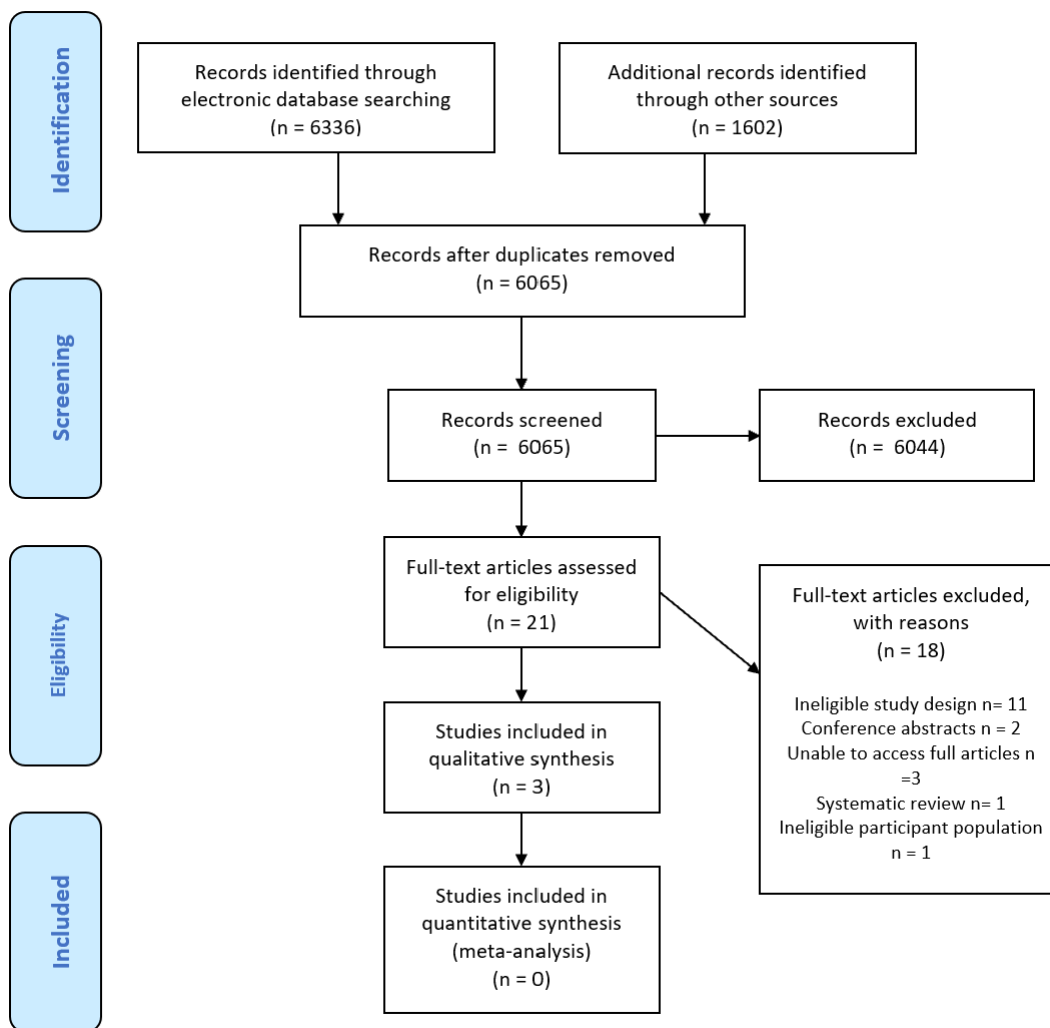
Conclusion

This qualitative study has highlighted the significant impact that long-term aerodigestive symptoms following oesophageal cancer surgery can have on quality of life for some survivors. The four main themes identified through reflexive thematic analysis, isolation, fear of ongoing symptoms, restricted social interactions, and restricted work capacity represent the self-perception of many oesophageal cancer survivors as they attempt to navigate a new life with long-term aerodigestive symptoms, even 10 years after surgery.

Our findings indicate a need for greater long-term support in the community to assist patients with managing aerodigestive symptoms so patients do not feel as alone, and with the hope that by minimising the symptoms, there will be reduced fear, and improved socialisation and working capacity. Increased access to specialist clinicians throughout survivorship may result in enhanced aerodigestive symptom management.

