DELAYS TO DIAGNOSIS AND TREATMENT OF OESOPHAGOGASTRIC CANCER AND ITS IMPACT ON TREATMENT OUTCOMES

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MBBS

Thesis

Submitted to Flinders University

for the degree of

Master of Surgery

College of Medicine and Public Health

16 August 2022

CONTENTS

ABSTRACT

Oesophageal and gastric carcinoma are the sixth and second leading cause of cancer-related mortality worldwide respectively. These cancers continue to have overall poor survival rates, partly due to late presentation with already advanced stage disease. Both cancers are frequently associated with a delay to diagnosis.

The aims of this study were to identify delays in diagnosis and treatment of oesophagogastric cancers in Australia, and to determine whether delays impacted outcomes and how these delays can be avoided.

The research methodology was approved by The Southern Adelaide Clinical Human Research Ethics Committee and involved collation of data for oesophagogastric cancer patients who underwent surgery with curative intent at Flinders Medical Centre from 2013 to 2018. Data was extracted from the Upper GI unit database containing patient demographic and procedural information, whilst remaining data around symptoms, dates of each timeframe, and outcomes was obtained via retrospective review of patient case notes and electronic records.

In the present study, most patients had delays to diagnosis and treatment (87.5% and 93% respectively). Most of the delay was in the symptom onset to referral time interval (12.5 weeks compared to 1-3 weeks for all other intervals). Most patients presented with late-stage disease (60%) and died within the first two years following diagnosis (66%).

Both cancers are quite different: oesophageal cancer presents mostly with dysphagia, in men peaking in the 60-69 age group whereas gastric cancer presents more with constitutional symptoms and blood loss. Most patients with oesophageal cancer (76%) had fulfilled the urgent referral criteria compared to only 33% of gastric cancer patients.

Despite dysphagia being included in the current urgent referral criteria, it was significantly associated with delays to diagnosis. GPs referred most patients to a Gastroenterologist for endoscopy (60%) which was associated with significant delays from referral to endoscopy (median of 32 days). Over a quarter of patients were diagnosed via the emergency department route and mostly had gastric cancer (63%) presenting with either blood loss or constitutional symptoms.

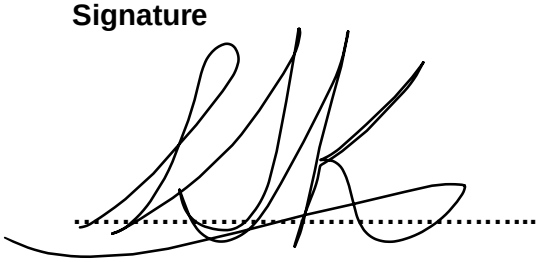
Most potentially curable patients with oesophageal and gastric cancer have delays to diagnosis and treatment. Most also presented with late-stage disease and died within the first two years, suggesting an association between delays and adverse outcomes. Delays predominantly occur in the interval from symptom onset to specialist referral and more often in patients with dysphagia despite being a symptom included in the urgent referral criteria. Oesophageal and gastric cancer differ significantly, indicating a need for separate referral guidelines for both cancers.

Recommendations for reduction in delays involve (1) New separate referral criteria for oesophageal and gastric cancer which includes gastrointestinal blood loss (anaemia, haematemesis or melena) and constitutional symptoms (nausea, weight loss or anorexia) for gastric cancer, and dysphagia for oesophageal cancer, (2) Education of GPs about the urgent referral criteria through incorporation into the medical and GP curricula, (3) Improving health literacy around symptoms and risk factors through public campaigning, (4) Increasing endoscopy availability through means of open access endoscopy or nurse endoscopists, and (5) Rapid utilization of barium swallow for initial diagnosis.

DECLARATION

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signature



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TERMS AND DEFINITIONS/GLOSSARY

NICE	National Institute for Care Excellence Guidelines
MDT	Multidisciplinary team
GP	General Practitioner
ED	Emergency Department
UGI or Upper GI	Upper Gastrointestinal
AIHW	Australian Institute of Health and Welfare Cancer statistics
IL-6	Interleukin-6
TNF	Tumour Necrosis Factor
OAE	Open Access Endoscopy
PPIs	Proton pump inhibitors
SAC HREC	Southern Adelaide Clinical Human Research Ethics Committee
TNM	T = tumour, N = node, M = metastases
ENT	Ear Nose and Throat
IQR	Interquartile range
OPD	Outpatient appointment
Hb	Haemoglobin
ASA status	American Society of Anaesthesiologists (ASA) status
OG cancer	Oesophagogastric cancer

ACKNOWLEDGEMENTS

Dr Jon Shenfine whose counsel and dedication to the project from its inception to completion was invaluable. I am grateful for his advice, critical reviews and guidance which has nurtured the project to fruition.

Dr Tim Bright and Prof David Watson who provided guidance, direction and critical reviews of the work done to achieve the final outcome for which I am greatly indebted.

Ms Feruza Kholmurodova for provision of statistical expertise throughout the data analysis and Mr Jeff Bull for assistance and guidance on data collection and retrieval. Their assistance is greatly appreciated.

The Flinders University Department of Surgery staff for their support of the project.

The Commonwealth Government's support of higher degree research projects such as this through the Australian Government Research Training Program Scholarship which allow for completion without financial burden to the student.

My parents for their support and encouragement throughout.

1 INTRODUCTION

1.1 Context

Oesophageal and gastric cancer have poor survival rates, in part due to late presentation with already advanced stage disease(1, 2). In response to this, referral guidelines for these cancers have been developed to encourage earlier detection. The first national UK guideline, established in the year 2000, was the “Two week wait” which outlined specific symptoms requiring urgent endoscopy referral within 14 days(3). These guidelines were upgraded in 2015 to include dyspepsia in the symptom criteria(4). Despite these implementations, no improvements have been achieved in survival rates(3, 5) nor detection of early-stage cancers(6-8). In fact, many studies have found that alarm symptoms have poor positive predictive value for upper gastrointestinal (GI) cancer detection(9).

This may be because oesophageal and gastric cancer have been viewed as one entity in most studies to date. This is despite significant differences in epidemiology, risk factors and clinical presentation between both cancers. Oesophageal cancer tends to present most commonly with reflux and dyspepsia followed by dysphagia(10) whilst gastric cancer has more non-specific symptoms such as abdominal or epigastric pain or discomfort, nausea and vomiting(11, 12). Such distinctions are expected given the differences in tumour location, surrounding structures and pattern of metastases. The current Australian urgent referral guideline however, view both cancers as one entity, which may confuse referring doctors. Perhaps more clarity is needed in terms of which symptoms would be specific for each cancer. There has not been a dedicated study highlighting and clarifying these differences.

Delays at any time between the development of symptoms to subsequent diagnosis and treatment could contribute to the poor overall survival for oesophageal and gastric cancer patients. A few studies have investigated the association between delays and outcomes: some report that in patients with oesophageal cancer, delay from diagnosis to surgery is associated with higher overall morbidity, mortality(13) and cancer of more advanced stages(14). Conversely, other studies have reported no effect of delay on survival(15) nor stage of gastric and oesophageal cancers(16). It is common sense

that for an individual, there is a certain duration between first symptoms to both diagnosis and treatment which, if exceeded, will lead to adverse outcomes such as those described above.

The main aim of this study was to determine if delays to diagnosis and treatment of oesophagogastric cancer could explain poor survival rates and outcomes and provide recommendations on reducing delays. It is hypothesized that optimisation of the current referral symptom criterion, timeframes and guidelines will help reduce delays.

1.2 Background

1.2.1 Oesophageal and gastric cancer epidemiology and classification

Oesophageal carcinoma is the eighth most common malignancy worldwide and the sixth leading cause of cancer-related mortality. The overall 5-year survival rates are 15% to 25%(17). Gastric carcinoma is deadlier, being the fourth most common malignancy worldwide and the second leading cause of cancer-related mortality worldwide. In European countries, survival rates vary from ~10% to 30%(18), similar to oesophageal cancer.

Oesophageal cancer and gastric cancer are quite different in terms of classification by virtue of their differences in anatomical location. Oesophageal cancer is most commonly classified based on histological subtype. The two primary histological subtypes are oesophageal adenocarcinoma and oesophageal squamous cell carcinoma(19). **Oesophageal adenocarcinoma** occurs more commonly in the lower third of the oesophagus and is associated with chronic acid exposure from gastro-oesophageal reflux disease(20) and obesity(21). **Oesophageal squamous cell carcinoma** often occurs in the middle to upper part of the oesophagus and correlates with a significant tobacco smoking history or alcohol consumption(22).

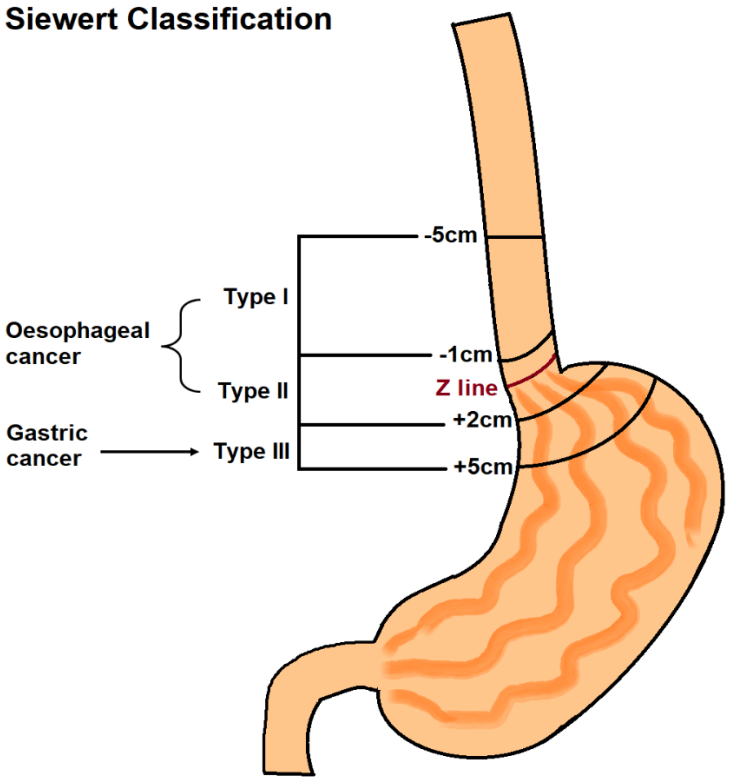
Gastric cancer is most commonly classified based on their anatomical region into cardia gastric cancer or non-cardia gastric cancer, as these have different aetiologies and epidemiological patterns(23, 24). **Cardia gastric cancer** is typically adenocarcinoma with similar risk factors and pathogenesis as oesophageal adenocarcinoma described above(24). **Non cardia gastric cancer** is most commonly due to H pylori infection which induces atrophic gastritis and a subsequent chronic inflammation that predisposes to malignant transformation of gastric mucosal cells(24). Risk factors

for non-cardia gastric cancer include several dietary factors including processed meats, broiled or smoked meats, high salt intake, and preserved or pickled foods(24). Although declining in incidence, non-cardia stomach cancer continues to be diagnosed twice as often as cardia(24).

Genetic gastric cancer syndromes. Inherited gastric cancer predisposition syndromes, such as Hereditary diffuse gastric carcinoma (HDGC) account for1-3% of gastric cancer cases(23)(25). The HDGC syndrome is associated with the CDH1 gene mutation, of which carriers confer a >80% lifetime risk of gastric carcinoma(26). Prophylactic total gastrectomy after confirmation through CDH1 molecular testing is therefore recommended(26, 27).

Whilst the gastro-oesophageal junction demarcates the oesophagus and stomach into two separate organs, classification of tumours at the gastro-oesophageal junction (GOJ) into oesophageal and gastric cancers can be challenging for several reasons. The squamocolumnar junction or Z-line as shown in figure 1 below could provide an anatomical separation for this however with Barrett's oesophagus, this Z-line shifts proximately(28). Gastric cardia mucosa can also be found in the distal oesophagus which is clearly above the Z-line and complicates this approach(28). **The Siewert Classification** helps to address this issue by dividing cancers at the GOJ into three groups:, where Type I and II are classified as oesophageal cancer and Type III tumours gastric(28). Type I refers to cancers occurring 1-5cm above the Z-line (regarded as the marker for the GOJ with this classification system), Type II refers to cancers with 1cm above and 2cm below the GOJ line, and Type III refers to cancers 2-5cm below the GOJ line(28). The best surgical approach for each of the Siewert groups still remains debatable and its application is often difficult in clinical practice(28). It does however provide standardisation for the purposes of research.

Figure 1: Siewert Classification for oesophageal and gastric cancers



1.2.2 Oesophageal and gastric cancer diagnosis

Oesophageal and gastric cancer are both diagnosed via endoscopic biopsy, which is the gold standard for diagnosis worldwide(29). Diagnosis can either be achieved via screening in certain risk groups or following clinical suspicion based on specific symptoms and signs.

1.2.2.1 Barrett's surveillance

Barrett's surveillance program is the only relevant surveillance program in Australia for detection of oesophagogastric cancer. Barrett's oesophagus is a pre-malignant condition with potential to transform into oesophageal adenocarcinoma(30). Barrett's oesophagus is defined as the presence of columnar epithelial cells in the oesophageal mucosa which have formed from metaplasia of the normal squamous cells of the oesophageal mucosa in response to chronic acid exposure(31). Barrett's oesophagus can subsequently transform into low grade dysplasia, followed by high grade dysplasia before progressing to oesophageal cancer.(30).

The British Society of Gastroenterology in 2014 Guidelines recommend that endoscopic screening is to be undertaken in patients with chronic gastro-oesophageal reflux symptoms, and at least three

other risk factors for Barrett's which includes (1) age 50 or older, (2) Caucasian background, (3) male gender(4) and obesity(32). This threshold of multiple risk factors should be lowered if the family history is positive for at least one first-degree relative with oesophageal adenocarcinoma or Barrett's (32). The annual incidence of Barrett's oesophagus is low but increasing in Australia from 0.3% in 1990 to 1.9% in 2002(33). The proportion of patients with oesophagogastric cancer who have a prior diagnosis of Barrett's oesophagus is low. According to a study in Ireland, only 7.3% of patients with oesophageal adenocarcinoma had known Barrett's oesophagus(34). Similarly, the proportion of patients with Barrett's oesophagus who develop oesophageal adenocarcinoma is low. A review of 47 studies reported an overall annual estimated cancer incidence of 0.61% in patients with Barrett's oesophagus(35). A meta-analysis of 41 studies reported an annual risk of progression from Barrett's oesophagus to oesophageal adenocarcinoma to be 0.7%, without significant geographic variation between UK, Europe, and the US(36).

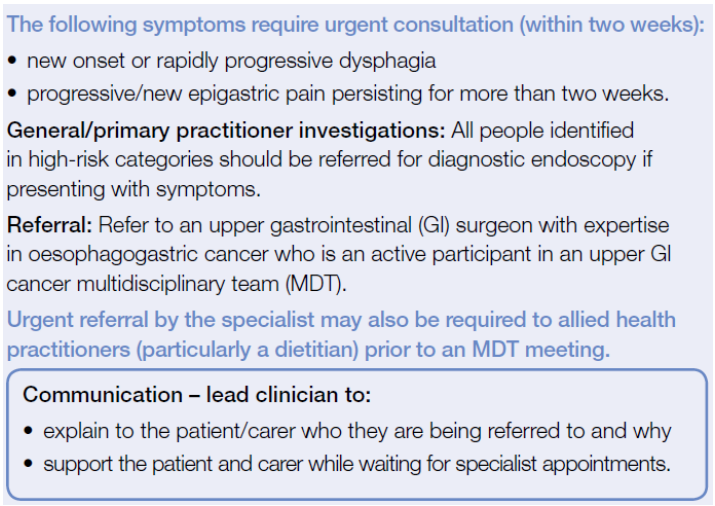
Most cases of oesophagogastric cancer are therefore not detected via the Barrett's screening program. Whilst some are detected incidentally and are more likely to be early cancers with better outcomes, the majority are diagnosed following recognition of symptoms or signs suggestive of oesophagogastric cancer that prompt referral for endoscopic diagnosis. These signs and symptoms must not only be recognised by the patient as concerning enough to present to the healthcare system for further investigation, but also by the General Practitioner (GP) who will need to refer to a specialist to perform an endoscopy. Sometimes when the GP does not have a strong enough suspicion to refer to a specialist, a barium swallow is often performed in practice. If the swallow test demonstrates a stricture or mass, this would strengthen need for referral for endoscopy. A barium swallow involves ingestion of barium sulphate which when passing through the oesophagus and stomach, can enhance the visibility of oesophageal pathology which is visualised in X-ray images(37). Barium swallow has been reported to have a sensitivity of 98% and positive predictive value of 42% for detection of cancers in the oesophagus and gastroesophageal junction(38). It is also a much less invasive test than endoscopy which carries a small risk of oesophageal perforation, bleeding, and infection with it(37). Patients with a negative barium swallow result however could still have malignancy(15) and therefore GPs should still refer for endoscopy if strong clinical suspicion (39).

A suitable screening test for early detection of oesophagogastric cancer that can be applied to the general public above an age threshold and not just for Barrett's, similar to that of the faecal occult blood test for bowel cancer screening or mammograms for breast cancer screening is not currently available or recommended in Western nations(40). Whilst endoscopy has the highest detection rates compared to any other test (including barium swallow, Helicobacter pylori serology and pepsinogen testing), its lack of adoption as a screening tool in Western nations is due to (a) lower incidence of gastric and oesophageal cancer and therefore not being cost-effective(40), and (b) it is an unpleasant test for patients with potentially serious complications as described above owing to its invasive nature and therefore risks outweigh the benefits. The absence of an ideal cost effective, minimally invasive screening tool that can be applied to those beyond just the Barret's oesophageal screening program is a possible reason for late detection and poor outcomes. Other than the production of an alternate screening tool, the development of urgent referral criteria which identifies those with early-stage oesophagogastric cancers before they progress could improve outcomes.

1.2.2.2 Urgent referral criteria

In Australia, there is an urgent referral criteria which is part of the current Australian national guideline titled 'Optimum care pathway for people with oesophagogastric cancer' which has been adapted from The National Institute for Care Excellence (NICE) Guidelines on suspected cancer recognition and referral(4) and established by the Oesophagogastric multidisciplinary experts group(41). This guideline states that patients with either: (1) rapidly progressive/new dysphagia or (2) epigastric pain for 2 weeks, must be urgently referred for endoscopy within 2 weeks (Figure 2)(41). These two criteria form the high-risk category(41). This recommendation serves as a guide to GPs and other clinicians on when to refer patients and facilitate diagnosis of cancers. All other 'alarm' symptoms have been listed in the guideline document as requiring 'prompt' investigation but unspecified and without a stipulated timeframe(41). More clarity on this would be helpful to referring clinicians.

Figure 2: Urgent referral criteria outlined in the Australian Guidelines 'Optimum pathway for people with oesophagogastric cancer'



Ideally, a patient with symptoms suggestive of oesophagogastric cancer should present at the outset to their GP who will refer directly to a specialist who can perform endoscopy in order to obtain a diagnosis. There are however patients who present to the Emergency Department directly and are subsequently referred either back to their GP for referral to a specialist or admitted, seen by a specialist and have the endoscopy as an inpatient in cases where symptoms are more severe and warrant urgent investigation. In any case, patients will either be referred to a specialist for endoscopy either from the GP or ED doctor.

At this point, the pathway does not necessarily get simpler. Direct referral to the appropriate specialist who can perform endoscopy (which includes Gastroenterologists, General Surgeons and General surgical subspecialists) may not always occur in the first instance. For example, a patient with retrosternal discomfort or epigastric pain, may be deemed as having cardiac related pain and referred to a Cardiologist for further work up. Once stress tests and ECGs are negative for a cardiac cause, then the Cardiologist may suspect an oesophageal pathology and subsequently refer on to the Gastroenterologist for endoscopy. Likewise the patient presenting with dysphagia who is referred to an Ear, Nose and Throat (ENT) specialist with suspicion for nasopharyngeal carcinoma or pathology will only later be referred to a General surgeon for endoscopy later once ENT causes are ruled out. Therefore, patients presenting to the healthcare system may end up having multiple consultations with a variety of specialists prior to referral for definitive, diagnostic endoscopy.

The specialist who performed the endoscopy will then subsequently refer the patient to an Upper GI surgeon which is a specialist with expertise in the management of oesophagogastric cancer. The upper GI surgeon will organise two things: (1) staging scans to determine the extent of spread of the disease, and (2) organise a multidisciplinary meeting to discuss treatment options. An upper GI cancer nurse can be helpful in providing information, guidance, and support around the new diagnosis and to help facilitate the above.

Staging investigations are imperative to planning treatment for oesophagogastric cancers. These investigations provide an indication of disease status, whether the cancer is resectable and suitability for radical surgery or palliation(37). Investigations usually include PET scans and CT scans(37). CT scans usually covering the chest, abdomen and pelvis are for assessment of stage and spread of cancer to detect metastatic or inoperable disease(37)If no metastatic disease is revealed on CT scanning, then a PET scan will likely be performed for those with oesophagogastric cancer but not for non-junctional gastric cancer. PET scan is a sensitive method of assessing distant metastases and lymph node involvement.. An endoscopic ultrasound (EUS) is typically indicated if a patient is medically fit for surgery and no evidence of metastases on the above investigations(37) and allows an estimation of the depth of tumour penetration to assist with preoperative work-up. Patients whose tumours may have involvement of the peritoneal cavity require a laparoscopy either prior to or at the time of radical surgery. (37).

The MDT meeting is the place for all involved health professionals to collaboratively develop individualised treatment recommendations for each patient. It involves consideration of specific patient circumstances and preferences and clinician expertise when coming to a decision around treatment. Any treatment of oesophagogastric cancer should only be performed after being deemed in accordance with this MDT group consensus(37). Once the decision is made for surgery, patients are required to undergo pre-operative evaluation, including an anaesthetic assessment, usually done in the preoperative outpatient clinics.

1.2.3 Oesophageal and gastric cancer treatment

Treatment approaches are different for oesophageal and gastric cancer. Surgical resection remains the primary curative treatment for locally advanced gastric cancer(42). For cancer in the proximal two thirds of the stomach, total gastrectomy is the gold standard. For cancer in the antral or pyloric region, a distal gastrectomy is the standard approach(42). Preoperative chemotherapy with historically MAGIC and now the FLOT regimen is the standard of care in many centres of Australia(43, 44).

The mainstay of treatment for locally advanced oesophageal carcinoma (stage I-III) is surgical resection(45). There are many different surgical approaches, the choice dependent on tumour location, extent of comorbidities and preference of the surgical unit(45). In addition, neoadjuvant chemoradiotherapy is the standard therapy in Australia for patients with T3 tumours and/or local nodal disease. This intends to treat micrometastases and reduce the size of the primary tumour prior to surgery(45). Whilst this result is possible in many, the downsides include disease progression in those with nonresponding tumours and treatment toxicity(45). If curative treatment is not possible, then Palliative care specialists will need to be involved with a shift in the focus of care on symptom control and quality of life rather than total disease eradication. Chemotherapy and radiotherapy can achieve this but other services like Psychology, Occupational Therapy and Social work will need to be involved to address every facet of care required extending to maintaining function and social support networks(37).

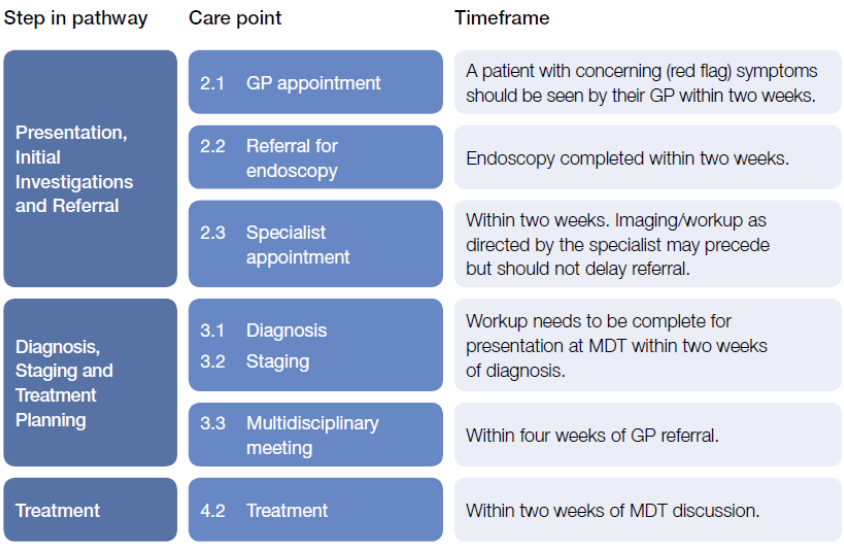
1.2.4 Australian Guidelines for oesophagogastric cancer diagnosis and management

As described in this chapter so far, the pathway from symptom onset to diagnosis to treatment can be both extensive and overwhelming for patients to follow. The smooth and timely progression from one step to another relies on efficiency of the following: (1) referrals being made, received, and triaged, (2) interactions between primary, secondary, and tertiary health care and (3) communication between specialists, nurses, administrative staff, and patients. Issues or mistakes in any one of these areas can result in significant delays along this pathway to diagnosis and treatment.

To make this journey easier for patients, and to reduce delays to diagnosis and treatment, the Australian guideline titled “The Optimum care pathway for people with oesophagogastric cancer”

was created(41). This guideline was a revised version of original patient management frameworks developed by the Department of Health in 2007 which for the first time had attempted to map the cancer pathway in a form more comprehensible to the wider public(41). The National Cancer Experts Reference Group (NCERG) is a panel of experts and consumer representatives established by the Council of Australian Governments in 2010, that have been working on this guideline as part of a national work plan aimed at improving cancer care in Australia(41). This guideline is therefore the result of consultations between a wide range of clinicians, consumers, carers and peak health organisations nationwide(41). It outlines the key steps along the path from symptom onset to treatment, with targeted timeframes at which each step must occur. According to these Australian guidelines, the timeline from first symptoms to diagnosis and treatment involves multiple stages: 1) first symptoms to presentation to a GP, 2) referral to endoscopy, 3) Upper Gastrointestinal Specialist appointment, 4), multidisciplinary (MDT) meeting, 5) treatment initiation(46) as shown in Figure 3 below(41). According to the guidelines, each stage must be met within 2 weeks. To summarise, time from symptom onset to diagnosis is to be no longer than 4 weeks and time from symptom onset to treatment no longer than 8 weeks(41).

Figure 3: Timeframes along path from symptom onset to diagnosis outlined within the Australian Guidelines 'Optimum pathway for people with oesophagogastric cancer'



With this background information on the diagnosis, treatment, and guidelines for managing oesophagogastric cancer, the following literature review provides a more detailed analysis of studies

on epidemiology and characteristics of oesophageal and gastric cancer as well as papers on delays to diagnosis and treatment with regards to its prevalence, causes or risk factors, impact on outcomes and strategies to reduce delays.

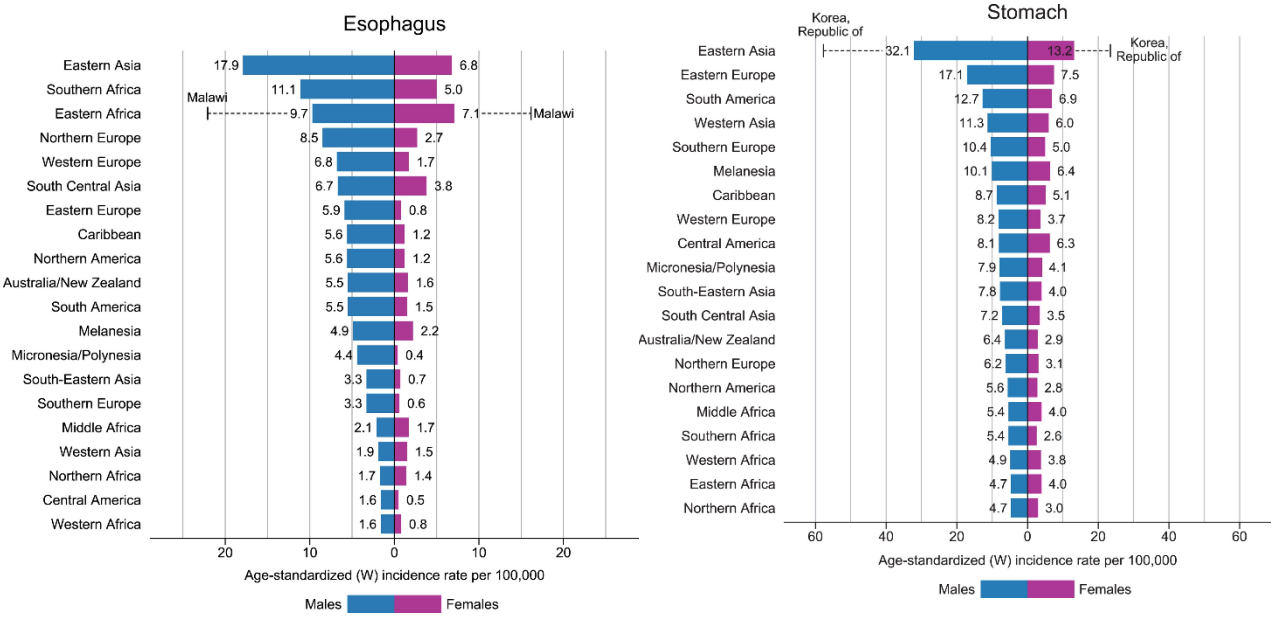
2 LITERATURE REVIEW

2.1 Incidence of oesophageal and gastric cancer

The incidence of oesophageal and gastric cancer is typically reported in the literature as age-adjusted standardised rates. In Australia, according to the Australian Institute of Health and Welfare Cancer (AIHW) statistics, the age-adjusted incidence rate in 2020 for oesophageal cancer was 8.2 per 100,000 in men and 2.6 per 100,000 in women(47). For gastric cancer, it was 11.0 per 100,000 in men and 4.9 per 100,000 in woman(48).

