

**A prospective analysis of factors influencing
outcome and survival in upper gastrointestinal
cancer in a centralised UK cancer network**

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For my wife Emily, son Charlie, and daughter Orla

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List of Abbreviations

ACA Adenocarcinoma
AJCC American Joint Committee on Cancer
ASA Association of Anaesthesiologists of America
ASGBI Association of Surgeons of Great Britain and Ireland
AT Anaerobic Threshold
AUGIS Association of Upper Gastrointestinal Surgeons
BASO British Association of Surgical Oncology
BF Body fat
BIA Bioelectrical Impedance Analysis
BRCA2 Breast Cancer 2
BSG British Society of Gastroenterology
CaNISC Cancer Network Information System Cymru
CCLOS Critical Care length of stay
CD Clavien-Dindo
CI Confidence Interval
CPEX Cardiopulmonary Exercise Testing
CRM Circumferential Resection Margin
CT Computerised Tomography
dCRT definitive Chemoradiotherapy
DoH Department of Health
ECF Epirubicin Cisplatin infused 5-Fluorouracil
ECV Extracellular volume
ECX Epirubicin Cisplatin Capecitabine
EMR Endoscopic Mucosal Resection
ERAS Enhanced Recovery after Surgery
EUS Endoscopic Ultrasound
FAP Familial Adenomatous Polyposis

FFM Fat Free Mass
GP General Practitioner
GFR Glomerular Filtration Rate
GORD Gastro Oesophageal Reflux Disease
HD Health Deprivation
HDU High Dependency Unit
HER Human Epidermal Growth Factor Receptor
HGD High Grade Dysplasia
HMSO Her Majesty's Stationary Office
HNPCC Hereditary Non Polyposis Colorectal Cancer
HR Hazard Ratio
HRQL Health Related Quality of Life
IARC International Agency for Research on Cancer
ICV Intracellular Volume
IMD Index of Multiple Deprivation
IOG Improving Outcomes Guidance
LGD Low Grade Dysplasia
LMM Lean Muscle Mass
LOHS Length of Hospital Stay
MDT Multi-Disciplinary Team
MIO Minimally Invasive Oesophagectomy
MRC Medical Research Council
NAEDI National Awareness and Early Diagnosis Initiative
NOGCA National Oesophago-Gastric Cancer Audit
OGD Oesophago-Gastro-Duodenoscopy
ONS Office for National Statistics
PET Positron Emission Tomography
PhA Phase Angle
POSSUM Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity

pTNM Pathological Tumour Node Metastasis
RCSE Royal College of Surgeons of England
RFA Radiofrequency Ablation
rTNM Radiological Tumour Node Metastasis
SCC Squamous Cell Carcinoma
SED Socio-economic Deprivation
SEMS Self-Expanding Metal Stents
SMD Submucosal Dissection
TBW Total Body Water
THO Trans-hiatal Oesophagectomy
TNM Tumour Nodes Metastasis
TTO Trans-thoracic Oesophagectomy
UGI Upper Gastrointestinal Cancer
UICC Union for International Cancer Control
USC Urgent Suspected Cancer
WIMD Welsh Index of Multiple Deprivation

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SUMMARY

This thesis investigates prognostic factors influencing outcome and survival in patients managed by the South East Wales Upper GI cancer network. The hypotheses tested were: Socio-economic deprivation and health deprivation adversely influence outcome in patients undergoing surgery for oesophageal and gastric cancer; Patient delay accounts for the majority of the total delay encountered in the diagnosis and treatment of oesophago-gastric cancer and deprivation is an important factor in this regard; Body composition and sarcopenia as measured by Bioelectrical Impedance Analysis (BIA) are important prognostic indicators; Centralisation of oesophago-gastric cancer services significantly improves outcome and survival.