Multidisciplinary team members should consider the findings in this study when developing outpatient services, and when implementing research. It is pertinent that medical and surgical interventions continue to measure and improve health-related quality of life outcomes with the intention of specifically enhancing the lives of the increasing number of survivors [793]. Further interdisciplinary research is required to expand upon our results, to minimise and prevent severe long-term aerodigestive impairments following oesophageal cancer treatment, and to develop improved solutions to residual symptoms.

10.13 Appendix N Systematic Review PRISMA 2020 Checklist



10.14 Appendix O Systematic Review Risk Of Bias Results

Case Control Study [69]

	FOAMS	Asp Pneu monia	Duration b/w op and oral intake	Dur b/w oral intake and d/c	Dur b/w sx and d/c	Pneum within 3 mo	Pharyng eal clearanc e	Max hyoid superior	Max hyoid anteri or	UOS
1.1 Potential for confounding of the effect of intervention?	PY	PY	PY	PY	PN	PY	PY	PY	PY	PY
1.2 Was analysis based on splitting participant's follow up time?	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
1.3 Were intervention discontinuations likely related to factors are prognostic for outcome?	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
1.4 Did authors use appropriate analysis ?	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
1.5 Were confounding domains controlled for measured validly and reliably?	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
1.6 Did authors control for any post-intervention variables?	N	N	N	N	N	N	N	N	N	N
1.7 Did authors use apt analysis methods that controlled for all confounding domains?	N	N	N	N	N	N	N	N	N	N
1.8 Were confounding domains measured validly and reliably	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

1. Risk:	Serious	Serious	Serious	Serious	Serious	Serious	Serious	Serious	Serious	Serious
2.1 Was participant selection after intervention?	N	N	N	N	N	N	N	N	N	N
2.3 Were post interv variables that influenced selection associated with interv?	/	/	/	/	/	/	/	/	/	/
2.4 Do start of f/u and interv coincide?	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
2.5 Were adjust techniques used that are likely to correct for bias?	N	N	N	N	N	N	N	N	N	N
2 Risk	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
3.1 Interv groups clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.2 Was info recorded at start?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.3 Could interv classification have been affected by outcome knowledge?	N	N	N	N	N	N	N	N	N	N
3 Risk	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
4. Deviations from intended interv beyond expected?	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
4.2 Were these unbalanced b/w groups?	N/NI	N/NI	N/NI	N/NI	N/NI	N/NI	N/NI	N/NI	N/NI	N/NI
4.3 Were co-interventions balanced?	N/NI	N/NI	N/NI	N/NI	N/NI	N/NI	N/NI	N/NI	N/NI	N/NI
4.4 Was interv implemented successfully for most?	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

4.5 Did participants adhere?	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
4.6 Apt analysis used to estimate effect?	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
4 Risk	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
5.1 Were outcome data available for (nearly) all?	N	N	N	N	N	N	Y	Y	Y	Y
5.2 Were participants excluded due to missing data needed for intervention status?	PN	PN	PN	PN	PN	PN	PN	PN	PN	PN
5.3 Were participants excluded due to missing data for analysis	N	NI	NI	NI	NI	NI	N	N	N	N
5.4 Are proportion of participants and reasons similar?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
5.5 Evidence that results were robust to missing data	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
5 Risk	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	PY	N	N	N	N	N	PY	PY	PY	PY
6.2 Were outcome assessors aware of the intervention received by study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6.3 Were the methods of outcome assessment	PY	NI	PY	PY	PY	NI	PY	PY	PY	PY

comparable across intervention groups?										
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
6 Risk	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
7 Is the reported effect estimate likely to be selected on the basis of the results from....										
7.1 multiple outcome measurements within the outcome domain?	NI	NI	NI	NI	NI	NI	NI	NI		NI
7.2....multiple analyses of the intervention-outcome relationship?	NI	NI	NI	NI	NI	NI	NI	NI		NI
7.3...different subgroups?	NI	NI	NI	NI	NI	NI	NI	NI		NI
7 Risk	NI	NI	NI	NI	NI	NI	NI	NI		NI

Key: FOAMS = Functional Outcomes Assessment Measure of Swallowing Asp = aspiration, dur = duration, b/w = between, op = operation, d/c discharge, sx = surgery, Pneum = pneumonia, Max = maximum, UOS = upper oesophageal sphincter, Interv = intervention, mo = months, fav = favourable

Overall Risk: Serious. The study is judged to be at a serious risk of bias in at least one domain, but not at critical risk of bias in any domain.