The incidence trends of each different subtype of oesophageal and gastric cancer differs significantly between different regions of the world as shown in Figure 4. These trends can be explained by the changing incidences of oesophageal carcinoma subtypes which have different underlying aetiologies, risk factors and pathogenesis.

Figure 4: Age adjusted incidence rates of oesophageal and gastric cancer in each region of the world as per the GLOBOCAN global cancer statistics



For oesophageal cancer, there has been an increase in incidence of oesophageal cancer in Africa(49) and Europe(50, 51) but decreased incidence in Asia(52, 53). This can be partly explained by the increase in incidence of oesophageal adenocarcinoma in many countries worldwide as

demonstrated in studies from Europe, New Zealand, Australia, North America, and Asia(52, 54-61). Oesophageal adenocarcinoma has also been increasing in Asia, but not as fast as the decline in oesophageal squamous cell carcinoma, hence the decreased overall incidence rate of oesophageal cancer in Asia. There has been a decrease in oesophageal squamous cell carcinoma in several countries globally as shown in studies from North America, Europe, and Asia (54, 55, 61). Oesophageal adenocarcinoma has overtaken squamous cell carcinoma as the most common subtype of oesophageal cancer mostly in high-income countries including United States, Australia, New Zealand, Brazil and parts of Europe(62, 63) whilst oesophageal squamous cell carcinoma persists as the most common subtype in Asia(53, 58, 64, 65). Studies from Europe and the West report squamous cell carcinoma rates to be 14.9% and 24.8% of all oesophageal cancer cases (13, 66) and at rates of 16.9% and 24.4% as a proportion of all oesophagogastric cancer cases, with the rest being adenocarcinoma(5, 67). Studies from India and China on the other hand report the proportion of squamous cell carcinoma to be 70.8 to 89% of all oesophageal cancer cases(14, 68, 69).

Incidence rates of gastric cancer have decreased worldwide(70). The incidence of non-cardia gastric cancer has been steadily declining in most countries in Europe, United States, (54, 55, 60, 71), followed by a plateau in China(72). There have been variable trends in incidence of gastric cardia cancer reported in different studies. Some studies report rising incidence rates in Europe and China(60, 72) whilst other studies from New Zealand, Switzerland and France report declining rates(59, 61, 73).

The reason for these differences in incidence rates of oesophageal and gastric cancer is due to the different underlying risk factors and pathogenesis for each subtype of cancer. The overall rise in oesophageal cancer in high income countries can be attributed the rise in oesophageal adenocarcinoma rising particularly in Western nations and this may be connected to rising rates of obesity(74). A busy lifestyle compromised with fast foods and high fat content and corresponding less physical activity have become more common here. Abdominal obesity is specifically associated with increased rates of oesophageal and gastric cardia adenocarcinoma(74). The abdominal obesity does this by two mechanisms: (1) through increasing intragastric pressure and the gastroesophageal

pressure gradient, increasing the flow of gastric juice into the oesophagus and reducing the clearance of gastric refluxate from the stomach(75) with resultant mutagenic effects of persistent acid reflux on the oesophageal mucosa leading to cancer formation(76, 77); and (2) the release of inflammatory adipokines (IL-6 TNF alpha, Leptin) which stimulates inflammation of the stomach lining and formation of carcinogenic mutations(78). Leptin also has been shown to stimulate cell proliferation and inhibit apoptosis in Barrett's derived oesophageal adenocarcinoma cells which is important for carcinogenesis due to promoting accumulation and persistence of genetic abnormalities(79).

The overall incidence of gastric cancer is decreasing due to the relative decrease in incidence of non-cardia gastric cancer. Non cardia gastric cancer is declining in developed countries due to a reduction in rates of H pylori infection, where H pylori eradication programmes have been more prevalent and well established. H pylori is the most common cause of non-cardia cancer. H pylori induced gastric inflammation causes DNA and cellular damage leading to atrophic gastritis with little or no acid secretion. This allows proliferation of H pylori further to induce carcinogenic mutations for cancer development. Whilst reduction in H pylori has reduced rates of non-cardia cancer, conversely this may to a lesser extent explain the higher incidence rates of oesophageal and cardia adenocarcinoma in high-income countries because these cancers are associated with increased acid production(80).

Table 1: Gender ratios for oesophagogastric cancers across different studies

Author	**Year**	**Country**	**Male: Female ratio**	**Cancer type**
Witzig	2006	Germany	2:1	Gastric
Eckardt	1990	Germany	1.4:1	Gastric
Suvakovic	1997	UK	1.6:1	Gastric
Hosseini	2007	Iran	3.2:1	Gastric
Crisan	2016	Romania	2:1	Gastric
Van Erp	2020	Netherlands	1.2:1	Gastric
Tata	2010	Malaysia	1.3:1	Gastric
Liang	2017	China	2.6:1	Gastric
Ahmed	2014	Canada	1.7:1	Gastric + GEJ
Maeda	2008	Japan	2.8:1 (Cardia) 1.7:1 (Non-Cardia)	Gastric
Author	**Year**	**Country**	**Male: Female ratio**	**Cancer type**
Martin	1997	UK	1.6:1	UGI
Lee	2017	China	2.4:1	UGI
Paterson	2006	Scotland	1.4:1	UGI

Table 1 (continued).

Phull	2006	Scotland	2.2:1	UGI
Fallon	2019	UK	2.4:1	UGI
Van Erp	2020	Netherlands	1.5:1	UGI
Author	**Year**	**Country**	**Male: Female ratio**	**Cancer type**
Kotz	2006	UK	2.5:1	OC
Tata	2010	Malaysia	2.7:1	OC
Grotenhuis	2010	Netherlands	4.3:1	OC
Van Erp	2020	Netherlands	2.4:1	OC
Cavalin	2018	Italy	4.3:1	OC
Krishnamurthy	2020	India	1.7:1	OC
Subasinghe	2010	India	1.2:1	OC
Coupland	2012	UK	3:1	OC
Witzig	2006	Germany	10:1	OA

It is also worth noting the higher male to female ratio of cancer, particularly for oesophageal cancer as shown in Figure 4 and demonstrated further above in Table 1. For upper gastrointestinal cancers in general, the male to female ratio is ranging from 1.5 to 2.4 (Table 1). Gastric cancer male to female ratios are quite similar with some going as high as 3.2:1(81). For oesophageal cancers, the male to female ratios are consistently higher than gastric, being mostly above 2:1 with several in the 3:1 and 4:1 range (Table 1). The study by Witzig reporting a male to female ratio of 10:1 was in a cohort of patients with only oesophageal adenocarcinoma, suggesting that ratios are even higher in this particular subtype(16). Likewise, the study by Maeda reported separate male to female ratios for cardia and non-cardia gastric cancer, with cardia having a higher ratio of 2.8:1 compared to 1.7:1 for non-cardia cancers(82). Cardia gastric cancer is very similar to oesophageal adenocarcinoma in risk factors and pathogenesis(83).

Whilst there are these slight variations between oesophageal and gastric cancer, it can be said that the overall proportion of cancers is higher in men than in women (Table 1). There may be different reasons for this. Whilst there is an equal prevalence of reflux between genders, the more severe or erosive subset of reflux is more common in men than women(84) and is a stronger risk factor for oesophageal cancer than the non-erosive or endoscopy-negative reflux subset.(85) Although there is an equal prevalence of obesity between genders, men have greater abdominal adiposity which has been hypothesized to contribute to the increased male predominance of oesophageal cancer(86). Nonetheless there has been no increase in oesophageal cancer overweight men compared to lean men in studies(87). The more plausible explanation may be the possibly protective effect oestrogen in women in reducing risk of oesophageal cancer(87). This also makes sense given

the later age of peak onset of oesophageal cancer in women that coincides with the drop in oestrogen levels post menopause. Potential mechanisms for this include the inhibitory effect of oestrogen on cell cycle induction and initiating apoptosis and growth arrest in cancer cells through estrogen receptor ligands. Androgen receptors are also expressed in oesophageal adenocarcinoma tissue(87). Ongoing research efforts are still required to comprehensively understand the reasons behind the male predominance of oesophagogastric cancer(87).All these mechanisms however only attempt to explain the increasing male predominance in the oesophageal adenocarcinoma subtype of oesophageal cancer as there are few studies looking at the male to female ratios separately for adenocarcinoma compared to squamous cell carcinoma. Squamous cell carcinoma is still a reasonable large subset of oesophageal cancer.

Table 2: The age of diagnosis for oesophagogastric cancer reported in different studies worldwide

Author	Year	Country	Cancer type	Age (median or mean)	Age range*
Boldys	2003	Poland	GC	44	35-54
Phull	2006	Scotland	UGI	46	44-48
Tata	2013	Malaysia	OC	58.4	25-84
Eckardt	1990	Germany	GC	59	49-70
Subasinghe	2010	India	OC	59.5	43-84
Wang	2008	China	OC	60	42-85
Tata	2013	Malaysia	GC	60.8	19-91
Hosseini	2007	Iran	GC	61.5	41-81
Witzig	2006	Germany	GC	62	30-91
Witzig	2006	Germany	OC	63.5	37-73
Lee	2017	China	UGI	64.6	+/-13.5
Martin	1997	UK	UGI	66	31-89
Kotz	2006	UK	OC + cardia	67	21-89
Marmo	2005	Italy	UGI	69.3	+/-12.8
Kapoor	2005	UK	UGI	69.84	-

The age of diagnosis of oesophageal and gastric cancers varies considerable across different studies (Table 2). Most studies reported the mean or median age of diagnosis for oesophagogastric cancers to be between 60-70 years old(14, 16, 66, 81, 88-92), with individual cases ranging from as young as 19 to as old as 91. Only two studies reported the median age to be within the younger age brackets of between 55-60 years old(69, 89), and between 40-50 years old(93, 94). When separating oesophageal and gastric cancer, the mean or median age of diagnosis ranges from 58.4 to 67 for oesophageal cancer(14, 16, 69, 91) and slightly younger for gastric cancer at 44 to 62 years old(16,

81, 89, 91, 94). When comparing Asian and European studies, the median or mean age of diagnosis seems to be less predictable with the European countries reporting ranges from 44 to 70 years old whilst all the Asian countries are within the narrower 58 to 64 age bracket(14, 69, 90, 91). This may be due to epidemiological differences between different continents where certain predominant risk factors require a certain length of time to be present before causing malignancy. In Asian countries, oesophageal cancers largely include squamous cell carcinomas of which alcohol and smoking are major risk factors(95). In European countries on the other hand, oesophageal cancers are mostly the adenocarcinoma subtype which are due to risk factors of obesity and reflux(95). The duration from the onset of these risk factors to the development of malignancy is unknown but likely to be different for each risk factor, thereby affecting the age of diagnosis.

Table 3: Tumour locations for oesophageal and gastric cancer across different studies

Author	Year	Country	Tumour location	Oesophageal cancer	Author	Year	Country	Tumour location	Gastric cancer
Witzig	2006	Germany	Proximal 1/3 Middle 1/3 Distal 1/3 Other	55 (53%) 11 (10.5%) 26 (25%) 12 (11.5%)	Martin	1997	UK	Proximal 1/3 Middle 1/3 Lower 1/3	27 (30.7%) 33 (37.5%) 28 (31.8%)
Wang	2008	China	Proximal 1/3 Middle 1/3 Distal 1/3 Cervical	10 (12.5%) 42 (52.5%) 26 (32.5%) 2 (2.5%)	Witzig	2006	Germany	Proximal 1/3 Middle 1/3 Distal 1/3 Other	33 (33%) 43 (43%) 20 (20%) 4 (4%)
Subasinghe	2010	India	Upper 1/3 Middle 1/3 Middle & lower 1/3 Lower 1/3 Other	1 (2%) 18 (37.5%) 5 (10.4%) 24 (50%) -	Eckardt	1990	Germany	Cardia Body Antrum	1 (2%) 25 (49%) 24 (47%)
Kotz	2006	UK	Proximal 1/3 Middle 1/3 Distal 1/3 OGJ Not specified	4 (0.6%) 71 (11.2%) 210 (33.2%) 324 (51.3%) 23 (3.6%)	Suvakovic	1997	UK	High gastric Low gastric Extensive	120 (66.3%) 46 (25.4%) 15 (8.3%)
Derakhshan	2004	Iran	Proximal Body Distal GOJ	22 (10.2%) 90 (41.7%) 57 (26.4%) 47 (21.7%)	Hosseini	2007	Iran	Cardia + upper Body Lower	31 (49.2%) 11 (17.5%) 21 (33.3%)
Camenita	2020	Romania	Upper thorax Middle thorax Lower thorax OGJ Cervical	1 (2.27%) 12 (27.3%) 8 (18.2%) 22 (50%) 1 (2.27%)	Derakhshan	2004	Iran	Cardia Corpus Antrum	126 (44.7%) 74 (26.2%) 82 (29.1%)
Asombang	2021	Zambia	Upper Middle Lower	41 (14.7) 105 (37.8) 88 (31.7)	Donida	2019	Italy	Cardias-GEJ Body-fundus Antrum-pylorus Not defined	106 (12.1%) 366 (41.8%) 304 (34.7%) 100 (11.4%)
Tinusz	2020	Hungary	Upper Middle Lower Lower-middle Upper-middle No data	399 (15.16%) 710 (26.98%) 1125 (42.7%) 158 (6%) 81 (3.08%) 159 (6.04%)	Wanebo	1993	USA	Upper Middle Distal Entire stomach Site unknown	5693 (31%) 2711 (14%) 4774 (26%) 1836 (10%) 3489 (19%)
Krishnamurthy	2020	India	Upper Middle-third Lower-third	152 (16.6%) 377 (41%) 388 (42.3%)	Liang	2017	China	Cardia Fundus Corpus Antrum Overlapping	59.59% 11.43% 13.92% 11.43% 4.17%
Grotenhuis	2010	Netherlands	Proximal Mid Distal GOJ	8 (1.6%) 27 (5.5%) 196 (39.9%) 260 (53.0%)	Coupland	2012	UK	Cardia Non-cardia Unspecified	18728 15340 37861
Coupland	2012	UK	Upper and middle Lower Not specified	18128 (29.5%) 35349 (57.6%) 7898 (12.9%)					

For oesophageal cancers, tumour locations have been generally categorized into thirds i.e. proximal or upper, middle or body and distal or lower (including the gastroesophageal junction)(14, 16, 49, 50, 68, 96). Some studies also provide a separate category for tumours in the gastro-oesophageal junction(13, 66, 96, 97), the cervical region(14, 97) and also accounting for tumours overlapping two or more areas(50, 69, 98) (Table 3). Most studies show the common trend of oesophageal cancers being most commonly located in the distal or lower third(14, 68, 69, 98), with a large proportion of these in the gastroesophageal junction(13, 66, 99). It is worth noting that in the Asian and African studies, there is either a greater proportion of tumours in the middle third of the oesophagus(14, 49, 96) or less of a gap between the proportions of lower and middle oesophageal cancers(68, 69). This can be explained by the fact that oesophageal adenocarcinomas most commonly occur in the distal part of the oesophagus whilst oesophageal squamous cell carcinomas occur most commonly in the middle third of the oesophagus(100). The study by Tinusz et al. (2020) reported that squamous cell carcinomas were located in the middle oesophagus in 36% and lower oesophagus in 26%, in comparison to adenocarcinomas which occurred in the lower oesophagus in 86% and less than 5% elsewhere(98). That is why in Asia which still has a significant proportion of squamous cell carcinomas(53, 58, 64, 65)., the rates of tumours located in the middle oesophagus is similar to or even higher than that of the lower oesophagus.

Gastric cancers on the other hand have greater variation in reporting of tumour locations between studies with some dividing areas of the stomach into thirds(16, 88, 101) or high vs low gastric(7) or cardia vs non-cardia(50) and others going with more recognized anatomical locations of cardia, fundus, body or corpus, antrum and pylorus(72, 81, 89, 96, 102). The proportions are also less predictable, but overall more studies report cardia or high gastric having the highest proportion of tumours(7, 50, 72, 81, 96, 103) compared to other older studies(16, 88, 89). Oesophageal adenocarcinoma and gastric cardia adenocarcinoma have the same risk factors of obesity and reflux, which are becoming increasingly more prevalent in developed countries(62). It is therefore not unexpected that gastric cardia adenocarcinoma would rise in the same way that oesophageal adenocarcinoma incidence has been rising(23).

In summary, when comparing epidemiology of oesophageal and gastric cancer in Australia to that worldwide, Australia has a rising incidence of oesophageal adenocarcinoma and gastric cardia cancer and a decreasing rate of oesophageal squamous cell carcinoma and gastric non-cardia cancer(104), similar to that of other Western nations described earlier (page 20-22). Whilst Australia has relatively lower incidence rates compared to Europe, South East Asia and South Africa (Figure 4), the incidence rates of gastrointestinal cancers have significantly risen in Australia over the last 28 years(105). Five-year survival rates in Australia for oesophageal and gastric cancer from 2013 to 2017 were only 23%(106) and 34%(107) respectively, which reflects the poor outcomes for these patients. The rising incidence and poor survival rates are compelling reasons for finding ways to achieve earlier diagnoses for oesophagogastric cancers.

2.2 Prevalence of delays to diagnosis and treatment

Around 9 studies have evaluated delays to diagnosis and/or treatment. There is great variability of methodology in reporting delays between these studies, which makes comparison extremely difficult. Some studies report duration of time from symptom onset to first presentation, which ranges from 1 to 3.5 months (14, 16, 69, 91). Others report time from symptom onset to diagnosis ranging from 17.1 weeks to 3 months (13, 88). The remaining studies report time from diagnosis to treatment(13), or from first presentation to treatment onset(108), or from referral to endoscopy(91) or from first presentation to referral to endoscopy to MDT to surgery (67). The study by Martin et al reports each time interval as a proportion of the total duration of time from symptom onset to diagnosis, in order to highlight which time interval has contributed the most to any delays if present i.e. symptom onset to GP presentation (18%), presentation to referral (33%), referral to hospital (13%) and hospital to diagnosis (36%)(88). Few other studies have reported delays using the same time interval proportions, but to the contrary demonstrate that the initial time interval from symptom onset to first consultation (either with GP or hospital) has by far the most significant contribution to total delays to diagnosis. The study by Wang et al (2008), reports the following time interval contributions to delays: delay from first symptoms to first contacting health-care system (69%), delay from first contacting

health-care system to histological diagnosis (20%), delay from histological diagnosis to end-point (11%)(14). The study by Subasinghe and Samarasekera (2010) reports the following time intervals: delay from first symptoms to first consultation is 12.29 weeks (82%), delay from consultation to upper GI endoscopy is 1.06 weeks (7.1%), and delay in histological diagnosis is 1.6weeks (upper GI endoscopy to histological report) (10.7%)(69). These studies by Wang et al (2008) and Subasinghe and Samarasekera (2010) however only included oesophageal cancer patients and not gastric cancer whilst the study by Martin included both oesophageal and gastric cancer (upper gastrointestinal cancer) patients in their reporting of intervals(14, 69).

The limitations of these studies are the different time intervals making comparison and generalisability of results difficult. This is also affected to a lesser extent by differences in the study cohorts as demonstrated above, being either gastric cancer(108), oesophageal cancer(13, 14, 69), oesophageal and cardia cancer(66) or upper gastrointestinal cancer(16, 67, 88, 91). These studies are also largely descriptive in that they only state time intervals rather than use a clear or consistent guideline to define delays to diagnosis or treatment. This lack of standardisation makes it hard to draw meaningful conclusions about the degree and impact of delays to diagnosis and treatment on outcomes. The current study proposes to look at time intervals based on a national guideline to create standardisation and objectivity in evaluation of delays to diagnosis, which is missing in other studies, with a view to applying these guidelines on an international scale to make global evaluation of delays to diagnosis and treatment more reliable and robust.

2.3 Causes of delays to diagnosis and treatment

2.3.1 Routes to diagnosis (GP vs ED)

There are typically two parts of the healthcare system that patients present to for further investigation and form two routes to diagnosis. In most cases patients are diagnosed via the GP (General Practitioner) route which involves presenting to the GP who will refer to a specialist for endoscopy.

Less commonly, patients can be diagnosed via the ED (Emergency Department) route, by presenting directly to the ED and subsequently getting referred for endoscopy through the hospital system.

The proportion of patients with oesophageal and gastric cancer combined presenting to ED with symptoms leading to their diagnosis, have been reported as 33%(109), 16.4%(110), and 32%(111). For oesophageal cancer alone, 29.4% had a diagnosis following ED presentation according to a single study(112). For gastric cancer alone, rates of ED presentation are slightly higher at 39.6%(112) and 38.7%(113). Overall, these rates of upper GI cancer following ED presentation are higher than that reported in studies looking at all cancers which range from 13.9 to 24%(114).

Cancer diagnosis following ED presentation is notoriously associated with adverse outcomes. For all cancers, diagnosis via the ED route is associated with lower 5-year survival rates, among which upper GI cancer has the second highest proportion of patients diagnosed via the ED route behind lung cancer(114). According to Fallon et al. (2019), upper GI malignancy has the highest proportion of diagnoses following ED presentation(5). For studies focussing on upper GI cancer, patients diagnosed following ED presentation have lower rates of curative treatment(109), lower 1 year survival, increased 5-year mortality and metastatic liver recurrence rates(112). According to Blackshaw et al. (2004), gastric cancer diagnosis following ED presentation is associated with increased advanced stage disease at resection, decreased rates of curative treatment, and lower cumulative 5-year survival rates(113).

Of patients diagnosed via the ED route, few studies have evaluated the proportion that had prior GP input. For all cancers, prior input from a GP occurred in 71%(115) and 80%(111) of ED presentations. For lung and colorectal cancer, a study by Mitchell et al (2015) reported 93.4% of ED presentations to have involved prior input from a GP, of which 52.3% arranged the ED admission, 29.3% were directly involved in managing the episode leading up to the admission, and 13.1% were involved in the care of the patient in the year before the diagnosis(116). There has not been a dedicated study on oesophagogastric cancer evaluating the proportion of ED presentations with prior GP input.

The most common risk factor reported for ED presentations is living in deprived areas(115, 117-119), due to the deficiency of primary care physicians in these areas. Other risk factors reported

include male gender(115), older age(117), GPs less able to offer appointments within 48 hours and no GPs with a primary UK qualification in UK study(119). A study by Markar et al. (2018) which focused on risk factors for diagnosis of oesophagogastric cancer following ED presentation reported age>70, female gender, non-white ethnicity, and Charlson comorbidity index score >3 as significant risk factors for ED presentation(112).

Adverse outcomes with cancer diagnoses following ED presentation are unsurprising given the unplanned nature of and considerable patient concern for symptoms which are significant enough to prompt an emergency presentation, often late in the disease course. It is therefore incumbent on the General Practitioner to be vigilant in recognising the symptoms and signs of oesophageal and gastric cancer early and referring for endoscopy before patients present late to the emergency department with significant symptoms.

2.3.2 Frequency and predictive value of symptoms

Determining the frequency of symptoms in upper GI cancer, particularly early upper GI cancer, helps in developing a prediction model for early cancer detection which in turn reduces delays to diagnosis. For example, if dysphagia was found to be a common presenting symptom in patients with early stage oesophagogastric cancer, then that may support the notion of early referral for endoscopic evaluation for cancer in those with dysphagia. This, however, is offset by the proportion of patients with dysphagia who also have other benign conditions which would not benefit from early endoscopic evaluation. Positive predictive value (sensitivity) of symptoms addresses this issue by identifying the proportion of these patients with a particular symptom, e.g., dysphagia, who have oesophagogastric cancer. Both frequency and positive predictive value of symptoms are still necessary in identifying the subset of patients who should be referred for urgent endoscopic evaluation and subsequently reduce their delays to diagnosis.

Of the studies reporting the frequency of individual symptoms in oesophageal and gastric cancer, only two studies reported the frequency of these symptoms for both cancers combined(88, 120), whilst the rest of the studies have looked at rates of symptoms occurring in either oesophageal cancer or gastric cancer(12, 16, 69, 81, 94, 121, 122).

Dysphagia was reported as the most common presenting symptom at 12% in one study (120) and the second most common presenting symptom at 24%(88) in the other study that looked at oesophageal and gastric cancer combined (upper GI cancer). For oesophageal cancer alone, dysphagia has been reported at rates of 46%(121), 50%(16, 122), 71%(14) and 100%(69). According to Gallo and Cha (2006), dysphagia is the most common complaint in oesophageal cancer, along with weight loss, but is often a sign of advanced disease(12). For gastric cancer however, dysphagia has been reported at much lower rates of 23%(16) and 20.6%(81). A study by Lee et al. (2017) which separates gastric cancer into upper and lower, reported dysphagia in 50% of upper gastric cancers (being in a location closer to the oesophagogastric junction/oesophagus) and 0% of lower gastric cancers(122).

Abdominal or epigastric pain has been reported at rates of 23%, 31%, and 30.8% in oesophageal cancer patients. For gastric cancer, abdominal pain occurs more frequently, at rates of 32%, 44%, and even 90.4%. According to Gallo and Cha (2006), epigastric pain is seen in 70% of early gastric cancers(12).

Other nonspecific symptoms such as weight loss, anorexia, nausea, and vomiting are all reported at variable rates in different studies and often tend to be reported in combination with each other rather than separately. For oesophageal cancer, weight loss was reported between50%(122) and 83.3% of cases(69), weight loss and anorexia combined in 6%(120), weight loss, nausea, vomiting and early satiety combined was reported in 12-16%(88), and fatigue alone reported in 14% of patients(16). For gastric cancer, a study by Boldys reported fatigue in 53%, anorexia in 43.4%, nausea in 37.3%, vomiting in 24.1% and weight loss in 10.8% of patients(94). Crisan et al. (2016) reported nausea and vomiting in 24% of gastric cancer patients(11) whilst Hosseini reported anorexia, cachexia, nausea and vomiting combined as occurring in 1.6 to 17.1% of gastric cancer patients(81).

Studies looking at positive predictive value and sensitivity of alarm symptoms as opposed to just frequency of symptoms have had mixed results. The term ‘alarm symptom’ refers to a symptom of suspected oesophagogastric cancer that warrants urgent investigation. Two meta-analyses by Vakil

et al (2006) and Fransen et al (2004) have concluded that alarm features have a limited predictive value for an underlying malignancy(9, 123). In a Danish study, the PPV for those who experienced at least one specific alarm symptom was 0.2%(124). In a UK study, the cancer detection rate in patients was low (7.1%), with all cancers clearly found at an advanced stage. Of the 42 patients in this study with alarm symptoms only 4 had gastric cancer and 1 with oesophagogastric cancer. Alarm symptoms are usually late manifestations of GI malignancy(125).

In contrast, a study by Crouwell et al. (2018) showed a considerably higher positive predictive value for alarm symptoms for detecting a malignancy compared to other studies (11.8% vs 5.9%), particularly for the alarm symptoms of dysphagia and weight loss combined, having a relatively high PPV of 28.1% and NPV of 99.2%(126). According to this study, a risk-prediction model based on the variables age, alarm symptoms (particularly dysphagia and weight loss) and male gender is a good predictor of upper GI malignancy(126). Two other studies reported a combination of dysphagia, weight loss, and age >50 or 55 to be a significant predictive factor for oesophagogastric cancer(127, 128). Dysphagia, weight loss and anaemia has been reported to show the strongest association to oesophagogastric cancer but with relatively low sensitivity and high specificity(129). Another study found dysphagia and weight loss to be significant positive predictive factors for malignancy(127).