In a consecutive cohort of 1185 patients survival was associated with multiple deprivation ($P < 0.0001$) and health deprivation ($P < 0.0001$). Total delay consisted of the following components: patient delay (76%); practitioner delay (1%) and hospital delay (23%). Factors influencing patient delay were deprivation ($p = 0.005$) and gender ($p = 0.030$). Survival was significantly related to overall delay ($p = 0.010$). In 125 patients who underwent BIA testing open and close laparotomy was significantly associated with FFM% ($p = 0.027$), and BF% ($p = 0.030$). Post-operative morbidity (Clavien-Dindo ≥ 3) was associated with intracellular fluid volume (ICV) ($p = 0.018$), total body water content ($p = 0.019$), and sarcopenia ($p = 0.045$). Critical care length of stay was associated with ICV ($p = 0.009$), lean muscle mass ($p = 0.006$), the phase angle ($p = 0.025$) and sarcopenia ($p = 0.011$). Treatment with curative intent increased from 21.6% to 29.6% of patients before and after centralisation respectively ($p = 0.002$). Serious post-operative morbidity (Clavien-Dindo ≥ 3) decreased after centralisation ($p = 0.194$), and there were significant reductions in critical care length

of stay ($p < 0.0001$), with overall length of hospital stay reduced by 2.5 days ($p = 0.008$). On univariate analysis of factors influencing two-year survival centralisation was statistically significant ($p = 0.001$).

Chapter 1

Introduction and a review of the literature

1.1 Historical Perspective

The earliest written description of oesophageal cancer appears to come from Egypt between 3000 and 2500BC after the discovery in 1862 of an ancient manuscript known as the Smith Surgical Papyrus. The document contains a case entitled “A Gaping Wound of the Throat Penetrating the Gullet” and includes the clinical observations, anatomy, and pathology of oesophageal cancer (Eslick 2009). Reports of oesophageal cancer also appear in China over 2000 years ago where it was referred to as “Ye Ge”, meaning dysphagia and belching, and the authors at the time suggested this particular cancer was the result of “heavy indulgence of heated liquors” (Qian 1961). The Roman physician and philosopher Galen (125-200 AD) subsequently published work describing the possibility of a fleshy growth partially or completely obstructing the passage of food down the gullet.

The word oesophagus is derived from the ancient Greek *oisophágos*, *oisein* meaning to carry and *phagos* meaning food. Middle age developments in the understanding and treatment of oesophageal cancer include the suggestion by the Spanish physician Avenzoar (1090-1162) to “introduce food into the stomach by a silver tube and the use of nutritive enemata”, and the subsequent development of the oesophagoscope by Kussmaul (1822-1902) in 1868. Kussmaul’s son-in-law Vincenz Czerny (1842-1916) performed the first successful resection of a human cervical oesophageal carcinoma in 1877, after which the patient survived for 1 year.

In 1946 Ivor Lewis, a pioneering Welsh surgeon trained in Cardiff, revolutionised oesophageal surgery after performing an oesophagectomy and oesophago-

gastrectomy through a right thoracotomy. Lewis published his seminal paper “The surgical treatment of carcinoma of the oesophagus with special reference to a new operation for growths of the middle third” in which he described seven such cases with an operative mortality of 29% and five-year survival of 19% (Lewis 1946). Humphrey Bogart, a renowned heavy drinker and smoker, died from oesophageal cancer in 1957, and the last words he uttered were “I should never have switched from scotch to martinis”.

The first possible reference to gastric cancer dates back to 1600 BC and was reported in the Ebers papyrus, found with an ancient Egyptian mummy at Luxor in 1873. The prominent Arabic physician and philosopher Avicenna also described a gastric cancer in his 11th century publication *Medical Encyclopaedia*. Further understanding of gastric anatomy and disease was however curtailed throughout the Dark and the Middle Ages due to the Catholic Church’s prohibition of the examination of human corpses, and the main anatomical reference for those times was the anatomy of a monkey’s stomach, described by Galen (Santoro 2005). It was only in the 18th century, and particularly during the Renaissance, that medieval concepts changed and theories regarding the origins of cancer were modified.

The modern concept of oncology was first proposed in a thesis entitled “Dissertatio Accademica de Cancro” by Peyrile in Lyon in 1774. Throughout the 18th century however, gastric cancer remained enigmatic until the description of benign and malignant gastric ulcers by Cruveilhier in 1835. In the interim, Napoleon Bonaparte died in May 1821 suffering from abdominal pain, vomiting, anorexia and diarrhoea. On autopsy a “cancerous ulcer” was discovered but debate persists to this day as to whether he died from gastric cancer or he was the victim of chronic arsenic poisoning. The French surgeon Jules Emile Pean performed the first gastric

resection for cancer in 1879 but the patient only survived until the 5th post-operative day.