Case series: [74]

	VFS findings	Independence with oral intake	Presence of laryngeal nerve palsy	Aspiration pneumonia
1.1 Potential for confounding of the effect of intervention?	Y	Y	Y	Y
1.2 Was analysis based on splitting participant's follow up time?	N	N	N	N
1.3 Were intervention discontinuations likely related to factors are prognostic for outcome?	NI	NI	NI	NI
1.4 Did authors use appropriate analysis ?	NI	NI	NI	NI
1.5 Were confounding domains controlled for measured validly and reliably?	N	N	N	N
1.6 Did authors control for any post-intervention variables?	NI	NI	NI	NI
1.7 Did authors use apt analysis methods that controlled for all confounding domains?	N	N	N	N
1.8 Were confounding domains measured validly and reliably	N	N	N	N
1. Risk:	Critical	Critical	Critical	Critical
2.1 Was participant selection after intervention?	N	N	N	N
2.3 Were post interv variables that influenced selection associated with interv?	N	N	N	N
2.4 Do start of f/u and interv coincide?	PY	PY	PY	PY
2.5 Were adjust techniques used that are likely to correct for bias?	-	-	-	-
2 Risk	Low	Low	Low	Low
3.1 Interv groups clearly defined?	N/A	N/A	N/A	N/A
3.2 Was info recorded at start?	Y	Y	Y	Y
3.3 Could interv classification have been affected by outcome knowledge?	PY	N	N	N
3 Risk	Low	Low	Low	Low
4. Deviations from intended interv beyond expected?	NI	NI	NI	NI
4.2 Were these unbalanced b/w groups?	-	-	-	-

4.3 Were co-interventions balanced?	NI	NI	NI	NI
4.4 Was interv implemented successfully for most?	NI	NI	NI	NI
4.5 Did participants adhere?	NI	NI	NI	NI
4.6 Apt anaylsis used to estimate effect?	NI	NI	NI	NI
4 Risk	NI	NI	NI	NI
5.1 Were outcome data available for (nearly) all?	N	Y	Y	N
5.2 Were participants excluded due to missing data needed for intervention status?	N	N	N	NI
5.3 Were participants excluded due to missing data for analysis	N	N	N	NI
5.4 Are proportion of participants and reasons similar?	-	-	-	-
5.5 Evidence that results were robust to missing data	—	—	—	—
5 Risk	Moderate	Low	Low	Low
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Y	N	N	N
6.2 Were outcome assessors aware of the intervention received by study participants?	PY	PY	PY	PY
6.3 Were the methods of outcome assessment comparable across intervention groups?	Y	Y	Y	Y
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	NI	NI	NI	NI
6 Risk	Moderate	Low/NI	Low/NI	Low/NI
7 Is the reported effect estimate likely to be selected on the basis of the results from....				
7.1 multiple outcome measurements within the outcome domain?	NI	NI	NI	NI
7.2....multiple analyses of the intervention-outcome relationship?	NI	NI	NI	NI
7.3...different subgroups?	NI	NI	NI	NI
7 Risk	NI	NI	NI	NI

Overall Risk: Critical. The study is judged to be at a critical risk of bias in at least one domain.

Retrospective Case Series [73]

	Start of Oral Intake	Length of Oral Intake rehabilitation	Length of postoperative stay
1.1 Potential for confounding of the effect of intervention?	Y	Y	Y
1.2 Was analysis based on splitting participant's follow up time?	N	N	N
1.3 Were intervention discontinuations likely related to factors are prognostic for outcome?	NI	NI	NI
1.4 Did authors use appropriate analysis ?	Y	Y	Y
1.5 Were confounding domains controlled for measured validly and reliably?	N	N	N
1.6 Did authors control for any post-intervention variables?	N	N	N
1.7 Did authors use apt analysis methods that controlled for all confounding domains?	N	N	N
1.8 Were confounding domains measured validly and reliably	Y	Y	Y
1. Risk:	Serious	Serious	Serious
2.1 Was participant selection after intervention?	N	N	N
2.3 Were post interv variables that influenced selection associated with interv?	N	N	N
2.4 Do start of f/u and interv coincide?	N	N	N
2.5 Were adjust techniques used that are likely to correct for bias?	N	N	N
2 Risk	Low	Low	Low
3.1 Interv groups clearly defined?	Y	Y	Y
3.2 Was info recorded at start?	Y	Y	Y
3.3 Could interv classification have been affected by outcome knowledge?	N	N	N
3 Risk	Low	Low	Low
4. Deviations from intended interv beyond expected?	NI	NI	NI
4.2 Were these unbalanced b/w groups?	NI	NI	NI
4.3 Were co-interventions balanced?	NI	NI	NI