Uncomplicated dyspepsia, whilst not an alarm symptom, is a commonly occurring symptom that is a potential precursor to upper GI cancer. It has however been reported as a poor predictor of cancer in older subjects (128) with only a small proportion of dyspeptic patients diagnosed to have malignancy after upper GI endoscopy(130). In a Chinese study of patients with uninvestigated dyspepsia aged between 36 and 74 years old, dysphagia was the only alarm feature strongly suggestive of potential upper GI malignancy in the Chinese population(127). Overall, it is rare for patients with upper GI cancer to experience significant dyspepsia before the onset of their alarm symptoms, therefore limiting the prospect of an earlier diagnosis (131).

2.3.3 Interspecialty cancer referral

Inter-specialty cancer referrals have been reported to triple the time to cancer diagnosis and occurs in a significant proportion of foregut cancer patients(132). A UK study found that oesophagogastric

cancer patients with more than two consultations prior to referral experienced greater delay to referral and a significantly poorer prognosis, including a higher mortality rate in those who underwent surgical resection with curative intent(133). In Australia, a referral to a specialist for outpatient review prior to endoscopy is often required and may contribute to delays in diagnosis. Not many studies, however, have assessed the frequency and burden of multiple consultations or inter-specialty cancer referrals in Australian centres for oesophagogastric cancer and its impact on outcomes.

2.3.4 Other reasons or risk factors for delays

Different other reasons for delays to diagnosis and treatment of oesophagogastric cancer have been reported in various studies. Empirical drug therapy with acid suppressants has been associated with a longer time from patient presentation to diagnosis(16, 91). This may be explained by the masking effect of acid suppressants on endoscopic visualisation of malignant tissue as described earlier, which can lead to diagnosis only occurring on a repeat endoscopy. It is also possible that a trial of therapy is undertaken prior to endoscopy which delays diagnosis. A negative barium meal study was the most common reason for delay from first consultation with doctor to diagnosis(15, 134). A large systematic review of 25 studies which specifically focussed on risk factors for delays to diagnosis in upper gastrointestinal cancer, reported a range of factors increasing delays to diagnosis but classified in terms of patient factors and practitioner factors(135). Patient factors included non-recognition of symptom seriousness, lower socioeconomic status, and being female. Practitioner factors included initial misdiagnosis, inappropriate/inaccurate tests, and a previous negative test result. Factors reported as decreasing delay included increasing comorbidity, first presentation to hospital, older patient age, use of referral guidelines and symptom type – abdominal pain and bleeding. It was noted that symptom seriousness appeared to be a double-edged sword, either prompting speedy presentation over patient concern or inducing fear in patients so as to increase their delay in presenting. This therefore presents a challenge in terms of raising awareness about upper gastrointestinal cancer in public health education, ensuring a balance is achieved between stressing the importance of early presentation versus inciting fear thereby deterring patients from presenting(135).

With regards to encouraging earlier presentation, several studies have in fact reported that a postponement in patients presenting to a GP is the primary reason for delay to diagnosis(13, 16, 69, 91) including two systematic reviews(6, 90). Few other studies have noted a lack of promptness in GP referral causing this delay instead(81, 88). Various strategies have been employed to address these causes as described below.

2.4 Impact of delays to diagnosis and treatment on outcomes

Few studies have investigated associations between delays and outcomes. Some studies reported that in patients with oesophageal cancer, delays from diagnosis to surgery are associated with higher overall morbidity, mortality(13) and cancer of more advanced stages(14, 88). For gastric cancer, delay in first specialist consultation to treatment is associated with higher post-operative mortality according to a study by Haugstvedt et al. (1991) (108). On the other hand, some studies have reported no effect of delays on survival(15) or the stage of gastric and oesophageal cancers(16).

The main outcomes analysed in studies include staging (stage of disease at resection), post operative complications or morbidity (largely classified into local, general or both), and mortality or survival. Again, there are a mix of studies looking at patient populations of either oesophageal or gastric cancer alone or combined, different time intervals from patient delay to hospital delay to physical delay to treatment delay etc. and classifications of staging typically from stage I to IV but also advanced stage disease or early-stage disease. Definitions of early and advanced stage disease also varied between studies with some defining stage I alone as early stage disease(7, 120, 136) whilst others defining stage I and II as early stage disease (5, 8). These different definitions and classifications make drawing conclusions from these studies difficult, but some inferences can be made as described below.

2.4.1 Staging

In terms of staging, three studies reported no association between delays and stage of disease at resection. These included the study by Witzig et al. (2006) which looked at effect of diagnostic delay

(symptom onset to diagnosis) in oesophageal and gastric cancer patients(16) and the study by Subasinghe and Samarasekera (2010) which included only oesophagogastric cancer patients of whom delays from symptom onset to treatment did not have an effect on staging(69). In the study by Grotenhuis et al (2010), hospital delay (delay from diagnosis to treatment) also did not affect staging in patients with oesophageal cancer alone(13).

Two other studies show some association with delays and staging. According to Kotz, a longer time interval from diagnosis to treatment is associated with greater proportion of stage IV disease in a cohort of patients with oesophageal and cardia cancer(66). The study by Martin showed that longer diagnostic delays in patients' oesophageal cancer were associated with higher rates of stage III and IV disease(88). These findings flow with the logic of increasing delays allowing more time for disease progression to occur prior to commencement of treatment, thus resulting in advanced stages at resection.

Conversely however, two studies report the reverse association between delays and staging. According to Van Erp, patients with oesophageal and gastric cancer who had shorter hospital delays tended to have higher rates of advanced stage disease (defined at stage III or IV in this study)(67). Likewise, according to the study by Haugsvedt et al. (1991), a shorter delay, that is patient delay and physician delay (from first consultation to treatment) were more likely to have advanced stage disease (defined as stage IV disease in this study). This study included only gastric cancer patients(108). Overall, these studies suggest that shorter delays to either diagnosis or treatment are associated with advanced stage disease. These findings could be explained by the fact that these patients had a more aggressive subtype of cancer involving a faster disease progression. Therefore, the shorter time from symptom onset to diagnosis and treatment still results in advanced stage disease compared to the less aggressive subtypes of cancer which may have had a longer time from symptom onset to diagnosis and treatment. Variations in tumour aggressiveness were not measured in these studies and are often impossible to objectify within the limitations of the current understanding of oesophagogastric cancer.

2.4.2 Postoperative complications, morbidity and survival

In terms of survival, morbidity and post operative complications, only few studies evaluated this in any detail and provided mixed results. According to Grotenhuis et al (2010), prehospital delay (symptom onset to diagnosis) had no impact on morbidity, in-hospital mortality or overall or 5-year survival, however longer hospital delay (diagnosis to treatment) did have a higher overall morbidity and mortality(13). Conversely according to Kotz, there was no association between time from diagnosis to treatment and post operative mortality (at 30- and 90-days post op) or survival at a median follow-up of 6.5 years in oesophageal cancer patients(66). In the study by Haugsvedt et al. (1991), post operative mortality was higher in those with longer patient delay but no difference in post operative complications, which were categorized into general (cardiovascular, pulmonary, thromboembolism), and local (post operative bleeding, intra-abdominal or wound infection, anastomotic leak, fistula, wound dehiscence)(108).

2.4.3 Comparison of delays and outcomes with other cancer types

Looking into the impact of delays and outcomes in other cancers for comparison also provides some further insights. A systematic review by Neal et al. (2015) compared the delays to diagnosis and treatment outcomes between a wide range of cancer types, including upper gastrointestinal cancer(137). The findings were that cancers with more reports of an association between shorter times to diagnosis and more favourable outcomes were breast, colorectal, head and neck, testicular and melanoma. Upper gastrointestinal cancers tended to show none or negative associations between shorter times to diagnosis and outcomes (of 18 papers, only 2 positive, 4 negative and 12 no association)(137). This perhaps reflects the overall complexity of upper gastrointestinal cancers in that there are so many factors affecting outcomes other than delays to diagnosis in comparison to the other cancers, such as differences in degree of tumour aggression between cancers, oesophageal vs gastric, adenocarcinoma vs squamous cell, etc. delays to diagnosis and its impact on outcomes may be hard to isolate in studies.

The variability of reporting outcomes of delays could be explained by differences in definition of what constitutes a delay to diagnosis and treatment between different studies based on their country's guidelines. Regardless of this or the above mixed findings, it makes sense that there is a certain

duration between first symptoms to diagnosis and treatment which, if exceeded in an individual patient, will lead to adverse outcomes such as those described above.

2.5 Strategies to reduce delays to diagnosis

2.5.1 Open Access Endoscopy

Over the last 5 decades, numerous initiatives have been created by the UK Government with the primary aim of detecting oesophagogastric cancer at an earlier stage to improve survival rates. It started with Open Access Endoscopy (OAE), which began to be offered unrestricted to GPs in 1974 (138). Open access endoscopy involves the ability for GPs to refer patients for endoscopy directly without the need for specialist consultation prior. Whilst specialist consultation has been intended to review, triage and divert unnecessary or inappropriate referrals, the entrance of 'open access' to endoscopy was intended to reduce delays to diagnosis and detect cancer earlier by removing the extra time associated with this triaging, reviewing and re-referring for endoscopy by the specialist. Despite this logical proposition, studies evaluating outcomes of open access endoscopy have reported a persistently low diagnostic yield for early stage cancers offset by a rise in endoscopy workload(7, 120, 121). The study by Suvakovic et al (1997) investigated the rates of early gastric cancer detection over a 5-year period in a South Tees Health district where open access endoscopy had been available for 7 years(7). There were no statistically significant differences in rates of early-stage gastric cancer detected between those referred through open access endoscopy and by those referred through conventional means. The primary reason cited for these were failure to recognize the disease early enough due to prior antacid treatment masking disease by facilitating mucosal healing resulting in a diagnosis occurring after multiple endoscopies(7). In the study by Broe et al. (2013), of 4262 patients referred for endoscopy by a primary care physician, the diagnostic yield for upper gastrointestinal cancers was 0.8%(121). The percentage of endoscopies with normal findings was 87.6%. One of the prime reasons for such a low diagnostic yield was felt to be inappropriate primary care referrals. When all referrals were retrospectively reviewed and appropriateness determined based on application of the NICE guidelines, only 22.8% of those referrals were deemed appropriate(121). This emphasizes the need for referral guidelines that are not only of a high quality but are actually utilized appropriately by primary care physicians in addition to just making endoscopy

more available. The other finding in this study was that 92.2% of endoscopies in patients less than 40 years old were normal, leading to the notion that perhaps an age threshold may be worth including in referral guidelines to improve the diagnostic yield. More studies are needed to identify factors that should be included in a referral guideline to improve upper gastrointestinal detection rates.

2.5.2 The Two Week Wait Rule

In the year 2000, the Two Week Wait Rule was introduced in the United Kingdom to streamline cancer care. The purpose of this rule was to reduce delays from referral to diagnosis in those patients with 'alarm symptoms' i.e., symptoms of suspected oesophagogastric cancer. This rule recommends maximum time-frame of 2 weeks between primary care (GP) referral and specialist review for any patient with alarm symptoms. The National Cancer Plan further specified recommended timeframes of 31 days between decision to treat and treatment and overall 62 days between primary care referral and first curative treatment for patients with alarm symptoms. (3). This two week wait rule sought to improve early cancer detection rates through encouraging greater utilisation of open access endoscopy. Nonetheless, several studies have shown a persistently low diagnostic yield for early stage cancers(3, 7, 8), no decrease in delay to diagnosis, and no improvement in survival(3, 5, 6). Reasons for this include alarm symptoms potentially being a reflection of late-stage disease rather than early stage disease, or a high proportion of inappropriate referrals by primary care physicians(8).

In 2004, the United Kingdom Department of Health advisory body, known as the National Institute of Health and Clinical Excellence (NICE) had developed guidelines that specified which alarm symptoms would warrant urgent endoscopy referral to help clinicians better identify patients with suspected oesophagogastric cancer. The alarm symptoms specified in these guidelines included gastrointestinal blood loss, progressive unintentional weight loss, progressive dysphagia, persistent vomiting, iron deficiency anaemia, epigastric mass, suspicious barium meal. Uncomplicated dyspepsia was also included in this urgent referral criteria if it occurred in those above 55 years old, or if it persisted despite the initially recommended treatment with antisecretory medications or H pylori eradication therapy(139). The inclusion of dyspepsia in this criteria was debated at the time due to some studies reporting it leading to a low diagnostic yield(140) whilst others reporting that it

resulted in missed cases of cancers due to a small percentage of cancers being in the setting of uncomplicated dyspepsia(141, 142).

According to the study by Bowrey et al. (2006), of the 123 patients diagnosed with oesophagogastric carcinoma, 85% (104 patients) had alarm symptoms and therefore 15% would have been missed because their symptoms were those of uncomplicated dyspepsia(139). Of those patients who had alarm symptoms, they often had advanced incurable stage disease.(142) According to the study by Sundar et al. (2006), of 228 patients with upper gastrointestinal cancer, 14 (6.2%) of patients presented without alarm symptoms, of which 11 had uncomplicated dyspepsia, suggesting again a small proportion of patients who would have had a missed diagnosis(141). On the contrary, according to the study by Patel and McNair (2019), over a 10-year period with 9012 endoscopies performed in the UK for uncomplicated dyspepsia, only 6 (0.46%) of patients had cancer(140).

In 2015, the 2 week wait guidelines were updated to include dyspepsia only in patients with weight loss and above 55 years old. According to the newer updated NICE guidelines in 2015, patients with treatment resistant dyspepsia or uncomplicated dyspepsia and above 55 years old were recommended for non-urgent endoscopy referrals instead. (4) There have not been many studies since evaluating these most recent changes specifically for oesophagogastric cancers. Changes in guidelines usually take time to implement into practice. Further long-term studies are required to evaluate the outcome of these changes.

2.5.3 Public campaigning

Public health campaigns had shown encouraging results. The Public Health England (PHE) has spent time on raising awareness of signs and symptoms of oesophagogastric cancer. It started with a series of seven local pilot campaigns run from the period of April to July 2012(143). These campaigns had shown encouraging results with statistically significant increases in urgent GP referrals by 26% and in oesophageal cancer diagnosed following a two-week wait referral by 20%(143). Nonetheless, at the end of it there was no change to oesophageal cancer conversion rate. Later, another regional pilot campaign followed from February to March 2014. Results from this campaign included a 52% increase in urgent general practitioner referrals for suspected

oesophagogastric cancer and a 29% increase in the proportion of oesophagogastric cancers diagnosed via a two-week wait referral amongst those aged 60-69 years old. The total number of oesophagogastric cancers diagnosed however, did not increase following this campaign(143).

After these preliminary trial results, the PHE proceeded to launch a larger-scale campaign titled 'Be Clear on Cancer Campaign' from 26 January to 22 February 2015(144). This involved advertising on television, radio and press across England for three weeks involving two key messages: 'Having heartburn, most days, for 3 weeks or more, could be a sign of cancer – tell your doctor' and 'Food sticking when you swallow could be a sign of cancer – tell your doctor'(144). The purpose of this campaign was to make the public aware of warning symptoms of oesophagogastric cancer such as dyspepsia and dysphagia.

A study by Siau et al. (2017) investigated the impact of the 2015 Be Clear on Cancer Campaign by retrospectively reviewing outcomes from patients referred via the two-week wait open-access endoscopy pathway three months following the start of the 2015 campaign and compared to the corresponding months in the prior year (2014) preceding this campaign(145). It found that the number of endoscopies performed rose by 48% from 777 to 1266. The incidence of target diagnoses (oesophagogastric cancer and Barrett's oesophagus) as a proportion of two-week wait referrals fell from 6.9% in 2014 to 6.1% in 2015, nor were there any significant increases in target diagnoses or cancer overall(145). There were no significant changes in tumour, node, metastases (TNM) staging or 1-year survival(145). The study by Koo, Awadelkarim, and Dhar (2017) evaluated the impact of the Be Clear on Cancer Campaign in the locality of Durham and found that there was a twofold increase in endoscopy workload without any change in detection of oesophagogastric cancers(146).

A systematic review by Lai et al. (2021) compared the results of 11 nationwide 'be clear on cancer' campaigns in England for different cancers(147). These included 2 bowel, 3 lung, 3 bladder and kidney, 2 breast and 1 oesophagogastric cancer campaigns that were run between 2012 and 2016. It revealed that there were significant increases in primary care attendances for campaign-related symptoms (9 of 10 campaigns), increases in relevant urgent referrals for suspected cancers (9 of 11 campaigns), increases in diagnostic tests (6 of 10 campaigns), and increases in cancer diagnoses resulting from urgent referrals (7 of 11 campaigns)(147). In fact, the oesophagogastric cancer campaign had the largest increase in urgent referrals compared to other cancers (84% vs 32% for

other cancer referrals). In terms of early-stage diagnoses however, only 4 of 10 campaigns demonstrated a higher-than-expected proportion of early-stage diagnoses for sustained periods. For the oesophagogastric cancer campaign alone, it had the least favourable outcomes compared to the other cancers in that it did not experience a significant change in the number of diagnostic tests, number of cancer diagnoses resulting from the urgent referrals. This is despite having the biggest increase in the number of urgent referrals. After all these campaigns there was no impact on survival for any of the cancers(147).

It is interesting to note how each cancer had different responses to the campaigns and this may reflect the ability for the public to understand and interpret the messages in the campaigns, particularly those pertaining to oesophagogastric cancer which has symptoms that may be harder to explain to people than others. According to a study by Humphries, which focused on patients' perception and understanding of symptoms, 41% of oesophagogastric cancer patients experienced heartburn prior to diagnosis, however many of them did not know what heartburn was, identifying it as either reflux or indigestion(148). Whilst the definition of either of these terms can vary depending in different countries, according to the American College of Gastroenterology and the Canadian Association of guidelines on dyspepsia, the definition of heartburn is a burning sensation in the retrosternal area behind the breastbone. Reflux is the presence of troublesome heartburn and/or regurgitation, with regurgitation defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx. Indigestion, otherwise known as dyspepsia, is predominant epigastric pain lasting at least 1 month. This can be associated with any other upper gastrointestinal symptom such as epigastric fullness, nausea, vomiting or heartburn, provided that epigastric pain is the patient's primary concern(149). There is obviously considerable overlap between these symptoms. It may be that the message of 'Having heartburn, most days, for 3 weeks or more, could be a sign of cancer – tell your doctor' as part of the Be Clear on Cancer Campaign was potentially misunderstood by several people. The effectiveness of a public campaign relies on ensuring the message is understood, which is equally dependent on the health literacy of the public in addition to how it is conveyed. Corresponding initiatives to improve health literacy within the wider public will aid in the value of such campaigns.

Another reason for lack of impact with this campaign is that heartburn or dyspepsia was potentially the wrong focus. Dyspepsia has been reported as a poor predictor of cancer (128) with only a small proportion diagnosed to have malignancy after upper GI endoscopy(130). It is definitely important to identify the correct symptoms that warrant endoscopy prior to development of a public campaign. These public health campaigns nonetheless serve as a learning lesson for developing effective future campaigns.

2.5.4 One stop dyspepsia clinic

To address the increasing demand for endoscopies in the UK following all the above initiatives, there have been proposals of a 'one stop dyspepsia clinic' with nurse endoscopists to provide additional endoscopy services. These clinics involve gastroenterologists initially seeing the referred patient, and then if the referral deemed appropriate, an endoscopy being performed by a trained nurse with the results discussed on the same day, either by the nurse endoscopist or the gastroenterologist. Abdominal ultrasounds or blood tests can also be performed on the same day if indicated. Whilst this provides GPs with direct access to a complete range of services all done on the same day, and a gastroenterologist to triage and avoid unnecessary referrals and tests, thus aptly described as the 'one stop dyspepsia clinic', the utilisation of nurses to perform endoscopies as opposed to just specialists proposes a unique approach to increasing availability for endoscopy. A randomised control trial by Meaden et al. (2006) evaluated the competency of nurse endoscopists in comparison to doctors, through use of an 'expert' consultant gastroenterologist to evaluate and compare the adequacy of views, rate of biopsies, and accuracy of endoscopic findings between both(150). This study found that nurses achieved greater adequacy of views than doctors (91.6% vs 53.4%), and there was no difference in rate of biopsy performance(150). Mean agreement with the 'expert' consultant gastroenterologist on endoscopy findings with doctors was 81%, and between nurse and expert was quite similar at 78.3%(150). Nurse endoscopists were therefore ultimately able to provide an accurate general diagnostic upper GI endoscopy service as competently as doctors. A study by Melleney and Willoughby (2002) also evaluated the efficacy of a one-stop dyspepsia clinic in the UK(125). It found that whilst preliminary consultation with a gastroenterological physician avoided

inappropriate tests in 16% of the referred patients, the waiting times for endoscopy progressively increases over the 6-month study period, from 8 days to over 3 weeks(125). The diagnostic yield for cancer was also quite low with only 6 cases (7.1%) of oesophageal or gastric cancer being detected(125). This is in comparison to the expected 40 cases of oesophagogastric cancer that would be dealt with over the same period at a general district hospital in a population of 300,000 people(125). It is likely that most cancers are detected through other means such as the direct access endoscopy. (125).

2.5.5 Centralisation of services

The centralisation of services was another initiative in 2001, which involved the extensive reorganisation of Oesophagogastric cancer services in England in 2001(151, 152). In the 1990s, it was perceived that oesophagogastric cancer services in England were poorly structured and disconnected. To address this the Improving Outcomes Guidance in Upper Gastrointestinal Cancer and the National Health Services (NHS) Cancer Plan implemented a strategy for reform which involved a number of specific approaches(151). According to this reform, all hospitals caring for cancer patients became integrated into regional cancer networks. Within each network, a specialist cancer centre provides appropriate access to staging investigations, curative surgical treatment, specialist radiology, oncology and palliative services to all patients living in the area. This allows for coordination of care between these services in a centralised specialist centre(151). Clinicians within each hospital are also required to work together as a Multidisciplinary team which involves collaboration and communication between the multiple above mentioned health professionals, all centred around caring for cancer patients.

There have been further studies to evaluate the progress of this reform since its inception. A study by Palser et al. (2009) reviewed adherence to the reforms over a 6-year period of its inauguration at all the 30 cancer networks and 156 NHS acute trusts in England(151). It found that there were still only 16 out of 30 cancer networks that discussed patients at a multidisciplinary meeting and 11 networks without a fully centralised curative surgery service available. They also still lacked availability of other health professionals such as dieticians, palliative care services and nurse specialists within some of the networks(151). Whilst this study was in 2007, i.e. 6 years post

implementation of centralisation of services, services had not reached their full restructuring as often these changes takes time. More recent studies evaluating its progress however have shown marked improvements.

According to the study by Groene et al. (2014), the survival of patients undergoing curative surgery has improved from 34% for oesophageal tumours and 40% for gastric tumours to 45% and 50% respectively(152). The study by Varagunam M et al. (2018) which investigated changes in surgical services for oesophagogastric cancer in England since centralisation over the period from 2003 to 2014 and found that the proportion of patients having their procedure at a cancer centre had increased from 40% to 80%(153). The annual 30-day, 90-day and 1 year mortality rates had decreased from 7.4%, 11.3% and 29.7% in 2003-04 respectively to 2.5%, 4.6% and 19.8% in 2013-14 respectively. Whilst the median annual surgical volume in NHS trusts did increase from 21 to 55 patients, this volume only explained a small proportion of the observed reduction in mortality rates, which can be largely attributed to the effect of centralisation and restructuring of services which had finally taken effect in the second decade after its implementation(153).

Centralisation of services was subsequently adopted in some centres throughout Australia and whilst it has not been around for as long as in the UK, the few studies evaluating its impact in Australia also demonstrate an improvement in outcomes. Three studies that evaluated outcomes in patients who underwent oesophagectomy or gastrectomy in high volume centres with access to centralised cancer services, demonstrated significantly better outcomes in terms of lower post-operative mortality(154, 155), better 5-year survival rates(155, 156) and superior surgical outcomes(154, 155) than those who underwent surgery in low volume centres.

Centralisation of services has probably been the most useful initiative out of all the initiatives established by the UK and subsequently introduced in Australia as reflected in the literature. Despite this, survival rates remain at 23% and 34% for oesophageal and gastric cancer respectively according to the latest data from 2013 to 2017. More still needs to be done therefore to improve survival rates in oesophagogastric cancer patients.

2.5.6 Utility of endoscopy as a diagnostic tool

From the poor survival of oesophagogastric cancer patients, arises the question of whether endoscopy is sufficiently accurate as the gold standard of diagnosis? According to two meta-analyses, the rate of missed upper GI cancer was 9.4% and 11.9% respectively(157, 158). The most cited reason was an insufficient number and inadequate quality of biopsies taken(157, 158). In the study by S Vradelis et al. (2011), endoscopy would achieve 100% diagnostic accuracy if at least six biopsy samples were taken, and insufficient biopsies (fewer than six) of a lesion are the only factor associated with a gastric cancer potentially being missed by an initial endoscopy(159). According to the review by A Pimenta-Melo et al. (2016), other risk factors for missed diagnoses were younger age (less than 55 years old), marked gastric atrophy, gastric adenoma, or ulcer(157). Perhaps specialists have a lower suspicion for cancer in the younger age-group which decreases their likelihood of looking any further for cancers and therefore missing them(157). Also, other gastric pathologies such as adenomas, ulcers, atrophy etc. are more likely to obscure visualisation of a true malignancy and lead to it being missed(157). Another issue is the use acid suppression therapy prior to endoscopy. Acid suppression medication promotes the overgrowth of normal mucosa in sites of malignant tissue, creating a benign appearance (7, 91, 160). According to a study by Bramble, Suvakovic and Hungin (2000), those without acid suppression therapy only had 1 out of 54 cases of cancer misdiagnosed compared to 22 of 62 who were on acid suppression therapy prior to endoscopy(160). This masking effect is more notable with proton pump inhibitors (PPIs) than with histamine 2 receptor antagonists (H2Ras)(160). Likewise, in the study by Suvakovic et al (1997), of 81 patients diagnosed with gastric cancer, 11 had an endoscopy within the three years prior to their diagnostic endoscopy, of which 9 were on symptomatic dyspepsia treatment prior to the endoscopy in which malignancy was not detected(7). This treatment was a H2 receptor antagonist alone or in combination with an antacid(7). This study by Suvakovic et al (1997) which was intended to investigate whether open access endoscopy reduced delays to diagnosis, found that open access endoscopy made no difference to delays over 5 years and one of the key reasons was attributed to prior symptomatic dyspepsia treatment with H2 receptor agonists masking malignancy by facilitating mucosal healing and making endoscopic diagnosis more difficult(7). Overall, a more rigorous

endoscopy protocol including specifications on the number and size of biopsies required and when to withhold acid suppression therapy prior could improve diagnostic accuracy of endoscopy(7).

Whilst these recommendations have been developed, there has been no formal study undertaken to investigate whether these guidelines have been adhered to or whether failure to adhere to these guidelines (delays to diagnosis or treatment) have a significant impact on treatment outcomes.

3 GAPS IN KNOWLEDGE

Overall, the following gaps in knowledge have been identified:

(1) **It is not clear as to whether delays to diagnosis impact treatment outcomes** due to the variations in definitions of delays, methodology and patient cohorts in different studies across different countries and hence the difficulty comparing them. There also has not been any studies in Australia that have evaluated delays to diagnosis and treatment of oesophagogastric cancer and its impact on treatment outcomes. This is the first project to evaluate the current Australian Guidelines for timeframes along the pathway from symptoms onset to treatment. If we find that patients who met these timeframes had better outcomes, then this would indicate that adherence to the guidelines is important. If the reverse were true, it may be an indication to reform the existing guidelines.

(2) **Causes and risk factors for delays to diagnosis are still not clear** in the literature and need to be further investigated, given that outcomes are still poor, and most are diagnosed at advanced stages. There specifically needs to be clarity around which time interval from symptom onset to treatment that the greatest delay is occurring i.e. is it the time from symptom onset to diagnosis or is it the time from diagnosis to treatment initiation that takes the longest and longer relative to the recommendations in the Australian guidelines also? Once this is known it is imperative to know which type of patient group or circumstances these delays are happening. Do demographical or personal patient factors such as gender, age etc. increase the risk of delay? Or other hospital factors such as delay in referrals, delays in endoscopy or specialist consultation? Or could it be disease factors such as tumour type, location, etc. that increases the risk of delays?

(3) **The current literature does not highlight differences in epidemiology and clinical presentation between oesophageal and gastric cancer in sufficient enough detail.** There are potentially some major differences and by identifying these differences in greater detail, we could develop a referral criteria that are separated for both oesophageal and gastric cancer and

therefore better at identifying patients with of higher risk of upper GI malignancy than the one described above.