The first successful operation, a subtotal resection with gastro-duodenal anastomosis, was performed in January 1881 by Theodor Billroth in Vienna. The patient was a 43-year-old female who had presented with gastric outlet obstruction secondary to a pyloric carcinoma. In modern terms the tumour would be described as a T3N2/3 Stage IIIb mucinous adenocarcinoma. The patient was discharged 26 days post-operatively but died of recurrence after some 4 months. When he retired fourteen years later Billroth had performed a total of 257 sub-total gastrectomies. The first total gastrectomy was performed in 1897 by Karl Schlatter, a 32 year old surgeon working in Zurich. He performed a total gastrectomy and oesophago-jejunosomy on a 56-year-old woman for a diffuse gastric cancer. The patient survived for 14 months before also succumbing to recurrent disease. These initial advances have since culminated in the contemporary practice of gastrectomy with radical D2 lymphadenectomy. Notable people to have died from gastric cancer include the actor John Wayne and the Irish writer James Joyce.

1.2 Epidemiology

1.2.1 Oesophageal Cancer

Oesophageal cancer, including both adenocarcinoma and squamous cell carcinoma (SCC), is the 8th most common cancer worldwide and ranks sixth in terms of mortality (Zhang 2013). Oesophageal adenocarcinoma was once an exceedingly rare histological type of oesophageal cancer but the incidence has increased greatly in recent times, by up to 600% since the 1970s (Rubenstein 2015). On a global scale however, SCC remains the predominant form (Arnold et al. 2014). In 2011 there were 8,332 new cases of oesophageal cancer in the UK accounting for nearly 3% of all new cases: 5,582 (67%) in men and 2,750 (33%) in women (Cancer Research UK 2015).

1.2.2 Gastric Cancer

According to the most recent estimates from the International Agency for Research on Cancer (IARC), gastric cancer is now the fifth most common cancer in the world after lung, breast, colorectal and prostate cancer respectively, with nearly one million new cases and 723,000 deaths in 2012 (Ferlay et al. 2013). The disease accounted for 7% of the total new cancer cases and 9% of the total cancer deaths, with over 70% of these deaths occurring in less developed regions (Oh et al. 2014). In the UK there were just over 7,000 new cases of gastric cancer diagnosed in 2011, accounting for 2% of all new cases: 4,615 (65%) in men and 2,474 (35%) in women (Cancer Research UK 2015).

1.3 Aetiology

1.3.1 Oesophageal Adenocarcinoma

The prevalence of oesophageal adenocarcinoma is increasing rapidly in Western society, presumably linked to the concurrent obesity epidemic. Recognised risk factors include gastro-oesophageal reflux disease (GORD), obesity, tobacco use, increasing age, and male gender. Furthermore, the disease is most common in industrialised countries with populations of predominantly Northern European origin (Bosetti et al. 2008). Barrett's oesophagus, whereby the normal squamous epithelium is replaced by specialised intestinal columnar epithelium, is the only known precursor lesion for this cancer (Rubenstein 2015).

Barrett's oesophagus develops secondary to GORD when recurrent reflux causes erosive oesophagitis and, after an aberrant healing process in predisposed individuals, the normal squamous cell lining of the distal oesophagus is replaced by a metaplastic columnar-lined epithelium (Souza et al. 2008). Previous research has shown a two to four-fold increased risk of developing cancer in patients with a history of GORD (Chow et al. 1995). Moreover, there is a linear relationship between risk of malignancy and severity of GORD as patients with recurrent and prolonged symptoms have an 8-fold increased risk of developing adenocarcinoma compared with patients who have minimal symptoms (Lagergren et al. 1999). The development of adenocarcinoma in a Barrett's segment follows a progressive sequence from intestinal metaplasia to low grade dysplasia (LGD), then high grade dysplasia (HGD) and finally to cancer (Jankowski et al. 1999).