4.4 Was interv implemented successfully for most?	NI	NI	NI
4.5 Did participants adhere?	NI	NI	NI
4.6 Apt anaylsis used to estimate effect?	NI	NI	NI
4 Risk	NI	NI	NI
5.1 Were outcome data available for (nearly) all?	Y	Y	Y
5.2 Were participants excluded due to missing data needed for intervention status?	NI	NI	NI
5.3 Were participants excluded due to missing data for analysis	NI	NI	NI
5.4 Are proportion of participants and reasons similar?	NI	NI	NI
5.5 Evidence that results were robust to missing data	NI	NI	NI
5 Risk	NI	NI	NI
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	PY	PY	PY
6.2 Were outcome assessors aware of the intervention received by study participants?	PY	PY	PY
6.3 Were the methods of outcome assessment comparable across intervention groups?	Y	Y	Y
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	NI	NI	NI
6 Risk	Low/NI	Low/NI	Low/NI
7 Is the reported effect estimate likely to be selected on the basis of the results from....			
7.1 multiple outcome measurements within the outcome domain?	NI	NI	NI
7.2....multiple analyses of the intervention-outcome relationship?	NI	NI	NI
7.3...different subgroups?	NI	NI	NI
7 Risk	NI	NI	NI

Overall Risk: Serious. The study is judged to be at a serious risk of bias in at least one domain, but not at critical risk of bias in any domain.

Downs & Black Methodological Quality Assessment Tool

Reporting		Case Control Study[69]	Case Series [74].	Retrospective Case Series [73]
1. Is the hypothesis/aim/objective of the study clearly described	yes 1 no 0	1	0	1
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	yes 1 no 0	1	0	1
3. Are the characteristics of the patients included in the study clearly described ?	yes 1 no 0	1	0	1
4. Are the interventions of interest clearly described?	yes 1 no 0	1	0	1
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	yes 2 partially 1 no 0	1	0	1
6. Are the main findings of the study clearly described?	yes 1 no 0	1	0	1
7. Does the study provide estimates of the random variability in the data for the main outcomes?	yes 1 no 0	0	0	1
8. Have all important adverse events that may be a consequence of the intervention been reported?	yes 1 no 0	0	0	0
9. Have the characteristics of patients lost to follow-up been described?	yes 1 no 0	1	0	0
10. Have actual probability values been reported(e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	yes 1 no 0	1	0	1
External validity				
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	yes 1 no 0 unable to determine 0	0	0	0
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	yes 1 no 0 unable to determine 0	0	0	0
13. Were those subjects who were prepared to participate representative of the recruited population?	yes 1 no 0 unable to determine 0	0	0	1
14. Were staff, places, and facilities where patients were treated representative of treatment most received?	yes 1 no 0 unable to determine 0	0	0	0

15. Was an attempt made to blind those measuring the main outcomes of the intervention?	yes 1 no 0 unable to determine 0	0	0	0
16. If any of the results of the study were based on "data dredging", was this made clear?	yes 1 no 0 unable to determine 0	1	1	1
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?	yes 1 no 0 unable to determine 0	1	0	0
18 Were the statistical tests used to assess the main outcomes appropriate?	yes 1 no 0 unable to determine 0	1	0	1
19 Was compliance with the intervention/s reliable?	yes 1 no 0 unable to determine 0	0	0	0
20. Were the main outcome measures used accurate (valid and reliable)?	yes 1 no 0 unable to determine 0	1	0	1
Internal validity - confounding (selection bias)				
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	yes 1 no 0 unable to determine 0	1	0	1
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	yes 1 no 0 unable to determine 0	0	0	0
23. Were study subjects randomised to intervention groups?	yes 1 no 0 unable to determine 0	0	0	0
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	yes 1 no 0 unable to determine 0	0	0	0
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	yes 1 no 0 unable to determine 0	0	0	0
26. Were losses of patients to follow-up taken into account?	yes 1 no 0 unable to determine 0	0	0	0
Power				
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? Sample sizes have been calculated to detect a difference of x% and y%.	Yes = 1 No = 0 Unable to determine = 0 * Modified as per Trac MH, McArthur E, Jandoc R, et al. Macrolide antibiotics and the risk of ventricular arrhythmia in older adults. CMAJ 2016. DOI:10.1503/cmaj.150901	0	0	0

TOTAL Scores		13	1	13

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