(4) **There is presently no risk stratification tool or urgent referral criteria that satisfactorily identifies early-stage oesophageal cancers.** At present, the Australian guidelines only outline epigastric pain and progressive dysphagia for 2 weeks as an indication for urgent referral, but should these symptoms be broadened out or even changed? Several studies demonstrate low rates of cancer detection on endoscopy for those with alarm symptoms and likewise in those with chronic dyspepsia. Perhaps a combination of certain alarm symptoms and other demographic variables such as gender, age may be able to better predict early stage oesophagogastric cancer? There needs to be more studies analysing whether a combination of alarm symptoms and demographic variables such as age and gender would be better at identifying early-stage oesophagogastric cancers. There needs to be a more sensitive and specific risk prediction model for early detection of upper GI cancers.

(5) **There is a lack of reporting on the proportion of oesophagogastric cancers diagnosed via presentation to the Emergency Department as well as the risk factors for these presentations and whether they are associated with delays to diagnosis and treatment, particularly in Australia**. In other words, are patients deferring presentation to the healthcare system until their symptoms are unbearable and disease is at an advanced stage warranting emergency admission? And in what group of patients is this happening in? It is also important to determine if there are any adverse outcomes associated with patients diagnosed following emergency presentation, and how to reduce this occurrence.

(6) **Strategies to improve survival rates and outcomes in oesophagogastric cancer patients have been insufficiently reported in the literature, particularly in Australia.** Whilst we can learn lessons from the initiatives undertaken in the UK, it is important to evaluate the efficacy of existing strategies in Australia as well as identify new ways to improve survival and outcomes by reducing delays to diagnosis.

(7)

3.1 Aims & Objectives

(1) To determine if there are delays to diagnosis and treatment of oesophagogastric cancer at an Australian tertiary hospital based on the Australian guidelines

(2) To determine if delays to diagnosis and treatment have an impact on treatment outcomes

(3) To identify causes and risk factors for delays to diagnosis and treatment

(4) To better delineate the differences between oesophageal and gastric cancer

(5) To develop an improved urgent referral criteria that is separate for oesophageal and gastric cancer and therefore potentially better at detecting early-stage cancers

(6) To determine whether delays to diagnosis occur more frequently in those diagnosed via the ED route

(7) To identify the proportion of patients diagnosed via the ED route and their risk factors and outcomes.

(8) To identify ways in which delays to diagnosis and treatment can be reduced to improve early cancer detection rates.

3.2 Hypotheses

(1) A greater proportion of oesophagogastric patients will have delays to diagnosis and treatment than those without delays.

(2) Delays to diagnosis are likely to be in patients with symptoms that are tolerable for long periods of time e.g. progressive dysphagia or dyspepsia or chronic reflux. Delays to diagnosis may occur more frequently in patients with symptoms that don't fulfill the urgent referral criteria because primary care physicians will be less likely to refer them.

(3) There will be more patients with advanced stage disease and deaths in patients with delays to diagnosis and treatment than those without delays.

(4) Oesophageal cancer is likely to be more associated with dysphagia, whilst gastric cancer may be more associated with epigastric pain and constitutional symptoms due to differences in tumour location.

(5) An improved referral criteria will involve having different criteria for both oesophageal and gastric cancer that reflects differences in their clinical presentations.

(6) It is likely that a significant proportion of patients will be diagnosed via the emergency department route due to delayed patient presentation in these patients, and this may result in greater adverse outcomes than patients diagnosed following GP presentation.

(7) Delays to diagnosis are likely to occur more frequently in patients presenting via the emergency department compared with patients diagnosed following GP presentation due to tolerating symptoms for too long before they become uncomfortable enough to present to the emergency department.

(8) A combination of initiatives is required to improve early detection rates and these will likely include education of both clinicians and the public about these rare but deadly cancers in terms of symptoms and risk factors warranting early investigation as well as increasing endoscopy availability in conjunction with improving the sensitivity of the current urgent referral guidelines.

4 COMPARISON OF OESOPHAGEAL AND GASTRIC CANCER IN THE EVALUATION OF URGENT ENDOSCOPY REFERRAL CRITERIA

Published as: Kumar, L., Kholmurodova, F., Bull, J., Bright, T., Watson, D.I. and Shenfine, J. (2021), Comparison of oesophageal and gastric cancer in the evaluation of urgent endoscopy referral criteria. ANZ Journal of Surgery. https://doi.org/10.1111/ans.16984

Contributions: Dr Liana Kumar contributed to the acquisition of data, data analysis, interpretation, drafting the article and incorporating suggestions from co-authors into the final version. This overall comprises eighty percent of the total work. Dr Jon Shenfine contributed to the design of the study, supervision and making critical revisions related to important intellectual content of the manuscript. Dr Tim Bright and Prof David Watson also made critical revisions related to important intellectual content of the manuscript. Mr Jeff Bull assisted with acquisition of some of the data extracted from the database. Ms Feruza Kholmurodova assisted with statistical analysis, survival graphs and interpretation of data.

4.1 Introduction

The poor survival rates in oesophageal and gastric cancer are partly due to late presentation with already advanced stage disease(1, 2). This is despite several initiatives already undertaken including open access endoscopy, two-week wait initiative, improvisations to NICE endoscopy referral guidelines, one stop dyspepsia clinics and centralisation of services. In order to improve survival rates and outcomes, it is imperative to have a better in depth understanding of the pathogenesis, development and clinical presentation of such cancers.

Oesophageal and gastric cancer are viewed as one entity in most studies to date and most guidelines despite significant differences in tumour location, epidemiology, risk factors, clinical presentation and management. There has not been however, a dedicated study highlighting and clarifying these

differences. Many studies have found that alarm symptoms have poor positive predictive value for upper gastrointestinal (GI) cancer detection(9), but again this is in studies that mostly look at both cancers as one entity.

The current Australian national guideline titled 'Optimum care pathway for people with oesophagogastric cancer' states that patients with either: (1)rapidly progressive/new dysphagia or (2)epigastric pain for 2 weeks, must be urgently referred for endoscopy within 2 weeks. It is not clear if these symptoms are truly reflective of all oesophagogastric cancer patients and are there other symptoms that should be included in this criteria? Should we have a separate referral criteria for oesophageal cancer and for gastric cancer which reflects their differences better and therefore improve early detection rates?

4.2 Aims

The aims of this study were to: 1) highlight differences in epidemiology, clinical presentation and management between oesophageal and gastric cancer, 2) suggest new referral criteria that consider oesophageal and gastric cancer as separate entities, to better facilitate early identification of patients at higher risk of upper GI malignancy. This should ultimately help with the education of General Practitioners and referring specialists and improve earlier recognition and referral of patients with suspected upper GI cancer.

4.3 Methods

This paper was an observational cohort study of all patients with oesophageal and gastric cancer that had surgery with curative intent from February 2013 to October 2018 at a single, tertiary, specialist, oesophagogastric cancer centre in the State of South Australia: Flinders Medical Centre. This centre is a high volume centre for oesophageal and gastric cancer care in Australia(161). Exclusion criteria consisted of patients without adenocarcinoma and squamous cell carcinoma, those who underwent prophylactic gastrectomy, or palliative resections, those on a Barrett's surveillance program and those referred following a diagnosis from an external endoscopy provider.

Palliative patients are more likely to have late-stage disease at diagnosis and delays to referral irrespective of fulfilling the referral criteria and hence their exclusion is to (a) avoid bias in determining the impact of referral criteria on time to referral (b) to characterise epidemiology and symptoms of patients with curative disease and (c) to make this study as standardised as possible.

Patients who underwent prophylactic gastrectomy were usually asymptomatic and identified via genetic screening and form a very small subset of oesophagogastric cancer patients which do not contribute to delays to diagnosis which this study is focussing on, hence their exclusion.

Patients on the Barrett's surveillance program are those generally identified through chronic reflux symptoms again only forming a small proportion of patients with oesophagogastric cancer that have their own separate guidelines for screening and endoscopy and are therefore unlikely to contribute to possible delays to diagnosis that we are trying to investigate in this study. These patients were also therefore excluded for standardization purposes.

Ethics approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC).Patients were identified from a prospectively maintained database that supports a South Australian Statewide Upper GI cancer multidisciplinary team meeting which manages more than 90% of new upper GI cancer presentations in South Australia. Information from MDT meetings at Flinders Medical Centre are entered into this database. Data on dates of birth, death, age, gender, ASA status, histological subtype (adenocarcinoma vs squamous cell), dates of endoscopy, operation, and MDT were able to be extracted from this database. All remaining data for public and private patients managed by clinicians working at Flinders Medical Centre was derived from retrospective review of patient case notes and electronic records.

Information regarding the nature and onset of symptoms were largely derived from review of GP referral letters and letters of first outpatient specialist consultation filed in the patients' case notes. Date of symptom onset was defined as the date when the patient first experienced symptoms that led to the diagnosis. In the case of patients with long-standing dyspepsia, the date was taken to be the point of significant worsening in these symptoms. This date was derived from the description of duration of first symptoms described in the referral or specialist outpatient letter. For example, a GP referral letter that stated the patient had epigastric pain for 4 months would then be taken as a symptom onset 4 months prior to the date of the referral letter being written. If the patient had multiple

symptoms including epigastric pain, nausea, and weight loss, then the symptom that started first was taken as the first presenting symptom.

First presenting symptoms were categorized into dysphagia, odynophagia, dyspepsia, abdominal pain, constitutional symptoms as one category (weight loss, nausea, vomiting), and blood loss as another category (anaemia, haematemesis, melena), abdominal pain, no or other symptoms. The symptom of dyspepsia was defined as indigestion or heartburn or worsening reflux. Abdominal pain included any pain within the abdomen, including epigastric pain. Anaemia included patients who had asymptomatic iron deficiency anaemia in addition to symptomatic anaemia.

For patients who presented directly to the emergency department, description of their symptoms in terms of duration and onset was obtained through their emergency admission note or specialist consultation note.

Stage of tumour at resection was according to the TNM classification and derived from review of all patient's electronic pathology reports from diagnostic endoscopy. Classification of GOJ tumours into oesophageal and gastric were based on the consensus from MDT discussions. Variables including age, gender, location, ASA status, tumour location, stage, and histology, and first presenting symptom were compared between patients with oesophageal cancer vs gastric cancer to identify differences in epidemiology and clinical presentation.

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The percentage of patients who fulfilled urgent referral criteria in the Australian Guidelines was compared between oesophageal and gastric cancer patients. This criteria for urgent endoscopy referral involved 2 weeks of epigastric pain or progressive dysphagia. In other words, of those that fulfilled these criteria, delays to referral were defined as those with the above criteria who were not referred within 2 weeks.

Stata15.1 (StataCorp, Texas) was used for analysis. Independent t-tests, Chi square, Mann Whitney or Wilcoxon rank sum tests were used to identify risk factors for delays. P values of <0.05 were taken to be statistically significant.

4.4 Results

Comparing epidemiology and clinical features of oesophageal and gastric cancer

Of the 126 patients included in this study, 78 had oesophageal cancer and 48 had gastric cancer. The mean age of symptom onset was 68.8 years for gastric cancer and 63.9 years for oesophageal cancer patients. The mean age of diagnosis was 69.6 years for gastric cancer, compared with 64.4 years for oesophageal cancer (p=0.01).

Age of symptom onset peaks in the 60-69 age bracket for oesophageal cancer, whilst gastric cancer peaks later in the 70-79 years age group (Figure 5). Oesophageal cancer symptom onset ranged from 43 to 82 years old with an increasing incidence up to the peak age bracket and no patients younger than 40 years old when symptoms commenced. This contrasts with a less predictable range of age of symptom onset for gastric cancer, from 39 to 92 years old (Figure 5).

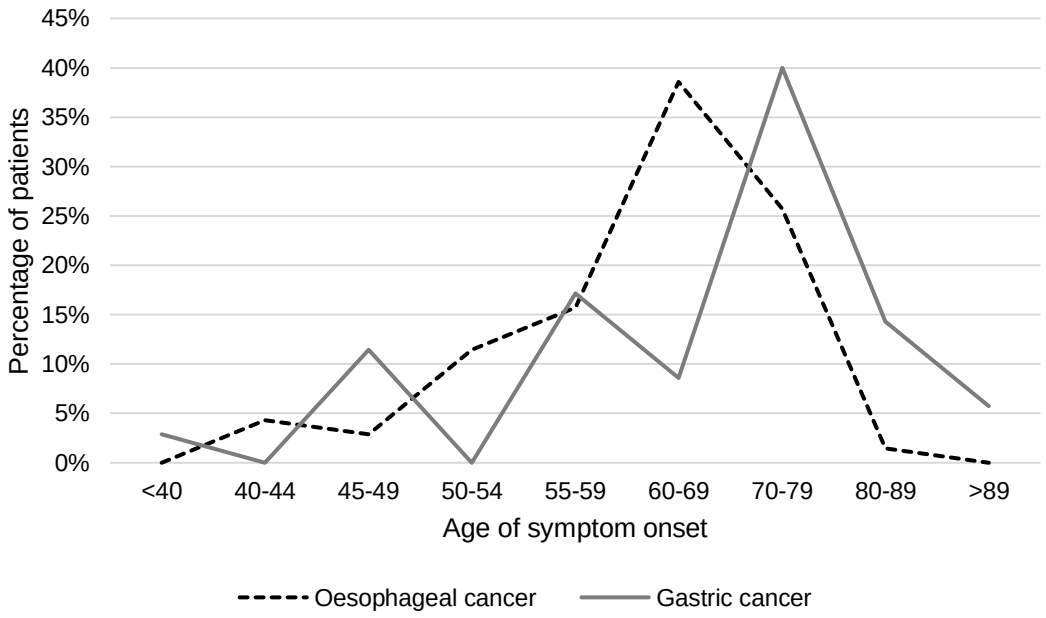


Figure 5: Comparison of age of symptom onset between oesophageal and gastric cancer patients

The male to female ratio is significantly higher for oesophageal cancer, being 6:1 compared with 2:1 for gastric cancer (p=0.01) (Table 4). Staging differed between both cancers (p=0.006), with one-

third of gastric cancer patients having stage IV disease at resection compared to 10% for oesophageal cancer.

Clinical presentation was significantly different between the two cancers (p=<0.001) (Table 4). The first symptoms or signs for gastric cancer were blood loss in 17 (36%) of which 13 had anaemia, and 4 with melena and/or haematemesis. This is followed by 6 (13%) abdominal pain, 6 (13%) dyspepsia, 5(11%) dysphagia and 3 (6%) with no or other non-specific symptoms. The first symptoms or signs for oesophageal cancer were dysphagia 46 (61%), abdominal pain 8 (11%), dyspepsia/indigestion 8 (11%), blood loss 5 (7%) which included anaemia in 2 and melaena in 3.

Table 4: Epidemiology and clinical presentation of oesophageal cancer vs gastric cancer

Characteristic	**Oesophageal cancer (n=78)**	**Gastric cancer (n=48)**	**p-value**
Age at symptom onset, mean (SD)	63.91 (9.33)	68.84 (13.13)	0.03
Age at diagnosis, mean (SD)	64.44 (9.27)	69.56 (13.31)	0.01
Gender			
Male	67 (85.9%)	32 (66.7%)	0.01
Female	11 (14.1%)	16 (33.3%)	
Location			
Rural	30 (38.5%)	12 (25.0%)	0.12
Local	48 (61.5%)	36 (75.0%)	
ASA Status			
1	7 (9.0%)	3 (6.3%)	0.38
2	38 (48.7%)	19 (39.6%)	
3	33 (42.3%)	25 (52.1%)	
4	0 (0.0%)	1 (2.1%)	
Histology			
Adenocarcinoma	68 (87.2%)	48 (100.0%)	0.01
Squamous cell carcinoma	10 (12.8%)	0 (0.0%)	
First symptom			
Dysphagia	46 (60.5%)	5 (10.6%)	<0.001
Odynophagia	4 (5.3%)	0 (0.0%)	
Dyspepsia/indigestion	8 (10.5%)	6 (12.8%)	

	Weight loss, nausea, anorexia	3 (3.9%)	10 (21.3%)	
	Anaemia, haematemesis, melena	5 (6.6%)	17 (36.2%)	
	Abdominal pain	8 (10.5%)	6 (12.6%)	
	No symptoms	1 (1.3%)	2 (4.3%)	
	Other	1 (1.3%)	1 (2.1%)	
Stage				
	I	34 (43.5%)	15 (33.3%)	0.006
	II	6 (7.69%)	7 (15.6%)	
	III	30 (38.5%)	9 (20.0%)	
	IV	8 (10.3%)	14 (31.1%)	

Of the gastric cancers, 22 were in the gastric antrum, 19 in the body and 7 in the cardia. This can be classified as 41 (85%) in the non-cardia region and 7 (15%) cardia region. For oesophageal cancers, 45 were in the distal oesophagus, 23 at the gastro-oesophageal junction (GOJ), 1 in the cardia, 5 in the mid oesophagus, and none in the upper oesophagus and 4 elsewhere unspecified. Overall, 80% of oesophageal cancers were therefore in the lower third (namely GOJ, cardia and distal third of oesophagus) (Figure 6).

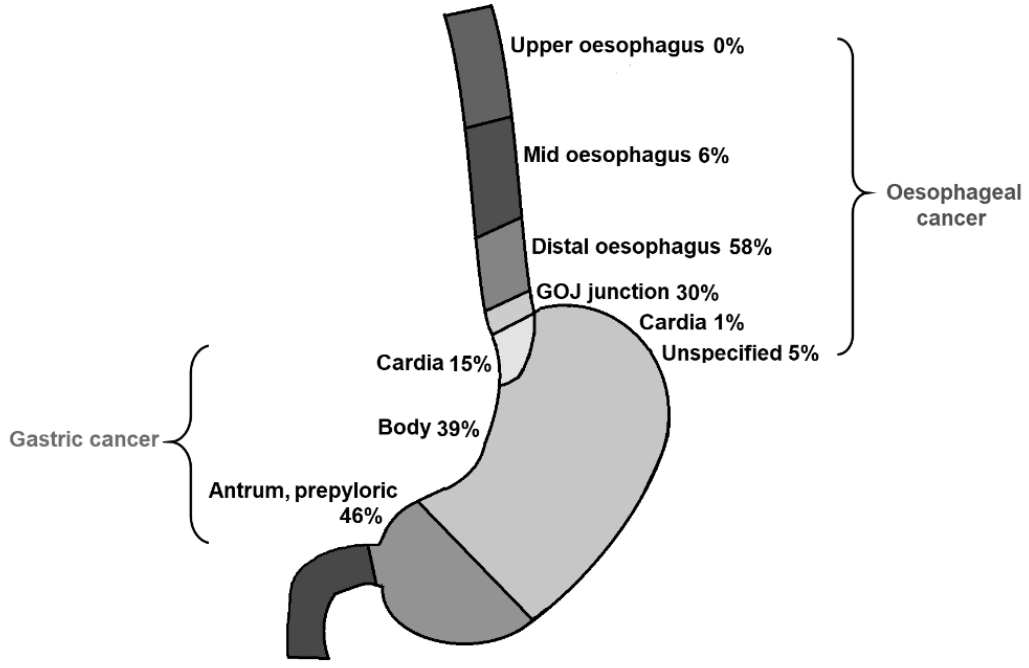


Figure 6: Tumour location of oesophageal and gastric cancer

Evaluation of the urgent referral criteria

Based on a recommended referral timeframe of 2 weeks from symptom onset the majority of patients had delays to referral. In oesophageal cancer patients, 74% (40 patients) had delayed referral; in gastric cancer patients, 54% (7 patients) had a delayed referral. A greater proportion of patients (76%) with oesophageal cancer fulfilled the urgent referral criteria compared with only 33% of gastric cancer patients (Table 5). Patients that fulfilled the urgent referral criteria for oesophageal cancer had a median duration of 10 weeks from symptom onset to referral (Table 6), which was longer than those who did not fulfill the urgent referral criteria (4 weeks). Similarly, patients that fulfilled the urgent referral criteria for gastric cancer had longer delay than those who did not fulfil the referral criteria, median 13 weeks compared to 8 weeks from symptom onset to referral.

Table 5:Sensitivity of urgent referral criteria in oesophageal cancer vs gastric cancer patients

	Oesophageal cancer, n=78	Gastric cancer, n=48	p-value
Patients who fulfilled the urgent referral criteria	58 (76%)	15 (33%)	<0.001
Patients who didn't fulfill the urgent referral criteria	18 (24%)	30 (67%)	

Table 6: Impact of urgent referral criteria on delays to referral and diagnosis in oesophageal cancer vs gastric cancer patients

	Median weeks from symptom onset to referral		
	Oesophageal cancer, n=78	Gastric cancer, n=78	p-value
Patients who fulfilled the urgent referral criteria	10 (4, 19)	13 (3, 20)	0.66
Patients who didn't fulfill the urgent referral criteria	4 (1, 17.5)	8 (1, 24)	0.40

4.5 Discussion

Statement of principal findings

The study confirms the median age of 64.4 for symptom onset for oesophageal cancer with no oesophageal cancer cases seen below 43 years. This is consistent with the several other epidemiological studies (16, 66, 90, 91). In contrast, gastric cancer peaked in the older 70-79 age group, with a median age of 69.6 years, and appears more unpredictable in age onset, with one case occurring in the third decade. This is significantly lower than two studies involving Caucasian patients (16, 94), and two studies with Asian patients (81, 91) which report a median age of late 50s to early 60s.

The fact that no oesophageal cancer cases were seen below the age of 43 would favour the idea of including an age cut off of 40 years old in the urgent referral criteria. This proposition however is challenged by the variability of age of diagnosis reported in several studies, including cases younger than 40 (Table 1). This variability is seen particularly between different continents due to differences in their predominant risk factors for cancer development. In Asian countries, oesophageal cancers largely include squamous cell carcinomas of which major risk factors are smoking and alcohol(95). In European countries oesophageal cancers are mostly the adenocarcinoma subtype largely due to risk factors of obesity and reflux(95). The time from risk factor onset to development of malignancy is likely different for each risk factor and therefore has an influence on age of diagnosis. The systematic review by De Jong evaluated the impact of age limits on detection of oesophagogastric cancer and found this intercontinental inequality in age of cancer onset(95). It recommended continent-specific age limits to improve the yield of upper gastrointestinal malignancy, that involved cut offs of age 40 in Africa, age 50 in Asia, and age 55 in Europe(95). In terms of the Australian guidelines, further studies would be needed in different Australian cohorts to further determine if an age cut off would be recommended.

Oesophageal cancer has a much higher male:female ratio of 6:1 compared to gastric cancer (2:1). This is comparable to other studies reporting high male:female ratios of 6:1(122), 10:1(16), 3.2:1(14), 2.7:1(91) and 2.5:1(66) for oesophageal cancer and lower ratios for gastric cancer of 1.1:1(89), 1.6:1(7), 2:1(16), 2.1:1(94) and 1.3:1(91). One reason for the higher male prevalence in oesophagogastric cancer may be the higher rates of erosive reflux in men(84) which is a stronger risk factor for oesophageal cancer than non-erosive reflux(87). The other reason may be the possible protective effect of oestrogen mediated through oestrogen receptors within oesophageal

cancers(87). More studies are needed to confirm the above theories. Whether men should be referred for endoscopy as part of the separate urgent referral criteria for oesophageal cancer, requires further research. Nonetheless, awareness of this significantly higher male prevalence in oesophageal cancer can help sharpen its recognition in clinical practice.

Whilst non-cardia cancers have always been more prevalent than cardia cancers, as demonstrated in this study (82%), the proportion of cardia vs non-cardia cancers reported vary depending on geographical location of the study (162). In studies from China, Iran and Japan the lower third of the stomach has the greatest proportion of tumours (81, 122) and cardia the least (82). In these areas, the higher use of pickled foods (163, 164) and persistent rates of H pylori are associated with non-cardia gastric cancer (24). European studies on the contrary report a higher proportion of tumours in the upper gastric or cardia region, at 66%, 53% and 30% (7, 16, 88). There has been an increase in cardia gastric cancer in from 33% to 53% over a 10-year period (1993 to 2003)(16). These changes are thought to be associated with changes in lifestyle, rising rates of reflux and increasing prevalence of obesity.

In this study, 87% of oesophageal cancer patients had adenocarcinoma, and the remaining were squamous cell carcinoma. This is similar to other UK studies which report between 70-75% (66) of oesophageal cancers are adenocarcinoma. In contrast, studies from China and India report reversed ratios, with 70-89% having squamous cancers and 7.5-29% adenocarcinoma (14, 69). Again, the higher prevalence of adenocarcinoma in Western countries is thought to be related to lifestyle factors, obesity, and reflux, and lower rates of squamous carcinoma correlating with lower smoking rates, achieved through years of public campaigning. Higher rates of squamous cell carcinoma in Asian countries could be partly due to persistent risk factors such as alcohol consumption, tobacco smoking, hot beverage drinking and poor nutrition(165). Comparison studies between Western and Asian populations however is lacking and is yet to be addressed(165). Furthermore, the reason for the significantly greater proportion of squamous cell carcinomas in oesophageal cancer compared to gastric cancer also needs further research.

Dysphagia is significantly more common in oesophageal cancer (61%). Most oesophageal tumours were located at the gastro-oesophageal junction or in the distal oesophagus (80%) in keeping with the higher proportion of adenocarcinoma. This is also where the lumen is narrower and less

compliant, and therefore dysphagia is more likely to manifest when the disease is locally advanced. Several studies on oesophageal cancer patients have reported high rates of dysphagia as a first presenting symptom, including 100%(69), 71%(14), 50%(16, 122). Studies that combine oesophageal and gastric cancers understandably report lower rates of dysphagia, including 24%(88), 12%(120), likely due to the lack of dysphagia in gastric cancer skewing the data. Dysphagia was only present in 11% of gastric cancer patients in this study. Given the high prevalence of dysphagia in oesophageal cancer and its indication of locally advanced disease, this should be included as a symptom in a separate urgent referral guideline for suspected oesophageal cancer patients only.

Gastric cancer presents with many non-specific symptoms including blood loss (35%), nausea, weight loss and anorexia (21%), making detection harder. This may explain the greater proportion of stage IV disease at resection (31%) for gastric cancer patients compared to oesophageal cancer patients (10%) ($p=0.006$) although this may also be skewed by more detailed selection criteria and investigations for surgical resection between these pathologies. The current urgent referral criteria for endoscopy includes epigastric pain, supported by a few studies where epigastric pain was a common presenting symptom of gastric cancer: occurring in 52-75%(89, 101). However, there are many other studies where epigastric pain is reported less commonly at rates of 31%(14), 32%(11) and 44%(81) and having no significant difference in rates when compared to symptoms of weight loss, GI bleeding, anorexia or fatigue(94). No one symptom stands out for gastric cancer. Nevertheless, epigastric pain in this study only occurred in 13% of gastric cancer patients, suggesting that it is of poor diagnostic accuracy and should not form part of the urgent referral criteria.

Part of the difficulty in diagnosis is the location of tumours away from the less compliant gastro-oesophageal junction, within the larger stomach cavity (82%). Considerable growth in tumour size would be needed before causing dysphagia from luminal narrowing, dyspepsia from disruption to the gastro-oesophageal junction pressure gradient, or abdominal pain from compressing other structures or invasion of local structures. However, release of inflammatory cytokines from gastric cancer can cause nausea, weight loss and anorexia and the presence of a highly vascular tumour in a strongly acidic environment is associated with friability and ulceration, with consequent

associated blood loss even in early stages. Early signs would include occult blood loss (anaemia) and constitutional symptoms (nausea, anorexia, weight loss) whilst later signs would be epigastric pain, dyspepsia, and dysphagia. Therefore, blood loss and a combination of nausea, anorexia and weight loss are recommended to be included as symptoms in a separate urgent referral recommendation for gastric cancer.

The Australian urgent referral criteria for oesophagogastric cancers specify new/progressive dysphagia or new/progressive epigastric pain for two weeks as warranting urgent specialist referral within 2 weeks of onset. In this study, these criteria had an 76% sensitivity for oesophageal cancer due to the high proportion of patients presenting primarily with dysphagia (61%). On the contrary, the majority of patients with gastric cancer had symptoms which did not fulfill these urgent referral criteria (67% vs. 33%), including blood loss (37%) and constitutional symptoms (27%). This suggests that these criteria would be better separated between these two very different upper gastrointestinal cancers for gastric cancer utilising blood loss (anaemia, haematemesis and melaena) as one defining criteria and constitutional symptoms such as nausea, weight loss and anorexia being more common between the cancers.

Despite a high proportion of oesophageal cancer patients who fulfilled the referral criteria (76%), delays to referral were still present in 75% of oesophageal cancer patients. This suggests that general practitioners (GPs) and referring doctors need to be educated more about the criteria and the importance of urgent endoscopy referral in any patient presenting with progressive dysphagia. This point needs greater emphasis in the training curriculum for medical students, junior doctors, and primary care trainees. Although it may also transpire that patients with dysphagia present late as they do not connect dysphagia with cancer and are willing to tolerate this symptom until it either limits oral intake or becomes uncomfortable. Public health campaigns are needed to raise awareness amongst the community about dysphagia as a symptom of oesophageal cancer to reduce delays to referral.