Obesity contributes to the development of a tumour by two mechanisms; mechanical and hormonal. Obesity-related hiatal herniation increases the risk of GORD with

resultant recurrent erosive oesophagitis. From a hormonal perspective obesity is associated with insulin resistance which in turn is linked with multiple epithelial cancers and the metabolic syndrome (Drahos et al. 2014; Lindkvist et al. 2014). Obesity also causes altered levels of circulating peptide levels which in turn are associated with Barrett's oesophagus (Garcia et al. 2014). Alcohol use and *Helicobacter pylori* however, are thought to protect against adenocarcinoma (Freedman et al. 2011; Islami et al. 2008).

1.3.2 Oesophageal Squamous Cell Carcinoma

Alcohol and tobacco are the main risk factors for SCC, and oesophageal squamous dysplasia has been identified as the precursor lesion. Patients with mild, moderate or severe dysplasia have a 3, 10 or 30 fold greater risk respectively of developing SCC (Wang et al. 2005). Oesophageal SCC is three to five times more likely among people who consume three or more alcoholic drinks daily (Rustgi and El-Serag, 2014), and up to seven times more likely in people who smoke tobacco (Kamangar et al. 2009). Furthermore, there appears to be a synergistic effect between the two whereby individuals who drink more than 1.5 bottles of wine and smoke 10 to 30 cigarettes daily have approximately a 150-fold increased risk (Salaspuro 2003).

Achalasia, an oesophageal motility disorder which causes oesophagitis due to stasis and resultant fermentation of food residue, is associated with a ten-fold increased risk of developing oesophageal SCC (Zendehdel et al. 2011). The rare autosomal dominant disorder Tylosis Palmaris et Plantaris, and Paterson-Brown-Kelly syndrome characterised by an inherent epithelial atrophy or hyperkeratinisation are also associated with developing oesophageal SCC (Blaydon et al. 2012; Chisholm 1974). In addition, the tumour suppressor gene p53 has been found to be abnormal

and responsible for the aberrant progression from normal oesophageal mucosa to cancer in up to half of cases of oesophageal SCC (Casson et al. 1998).

1.3.3 Gastric Cancer

Gastric carcinoma has a complex and multifactorial pathogenesis with both an environmental and genetic aetiology. It was previously thought that N-nitroso compounds (mostly nitrosamines) were the principal causal factor but no proof of this causality has been found. In more recent times the emphasis on investigation has shifted to bacterial aetiology, and more specifically the role of *Helicobacter Pylori* (*H.Pylori*) (Correa and Schneider, 2015). In 1994 the IARC classified *H. pylori* as a class I human carcinogen (IARC 1994). The chronic active inflammatory response to the infection caused by *H. Pylori* is thought to induce gastric neoplasia via both the immune response elicited and the resulting damage from oxidative stress. More latterly, the long suspected influence of genetic susceptibility and the role of polymorphisms in the inflammatory cytokine genes of the host have come to the forefront (Correa and Schneider, 2015). The gastric microenvironment and acid secretion are also thought to play a key role in the pre-cancerous process. Patients with gastric ulcers have a tendency towards hypochlorhydria and the pro-inflammatory cytokine Interleukin-1 β . IL1 β is a potent inhibitor of acid secretion (100 times more potent than proton pump inhibitors), and previous studies investigating the IL1 β gene cluster in gastric cancer patients have shown a four-fold increased risk of developing a tumour (El-Omar et al. 2003).

Gastric cancer has also been attributed to a number of dietary and lifestyle factors. Salted, smoked and preserved foods are associated with an increased risk of gastric cancer, whereby prolonged or excessive consumption leads to atrophic gastritis and

the generation of carcinogenic N-nitroso compounds (Gore 1997). Cigarette smoking is associated with a 2 to 3 times increased risk of proximal gastric cancer (Devisa et al. 1998; Haung et al. 2000).

The US National Cancer Institute examined ethnicity as a risk factor for gastric cancer and found people of Japanese and Korean origin at particularly high risk compared with Caucasians. Gastric carcinoma can occasionally develop in families with germline mutations in the p53 tumour suppressor gene, e.g.; Li-Fraumeni syndrome and BRCA2, or as part of the hereditary non-polyposis colon cancer (HNPCC) syndrome, familial adenomatous polyposis (FAP) and Peutz-Jeghers syndrome (Fenoglio-Preiser et al. 2000). Other factors associated with an increased risk of gastric cancer include chronic atrophic gastritis (e.g. pernicious anaemia), previous gastric surgery, hypertrophic gastropathy (Menetrier's disease), gastric polyps, low socioeconomic status, and obesity (Gore 1997).