4.6 Conclusion

This findings from this chapter clearly indicates that oesophageal cancer and gastric cancer are very different in terms of epidemiology and clinical features. These include differences in (1) age, (2) gender ratios, (3), histological subtypes, (4) tumour locations, (5) presenting symptoms and (6) stage at resection. Oesophageal cancer has a median age of 65 years old, a much higher male to female ratio of 6:1, most tumours located in the gastroesophageal junction or distal oesophagus (80%), and largely presents with dysphagia (61%). Gastric cancer has a much more unpredictable age trend, peaking at 70 years old, presenting largely with blood loss or constitutional symptoms, and having a greater proportion of patients with stage VI disease at resection (31%). Such a spectrum of differences between both cancers reflects disparities in surrounding structures and pattern of dissemination. This clearly indicates the need for separate referral guidelines for both cancers being treated as separate entities.

With application of the current referral guidelines in this study, most patients with oesophageal cancer (76%) had fulfilled the urgent referral criteria compared to only 33% of gastric cancer patients. The urgent referral criteria appropriately include dysphagia as reflected by the large proportion of oesophageal cancer patients with this symptom (61%). The referral criteria however needs to also include gastrointestinal blood loss (anaemia, haematemesis or melena) as one criteria and vague constitutional symptoms of nausea, weight loss and anorexia as another criteria in order to detect more gastric cancer patients. Epigastric pain may be excluded as it is not as prominent a symptom of either cancer. These changes to the urgent referral criteria could improve early detection rates. GPs, trainees, and the public should be educated about these rare but deadly cancers.

5 DELAYS TO DIAGNOSIS AND TREATMENT OF OESOPHAGEAL AND GASTRIC CANCER AND ITS IMPACT ON TREATMENT OUTCOMES

Contributions: Dr Liana Kumar contributed to the acquisition of data, data analysis, interpretation, drafting the article and incorporating suggestions from co-authors into the final version. This overall comprises eighty percent of the total work. Dr Jon Shenfine contributed to the design of the study, supervision and making critical revisions related to important intellectual content of the manuscript. Dr Tim Bright and Prof David Watson also made critical revisions related to important intellectual content of the manuscript. Mr Jeff Bull assisted with acquisition of some of the data extracted from the database. Ms Feruza Kholmurodova assisted with statistical analysis, survival graphs and interpretation of data.

5.1 Introduction

Oesophageal and gastric carcinoma are the sixth and second leading cause of cancer-related mortality worldwide respectively. It is therefore incumbent that more be done to improve adverse outcomes. Although there have been mixed conclusions from studies investigating associations between time to diagnosis and adverse outcomes in oesophagogastric cancer, it is obvious that if time between first symptom onset to diagnosis and from diagnosis to treatment exceeds a certain duration, then adverse outcomes will ensue. The question then is what the optimum timeframes should be to prevent this?

This study focuses on the timeframes outlined in the Australian guidelines ‘Optimal care pathway for people with oesophagogastric cancer’ published in 2016, in which the timeline from first symptoms to diagnosis and treatment are separated into multiple stages: (1) First symptoms to presentation to a general practitioner (GP); (2) Referral for endoscopy; (3) Upper gastrointestinal (GI) specialist appointment; (4) Multidisciplinary (MDT) meeting; and (5) Treatment initiation. According to the guidelines, each stage must be met within 2 weeks. This sets a benchmark for what constitutes a

delay in Australia. There have not been any studies to date evaluating this guideline in terms of adherence to it, as well as if there is a greater occurrence of adverse outcomes for patients where delays occurred. This is the first study to evaluate adherence to the timeframes outlined in the Australian guidelines and use it to define, determine and investigate delays to diagnosis and treatment and its effect on outcomes.

5.2 Aims

The aims of this study were to 1) assess whether these Australian standards are being met in oesophageal and gastric cancer patients managed surgically at Flinders Medical Centre, 2) to identify whether there were any delays in diagnosis and treatment, 3) to determine whether delays impacted outcomes and 4) determine what factors may be causing these delays.

5.3 Methods

This was an observational cohort study of patients with oesophageal and gastric cancer who had surgery with curative intent at Flinders Medical Centre: a single, tertiary, specialist, oesophageal and gastric cancer centre, from the period of February 2013 to October 2018.

Exclusion criteria consisted of patients on a Barrett's oesophagus surveillance program, those who underwent prophylactic gastrectomy for known genetic CDH1 gene mutations, or palliative resections, and those without adenocarcinoma and squamous cell carcinoma. Determination of risk factors and adverse outcomes from delays to diagnosis requires a comparison between patients with delays to diagnosis and patients without delays to diagnosis.

Data for private and public patients managed by clinicians working at Flinders Medical Centre was derived from review of clinical records. Patients were selected from a prospectively maintained database that supports a South Australian Statewide oesophageal and gastric cancer multidisciplinary team meeting which discusses over 90% of new oesophageal and gastric cancer presentations in South Australia. Ethics approval was obtained from the Southern Adelaide Clinical

Human Research Ethics Committee (SAC HREC). The duration of time from symptom onset to treatment initiation in weeks were recorded at these time intervals:

(1) Symptom onset to initial referral to healthcare system (from general practitioner or hospital)
(2) Referral to healthcare system for endoscopy (resulting in histological diagnosis)
(3) Endoscopy to upper gastrointestinal (GI) specialist consultation
(4) Upper GI specialist consultation to first multidisciplinary meeting (MDT)
(5) First MDT to treatment initiation (date of first neoadjuvant therapy session or date of surgery)

The above intervals, demographics and outcome variables were compared between the following groups: (1) delays to diagnosis vs no delays to diagnosis, (2) delays to treatment vs no delays to treatment.

Delays were defined by the Australian national guidelines titled 'Optimal care pathway for people with oesophagogastric cancer' which states that the duration of each time interval must not exceed 2 weeks. And overall, delay to diagnosis and treatment was defined as exceeding 4 weeks and 8 weeks from symptom onset to histological diagnosis respectively. Date of symptom onset was defined as the date when the patient first experienced symptoms that led to the diagnosis. For patients with long-standing dyspepsia, this date was recorded as the point of significant change in these symptoms.

Date of histological diagnosis was defined as the date of the endoscopy from which the histology first showed upper GI cancer. This value does not include the time taken for histological confirmation by pathologist.

Date of treatment initiation was reported as the date of the first session of neoadjuvant therapy commencing in those patients who had neoadjuvant therapy. In those without neoadjuvant therapy, treatment initiation was reported as the date of surgery.

Tumour location was classified by surgeons at the MDT meetings based on the consensus on approach to treatment. Staging was defined by the TNM classification system and defined from

histological report from resected specimens. Late-stage disease was defined as patients with disease stage II, III or IV.

Post-operative complications were classified as general, local (specific to wound or surgical site), both or none. General complications included cardiac complications (rapid atrial fibrillation, bradycardia), respiratory complications (pneumothorax, atelectasis, pleural effusion, hospital acquired pneumonia), sepsis, delirium, deep vein thrombosis, electrolyte disturbances, urinary tract infections, post-operative ileus, and small bowel obstructions. Local complications include anastomotic leak, chyle leak, recurrent laryngeal nerve palsy, dumping syndrome, oesophageal stricture, wound infections, splenic infarct, diaphragmatic herniation, and conversion from minimally invasive approach to open surgery.

Number of total and positive lymph nodes resected were derived from review of surgical specimen pathology reports and the number of patients with a positive to negative lymph node ratio of >0.20 was calculated from this.

Overall survival was defined as duration from date of symptom onset to date of death or date at which data collection commenced (for those that were still alive at the time of the study). Survival post resection was defined as duration from date of surgery to date of death or date at which data collection commenced. Both durations were reported in weeks.

Using Stata15.1 (StataCorp, Texas) software, independent t-tests, Chi square, Mann Whitney and Wilcoxon rank sum tests were used to identify risk factors for delays. The Kaplan Meyer survival curve was presented using survival from date of diagnosis to date of death. Statistical review was performed by a biomedical statistician. $P < 0.05$ was considered statistically significant.

5.4 Results

Demographics

A total of 126 patients were included in this study, 78 with oesophageal cancer and 48 gastric cancer. The median age of the patients when they first developed symptoms was 66 years (range from 39

to 92 years). There were 99 (78.6%) men and 27 (21.4%) women, giving a male to female ratio of 4:1.

First presenting symptom

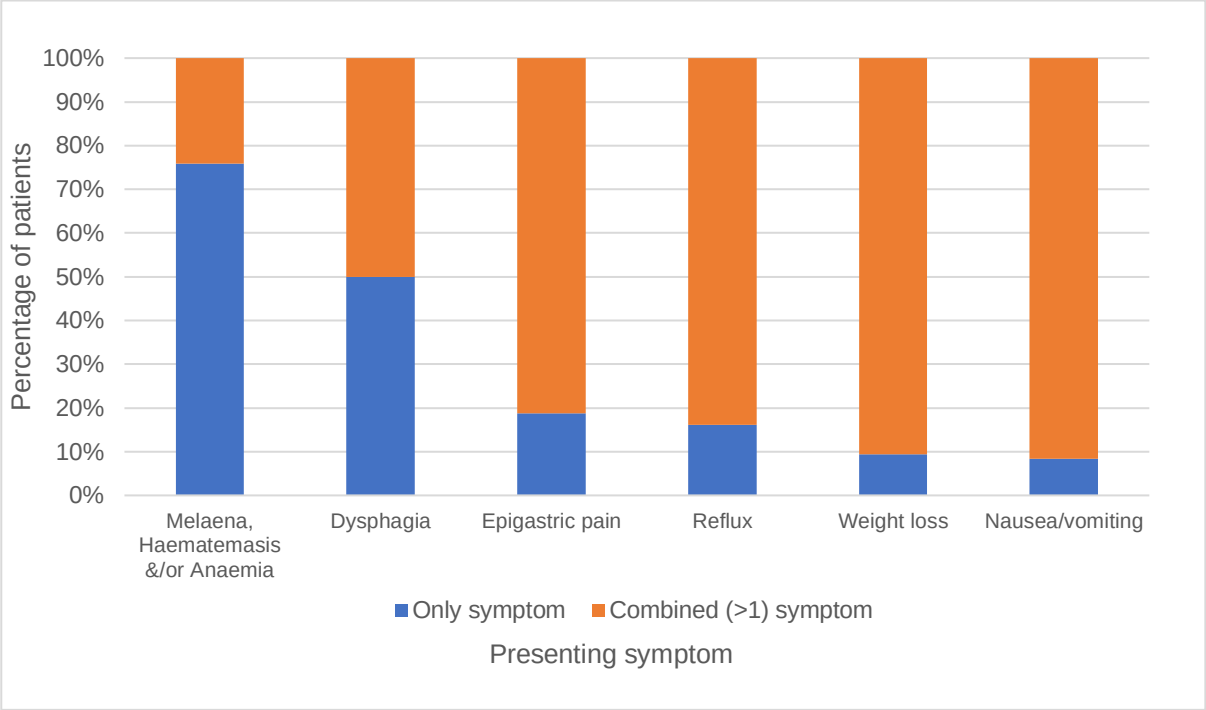
The first symptoms leading to presentation to a General Practitioner (GP) or Emergency Department (ED) were dysphagia in 51 (41.5%) followed by blood loss (anaemia, haematemesis, melaena) in 22 (17.9%), dyspepsia/reflux in 14 (11.4%), epigastric pain in 14 (11.4%), weight loss, nausea, anorexia in 13 (10.6%), odynophagia in 4 (3.3%), no symptoms in 3 (2.4%) and 2 (1.6%) with other nonspecific uncategorised symptoms. Of the 22 patients presenting with blood loss, this included 15 with anaemia and 7 with melaena or haematemesis.

Frequency of symptoms at presentation

Many patients had more than one symptom at the time of presentation. In terms of frequency of these symptoms at the time of presentation, dysphagia occurred in 58 (44%), blood loss in 29 (23%), weight loss in 32 (25%), reflux 31 (25%), epigastric pain in 26 (21%), and nausea/vomiting in 12 (9.5%).

For the 58 patients who presented with dysphagia, half had this as their only symptom on presentation. For the 29 patients who presented with blood loss, 22 (76%) had this as their only symptom on presentation. Each of the other symptoms mostly occurred in combination with each other, and rarely in isolation as demonstrated in Figure 7.

Figure 7: Comparison of each symptom of oesophageal and gastric cancer in terms of prevalence in isolation vs with other symptoms on presentation, n=123



Other characteristics

At least one third of patients were from rural areas. Most cancers were in the distal oesophagus 45 (36%) and gastroesophageal junction 26 (20%). The histological subtypes included 116 (92.1%) with adenocarcinoma and 10 (7.9%) being squamous cell carcinoma.

Delays to diagnosis and treatment

Of 104 patients, in whom there was an accurate symptom onset date, 91 (87.5%) had a delay to diagnosis. Of 98 patients, in whom there was an accurate treatment onset date, 91 (93%) had a delay to treatment. The median duration from onset of symptoms to definitive histological diagnosis was 12.5 weeks (7-27.5 weeks) for all patients, of which 8.5 weeks (3-21.5 weeks) was from symptom onset to referral. The other time intervals did not exceed 3 weeks. Therefore, duration from symptom onset to referral accounts for 68% of the total time to diagnosis.

Oesophageal cancer patients had significantly longer median delays in the interval from first MDT to treatment initiation (3 vs 2 weeks, p=0.001, Table 7) and a significantly greater proportion of patients had delays for this interval (72% vs 46%, p=0.004, Table 8) when compared to gastric cancer.

Table 7. Median (interquartile range) duration from first symptoms to treatment in weeks.

Time interval	All patients (n = 126)	Oesophageal cancer (n = 78)	Gastric cancer (n = 48)	p-value
From symptom onset to referral to healthcare system	8.5 (3, 21.5)	9 (4, 19)	8 (3, 24)	0.72
From referral to healthcare system to endoscopy	3 (0, 7)	3.5 (1, 7)	3 (0, 6)	0.56
From endoscopy to Upper GI OPD	1 (0, 2)	1 (0, 2)	1 (0, 1)	0.26
From Upper GI OPD to MDT	1 (0, 2)	1 (0, 2)	1 (1, 2)	0.83
From MDT to treatment initiation	3 (1, 4)	3 (2, 4)	2 (1, 3)	0.001
From MDT to neoadjuvant therapy	3 (2, 4)	3 (2, 4)	3 (1, 4)	0.17
From MDT to surgery without neoadjuvant therapy	1 (1, 3)	2.5 (1, 11.5)	1 (1, 3)	0.24
From symptom onset to diagnosis	12.5 (7, 27.5)	12 (8, 28)	13 (5, 25)	0.29
From symptom onset and treatment initiation	18 (12, 34)	18 (13, 38)	16 (9, 31)	0.12

Table 8: Number (percentage) of patients with delays at each time interval.

Time interval	Total (n=126)	Oesophageal cancer (n=78)	Gastric cancer (n=48)	p-value
From symptom onset to referral to healthcare system	71 (69.6%)	48 (71%)	23 (68%)	0.76
From referral to healthcare system to endoscopy	61 (59.2%)	41 (62%)	20 (54%)	0.42
From endoscopy to Upper GI OPD	20 (16.8%)	13 (17%)	7 (16%)	0.84
From Upper GI OPD to MDT	32 (26.9%)	19 (25%)	13 (30%)	0.62
From MDT to treatment initiation	73 (61.3%)	51 (72%)	22 (46%)	0.004
From MDT to neoadjuvant therapy	62 (70%)	48 (74%)	14 (61%)	0.24
From MDT to surgery without neoadjuvant therapy	14 (45%)	5 (63%)	9 (39%)	0.25
From symptom onset to diagnosis	91 (87.5%)	63 (91%)	28 (80%)	0.10
From Symptom onset and treatment initiation	91 (93%)	61 (97%)	30 (86%)	0.04

Risk factors for delays to diagnosis

The variables identified as significant risk factors for delay to diagnosis include the first presenting symptom (p=0.002) and tumour location (p=0.05) with borderline significance as shown in Table 9.

In terms of first presenting symptom of those with a delay to diagnosis, 46 (51%) had dysphagia whilst only 8 (9%) presented with anaemia, haematemesis or melaena. Conversely, of those without a delay to diagnosis, only 2 (15%) had dysphagia, whilst 7 (54%) had anaemia, haematemesis or melena. Almost all patients with dysphagia (46 out of 48) had a delay to diagnosis and median time to diagnosis was longer when dysphagia (13 weeks) was the initial presenting symptom compared to anaemia, haematemesis and melaena (7 weeks respectively). All other presenting symptoms did not differ much in frequency between those with and without delays and in terms of duration from symptom onset to diagnosis (Table 10).

Tumour location had borderline significance as a risk factor for delays to diagnosis. Those with delays to diagnosis has a much higher proportion of cancers in the GOJ compared to those without delays to diagnosis (22% vs 8%, p=0.05). On the contrary, those with delays to diagnosis had a much lower proportion of cancers in the body and antrum compared to those without delays to diagnosis (11% and 8% vs 16% and 31% respectively, p=0.05).

Table 9: Risk factors for delays to diagnosis

Characteristics	No Delay (n = 13)	Delay >4 weeks (n= 91)	p-value
Age	72.3 (12.0)*	65.6 (10.9)	0.12
Gender			
Male	10 (77%)^	74 (81%)	0.71
Female	3 (23%)	17 (19%)	
Location			
Rural	5 (38%)	32 (35%)	0.82
Local	8 (62%)	59 (65%)	
Type of cancer			
Oesophageal cancer	6 (46%)	63 (69%)	0.10
Gastric cancer	7 (54%)	28 (31%)	
ASA Status			
1	1 (8%)	8 (9%)	0.68
2	4 (31%)	42 (46%)	
3	8 (62%)	40 (44%)	
4	0 (0%)	1 (1%)	
First symptom			
Dysphagia	2 (15%)	46 (51%)	0.002[a]
Odynophagia	0 (0%)	4 (4%)	
Dyspepsia/indigestion	1 (8%)	9 (10%)	
Weight loss, nausea, anorexia	2 (15%)	10 (11%)	
Anaemia, haematemesis, melena	7 (54%)	8 (9%)	
Abdominal pain	1 (8%)	12 (13%)	
Other	0 (0%)	2 (2%)	
Histology			
Adenocarcinoma	13 (100%)	81 (89%)	0.21
Squamous cell carcinoma (SCC)	0 (0%)	10 (11%)	
Tumour location			
Cardia	1 (8%)	7 (8%)	0.05[b]
Body	2 (16%)	10 (11%)	
Antrum	4 (31%)	7 (8%)	
Prepyloric	0 (0%)	2 (2%)	
GOJ	1 (8%)	20 (22%)	
Upper oesophagus	0 (0%)	0 (0%)	
Middle oesophagus	0 (0%)	4 (4%)	
Distal oesophagus	5 (38%)	37 (41%)	
Undetermined	0 (0%)	4 (4%)	

*Age expressed as mean (and standard deviation), ^The remaining variables expressed as number (and percentage)

Table 10. Relationship between duration of time to diagnosis and patient characteristics.

Characteristic	No	Median weeks from symptom onset to diagnosis	P-value
Age			
<60	36	11.9 (6.1, 20.7)~	0.64
60-75	57	13.8 (8.0, 29.1)	
>75	33	10.7 (6.3, 32.3)	
Gender			
Male	99	12.9 (7.4, 27.8)	0.68
Female	27	13.9 (6.0, 27.4)	
Location			
Rural	42	14.6 (8.6, 36.3)	0.62
Local	84	12.1 (6.7, 27.1)	
Type of cancer			
Oesophageal	78	12.7 (8.0, 28.4)	0.27
Gastric	48	13.1 (5.6, 25.7)	
ASA Status			
1&2	67	12.1 (7.3, 25.7)	0.79
3&4	59	13.1 (7.3, 35.0)	
First Symptom			
Dysphagia	51	12.9 (8.6, 27.1)	0.12
Odynophagia	4	18.2 (9.4, 37.4)	
Dyspepsia/indigestion	14	12.5 (7.4, 50.1)	
Weight loss/anorexia/night sweats	13	17.1 (5.9, 31.1)	
Haematemesis/melaena/anaemia	22	6.6 (1.6, 24.9)	
Abdominal pain	14	15.7 (10.6, 25.7)	
None/other/unknown	8	60.4 (42.3, 78.6)	
Histology			
Adenocarcinoma	116	12.1 (6.7, 27.1)	0.13
SCC	10	20.4 (12.0, 50.1)	
Tumour location			
Cardia	8	16.7 (6.4, 23.2)	0.86
Body	17	8.6 (5.0, 29.9)	
Antrum-prepyloric	21	8.6 (2.9, 29.6)	
GOJ	26	13.6 (10.7, 25.9)	
Distal/middle oesophagus	50	13.4 (7.4, 29.1)	
Other	4	8.8 (8.0, 56.4)	

~All variables expressed as median (and interquartile range)

Impact of delays on treatment and Outcomes

Of all patients, 49 (39.8%) had early-stage disease (stage I disease) whilst 74 (60.2%) had locally advanced disease (stage II – IV disease). Patients with delays to diagnosis and treatment did not have a significantly higher proportion of late-stage disease than those without delays (p=0.53).

Post-operative complications occurred in 78 (61.9%) patients, of which 38 (30.2%) had general complications, 16 (12.7%) had local complications, and 24 (19.0%) had both local and general complications. There was no significant difference in post-operative complication rates between those with delays to diagnosis and treatment vs without delays.

The median duration of follow-up was 3.68 years (IQR 2.24 to 5.28 years). The median duration of survival post resection was 1.32 years (IQR 0.7 to 2.4 years). The overall mortality rate was 32.5% (41 of 126 patients). Of all deaths, 68% occurred within the first 2 years following diagnosis and all occurred within 5 years of diagnosis (Figure 8).

No outcome markers were significantly associated with delays to diagnosis and treatment (Table 11) or time from symptom onset to diagnosis (Table 12), including survival (Figure 8 and Figure 9).

Table 11: Outcomes of patients with delays to diagnosis compared to those without delays

Characteristics	No Delay (n = 13)	Delay >4 weeks (n= 91)	p-value
Post-operative complications			
General	5 (38%)	26 (29%)	0.68
Local	2 (15%)	9 (10%)	
Both	3 (23%)	20 (22%)	
None	3 (23%)	36 (40%)	
Stage			
I	2 (18%)	36 (40%)	0.53
II	2 (18%)	9 (10%)	
III	5 (45%)	31 (34%)	
IV	2 (18%)	15 (16%)	
Deceased			
Yes	5 (38%)	34 (37%)	0.94
No	8 (62%)	57 (63%)	
Overall 5-year survival			
Yes	0 (0%)	11 (24%)	0.21
No	5 (100%)	34 (76%)	
30-day mortality			
Yes	1 (8%)	1 (1%)	0.11
No	12 (92%)	90 (99%)	
Duration of survival post resection[1]	614 (474, 1282)	418 (259, 850)	0.40
Overall survival, mean (SD)[2]	233.7 (70.0)	245.9 (93.3)	0.65
No with +ve LN			
Yes	3 (25%)	44 (48%)	0.13
No	9 (75%)	47 (52%)	
No with LN +Ve ratio ≥0.20			
Yes	9 (75%)	70 (77%)	0.88
No	3 (25%)	21 (23%)	
No with LN +ve ≥4			
Yes	9 (75%)	73 (80%)	0.67
No	3 (25%)	18 (20%)	
Neoadjuvant chemotherapy			
Yes	72 (92%)	23 (48%)	<0.001
No	6 (8%)	25 (52%)	

[1] Duration expressed in days as median (and interquartile range). [2.] Duration expressed in days as mean (and standard deviation)

Table 12. Relationship between duration of time to diagnosis and treatment outcomes

Characteristic	No	Median weeks from symptom onset to diagnosis	p-value
Post-operative complications			
Local	38	11.3 (6.1, 24.1)[1]	0.18
General	16	9.3 (5.4, 20.3)	
Both	24	14.3 (6.6, 30.6)	
None	48	17.9 (9.1, 51.4)	
Stage			
I and II	62	13.6 (7.4, 25.9)	0.57
III and IV	61	12.1 (6.7, 29.6)	
Deceased			
Yes	41	12.1 (7.3, 24.9)	0.67
No	85	13.1 (7.3, 29.6)	
Overall 5-year survival			
Yes	14	51.1 (12.0, 62.6)	0.03[a]
No	41	12.1 (7.3, 24.9)	
30-day mortality			
Yes	3	4.9 (1.3, 8.6)	0.12
No	123	13.1 (7.3, 28.4)	
Positive (+ve) LN			
No	62	13.1 (7.4, 25.7)	0.75
Yes	63	12.6 (6.4, 30.1)	
LN +Ve ratio >20			
No	98	14.3 (7.3, 29.6)	0.30
Yes	27	11.0 (7.0, 18.2)	
LN +ve>4	N		
No	101	15.0 (7.3, 29.1)	0.28
Yes	24	10.1 (7.3, 14.0)	

[1]Duration of time expressed as median (and interquartile range)

Figure 8: Percentage of deaths at each time interval following diagnosis as a proportion of total deaths across the whole study period

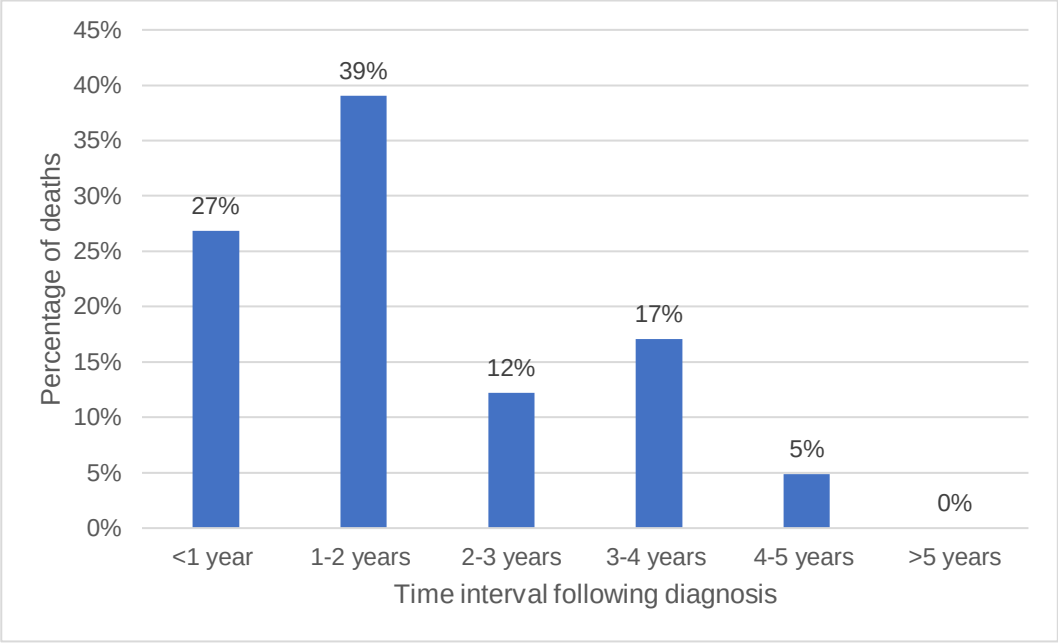
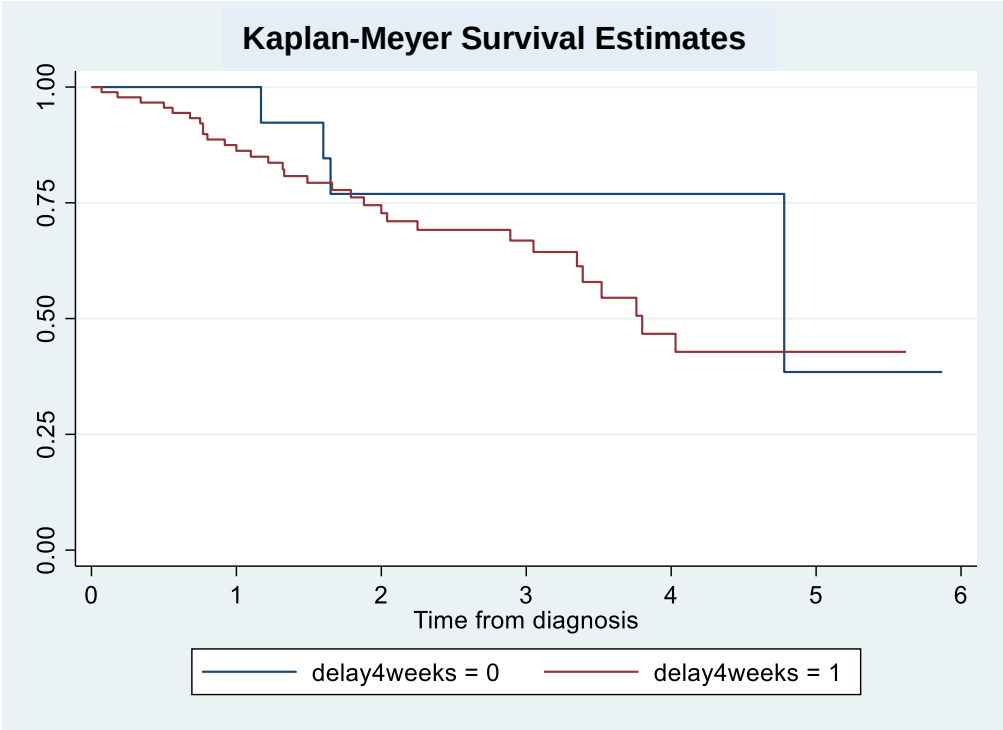


Figure 9: Kaplan-Meyer Survival Estimates:

Survival rates in patients with delays to diagnosis vs without delays to diagnosis



5.5 Discussion

Statement of principal findings

Were there delays to diagnosis or treatment?

Despite the data coming from a major tertiary, specialist, oesophageal and gastric cancer centre, the majority of patients had delays to diagnosis (87.5%) and treatment (93%) in accordance with the standards set by the Australian guidelines 'Optimal care pathway for people with oesophagogastric cancer'. Most of the delays occur between symptom onset to referral. This may be due to: (1) delay in patient presentation (patient delay); (2)delay in GP referral (doctor delay). Several oesophageal and gastric cancer studies cite delayed patient presentation as the primary reason for any delay in diagnosis(14, 69, 91) including two systematic reviews(6, 90). Delayed patient presentation following symptom onset had been reported to account for 82%, and 69% of the total duration from symptom onset to diagnosis in studies by Subasinghe and Samarasekera (2010) and Wang et al (2008) respectively(69) and 47% of time from symptom onset to treatment according to the study by Tata et al (2013)(91). Patient factors contributing to delayed patient presentation were lack of awareness of symptom seriousness and self-treatment with antacids for perceived benign symptoms before presenting later(91).

There are also few studies that note tardiness in GP to specialist referral as the major factor in delay(81, 88). Delay from GP referral to diagnosis accounted for 68% of the total time from symptom onset to treatment in the study by Hosseini(81). According to the study by Hosseini, the delay from GP referral to diagnosis accounted for 68% of the total time from symptom onset to treatment(81). Reasons cited for this included lack of physician training regarding referral to endoscopy(81). Certainly, making GPs of the Australian urgent referral criteria is a good approach to addressing doctor delay.

In contrast to their high associated cancer mortality, oesophageal and gastric cancers are not common and may therefore be overlooked. It is likely that both patients and GPs require more awareness of the conditions.

The ‘Optimum Care Pathway for Oesophagogastric Cancer’ Urgent Referral Guidelines states those with new/progressive dysphagia and/or epigastric pain for 2 weeks should be urgently referred for endoscopic evaluation. Dysphagia was the most common first presenting symptom (42%), which is explained by the presence of most cancers in the study being in the GOJ and distal oesophagus (56%). This is supported by studies in several other countries in Europe and Asia reporting high incidences in oesophageal cancer patients of dysphagia as a first presenting symptom in 100%(69), 71%(14) and 50%(16, 122). Dysphagia and blood loss tended to present more commonly as the only symptom of oesophageal and gastric cancer. This supports the premise that dysphagia and blood loss are surprisingly strong signs of the presence of these cancers and warrant early endoscopy.

However, evidence of blood loss alone was surprisingly common as the only sign of an oesophageal and gastric cancer and perhaps should be included in this criteria as a sole diagnostic sign. In contrast, despite its inclusion in the guidelines, epigastric pain was not strongly associated with oesophageal and gastric cancers in this study, only occurring in 14% of cases.

Despite the strong pathognostic association, dysphagia as a first presenting symptom was significant associated with delay to diagnosis (p=0.002). Conversely, blood loss (anaemia, melena or haematemesis) as the first presenting symptom was more likely to occur in those without delays to diagnosis (p=0.002). This explains the higher proportion of tumours in the body and antrum in those without delays to diagnosis (p=0.05, 31% vs 10%), which perhaps have greater room for rapid tumour expansion, necrosis, ulceration, and thus bleeding. Referring doctors may also perceive anaemia as a stronger indication for endoscopy referral compared to other symptoms.

It appears then, that dysphagia may be deemed less alarming and therefore overlooked by patients, who may defer presentation to their General Practitioner (GP) until this progresses to the point of exceeding tolerability. In contrast, overt blood loss or the symptoms of anaemia may be deemed more alarming and perhaps interfere more with daily function e.g., fatigue and shortness of breath from symptomatic anaemia. Alternatively, a blood test may give some objective evidence of an issue

that the GP find more concrete to follow up than dysphagia, which at first may be vague and non-progressive.

Public campaigns have been shown to create significant improvements in health outcomes, for example, reducing smoking and reducing rates of cervical cancer through pap smears(166). A similar targeted public campaign for oesophageal and gastric cancer could improve patient awareness about new/progressive dysphagia and the need for patients to present earlier for investigation. Likewise, GPs as well as gastroenterologists, general and upper GI surgeons and any specialists encountering a patient with dysphagia needs to be made aware of the current guidelines which require promptness in referring patients with dysphagia for endoscopy. Perhaps the emphasis on endoscopy is also harmful. Given the invasive nature of endoscopy and associated waiting lists for the procedure both patients and their GPs may avoid a referral. Perhaps guidelines should instead highlight the use of a simple contrast swallow for diagnosis in dysphagia since these are readily available in Australia and of high sensitivity and specificity for oesophageal and gastric cancer(38, 167). Incorporation of these improved guidelines into the medical and general practitioner curricula and online can only improve the pick-up rate and reduce delay.

Any impact of delays on outcomes?

There was no impact of delays to diagnosis and treatment on outcomes in this study, including post-operative complications, stage at resection, 30-day, 5-year, post-resection, and overall survival. This could be explained by lead-time bias and the converse relationship of cancer stage with symptoms i.e., those with late-stage disease at diagnosis have a worse outcome despite a shorter time from symptom onset to diagnosis. Conversely earlier stage with better outcomes will be picked up later with a longer symptom duration (168). Hence time from symptom to diagnosis may be a poor predictor of adverse outcome. This is explained through the difference in aggressiveness of tumours, with some progressing more rapidly than others, and therefore having a shorter time course from symptom onset to advanced stage disease. Conversely other tumours have a slower tumour growth and progression with a greater likelihood of low-grade symptoms continuing for a longer period before being acted upon or becoming concerning to the individual or primary care physician. Either

way, present research has not reached the stage of being able to identify specific subtypes of oesophageal or gastric cancer that are more or less aggressive yet, nor has the present study investigated this. This area of research relies on large-scale genomic analysis to identify differences at a molecular and DNA level and warrants consideration for future research.

The lack of association between time from symptom onset to diagnosis and adverse outcomes has been found in several other studies across Europe and Asia which show no impact on stage at resection(16, 88, 169), post-operative complications(13, 88, 169), or survival(13, 15, 169, 170). The diagnosis to treatment interval has also been reported to have no impact on staging, post-operative complications, and survival in several studies worldwide (16, 66, 108, 136). Conversely, a few studies report increased delay to treatment leads to a greater proportion of late-stage disease at resection(14), morbidity and in-hospital mortality(13). Whilst outcomes between those with vs without delays did not demonstrate statistically significant differences in this study, the vast majority of patients had delays to diagnosis and treatment (87% and 93% respectively) which may bias the data. In this cohort where most patients had delays to diagnosis and treatment, most patients also died within the first two years following diagnosis (66%), and none survived beyond the fifth year following diagnosis. Most patients also had locally advanced disease at resection (60%). Overall then, regardless of the absence of statistically significant differences between patients with delays to diagnosis and treatment and those without delays, the simple fact that the majority of patients have locally advanced disease at resection, and most died within the first two years (66%) alone suggests that delays do impact outcomes.

Other findings?

There was a significantly longer delay from MDT to treatment for oesophageal cancers compared to gastric cancers (p=0.001). This may be due to a significantly higher proportion of unimodality, straight to surgical resection patients in the gastric cancer cohort (52% vs 8%, p=<0.001). Delays relating to provision of Oncological services within South Australia may explain this, but this requires further examination.

In comparison to the findings from chapter one, it is noted that the demographics i.e., age, gender, and symptoms differ significantly when evaluating oesophagogastric cancer as one entity compared with gastric and oesophageal cancer as separate entities. For oesophageal cancer, the male to female ratio is 6:1 compared with 2:1 for gastric cancer. Likewise, dysphagia is present in 60% of oesophageal and 10.6% of gastric. Bloods loss occurs in 6.6% of oesophageal cancers and 36.2% for gastric cancer. Constitutional symptoms of weight loss, nausea or anorexia occur in 3.9% of oesophageal cancer and 21.3% of gastric cancer patients. Ratios of adenocarcinoma to squamous cell carcinoma are 6.8:1 for oesophageal cancer and 1:0 for gastric cancer. Stage IV disease at resection is present in around one tenth of oesophageal cancer and one third of gastric cancer cases. These findings again further emphasizes the need for both cancers to be viewed as separate entities, not just in the referral guidelines, but also in the way they are viewed in future studies.

5.6 Conclusion

It is evident that majority of patients with oesophagogastric cancer had delays to diagnosis (87.5%) and treatment (93%) in accordance with the standards set by the Australian guidelines ‘Optimal care pathway for people with oesophagogastric cancer’.

The primary interval responsible for these delays was in the symptom onset to referral time period. This interval far exceeded any other interval along the pathway from symptom onset to treatment in terms of delay, i.e. 8.5 weeks compared to 3 weeks for any other interval. Efforts to reduce delays to diagnosis should specifically target this interval.

Despite dysphagia being the most common first presenting symptom (42%), as well as being already included in the urgent referral criteria, it was significant associated with delay to diagnosis (p=0.002). This indicates a strong need for greater education of GPs and the public around the importance of early investigation of dysphagia.

There are also a number of amendments to the current guidelines for improvement is suggested. An emphasis on the rapid utilisation of contrast radiology for diagnosis in dysphagia over endoscopy

may help. Given that blood loss alone was surprisingly common as the only sign of an oesophageal and gastric cancer, it perhaps should be included in this criteria as a sole diagnostic sign. Epigastric pain may conversely be removed from the criteria given its less common occurrence (11%) in patients with oesophageal and gastric cancers in this study.

The vast majority of patients within this study had delays to diagnosis and treatment, and the fact that most of these patients had locally advanced disease at resection, and most deaths occurred within the first two years (66%) alone suggests that delays do impact outcomes. Delays and survival remain poor, but education and the recommendations on guideline reform described in this study are promising.

6 REFERRAL PATHWAYS FOR PATIENTS WITH OESOPHAGEAL AND GASTRIC CANCER AND THEIR IMPACT ON DELAYS TO DIAGNOSIS AND OUTCOMES.

Contributions: Dr Liana Kumar contributed to the acquisition of data, data analysis, interpretation, drafting the article and incorporating suggestions from co-authors into the final version. This overall comprises eighty percent of the total work. Dr Jon Shenfine contributed to the design of the study, supervision and making critical revisions related to important intellectual content of the manuscript. Dr Tim Bright and Prof David Watson also made critical revisions related to important intellectual content of the manuscript. Mr Jeff Bull assisted with acquisition of some of the data extracted from the database. Ms Feruza Kholmurodova assisted with statistical analysis, survival graphs and interpretation of data.

6.1 Introduction

Patients with oesophageal or gastric cancer continue to have overall poor survival rates(17, 18) and are both frequently associated with a delay to diagnosis(69, 81). Ideally, patients would present promptly to their General Practitioner (GP) with early onset symptoms, but this is not the case for many patients who present directly to the Emergency Department (ED). This route of presentation may result in a faster specialist review and inpatient investigations such as endoscopy. However, several studies report worse outcomes in these patients with a higher stage of disease at presentation(113), lower 5-year survival rates(113), and lower rates of operability(109). According to Fallon et al. (2019), emergency presentation is in fact the most common presenting route in upper gastrointestinal (GI) malignancy(5).

Patients presenting to the healthcare system may end up having multiple consultations with a variety of specialists prior to referral for definitive, diagnostic endoscopy. According to a study by Arhi et al.(2019), both oesophageal and gastric cancer patients with more than two consultations experienced greater delay to referral and a significantly poorer prognosis, including a higher mortality

rate in those who underwent potentially curative resection(133). Inter-specialty cancer referrals have been reported to triple the time to cancer diagnosis and this happens in a significant proportion of patients with foregut cancers(132). In several countries, including Australia, a referral to a specialist for outpatient review is often required prior to endoscopy. Whilst there are many different specialists who can perform endoscopy in Australia (General Surgeons including their subspecialists, Gastroenterologists), this means that the pathway to diagnosis becomes quite varied. On top of this, referral to an Upper GI specialist would be required following diagnosis which again leads to involvement of multiple types of specialists within a fragmented system that still relies on the traditional faxed referrals and associated clerical work. All of this increases the risk of inter-specialty cancer referrals and may further contribute to delays in diagnosis.

This objective of this study is to compare the two routes to diagnosis (ED vs GP) and to identify any causes of delays to diagnosis within these pathways.

6.2 Aims

The aims of this study were (1) To identify different characteristics or risk factors for patients diagnosed with oesophagogastric cancer following presentation via the General Practitioner route vs the Emergency department route, (2) To identify any delays to diagnosis within these pathways and (3) To identify causes for delays in each of these routes, and (4) To identify other referral pathways and patterns and determine if these contribute to delay to diagnosis.

6.3 Methods

This was a retrospective observational cohort study at a single tertiary centre. It included patients with oesophageal and gastric cancer who had surgery with curative intent between the period of February 2013 and October 2018 at Flinders Medical Centre, South Australia.

Study group and data collection

Exclusion criteria included patients diagnosed through the hospital Barrett's oesophagus surveillance program, those who underwent palliative resections or prophylactic gastrectomies for

known genetic CDH1 gene mutations, and patients with less common non-carcinoma histological subtypes (e.g., gastrointestinal stromal or carcinoid tumours, high-grade dysplasia). Patients without a discernible source or date of referral and those with outpatient referrals from a specialist who they were routinely seeing for a separate chronic condition were also excluded from this study to confine participants to only those diagnosed via the GP or ED routes.

A prospectively maintained database was used to identify suitable patients. This database compiles data on over 90% of new upper GI cancer presentations in South Australia who are discussed at the South Australian Statewide Upper GI cancer multidisciplinary team meeting. Data for public and private patients managed by upper GI specialists working at Flinders Medical Centre was derived from review of patient clinical records. The Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC) provided ethics approval for this study (Reference number 257.18).

Variables and definitions

The 'pathway or route to diagnosis' refers to the series of interactions between the patient and the healthcare system that led to their cancer diagnosis (Figure 10). Patients were divided into 2 groups depending on their pathway to diagnosis: (1) GP group, (2) ED group. Patients diagnosed with cancer following a GP referral were in the GP group whilst patients diagnosed following an emergency presentation were in the ED group. Patients who presented to their GP who referred them directly to ED at the time of consultation were still placed in the ED group. This is because this subset of patients were more likely to have a delayed presentation to the GP and therefore any delays to diagnosis in this group should not be attributed to a delay in GP referral, thereby skewing the data. This was also done to allow this study to focus on factors within referral pathways and the healthcare system that are contributing to delays as opposed to delayed patient presentation.

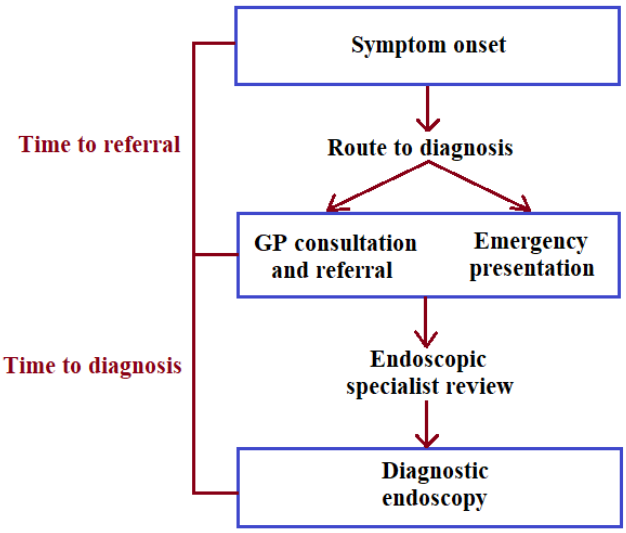


Figure 10: Referral pathways or routes to diagnosis

Various characteristics were compared between these two groups including demographic variables (including age, gender, tumour location, stage at resection, and first presenting symptom), outcome variables (including post-operative complications, and mortality rates), delays to diagnosis and referral, and proportion of patients fulfilling the urgent referral criteria as defined in the Australian Guidelines 'Optimum care pathway for people with oesophagogastric cancer'.

Time from referral being made by the primary care physician to being received and triaged by the outpatient specialist department were also obtained and reviewed. Types of specialists initially referred to were compared in terms of delays to referral, endoscopy waiting times and proportion of patients referred to each specialist for endoscopy. Type of specialist initially referred to were categorized into Gastroenterologists, Upper GI surgeons, General surgeons and 'Others'. General surgeons included those surgeons with General Surgical qualifications practicing as General surgeons and other General surgical subspecialists including Hepatobiliary and Colorectal surgeons. In Australia these specialists can perform flexible endoscopies. The 'Others' group included all other specialists who could not perform endoscopies, i.e., Cardiology, ENT, Head and Neck, and General physicians etc.

Delay to referral was defined as a duration of greater than 2 weeks from symptom onset to referral to a specialist for endoscopy. Date of symptom onset was defined as the date when the patient first experienced symptoms that led to the diagnosis as determined from GP referral letters or patient clinical records. Date of diagnosis was the date of endoscopy that confirmed the histological diagnosis of cancer.

Statistics

Data are expressed as mean ± SD, medians and interquartile ranges, or frequencies. Baseline comparisons between the groups were performed by independent t-tests, Mann-Whitney U-tests, or chi-squared tests. The type 1 error rate was set at $P<0.05$. Analyses were performed using STATA version 16.0 (StataCorp, College Station, TX, USA)

6.4 Results

Characteristics of GP and ED pathways

Of 103 patients in this study 66 had oesophageal cancer and 37 gastric cancer. 76 (74%) patients were diagnosed via the GP route, and 27 (26%) via the ED route. There were significant differences between the GP and ED groups, in terms of type of cancer ($p<0.001$), tumour location ($p=0.037$) and first presenting symptom ($p<0.001$) (Table 13). The majority of gastric cancers were diagnosed following an ED presentation (63%), whereas the majority of patients found to have an oesophageal cancer presented via their GP (73%). Over half of patients in the GP group had tumours located in the distal oesophagus and GOJ (64.5%), compared with 36% in the ED group. Around 63% of patients in the ED group had tumours in the stomach compared to only 26% in the GP group.

As a result, dysphagia was the most common symptom in those being referred by the GP group (50%) compared to only 14.8% in the ED group ($p<0.001$), so that of the 42 patients with a dominant symptom of dysphagia, 38 were referred by the GP whereas 4 presented to the ED. The patients presenting to ED first with dysphagia had mostly advanced or rapidly progressive disease including 2 patients with a food bolus obstruction and 2 patients had rapidly progressive dysphagia associated with epigastric pain, weight loss, and reflux.

Blood loss (melena, haematemesis, anaemia) was in contrast, the more common presenting symptom for those diagnosed via the ED route (44.4% compared to 10.5% in the GP group, $p<0.001$, Table 13). Of the 20 patients who had dominant symptoms of blood loss, 12 presented to ED, mostly with obvious symptoms or signs of blood loss, including 8 with haematemesis and melena and 2 with dizziness from symptomatic anaemia. The other 2 had an anaemia of unclear aetiology. Of the 8 patients presenting to the GP with blood loss, 5 had asymptomatic anaemia and 3 had symptomatic anaemia (2 with fatigue and dizziness), and 1 had noticed melena for 2 weeks.

Most patients (over 60%) in this study were initially referred to a Gastroenterologist and less than a fifth were referred directly to an Upper GI surgeon. The referral criteria was fulfilled in a significantly higher proportion of patients presenting via the GP route ($p<0.001$, Table 13). For those diagnosed

via the GP pathway, 52 of 76 (70.3%) had symptoms which fulfilled the urgent referral criteria. On the contrary, only 7 of 27 diagnosed via the ED pathway (25.9%) had symptoms which met the urgent referral criteria (p<0.001, Table 13).

Table 13: Comparison of demographics between patients diagnosed via GP vs ED routes

Demographic /outcome variables		**GP (n=76)**	**ED (n=27)**	**p-value**
Type of cancer	Oesophageal cancer	56 (73.7%)	10 (37.0%)	<0.001
	Gastric cancer	20 (26.3%)	17 (63.0%)	
Tumour location	Cardia	4 (5.6%)	3 (11.1%)	0.037
	Proximal-mid stomach	7 (9.72%)	6 (22.2%)	
	Antrum, pylorus	8 (11.1%)	8 (29.6%)	
	Gastro-oesophageal junction	18 (25%)	3 (11.1%)	
	Upper oesophagus	0	0	
	Mid oesophagus	5 (6.94%)	0	
	Distal oesophagus	30 (39.5%)	7 (25.9%)	
	Unknown	4	0	
Histology	Adenocarcinoma	69 (90.8%)	26 (96.3%)	0.36
	Squamous cell carcinoma	7 (9.21%)	1 (3.70%)	
First presenting symptom	Dysphagia	38 (50%)	4 (14.8%)	<0.001
	Odynophagia	2 (2.63%)	1 (3.70%)	
	Dyspepsia/indigestion	10 (13.2%)	1 (3.70%)	
	Early satiety	0 (0%)	0 (0%)	
	Weight loss/anorexia/nausea	5 (6.58%)	6 (22.2%)	
	Haematemesis/melena/anaemia (blood loss)	8 (10.5%)	12 (44.4%)	
	Abdominal pain	9 (11.8%)	3 (11.1%)	
	None	2 (2.63%)	0 (0%)	
	Other	1 (1.31%)	0 (0%)	
Age	<55	13 (17.1%)	4 (14.8%)	0.55
	55-64	21 (27.6%)	4 (14.8%)	
	65-74	22 (28.9%)	10 (37.0%)	
	75-84	18 (23.7%)	7 (25.9%)	
	>/=85	2 (2.63%)	2 (7.41%)	
Age	Median (IQR)	67.5 (57.0, 75,2)	72 (61.5, 76)	0.27
Gender	1=Male	60 (78.9%)	17 (63.0%)	0.10
	2=Female	16 (21.1%)	10 (37.0%)	
Location	Rural	28 (36.8%)	6 (22.2%)	0.17
	Local	48 (63.2%)	21 (77.8%)	

Table 13 (continued).

ASA grading	1	8 (10.5%)	2 (7.41%)	0.32
	2	34 (44.7%)	10 (37.0%)	
	3	34 (44.7%)	14 (51.9%)	
	4	0	1 (3.7%)	
Hospital admissions prior	>/=1	19 (32.2%)	12 (48%)	0.34
	0	40 (67.8%)	13 (52%)	
Specialist referred to initially	Gastroenterology	46 (60.5%)	18 (66.7%)	0.31
	General Surgery	9 (11.8%)	1 (3.7%)	
	Upper GI Surgery	13 (17.1%)	5 (18.5%)	
	ENT	3 (3.95%)	0	
	Cardiology	1 (1.32%)	2 (7.41%)	
	General Physician	0	1 (3.70%)	
	Hepatobiliary	1 (1.32%)	0	
	Colorectal	2 (2.63%)	0	
	Head/neck	1 (1.32%)	0	
Patients who fulfilled the referral criteria	Yes	52 (70.3%)	7 (25.9%)	<0.001
	No	22 (29.7%)	20 (74.1%)	

Outcomes in GP and ED pathways

In hospital mortality occurred in 2 out of 103 patients in this study. Both these patients were diagnosed with gastric cancer via the ED route. One patient presented with haematemesis and the other presented with a gastric outlet obstruction. All other outcomes were not significantly different between those diagnosed via the ED and GP pathways (Table 14).

Table 14: Comparison of outcome variables between patients diagnosed via the GP vs ED route

Demographic /outcome variables		GP (n=76)	ED (n=27)	p-value
Stage at resection	I	32 (42.1%)	8 (29.6%)	0.52
	II	7 (9.21%)	4 (15.4%)	
	III	26 (34.2%)	8 (29.6%)	
	IV	11 (14.5%)	6 (22.2%)	
LN positive (number)	Yes	36 (47.4%)	17 (63.0%)	0.16
	No	40 (52.6%)	10 (37.0%)	
LN positive (number) >/= 4	Yes	15 (19.7%)	4 (14.8%)	0.57
	No	61 (80.3%)	23 (85.2%)	
Neoadjuvant chemotherapy	Yes	61 (80.3%)	18 (66.7%)	0.15
	No	15 (19.7%)	9 (33.3%)	
Radiotherapy	Yes	42 (55.3%)	9 (34.6%)	0.069
	No	34 (44.7%)	17 (65.4%)	
Deceased (died)	Yes	23 (30.3%)	11 (40.7%)	
	No	53 (69.7%)	16 (59.3%)	
In hospital mortality	Yes	0 (0%)	2 (7%)	0.017
	No	76 (100%)	25 (93%)	
Post-operative complications	Yes	48 (63.2%)	18 (66.7%)	0.74
	No	28 (36.8%)	9 (33.3%)	
	General	22 (29.9%)	11 (40.7%)	0.34
	Local	12 (15.8%)	1 (3.7%)	
	Both	14 (18.4%)	6 (22.2%)	
	No	28 (36.8%)	9 (33.3%)	
Reoperation	Yes	5 (6.58%)	2 (7.41%)	0.88
	No	71 (93.4%)	25 (92.6%)	
5-year survival	Yes	11 (32.4%)	2 (15.4%)	0.22
	No	23 (74.2%)	11 (84.6%)	
Duration of survival (from symptom onset)*		2.32 (1.65, 4.16)	2.87 (1.32, 3.79)	0.32
Duration of survival (from diagnosis)*		1.94 (1.27, 3.37)	2.63 (.96, 3.52)	0.71
Duration of survival (post resection)*		1.595 (.93, 3.21)	2.33 (.62, 3.21)	0.76
Overall follow-up time*		3.44 (2.11, 5.12)	3.64 (2.33, 5.13)	0.74

*Years, median (IQR)

Delays to referral and diagnosis for GP vs ED pathways

Delays from symptom onset to referral were significantly more common when patients were referred by GPs (89% vs 58%, p=0.01) (Table 15). Duration from symptom onset to GP referral was three times that of the ED patients (73 days vs 34.5 days, p=0.014) (Table 16). Of note, in GP referred patients, the time to referral appeared to be steadily increasing year on year, going from 64 days in 2013 to 90 days in 2018 (Figure 11).

As a result, a significantly larger proportion of patients in the GP group had a delay from referral to endoscopy (72% vs 22%, p<0.001), with a median of 32.5 days (14.3 to 59.5 days) in comparison to only 1 day (1 to 4 day) for those referred by ED (Table 5).