1.4 Diagnosis

1.4.1 Symptoms

The most important prognostic factor in patients diagnosed with oesophageal or gastric cancer is the stage of disease at presentation, yet incurable metastatic disease is still diagnosed in as many as 50% of patients at first presentation (Allum et al. 2002). Patients with upper gastrointestinal cancer typically present with dyspepsia, progressive dysphagia often associated with weight loss and fatigue, or on occasion with iron deficiency anaemia.

British Society of Gastroenterology (BSG) guidelines recommend that all patients over 55 years of age with recent onset dyspepsia, and all patients with alarm symptoms suggestive of UGI cancer irrespective of age should be referred for rapid access endoscopy and biopsy (Allum et al. 2011). Moreover, the UK Department of Health has specified that these urgent investigations be performed within two weeks of referral (Dept of Health 2000).

1.4.2 Screening

At present there is no screening programme for UGI cancer in the UK, but in countries with a high burden of disease such as Japan and the Republic of Korea barium-meal photofluorography and upper endoscopy were introduced in 1960 and 1999 respectively. The relative 5-year survival rates for gastric cancer in these countries is around 70%, compared with less than 30% in most other countries without national screening programmes (Park et al. 2014). Endoscopic screening and non-endoscopic balloon brush cytologic testing have previously been performed in regions of China and may have merit (Rustgi and El-Serag 2014).

For patients with known Barrett's oesophagus however, endoscopic surveillance is recommended every three years. Patients in whom adenocarcinoma is detected through surveillance for Barrett's are more likely to have early-stage disease, receive curative therapy, and survive longer than patients who present with symptoms and in whom cancer is then subsequently detected (Kearney et al. 2003; Cooper et al. 2009).

1.4.3 Endoscopy

The gold standard for diagnosis of UGI cancer is oesophagogastro-duodenoscopy (OGD), allowing direct visualisation of the lesion and biopsy or cytological brushings for histological confirmation. As discussed previously the UK Department of Health has recommended patients older than 55 years of age with new onset or persistent dyspepsia, or patients of any age who present with alarm symptoms should undergo endoscopy, and furthermore recommends these investigations be performed within two weeks of referral (Allum et al. 2011). For patients suspected of having a gastric tumour endoscopy is the most sensitive and specific method of diagnosis (Karpeh et al. 1998).

In cases where OGD is not indicated or tolerated a barium swallow will outline any mucosal irregularities or strictures, but carries the inherent disadvantage of being unable to obtain a biopsy for histological diagnosis. Barium studies for the detection of carcinoma of the oesophagus and oesophago-gastric junction have been found to have a positive predictive value of 42% (Levine et al. 1997).

1.5 Staging Classification

1.5.1 Tumour Nodes Metastases (TNM) Classification

The contemporary TNM classification system for staging solid tumours was originally devised by Professor Pierre Denoix between 1946 and 1952 (Denoix 1946) and has subsequently been accepted for use by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC). The TNM system describes the anatomic extent of cancer and is based on three factors; the size and extent of the primary tumour (T stage), the number of regional lymph node metastases (N stage), and the presence or absence of distant metastases (M stage). Such an accurate and unified classification system facilitates the planning of appropriate treatment, estimating prognosis and exchange of information between trial centres.

1.5.2 T Stage

The T stage describes the depth of invasion of the primary tumour and is essentially similar for both oesophageal (Table 1.1) and gastric cancer (Table 1.2). The least invasive tumours are limited to the lamina propria and/or the submucosa and are classified as T1 tumours. Tumours which invade the muscularis are T2, T3 tumours traditionally invaded the serosa or adventitia for gastric or oesophageal cancers respectively, and T4 tumours have spread to invade adjacent structures.

The 7th edition of the TNM classification system however introduced some modifications whereby T3 gastric cancer represents subserosal invasion, T4a serosal penetration and T4b invasion of adjacent structures. For oesophageal cancer, Tis denotes carcinoma in-situ or HGD, T1a represents invasion of the lamina

propria, and T1b submucosal invasion. T4 has been sub-classified whereby T4a represents invasion of the pleura, pericardium, peritoneum or diaphragm and T4b invasion of the aorta, trachea or bone (Sobin 2009). Early tumours confined to the mucosa and submucosa have previously been shown to confer a significantly better prognosis than more advanced tumours (Tachibana et al. 2000), and T stage has been found to be an independent predictor of survival after surgery (Khan et al. 2004).