Table 15: Delays from symptom onset to referral (GP vs ED)

Time interval from symptom onset to MDT		**GP (n=76)**	**ED (n=27)**	**p-value**
Delay from symptom onset to referral	**yes**	58 (89.2%)	14 (58.3%)	0.01
	no	7 (10.8%)	10 (41.7%)	
Delay from endoscopy to UGI OPD	**yes**	8 (11.1%)	3 (11.5%)	0.953
	no	64 (88.9%)	23 (89.5%)	
Delay from symptom onset to endoscopy	**yes**	62 (95.4%)	16 (64%)	<0.001
	no	3 (4.61%)	9 (36%)	
Delay from referral to endoscopy	**yes**	55 (72.4%)	6 (22.2%)	<0.001
	no	21 (27.6%)	21 (77.8%)	

Table 16: Duration of time intervals from symptom onset to UGI OPD

Time interval in weeks	**GP (n=76)**	**ED (n=27)**	**p-value**
Time from symptom onset to referral	73 (30-138)	24.5 (9.25-80.25)	0.014
Time from referral to endoscopy	32.5 (14.3-59.5)	1 (1-4)	<0.001
Time from endoscopy to Upper GI OPD	7 (5-9.5)	7 (3.5-13)	0.22

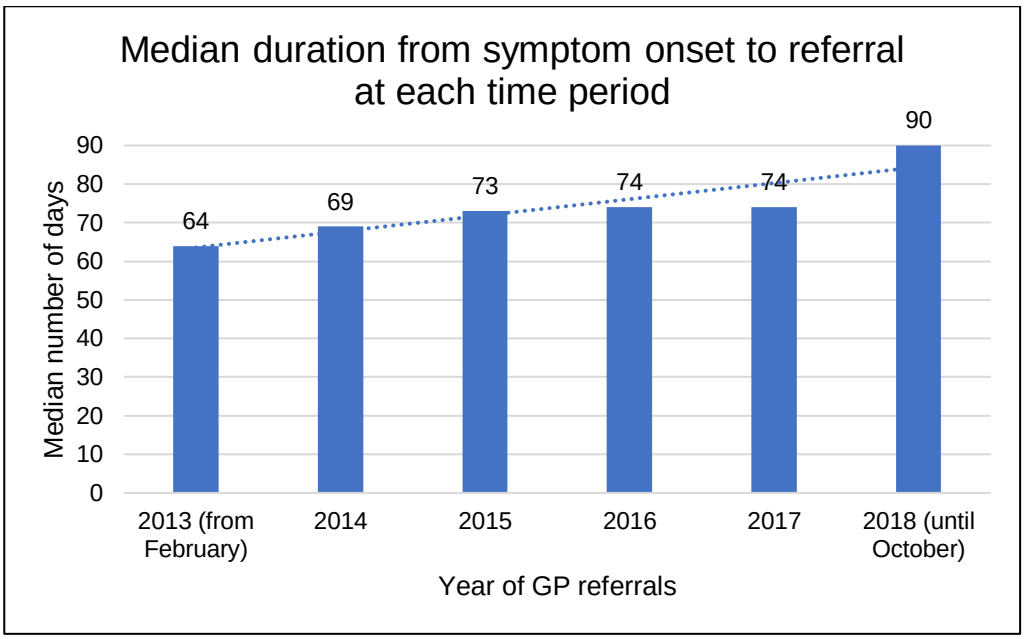


Figure 11: Median duration from symptom onset to referral at each year from 2013 to 2018

For patients in the GP group, patients referred to an Upper GI surgeon in the first instance had the shortest endoscopy waiting time of 8 days (p=0.035) (Table 17). For the other specialists who could perform endoscopy, i.e., Gastroenterologists and General surgeons, these had much longer times from referral to endoscopy (32 and 42 days respectively) whilst the other specialists who could not perform endoscopies had the longest waiting time at 55 days.

Table 7: Comparison of delay from referral to endoscopy between type of specialist initially referred to by GP

Type of specialty initially referred to by GP	**Delay from referral to endoscopy**	**Duration of delay (days)**	**p-value**
Gastroenterology	36/45 (80%)	32 (20, 61)	0.035
General Surgery[1]	10/11 (90.9%)	42 (29, 51.5)	
Upper GI	4/9 (44.4%)	8 (5, 34)	
Others[2]	5/5 (100%)	55 (33, 316)	

[1]General surgery refers to those surgeons with General Surgical qualifications practicing as General surgeons and other General surgical subspecialists including Hepatobiliary and Colorectal surgeons.

[2]Others includes cardiology, ENT, Head and neck, general physicians

Date of referrals being received for triaging by the hospital was available for 44 patients. Of these patients, 24 patients had ED referrals and 20 had GP referrals. Of the ED referrals all but one was received within less than 24 hours (96%). Of the GP referrals, 12 (60%) were received within 24 hours, 2 (10%) within 72 hours) and 6 (30%) within 2 months. Of the 6 received within 2 months, these durations were 6, 10, 13, 27, 50 and 54 days from date of referral made to referral received.

6.5 Discussion

In this study, around a quarter of patients with oesophageal or gastric cancer first presented to the Emergency Department (26%). This is lower than in other studies which report rates of emergency diagnosis of 38.7%(113) for gastric cancer and in another study, 33%(109) for oesophageal and gastric cancer combined. Other studies that report rates of between 13.9-24%(116, 117) for cancers in general. The proportion of emergency presentations that involved direct GP referral or the proportion of patients referred by an alternate outpatient specialist route were not evaluated in this study. Regardless of this, ED and GP referral pathways are by far the commonest routes to diagnosis(114).

This study found significant differences between patients presenting via the ED and GP pathways, in terms of cancer type ($p<0.001$), tumour location ($p=0.037$) and first presenting symptom ($p<0.001$). Patients referred by a GP had mostly oesophageal cancer (73.7%) and presented with dysphagia (50%). The proportion of patients who fulfilled the referral criteria for patients in the GP group was 70.3%, likely due to the high prevalence of dysphagia in this group, which is more common in oesophageal than gastric cancer patients(16) and is one of the two symptoms included in the referral criteria.

Patients referred following direct presentation to ED were mostly those with gastric cancer (63%) and a large proportion presented with either blood loss (44%) or associated constitutional symptoms such as weight loss, anorexia, or nausea (22%). These findings are supported by several other studies(110, 112, 171). The study by Palser et al. (2013) also reports a much higher proportion of gastric cancer patients diagnosed via the ED route compared to oesophageal cancer (64.9% gastric cancer patients vs 36.1% oesophageal cancer patients)(110). Likewise, the study by Markar et al.

(2018) reports a greater proportion of emergency diagnosis for gastric cancer compared to oesophageal cancer (39.6% compared to 29.4% respectively)(112). According to Solsky et al (2018), over half of gastric cancer diagnoses are made following emergency presentations(171). The main reason cited for this was the non-specific nature of symptoms not prompting the GP to start a cancer work up whilst ED physicians would be more likely to order a CT scan that could initiate the diagnostic process(171). In this study by Solsky et al (2018), bleeding and non-specific symptoms such as weakness, fatigue and anaemia related symptoms occurred in 21% and 20% of gastric cancer patients diagnosed following emergency presentation and together these were the more common than any other presenting symptom(171). These studies along with the findings in this study highlight the fact that oesophagogastric cancer patients diagnosed following emergency presentation are typically those with gastric cancer, presenting with blood loss and constitutional symptoms. Despite this, none of these symptoms are in the urgent referral criteria. Hence, the proportion of patients diagnosed via emergency presentation who fulfilled this criteria was only 22.6%.

There was a statistically significant difference in in-hospital mortality rates between the ED and GP groups, in which all deaths, occurred in patients of the ED group, perhaps demonstrating an increased risk of in-hospital mortality in those presenting via the ED pathway (p=0.017). This clearly could be a statistical error with such low numbers, but it is consistent with the large volume of literature that report worse outcomes in patients presenting via the ED route, not only for upper GI cancers(5, 109, 110, 112-114, 171, 172). In this study, although there was no difference in staging between ED and GP groups, when comparing staging between oesophageal and gastric cancer patients (chapter one), gastric cancer still had a much higher proportion of stage IV cancers than oesophageal cancer (31% vs 10%). Given that most patients diagnosed following emergency presentation had gastric cancer, reducing the number of emergency diagnoses could help reduce the incidence of late-stage diagnoses in these patients.

Whilst other studies on routes to diagnosis found older age(117), comorbidity(112), worse performance status(110) and living in deprived areas including rurally (115, 117-119) as significant risk factors for emergency route diagnoses(110), none of these were shown to be significant risk factors in this study.

Delays to referral were significantly greater for patients referred by a GP compared with those presenting directly to ED. The duration from symptom onset to referral was three times as much for patients referred by GP (73 days vs 24.5 days, p=0.014). The proportion of those with delays to referral was also significantly higher for patients in the GP group compared to the ED group (89.2% vs 58.3%, p=0.01). Whilst the most common presenting symptom in the GP group was dysphagia (50% compared to 14.8% in the ED group) owing to the higher proportion of oesophageal cancer patients in this group (73.7%), dysphagia is included in the urgent referral criteria and significant delays to referral may reflect a lack of adherence of GPs to these criteria. There might be a lack of awareness of the symptoms of oesophageal and gastric cancer in the general population.

It is also worth noting that the time from symptom onset to referral has been steadily increasing every year, starting at 64 days in 2013 to 90 days in 2018. Both significantly exceed the target timeframe of 2 weeks but nonetheless, causes for the increase in time to referral each year needs further investigation, which is outside the scope of this study. One of the most obvious ways in which to address this issue is by educating GPs about the epidemiology and clinical features of oesophagogastric cancers and the need to refer within 2 weeks in those who meet the criteria for referral.

Unfortunately, the date of initial patient presentation to the GP and the number of GP consultations prior to GP referral were unable to be determined and is therefore a limitation in this study. Regardless, it is likely that both factors contribute to delays to referral. Perhaps increasing public and GP awareness of these uncommon cancers and the implications of progressive dysphagia would help reduce delays to referral.

Delays from referral to endoscopy were also significantly higher in patients presenting via the GP pathway compared to the ED pathway. It took a median of 1 month from GP referral to endoscopy as opposed to 1 day from ED referral to endoscopy (32.5 days vs 1 day, p=<0.001). Patients in the GP groups had a lower proportion of referrals being received for triaging within 72 hours (70% vs 96%) and this took between 6 and 54 days for 6 patients (30% vs 4%) compared with all but one patient having a referral received within 24 hours from ED. Whilst being limited by a smaller sample

size of available date for referral processing, this difference reflects the greater complexity of administration and organisation required for those being referred via the GP pathway as opposed to the direct hospital presentations where inpatient specialist reviews are readily available.

Most patients (>60%) were referred to a Gastroenterologist for further investigation. However, the waiting time from referral to endoscopy was almost four times longer for Gastroenterology compared to Upper GI surgeons (p=0.012). This may be because gastroenterologists have a broad scope of practice and receive a higher volume of referrals relative to other specialties. As such, the increased number of referrals to a single specialist will increase the waiting time for the endoscopy according to a demand-supply principle. In this study, patients referred directly to an upper GI surgeon for endoscopy had a faster median time from referral to endoscopy (8 days vs >32 days for other groups) and a lower proportion of delays from referral to endoscopy (44% vs >80% for the other specialist groups; p=0.035).

Whilst these findings may suggest that referral of these suspected oesophageal or gastric cancer cases to an Upper GI surgeon in the first instance may offload the burden of referrals on Gastroenterologists and General surgeons, avoid inter-specialty referrals, and streamline the path to discussion around treatment, the proportion of available Gastroenterologists in Australia is far more extensive than the proportion of upper GI surgeons. Therefore, it may not be feasible to advise all GPs to refer to an upper GI surgeon in the first instance as it may likely create the same, if not a worse issue of demand exceeding supply and a blow-out of waiting times for endoscopy.

Of the specialists initially referred to by primary care physicians who were unable to offer endoscopy services, e.g. Cardiologists etc., all these involved a delay to endoscopy, and had the longest duration from referral to endoscopy. This is expected given that they would have needed to re-refer to specialists who could perform endoscopy, leading to multiple specialist appointments, triaging, and waiting prior to endoscopy. Perhaps increasing the number of trained endoscopists, having nurse endoscopists, or open access endoscopy, which is not currently available in Australia, could all be methods of reducing endoscopy waiting times. In addition to this however, improvising the above urgent referral criteria as described would be equally required to genuinely increase early

detection rates. The studies on open access endoscopy(121) and nurse endoscopist clinics(125) that demonstrated no improvement in diagnostic yield, were due to failure to simultaneously utilise appropriate referral guidelines. Therefore, the combination of increasing endoscopy availability and improving sensitivity of referral guidelines is vital to improving early oesophagogastric cancer detection rates, and thereby improving outcomes.

6.6 Conclusion

In this study, which focuses on different referral pathways indicated that over a quarter of patients with oesophageal or gastric cancer first presented to the Emergency Department (26%) and was associated with greater in-hospital mortality. Patients presenting via the Emergency Department were mostly patients with gastric cancer who presented with blood loss or constitutional symptoms. Inclusion of these symptoms in the current urgent referral criteria may significantly improve chances of early cancer detection and reroute diagnosis of patients towards the GP pathway.

Patients diagnosed following GP presentation were most commonly oesophageal cancer patients (73.7%) with dysphagia (50% vs 14% in ED group). Despite dysphagia being included in the current urgent referral criteria, there were surprisingly significant delays from symptom onset to referral in the GP group. This delay has also been steadily increasing every year, starting at 64 days in 2013 to 90 days in 2018. This clearly indicates a need for education of GPs about the referral criteria and its importance.

Delays from referral to endoscopy were also significantly higher in patients presenting via the GP pathway compared to the ED pathway. Most patients (>60%) were referred to a Gastroenterologist for further investigation, despite the endoscopy waiting time being over a month for Gastroenterologists. Waiting times were even longer for most other specialists able to offer endoscopy services in Australia including General surgeons. Incorporation of open access endoscopy or one stop dyspepsia clinics in Australia may assist in increasing endoscopy availability and reducing such waiting times. Additionally, utilisation of a less invasive barium swallow test in the interim whilst awaiting endoscopy can also be a tool in aiding identification of a cancer.

It appears then that a combination of increasing endoscopy availability and improving sensitivity of referral guidelines may significantly improve early oesophagogastric cancer detection rates, and thereby improve outcomes.

7 SUMMARY

7.1 Rationale

The main aim of this study is to assess diagnostic and treatment delay in oesophagogastric cancer, possible reasons for it and options to minimize it. The lack of standardisation in studies on delays to diagnosis for upper GI cancer across different countries makes it difficult to draw conclusions on the prevalence of delays to diagnosis and subsequent impact on outcomes. Whilst the emergency route to cancer diagnosis is associated with adverse outcomes, and accounts for around one-third of oesophagogastric cancer diagnoses, risk factors or reasons for emergency diagnosis and whether it is associated with delays to diagnosis is not clear. Differences between oesophageal and gastric cancer in terms of symptom profile include dysphagia being more common in oesophageal cancer, but other differences are not well established, and positive predictive value of these symptoms alone are insufficient in detecting early-stage cancers. Whilst the two week wait in England has been used as a referral criteria, it has not reduced delays to diagnosis and does not have a strong predictive value for oesophagogastric cancer detection. A better criteria at detecting early cancers needs to be identified. Initiatives to reduce delays to diagnosis so far, including the two week wait, open access endoscopy, dyspepsia guidelines, and public campaigning have not reduced delays to diagnosis or treatment, save for marginal improvement following centralisation of services. More may need to be done to reduce delays to diagnosis to improve outcomes. To achieve the main aim, this study has focused on specific objectives. These objectives and their respective findings are detailed below.

7.2 Key objectives, findings, and implications

The **first objective** is to determine if there are delays to diagnosis and treatment of oesophagogastric cancer at an Australian tertiary hospital based on the Australian guidelines. This study found that most patients had delays to diagnosis (87.5%) and treatment (93%) in accordance with the standards set by the Australian guidelines ‘Optimal care pathway for people with oesophagogastric cancer’. Most of the delays occur between symptom onset to referral (which

accounts for 68% of the total delay from symptom onset to treatment). The implications are that to reduce delays to diagnosis, we need to reduce delays from symptom onset to referral.

The **second objective** is to identify causes and risk factors for delays to diagnosis and treatment. This study found first symptom (p=0.002) and tumour location (p=0.05) to be significant risk factors for delays to diagnosis. More specifically, patients with dysphagia and tumours in the distal oesophagus or gastroesophageal junction experienced more frequently delays to diagnosis. The implications of these findings are the need for education of GPs and referring doctors about the connection between dysphagia and malignancy and the need to promptly refer for diagnostic evaluation either through barium swallow initially followed by prompt endoscopic evaluation.

The **third objective** is to determine if delays to diagnosis and treatment have an impact on treatment outcomes. This study found that most patients presented with late-stage disease (60%) and most deaths occurred in the first two years (66%) in the overall cohort. Despite no statistically significant difference in tumour stage, post-operative complications, and survival between patients with vs without delays to diagnosis and treatment, outcomes are still suboptimal within the overall cohort of patients who have been managed surgically with curative intent. The fact that most patients in this cohort had delays to diagnosis and treatment and poor outcomes suggests a likely correlation between the two. The implications of these findings are that delays to diagnosis are significant and there may be benefit in reducing such delays.

The **fourth objective** is to highlight the differences between oesophageal and gastric cancer. This study found that both have several differences. Although originating from the gastrointestinal tract, this study demonstrates that both cancers behave quite differently as reflected by their different tumour locations and pattern of dissemination. Oesophageal cancers are much more common in men (6:1 ratio compared with 2:1 for gastric cancer) and therefore warrants greater clinical suspicion in men with symptoms. Dysphagia is more common in oesophageal cancer due to the higher propensity for luminal narrowing that occurs in the oesophagus and gastro-oesophageal junction as opposed to the stomach. Gastric cancers on the other hand are more likely to bleed due to the tumour growing in a corrosive environment prior to impinging on surrounding structures to cause

epigastric pain. The non-specific nature of gastric cancers means that they are harder to detect and therefore more likely to present at advanced stages. We therefore now because of this study, have a better understanding of the pathogenesis, presentation and behaviour of oesophageal and gastric cancers and the significant differences between them highlights the need for separate referral criteria.

The **fifth objective** was to develop an improved urgent referral criteria that is separate for oesophageal and gastric cancer and therefore better at detecting early-stage cancers. Based on the above differences and symptom profiles of oesophageal and gastric cancer, the urgent referral criteria outlined in the Australian guidelines should be changed in the following ways to improve early cancer detection rates: (a) there should be a separate referral criteria for oesophageal and gastric cancer, (b) oesophageal cancer should include dysphagia as a defining criteria, (c) gastric cancer should include blood loss (anaemia, haematemesis and melaena) as one defining criteria, (d) epigastric pain should be removed as a criteria for referral, (e) constitutional symptoms such as nausea, weight loss and anorexia can be criteria common between the cancers. Whilst age and gender ratios were different between the two cancers, these factors are best left as a guide to clinicians and GPs in strengthening their recognition of them in clinical practice.

The **sixth objective** was to identify the proportion of patients diagnosed via the emergency route, their risk factors and if associated with adverse outcomes. This study found that around a quarter of patients with oesophageal or gastric cancer first presented to the Emergency Department (26%). Patients diagnosed via the emergency department had significantly different characteristics compared to those diagnosed following GP presentation. Most patients diagnosed via the emergency route had gastric cancer (63%). They also most commonly presented with symptoms not included in the urgent referral criteria, which were blood loss (44.4%) and constitutional symptoms (22.2%). Therefore only 25.9% of emergency route patients in total fulfilled the urgent referral criteria compared to 70.3% diagnosed following GP presentation. All three patients with in-hospital mortality were those diagnosed via the ED route, suggesting a possible association to adverse outcomes.

The **seventh objective** was to determine whether delays occur more frequently in those diagnosed via the emergency route. Delays from symptom onset to referral were significantly shorter for patients diagnosed via the emergency department route (14 days vs 58 days for GP route). This contrasts with the original hypothesis that delays would be longer in such patients due to delayed patient presentation until symptoms became severe. This is likely explained by the fact that a large proportion of patients presenting via the ED route presented with obvious signs of blood loss, i.e., haematemesis and symptomatic anaemia. It is likely that these patients had asymptomatic iron deficiency anaemia for a significantly longer period prior to detection or becoming symptomatic and therefore the duration from symptom onset to presentation and referral in these patients could be underestimated. Endoscopy to referral was significantly shorter in duration for patients diagnosed via the Emergency route, whereas the GP route had significant delays to endoscopy when referrals were to all other specialists (>30 days) except Upper GI surgeons (8 days). Whilst at the outset it may seem logical to encourage more direct referrals to upper GI surgeons given the associated shorter endoscopy waiting time, there are much less upper GI surgeons than Gastroenterologists, and therefore based on a demand-supply principle, endoscopy waiting times would adversely increase if more referrals were directed to Upper GI surgeons. There are other more practical ways to increase endoscopy availability such as open access endoscopy, and training nurse endoscopists.

The **eighth objective** is to identify ways in which delays to diagnosis and treatment can be reduced to improve early cancer detection rates. To reduce delays to diagnosis, which is the key goal of this research, this study has led to the creation of a multifaceted approach. This approach involves five key strategies, of which all should be employed simultaneously in order to achieve the desired outcome of improving early cancer detection rates. As this study has found, delays to diagnosis can be attributed to a number of reasons such as lack of patient and GP cancer awareness, endoscopy availability issues, failure to utilise other readily available non-invasive tests, the need for a more sensitive referral guideline etc. The five strategies seek to address these issues and implementing only one of the five strategies will only address one problem and potentially exacerbate other problems, thereby nullifying any positive impact. This multifaceted approach is described in further detail below and illustrated in Figure 11.

7.3 Recommendations

Based on the study results, there are five recommendations to reducing delays to diagnosis. The first and key recommendation is derived directly from the literature review findings and results of the data analysis. The remaining four recommendations are additional measures to maximise the beneficial outcome of the first recommendation. It has been noted from the literature review, that many strategies to reduce delays to diagnosis were not successful when implemented in isolation. It may be more likely that when all strategies are simultaneously implemented, they will be able to reduce delays to diagnosis. This is due to the interdependency of these particular strategies and their effects, as clearly highlighted in figure 11.

7.3.1 Education of primary care physicians

One issue identified as causing delays is the failure for GPs to be aware of the need to refer patients with suspected oesophagogastric cancer for endoscopy. This is demonstrated by the following findings in this study: (1) that that were significant delays to diagnosis in patients with dysphagia despite it being a common symptom of oesophageal cancer and included in the Australian urgent referral criteria; (2) that whilst 76% of oesophageal cancer patients had symptoms fulfilling the urgent referral criteria, there was a delay to referral in 74% of oesophageal cancer patients. Whilst delays to referral could also be due to delayed patient presentation, from the literature review, studies have shown that delays in GP referral have been a reason for delays to diagnosis(81, 88). The first strategy proposed that will address this issue is the educate GPs about the current urgent referral criteria through its incorporation into the medical school curriculum and GP training curriculum and manuals. Whilst this will result in an increased identification of patients with potential oesophagogastric cancer for referral leading to more referrals, it can also result in the problem of increasing the endoscopy workload at rates that will increase endoscopy waiting times and increase delays to diagnosis again.

7.3.2 Increasing endoscopy availability

In order to address this second issue, there needs to be a means to increase endoscopy availability in Australia. This can be achieved through either allowing open access endoscopy or by training

more endoscopists including nurses. Whilst this will reduce endoscopy waiting times, it will allow for an increase in the number of endoscopies which can be associated with a lower diagnostic yield for oesophagogastric cancer if the referrals are inappropriate. This was already demonstrated following the open access endoscopy initiative in the UK(121).

7.3.3 Rapid utilisation of barium swallow

There are two strategies to overcome this problem of increased inappropriate endoscopy referrals. One is the utilisation of barium swallow as an initial investigation, being readily available, quickly accessible, and of high sensitivity and specificity for diagnosis of oesophagogastric cancer(38, 167). A positive finding will further consolidate the referral for endoscopy which is still required for definitive histological diagnosis. A negative finding can aid the primary care physician in making a decision about endoscopy referral and avoid any potentially unnecessary referrals. The only issue with this is that patients with a negative barium swallow result can still have an oesophagogastric cancer (15, 134). This is where a proper sensitive urgent referral guideline is needed which outlines symptoms that still warrant urgent referral irrespective of a negative barium swallow result.

7.3.4 New separate urgent referral criteria

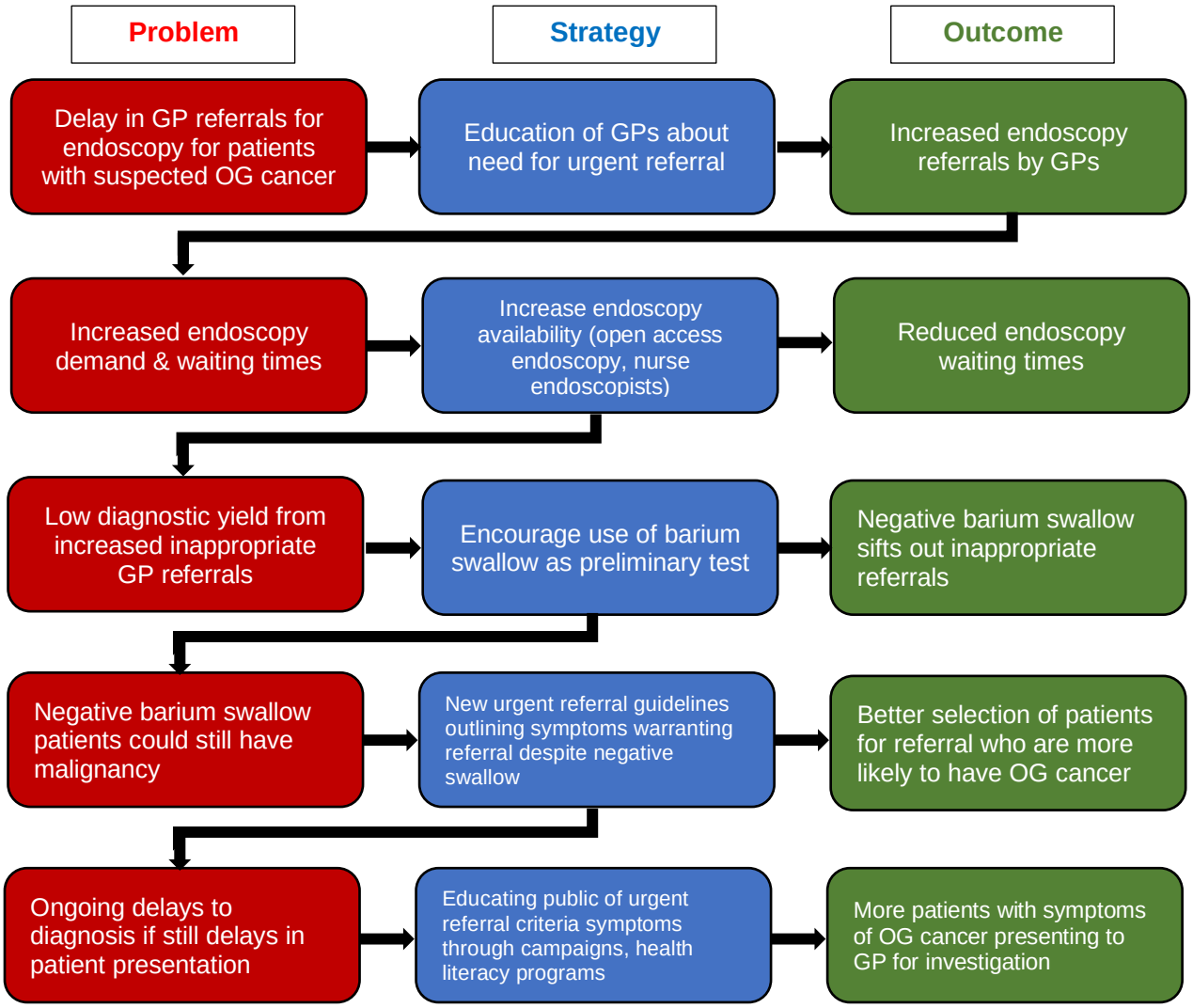
This study recommends that the urgent referral criteria be changed to separate criteria for each cancer. Dysphagia is an appropriate symptom warranting urgent referral for oesophageal cancer. Blood loss and constitutional symptoms should be included as criteria for gastric cancer. Epigastric pain should be excluded as it was a less common symptom of either cancer and also has several other causes that could be investigated first via different non-invasive means. Whilst age and gender are not recommended to be included in this referral criteria, it is worth GPs being aware that oesophagogastric cancer occurs six times more commonly in men, and generally over the age of 40. These new referral guidelines can help primary care physicians refer patients which are much more likely to have oesophageal and gastric cancer, but in order for this guideline to be effective, it is not only a requirement for GPs to be aware and educated about them, but also the public. The final issue to be addressed is the failure for patients to present to GPs soon enough with symptoms. This needs to be addressed by public campaigning and improvements in public health literacy.

7.3.5 Public campaigning and improving health literacy

Failure for previous public campaigns to improve early detection rates can be overcome by ensuring that the message is (a) clear and understood by the public, (b) reaches as many people as possible, particularly those at greatest risk, and (c) focuses on the symptoms outlined in the new urgent referral criteria. In order for the message to be clearly understood by the public, people need to have a reasonable degree of health literacy. Education around the basics of health and cancer can be incorporated into a school curriculum or by having public campaigns that target high schools and universities. In order to reach as many people as possible with the campaign message, other modes of communication that go beyond television and radio need to be utilised such as Facebook and other social media platforms.

This multifaceted five strategy approach is promising, and further research should be undertaken to review the outcome following implementation of this.

Figure 11: Five strategy approach to reducing delays to diagnosis



OG cancer = oesophagogastric cancer

This flowchart illustrates the five-strategy approach to reducing delays to diagnosis. It demonstrates the need for implementation of all strategies (blue boxes), as one strategy addresses only one issue, and can lead to exacerbation of other issues (red boxes) if not addressed.