1.5.3 N Stage

The N stage describes the extent or absence of regional lymph node metastasis and is used to determine the most appropriate treatment using multi-modal therapy (Mariette et al. 2003; Kunisaki et al. 2005). A description of the TNM 7 N stage classification for oesophageal and gastric cancer is provided in Tables 1.1 and 1.2 respectively.

By tradition an operable tumour has been defined as of radiological stage N0 or N1 (Earlam 1980). The accuracy of the N stage is dependent on the number of lymph nodes harvested, and a minimum count of 10 nodes should be examined to designate stage N0 in oesophageal cancer (Twine et al. 2009) and 15 nodes for gastric cancer (Bouvier et al. 2002). Furthermore, the number of malignant lymph node metastases is a key prognostic factor predicting outcome after surgical resection for oesophageal cancer (Kawahara et al. 1998). In oesophageal disease carcinomas arising in the upper oesophagus drain to cervical or upper mediastinal nodes while those arising from the mid or lower oesophagus spread to lower mediastinal or perigastric nodes, and skip metastases are not infrequent (Glickman 2003).

1.5.4 M Stage

The M stage is the assessment of distant metastases whereby M0 represents tumours with no metastases and M1 tumours with distant metastases. In gastric cancer the M stage is simply divided into M0 and M1 representing the absence or presence of distant metastases respectively. This classification has now also been adopted in staging oesophageal cancer whereby metastases in the coeliac lymph nodes are no longer classified as M1a (Sobin 2009), thereby simplifying oesophageal cancer into M0 or M1, as for gastric cancer.

Table 1.1 TNM 7 for Oesophageal cancer

T stage	N Stage
Tis = Carcinoma in-situ	
T1a Tumour invades Lamina propria	N1=1-2 nodes
T1b Tumour invades Submucosa	N2=3-6 nodes
T2 Tumour invades Muscularis propria	N3=>6 nodes
T3 Tumour invades Adventitia	
T4a Tumour invades pleura, pericardium, peritoneum, diaphragm	
T4b Tumour invades trachea, aorta, vertebrae	

Table 1.2 TNM 7 for Gastric Cancer

T stage	N Stage
T1a Tumour invades Lamina propria	N1=1-2 nodes
T1b Tumour invades Submucosa	N2=3-6 nodes
T2 Tumour invades Muscularis propria	N3a=7-15 nodes
T3 Tumour invades subserosa	N3b=16 nodes
T4a Tumour perforates serosa	
T4b Tumour invades adjacent structures	

1.6 Pre-operative Staging

Approximately 50% of patients with upper GI cancer have metastatic disease at first presentation, and the two most important prognostic indicators for oesophageal cancer are depth of tumour penetration and lymph node involvement (Iyer 2004). Initial assessment must therefore stage the disease as accurately as possible in order to determine which patients may be suitable for surgical resection. In the case of early tumours precise localised staging is performed to assess suitability for endoscopic mucosal resection (EMR). For more advanced tumours depth of invasion with reference to surgical margins, clear delineation of cranio-caudal and radial margins, and the presence and extent of lymph node metastases are assessed before tailoring an individual patient's treatment. The principal imaging modalities are computed tomography (CT), positron emission tomography combined with CT (PET/CT), endoscopic ultrasonography (EUS) and diagnostic laparoscopy.

1.6.1 Computed Tomography

The first line of multimodal investigation is CT imaging of the thorax, abdomen and pelvis to look for metastatic disease. CT studies should be performed with intravenous contrast and anti-peristaltic agents may be given to achieve maximum distension. CT has limited value in staging early disease due to an inability to reliably delineate the individual layers of the oesophageal wall and therefore cannot distinguish between T1 and T2 lesions. The use of CT multi-planar images combined with axial imaging however is particularly accurate when differentiating between T3 and T4 disease as the multi-planar re-formatted images increases the ability to determine any loss of the fat plane around the oesophagus and stomach (Bhandari et al. 2004). The reported accuracy of CT in diagnosing mediastinal invasion ranges

from 59% to 82% (Saunders et al. 1997; Rankin 1998). The accuracy in predicting lymph node metastases in the abdomen is in the order of 85% (Saunders et al. 1997), and the overall accuracy of CT for predicting regional lymphadenopathy ranges from 50% to 70% (Iyer 2004). The main strength of CT is the detection of distant metastases with a sensitivity and specificity of 52% and 91% respectively (van Vliet et al. 2008). Small volume metastatic disease can however be missed by CT and investigations such as PET/CT and laparoscopy can improve the accuracy of M staging.

1.6.2 Positron Emission Tomography

Positron Emission Tomography (PET) is a nuclear medical imaging technique which uses a labelled glucose analogue, 2-[¹⁸F] fluoro-2-deoxy-D-glucose (18F-FDG), combined with CT imaging to provide both functional and anatomical data. The radioactive tracer 18F-FDG is taken up by the more metabolically active tumour cells, the rate of uptake being proportional to metabolic activity, and malignant tumours usually have higher metabolic rates compared with normal tissue (Branstetter et al. 2005). The main advantage of PET/CT is that the patient position remains unchanged between each procedure thereby allowing for reliable co-registration of the PET and the CT data. For previously unsuspected metastatic disease PET/CT significantly improves detection rates with a sensitivity of 69-78% and specificity of 82-88% (Allum et al. 2011), and establishes a more advanced stage in 10-20% of cases (Rustgi et al. 2014).

PET/CT also has potential benefits when planning radiation therapy as it is now possible to treat tumours while reducing radiation doses to non-target organs compared with traditional techniques (Allesio et al. 2004). However, studies with

PET/CT have reported a failure to detect early stage tumours (T1 and T2) and mucinous tumours (Allum et al. 2011). Furthermore, while PET/CT can identify local lymph node metastases, avid uptake by the adjacent tumour can obscure uptake in nearby small volume metastatic lymph nodes, and The American College of Surgical Oncology Group trial of PET to identify unsuspected metastatic lesions demonstrated a 3.7% false-positive and a 5% false negative rate (Meyers et al. 2007).

1.6.3 Endoscopic Ultrasonography

Endoscopic ultrasonography is most accurate for T staging in more advanced tumours because of the precise visualisation of the individual layers of the oesophageal and gastric walls. A previous meta-analysis found EUS could detect T1b disease with 80% sensitivity and 70% specificity, and the added ability to perform fine needle aspiration further improves the sensitivity of lymph node staging (van Vliet et al. 2008). EUS has previously been shown to be the most accurate method of assessing nodal status (Foley et al. 2014), and on meta-analysis the sensitivity and specificity of detecting regional lymph node metastases is also reported as 80% and 70% respectively (van Vliet et al. 2008). The accuracy of overall N-staging is 66%, compared with 68% for PET/CT (Choi et al. 2010).

Further to these diagnostic roles, EUS defined tumour characteristics such as tumour length (Twine et al. 2010), total length of disease (Davies et al. 2012), and tumour volume (Twine et al. 2010) also provide important prognostic information. EUS is limited however as an imaging modality if strictures prevent passage of the scope to the full extent of the tumour, and dilatation carries a high risk of perforation (Pfau et al. 2000). EUS is not suitable for M staging, but in combination with fine

needle aspiration it is an accurate and safe method for the assessment of solid lesions such as liver metastases or for aspiration of ascites (Wallace et al. 2001; Eloubeidi et al. 2004).

1.6.4 Staging Laparoscopy

Staging laparoscopy should be undertaken in all gastric cancers and in selected patients with lower oesophageal and oesophago-gastric junctional tumours (Allum et al. 2011). Laparoscopy may establish the presence of previously undetected peritoneal or pancreatic metastases in addition to assessing the operability of locally spread disease. Previous studies have shown laparoscopy provided additional treatment information in 17% of distal oesophageal and oesophago-gastric junctional tumours and 28% of gastric tumours (de Graaf et al. 2007).