7.3.6 Future research

From the literature review, it was noted that increasing endoscopy accuracy involves taking an adequate number of biopsies and withholding antacid medication prior to endoscopy. At present there are no national guidelines that provide further clarity on either of these points in terms of how many biopsies should be taken to ensure diagnostic accuracy and the duration and conditions upon which the antacids should be withheld prior to endoscopy. Further research and initiatives should be undertaken to establish these guidelines. In terms of delays to diagnosis in oesophagogastric cancer,

future studies should have greater standardization. This study used the Australian guidelines to provide a clear definition of delays to diagnosis and involved selection of patients undergoing surgery with curative intent. This is opposed to the many studies that involved different definitions and measurements of delays, palliative patients and other rarer histological subtypes which made comparison hard. There should be a goal to achieve an international standardized measurement for delays to diagnosis and treatment applied to various studies in order to strengthen our understanding of the causes and outcomes of delays to diagnosis.

Whilst the five key recommendations listed in section 7.3 and summarised in Figure 11 are derived from a comprehensive literature review as well as data from oesophagogastric cancer patients at Flinders Medical Centre in South Australia, there needs to be further dedicated research in an Australian setting to evaluate the efficacy of these interventions prior to widespread implementation.

7.4 Limitations

Comparison of the results in this Australian study with that of other international studies, is limited by variations in methodology in determining delays to diagnosis, and differences in subtype and pathogenesis of oesophagogastric cancer in many countries.

Generalisability is also limited by differences in accessibility of endoscopy across many countries. Open access endoscopy, whilst available in many other countries is largely not available in Australia. General surgeons can also perform endoscopy in Australia whilst in many other countries, endoscopy is performed exclusively by Gastroenterologists.

Data being collected from a single centre study, although the largest centre in the state, may limit generalisability of findings. Detailed analysis of causes of delays to diagnosis were limited by the absence of data on date of initial patient presentation to the GP, the number of GP consultations prior to referral and the proportion of emergency presentations that involved a direct GP referral to ED. Data on patients who had more than one endoscopy prior to diagnosis and the number of interspecialty cancer referrals (number of consultations with specialists prior to seeing an upper GI

surgeon) were unable to be collected in this study, also preventing detailed analysis of delays. Some patients also may have presented to private or other hospitals for treatment of their post-surgical complications, of which data from private hospitals was unable to be accessed and may underestimate the complication rates reported. The fragmented nature of the way medical information is stored and accessed in Australia, particularly the different electronic software systems that vary between private and public hospitals and GP practices makes collection of certain data difficult.

The sample size of those without delays, was small in comparison to those with delays and therefore comparing these groups may be subject to Type II statistical error. Particularly with the comparison of patients with delays to diagnosis and those with no delays, the sample size was not large enough to undertake a multivariate analysis and possibly subject to underpowering. Determination of time from referral being made to being triaged as well as comparison of type of specialties who were initially referred to was limited by a smaller sample size of available data.

Our study cohort excluded non-curative patients, who at time of presentation already had stage IV disease. Common sense dictates that these patients are likely to have experienced even greater delays to diagnosis, but these are an ethically difficult cohort to study with limited data available and the premise of the study was to characterise the delays in curable patients in as standard a fashion as was possible. If these patients would be more likely to have delays to diagnosis, then their exclusion from this study may underestimate the proportion of patients with delays.

For those with anaemia as the first presenting sign, the proportion of symptomatic vs asymptomatic patients as well as duration of symptoms prior to detection of Hb was indeterminable from GP referral letters. The absence of this data may underestimate the duration of delay to diagnosis in those with blood loss in this study.

Symptom onset is a subjective measurement, and it is possible that patients are not able to recall the exact time that they first experienced a particular symptom or which symptom occurred first if they were close together in onset. When the primary care physician or specialist is taking the history

from the patient and documenting the symptom onset in their referral letters, from which the data in this study was derived, these variations in timing of symptom onset could influence the results.

Classification of tumours at the GOJ or cardia into oesophageal or gastric cancers was determined in this study from multidisciplinary meeting opinions. These opinions are often influenced by treatment approach as opposed to direct endoscopic visualisation only or the Siewert Scale, which affects standardisation.

7.5 Conclusion

There are three main conclusions derived from this study. The first concluding point is that most potentially curable patients with gastric and oesophageal cancer have delays to diagnosis and treatment according to the Australian guidelines. They therefore present with advanced stage disease. Delays predominantly occur in the interval from symptom onset to specialist referral and more often in patients with dysphagia. Therefore, education about the need for urgent investigation in patients with dysphagia, either through public campaigning or incorporation in the medical and GP curriculum would help reduce delays. Reiterating the prompt utilisation of contrast radiology for diagnosis over endoscopy may also improve early detection of these cancers.

A second point is that oesophageal and gastric cancer differ significantly in epidemiological and clinical features due to differences in tumour location and pattern of dissemination. This clearly suggests the need for separate referral guidelines for both cancers. The urgent referral criteria for oesophageal cancer appropriately include dysphagia. For gastric cancer, the criteria should emphasise gastrointestinal blood loss (anaemia, haematemesis or melena) and vague constitutional symptoms of nausea, weight loss and anorexia and exclude epigastric pain. GPs, trainees, and the public should be educated about these rare but deadly cancers and these referral criteria to improve early detection rates.

The third conclusion is that patients diagnosed following an emergency presentation are more likely patients with gastric cancer. This again reiterates the importance of the inclusion of symptoms of blood loss and constitutional symptoms in the referral criteria to diagnose more gastric cancers and

subsequently reroute patients from emergency presentation to the GP pathway. Significant delays from GP referral to endoscopy were noted, with most referring to Gastroenterologists who had an endoscopy waiting time of over one month. This could be addressed through evaluating ways to increase endoscopy availability in Australia.

In summary, delays to diagnosis occur in most patients and we conclude that the five main recommendations to reduce delays involve (a) education and awareness of dysphagia as a symptom of malignancy that needs urgent investigation, (b) a new improved referral criteria developed from a better understanding of the epidemiology, pathogenesis of oesophageal and gastric cancer, (c) rapid utilisation of barium swallow as an initial diagnostic test, (d) increasing endoscopy availability through open access endoscopy and training nurse endoscopists, and (e) educating the public about symptoms warranting urgent referral through campaigns and health literacy programs

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9 APPENDICES: PEER REVIEWED PUBLICATIONS

UPPER GUT

Royal Australasian College of Surgeons

Comparison of oesophageal and gastric cancer in the evaluation of urgent endoscopy referral criteria

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Key words
endoscopy, gastric neoplasms, guideline, oesophageal neoplasms, referral and consultation.

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Accepted for publication 10 May 2021.

doi: 10.1111/ans.16984

Abstract

Background: The objective of the study is to identify differences in epidemiology and clinical presentation between oesophageal and gastric cancer and to evaluate the sensitivity of the Australian urgent endoscopy referral guidelines.
Methods: Design; Observational cohort study from February 2013 to October 2018. Setting: A single tertiary specialist oesophago-gastric cancer centre: Flinders Medical Centre, South Australia. Participants: Patients with oesophageal and gastric cancer that had surgery with curative intent 61.9% oesophageal cancer, 38.1% gastric cancer. Main outcome measures: Differences between oesophageal and gastric cancer in terms of demographical variables, first presenting symptoms and sensitivity of the Australian urgent endoscopy referral guidelines.
Results: Oesophageal cancer presented at a median age of 64.4 years old, with a male: female ratio of 6:1, and dysphagia as the first presenting symptom in 61%. Gastric cancer presented at a median age of 69.5, with a 2:1 male: female ratio and predominantly non-specific symptoms—blood loss (36%), weight loss, nausea, and anorexia (21%) and epigastric pain (13%). The Australia urgent endoscopy referral guidelines had 76% sensitivity for oesophageal cancer detection compared with a 33% sensitivity for gastric cancer in this cohort. Delays from symptom onset to referral occurred for most patients with timeframes over four times the recommended 2-week timeframe.
Conclusion: There should be a separate urgent referral guideline for oesophageal and gastric cancer. These should include dysphagia for oesophageal cancer and blood loss (anaemia, haematemesis, melaena) for gastric cancer. Delays from symptom onset to referral indicate the need for further education of the public and general practitioners on symptoms warranting urgent referral.

Introduction

Oesophageal and gastric cancer have poor survival rates, in part due to late presentation with already advanced stage disease.[1,2] In response to this, referral guidelines for these cancers have been developed to encourage earlier detection. The first national UK guideline, established in the year 2000, was the 'Two week wait' which outlined specific symptoms requiring urgent endoscopy referral within 14 days.[3] These guidelines were upgraded in 2005 to include dyspepsia in the symptom criteria.[4] Despite these implementations, no improvements have been achieved in survival rates[3,5] nor detection of early-stage cancers.[6–8] In fact, many studies have found that alarm symptoms have poor positive predictive value for upper gastrointestinal (GI) cancer detection.[9]

One reason for this may be that oesophageal and gastric cancer are viewed as one entity in most studies to date. This is despite significant differences in epidemiology, risk factors and clinical presentation between both cancers. Oesophageal cancer tends to present most commonly with reflux and dyspepsia followed by dysphagia[10] whilst gastric cancer has more non-specific symptoms such as abdominal or epigastric pain or discomfort, nausea and vomiting.[11,12] Such distinctions are expected given the differences in tumour location, surrounding structures and pattern of dissemination. There has not been, however, a dedicated study highlighting and clarifying these differences.

The current Australian national guideline titled 'Optimum care pathway for people with oesophagogastric cancer' is adapted from The National Institute for Care Excellence Guidelines on suspected cancer recognition and referral[4] and established by the Oesophagogastric multidisciplinary experts group.[13] This guideline states that patients with either: (1) rapidly progressive/new dysphagia or (2) epigastric pain for 2 weeks, must be urgently referred for endoscopy within 2 weeks. These two criteria form the high-risk category. All other 'alarm' symptoms have been listed as requiring 'prompt' investigation but unspecified and without a stipulated timeframe. More clarity on this would be helpful to referring clinicians.

The aims of this study were to: (1) highlight differences in epidemiology and clinical presentation between oesophageal and gastric cancer, (2) suggest new referral criteria that consider oesophageal and gastric cancer as separate entities, to better facilitate early identification of patients at higher risk of upper GI malignancy. This should ultimately help with the education of general practitioners and referring specialists and improve earlier recognition and referral of patients with suspected upper GI cancer.

Methods

This paper was an observational cohort study of all patients with oesophageal and gastric cancer that had surgery with curative intent from February 2013 to October 2018 at a single, tertiary, specialist, oesophago-gastric cancer centre which accounts for a majority of cases in the State of South Australia: Flinders Medical Centre. Exclusion criteria consisted of patients without adenocarcinoma and squamous cell carcinoma, those who underwent prophylactic gastrectomy, or palliative resections, those on a Barrett's surveillance programme and those referred following a diagnosis from an external endoscopy provider. Palliative patients are more likely to have late-stage disease at diagnosis and delays to referral irrespective of fulfilling the referral criteria and hence their exclusion is to (a) avoid bias in determining the impact of referral criteria on time to referral (b) to characterise epidemiology and symptoms of patients with curative disease and (c) to make this study as standardised as possible. Ethics approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee.

Patients were identified from a prospectively maintained database that supports a South Australian Statewide Upper GI cancer multidisciplinary team meeting which manages more than 90% of new upper GI cancer presentations in South Australia. Data for public and private patients managed by clinicians working at Flinders Medical Centre was derived from a retrospective review of patient case notes and electronic records.

Variables including age, gender, location, American Society of Anaesthesiologists Physical Status Classification System grade (ASA status), tumour location, stage, and histology, and first presenting symptom were compared between patients with oesophageal cancer versus gastric cancer to identify differences in epidemiology and clinical presentation. Date of symptom onset was defined as the date when the patient first experienced symptoms that led to the diagnosis. In the case of patients with long-standing dyspepsia, the date was taken to be the point of significant worsening in these symptoms.

The percentage of patients who fulfilled urgent referral criteria in the Australian Guidelines was compared between oesophageal and gastric cancer patients. Of those that fulfilled these criteria, delays to referral were defined as those not referred within 2 weeks.

Stata15.1 (StataCorp, Texas) was used for analysis. Independent *t*-tests, chi-square, Mann Whitney or Wilcoxon rank sum tests were used to identify risk factors for delays.

Results

Comparing epidemiology and clinical features of oesophageal and gastric cancer

Of the 126 patients included in this study, 78 had oesophageal cancer and 48 had gastric cancer. The mean age of symptom onset was 68.8 years for gastric cancer and 63.9 years for oesophageal cancer patients. The mean age of diagnosis was 69.6 years for gastric cancer, compared with 64.4 years for oesophageal cancer ($p = 0.01$).

Age of symptom onset peaks in the 60–69 age bracket for oesophageal cancer, whilst gastric cancer peaks later in the 70–79 years age group (Fig. 1). Oesophageal cancer symptom onset ranged from 43 to 82 years old with an increasing incidence up to the peak age bracket and no patients younger than 40 years old when symptoms commenced. This contrasts with a less predictable range of age of symptom onset for gastric cancer, from 39 to 92 years old (Fig. 1).

The male to female ratio is significantly higher for oesophageal cancer, being 6:1 compared with 2:1 for gastric cancer ($p = 0.01$) (Table 1). Staging differed between both cancers ($p = 0.006$), with one-third of gastric cancer patients having stage IV disease at resection compared to 10% for oesophageal cancer.

Clinical presentation was significantly different between the two cancers ($p = <0.001$) (Table 1). The first symptoms or signs for gastric cancer were blood loss in 17 (36%) of which 13 had anaemia, and four with melena and/or haematemesis. This is followed by six (13%) abdominal pain, six (13%) dyspepsia, five (11%) dysphagia and three (6%) with no or other non-specific symptoms. The first symptoms or signs for oesophageal cancer were dysphagia in 46 (61%), abdominal pain in eight (11%), dyspepsia/indigestion in eight (11%), blood loss in five (7%) which included anaemia in two and melaena in three.

Of the gastric cancers, 22 were in the gastric antrum, 19 in the body and seven in the cardia. This can be classified as 41 (85%) in the non-cardia region and seven (15%) cardia region. For oesophageal cancers, 45 were in the distal oesophagus, 23 at the gastro-oesophageal junction (GOJ), one in the cardia, five in the mid oesophagus, and none in the upper oesophagus and four elsewhere unspecified. Overall, 80% of oesophageal cancers were therefore in the lower third (namely GOJ, cardia and distal third of oesophagus) (Fig. 2).

Evaluation of the urgent referral criteria

Based on a recommended referral timeframe of 2 weeks from symptom onset the majority of patients had delays to referral. In

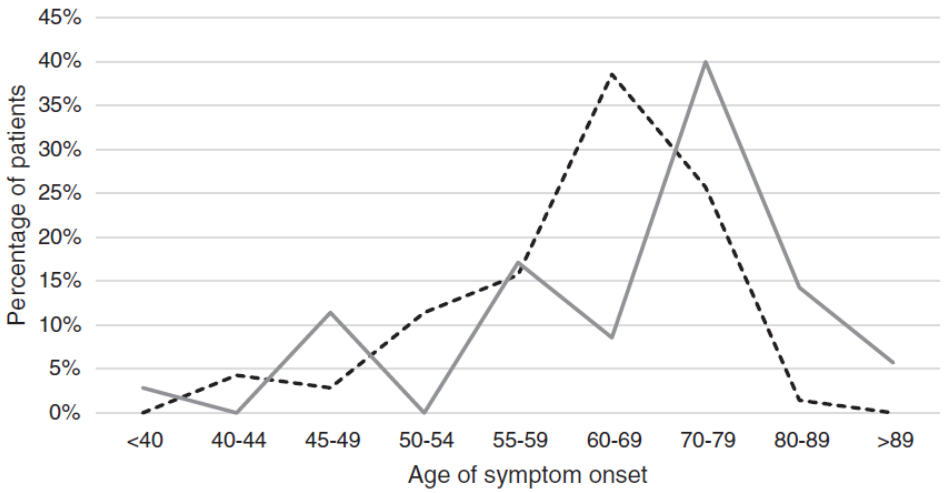

Fig 1. Comparison of age of symptom onset between oesophageal and gastric cancer patients. (----), Oesophageal cancer; (——) gastric cancer.

oesophageal cancer patients, 74% (40 patients) had delayed referral; in gastric cancer patients, 54% (seven patients) had a delayed referral. A greater proportion of patients (76%) with oesophageal cancer fulfilled the urgent referral criteria compared with only 33% of gastric cancer patients (Table 2). Patients that fulfilled the urgent referral criteria for oesophageal cancer had a median duration of 10 weeks from symptom onset to referral (Table 3), which was longer than those who did not fulfil the urgent referral criteria (4 weeks). Similarly, patients that fulfilled the urgent referral criteria for gastric cancer had longer delay than those who did not fulfil the referral criteria, median 13 weeks compared to 8 weeks from symptom onset to referral.

Discussion

Statement of principal findings

The study confirms the median age of 64.4 for symptom onset for oesophageal cancer with no oesophageal cancer cases seen below 43 years. This is consistent with the majority of other

Table 1 Epidemiology and clinical presentation of oesophageal cancer compared to gastric cancer

Characteristic	Oesophageal cancer ($n = 78$)	Gastric cancer ($n = 48$)	p-value
Age at symptom onset, mean (SD)	63.91 (9.33)	68.84 (13.13)	0.03
Age at diagnosis, mean (SD)	64.44 (9.27)	69.56 (13.31)	0.01
Gender, *n* (%)			
Male	67 (85.9)	32 (66.7)	0.01
Female	11 (14.1)	16 (33.3)	
Location, *n* (%)			
Rural	30 (38.5)	12 (25.0)	0.12
Local	48 (61.5)	36 (75.0)	
ASA status, *n* (%)			
1	7 (9.0)	3 (6.3)	0.38
2	38 (48.7)	19 (39.6)	
3	33 (42.3)	25 (52.1)	
4	0 (0.0)	1 (2.1)	
Histology, *n* (%)			
Adenocarcinoma	68 (87.2)	48 (100.0)	0.01
Squamous cell carcinoma	10 (12.8)	0 (0.0)	
First symptom, *n* (%)			
Dysphagia	46 (60.5)	5 (10.6)	<0.001
Odynophagia	4 (5.3)	0 (0.0)	
Dyspepsia/indigestion	8 (10.5)	6 (12.8)	
Weight loss, nausea, anorexia	3 (3.9)	10 (21.3)	
Anaemia, haematemesis, melena	5 (6.6)	17 (36.2)	
Abdominal pain	8 (10.5)	6 (12.6)	
No symptoms	1 (1.3)	2 (4.3)	
Other	1 (1.3)	1 (2.1)	
Stage, *n* (%)			
I	34 (43.5)	15 (33.3)	0.006
II	6 (7.69)	7 (15.6)	
III	30 (38.5)	9 (20.0)	
IV	8 (10.3)	14 (31.1)	

SD, standard deviation.

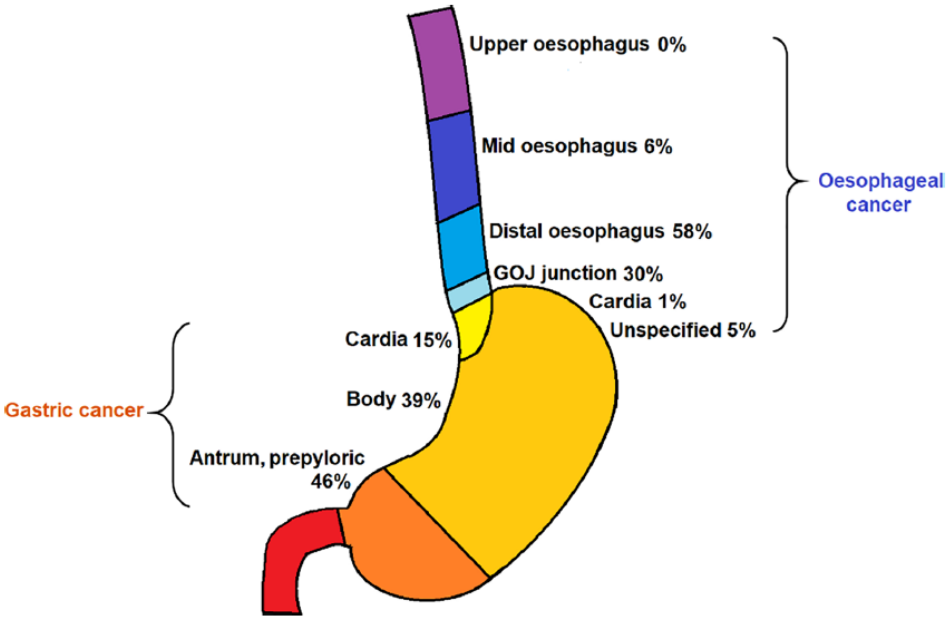

Fig 2. Tumour location comparison for oesophageal and gastric cancer.

epidemiological studies.[14–17] In contrast, gastric cancer peaked in the older 70–79 age group, with a median age of 69.6 years, and appears more unpredictable in age onset, with one case occurring in the third decade. This is significantly lower than two Caucasian studies,[14,18] and two Asian studies[17,19] which report a median age of late 50s to early 60s.

Oesophageal cancer has a much higher male: female ratio of 6:1 compared to gastric cancer (2:1). This is comparable to other studies reporting high male: female ratios of 6:1,[20] 10:1,[14] 3.2:1,[21] 2.7:1[17] and 2.5:1[15] for oesophageal cancer and lower ratios for gastric cancer of 1.1:1,[22] 1.6:1,[7] 2:1,[14] 2.1:1[18] and 1.3:1.[17] Awareness of this significantly higher male prevalence in oesophageal cancer can help sharpen its recognition in clinical practice.

Whilst non-cardia cancers have always been more prevalent than cardia cancers, as demonstrated in this study (82%), the proportion of cardia versus non-cardia cancers reported vary depending on geographical location of the study.[23] In studies from China, Iran and Japan, the lower third of the stomach has the greatest proportion of tumours[19,20] and cardia the least.[24] In these areas, the higher use of pickled foods[25,26] and persistent rates of *Helicobacter pylori* are associated with non-cardia gastric cancer.[27] European studies on the contrary report a higher proportion of tumours in the upper gastric or cardia region, at 66%, 53% and 30%.[7,14,28] There has been an increase in cardia gastric cancer in from 33% to 53% over a 10-year period (1993–2003).[14] These changes are thought to be associated with changes in lifestyle, rising rates of reflux and increasing prevalence of obesity.

In this study, 87% of oesophageal cancer patients had adenocarcinoma, and the remaining were squamous cell carcinoma. This is similar to other UK studies which report between 70% and 75%[15] of oesophageal cancers are adenocarcinoma. In contrast, studies from China and India report reversed ratios, with 70%–89% having squamous cancers and 7.5%–29% adenocarcinoma.[21,29] Again, the higher prevalence of adenocarcinoma in Western countries is thought to be related to lifestyle factors, obesity and reflux, and lower rates of squamous carcinoma correlating with lower smoking rates, achieved through years of public campaigning.

Dysphagia is significantly more common in oesophageal cancer (61%). Most oesophageal tumours were located at the gastro-oesophageal junction or in the distal oesophagus (80%) in keeping with the higher proportion of adenocarcinoma. This is also where the lumen is narrower and less compliant, and therefore dysphagia is more likely to manifest when the disease is locally advanced. Several studies on oesophageal cancer patients have reported high

Table 2 Sensitivity of urgent referral criteria in oesophageal cancer versus gastric cancer patients

	Oesophageal cancer, $n = 78$, n (%)	Gastric cancer, $n = 48$, n (%)	p-value
Patients who fulfilled the urgent referral criteria	58 (76)	15 (33)	<0.001
Patients who did not fulfil the urgent referral criteria	18 (24)	30 (67)	

Table 3 Impact of urgent referral criteria on delays to referral and diagnosis in oesophageal cancer versus gastric cancer patients

	Median weeks from symptom onset to referral		
	Oesophageal cancer, $n = 78$	Gastric cancer, $n = 78$	p-value
Patients who fulfilled the urgent referral criteria	10 (4, 19)	13 (3, 20)	0.66
Patients who did not fulfil the urgent referral criteria	4 (1, 17.5)	8 (1, 24)	0.40

rates of dysphagia as a first presenting symptom, including 100%,[29] 71%[21] and 50%.[14,20] Studies that combine oesophageal and gastric cancers understandably report lower rates of dysphagia, including 24%,[28] 12%,[30] likely due to the lack of dysphagia in gastric cancer skewing the data. Dysphagia was only present in 11% of gastric cancer patients in this study. Given the high prevalence of dysphagia in oesophageal cancer and its indication of locally advanced disease, this should be included as a symptom in a separate urgent referral guideline for suspected oesophageal cancer patients only.

Gastric cancer presents with many non-specific symptoms including blood loss (35%), nausea, weight loss and anorexia (21%), making detection harder. This may explain the greater proportion of stage IV disease at resection (31%) for gastric cancer patients compared to oesophageal cancer patients (10%) ($p = 0.006$) although this may also be skewed by more detailed selection criteria and investigations for surgical resection between these pathologies. The current urgent referral criteria for endoscopy include epigastric pain, supported by a few studies where epigastric pain was a common presenting symptom of gastric cancer: occurring in 52%–75%.[22,31] However, there are many other studies where epigastric pain is reported less commonly at rates of 31%,[21] 32%[11] and 44%[19] and having no significant difference in rates when compared to symptoms of weight loss, GI bleeding, anorexia or fatigue.[18]No one symptom stands out for gastric cancer. Nevertheless, epigastric pain in this study only occurred in 13% of gastric cancer patients, suggesting that it is of poor diagnostic accuracy and should not form part of the urgent referral criteria.

Part of the difficulty in diagnosis is the location of tumours away from the less compliant gastro-oesophageal junction, within the larger stomach cavity (82%). Considerable growth in tumour size would be needed before causing dysphagia from luminal narrowing, dyspepsia from disruption to the gastro-oesophageal junction pressure gradient, or abdominal pain from compressing other structures or invasion of local structures. However, release of inflammatory cytokines from gastric cancer can cause nausea, weight loss and anorexia and the presence of a highly vascular tumour in a strongly acidic environment is associated with friability and ulceration, with consequent associated blood loss even in early stages. Early signs would include occult blood loss (anaemia) and constitutional symptoms (nausea, anorexia, weight loss) whilst later signs would be epigastric pain, dyspepsia and dysphagia. Therefore, blood loss and a combination of nausea, anorexia and weight loss are recommended to be included as symptoms in a separate urgent referral recommendation for gastric cancer.

The Australian urgent referral criteria for oesophago-gastric cancers specify new/progressive dysphagia or new/progressive epigastric pain for 2 weeks as warranting urgent specialist referral within 2 weeks of onset. In this study, these criteria had 76% sensitivity for oesophageal cancer due to the high proportion of patients presenting primarily with dysphagia (61%). On the contrary, the majority of patients with gastric cancer had symptoms which did not fulfil these urgent referral criteria (67% vs. 33%), including blood loss (37%) and constitutional symptoms (27%). This suggests that these criteria would be better separated between these two very different upper GI cancers for gastric cancer utilising blood loss (anaemia, haematemesis and melaena) as one defining criteria and constitutional symptoms such as nausea, weight loss and anorexia being more common between the cancers.

Despite a high proportion of oesophageal cancer patients who fulfilled the referral criteria (76%), delays to referral were still present in 75% of oesophageal cancer patients. This suggests that general practitioners (GPs) and referring doctors need to be educated more about the criteria and the importance of urgent endoscopy referral in any patient presenting with progressive dysphagia. This point needs greater emphasis in the training curriculum for medical students, junior doctors and primary care trainees. Although it may also transpire that patients with dysphagia present late as they do not connect dysphagia with cancer and are willing to tolerate this symptom until it either limits oral intake and becomes uncomfortable. Public health campaigns are needed to raise awareness amongst the community about dysphagia as a symptom of oesophageal cancer to reduce delays to referral.

Limitations include the absence of data on date of first GP consultation, preventing detailed analysis of causes of delays to referral, and data being collected from a single centre study, albeit the largest centre in the state, which may limit generalisation of findings to the wider population.

Conclusion

Oesophageal and gastric cancer differ significantly in clinical and epidemiological features due to disparities in tumour location, surrounding structures and pattern of dissemination. This clearly indicates the need for separate referral guidelines for both cancers.

The urgent referral criteria for oesophageal cancer appropriately include dysphagia. However, the criteria for gastric cancer should emphasise GI blood loss (anaemia, haematemesis or melena) and vague constitutional symptoms of nausea, weight loss and anorexia and exclude epigastric pain. GPs, trainees and the public should be educated about these rare but deadly cancers.

Conflict of interest

None declared.

Author contributions

Feruza Kholmurodova: Formal analysis; software. **Jeff Bull:** Data curation; investigation; resources. **Tim Bright:** Supervision; writing-review & editing. **David Watson:** Conceptualization; supervision; writing-review & editing.

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