1.7 Risk Stratification

Despite the increased efficacy associated with chemoradiotherapy, oesophagectomy remains the mainstay of potential curative treatment for oesophageal cancer. Oesophagectomy is however, a highly invasive procedure with serious potential post-operative complications including pneumonia, anastomotic leak, and sepsis. A McKeown total oesophagectomy involves entering three separate body cavities, and trans-thoracic oesophagectomy with 3-field lymph node dissection is one of the most invasive gastrointestinal operations performed (Fujita et al. 1995; Kinugasa et al. 2004; Fang et al. 2007). Upper gastrointestinal cancer resection therefore falls within the category of high risk surgery as defined by the Royal College of Surgeons of England (RCSE 2011). In order to predict and thereby protect patients at greater risk of post-operative morbidity and mortality there are several operative risk stratification tools including the American Society of Anaesthesiologists (ASA) Physical Status Classification System, the Physiological and Operative Severity Score (POSSUM), and Cardio-Pulmonary Exercise Testing (CPEX).

1.7.1 American Society of Anaesthesiology Physical Status Classification

The ASA system was designed in 1963 to assess the fitness of patients pre-operatively and uses a six category classification system as follows:

I equates to a normal healthy patient,

II equates to mild systemic disease,

III equates to severe systemic disease,

IV equates to severe systemic disease that is a constant threat to life,

V equates to a moribund patient not expected to survive without operation,

VI equates to a patient declared braindead awaiting organ removal for donor purposes (Dripps, 1963). Although used globally the correlation of ASA grade with peri-operative risk does however have limitations. It does not consider inter-tester reliability between individual anaesthetist`s assessments when describing common clinical problems (Daabiss, 2011), nor does it consider the nature of the planned operation, the skill of the anaesthetist or the surgeon, or the post-operative facilities.

1.7.2 Physiological and Operative Severity Score

The POSSUM system was devised in 1991 and uses linear analysis, based on 12 physiological and 6 operative variables, to give a predicted risk of operative morbidity and mortality (Copeland et al. 1991). A strength of the POSSUM model is the combined assessment of physiological status (physiological score) with a measure of the magnitude of a particular operation (operative severity score). Though widely used and validated in many surgical specialities POSSUM has been reported to have a poor predictive accuracy related to oesophagectomy (Zafirellis et al. 2002). A modified O-POSSUM version was therefore subsequently derived specifically for oesophago-gastric surgery (Tekkis et al. 2004). The value of the various POSSUM models in oesophago-gastric surgery however remains controversial, with some studies finding O-POSSUM to be of greater predictive accuracy (Bosch et al. 2011), while others continue to debate the degree of overestimation of mortality risk (Nagabushan et al. 2007; Lagarde et al. 2007; Dutta et al. 2010).

1.7.3 Cardiopulmonary Exercise Testing

CPEX is a non-invasive, dynamic and objective measurement of cardiovascular and respiratory function during exercise that can be used to assess the ability of a patient to adapt to the increased oxygen demand required during and following surgery (Saito et al. 2007). A reduced anaerobic threshold, the point at which increasing exercise results in oxygen consumption exceeding supply and a consequent switch to anaerobic metabolism, has been reported to predict greater mortality following major abdominal surgery (Older et al. 1999). Further physiological variables measured by CPEX include the peak oxygen uptake (VO_2 max) and ventilatory equivalent for carbon dioxide (VE/VCO_2). Few studies have investigated the association between CPEX derived variables and outcome in oesophago-gastric cancer surgery. Previously VO_2 max has been reported to be significantly lower in patients who experience cardiopulmonary morbidity following oesophagectomy (Nagamatsu et al. 1994 and 2001; Forshaw et al. 2008), but there remains a need for a large-scale study of CPEX in oesophago-gastric surgery (Hennis et al. 2011).

1.8 Bioelectrical Impedance Analysis

Patients with upper gastrointestinal cancer and particularly patients with oesophageal or junctional tumours are at significant risk of dysphagia, weight loss and cachexia. It has been reported that cachexia itself rather than the underlying tumour is responsible for a significant number of cancer-related deaths (Ottery 1994). Sarcopenia has been defined as the degenerative loss of skeletal muscle mass, quality, and strength and is often a component of cachexia.

A deficiency in pre-operative nutritional status (malnutrition) is associated with higher rates of surgical morbidity and mortality (Deans et al. 2007), but is also potentially identifiable and reversible. Considering UGI cancer resection falls within the Royal College of Surgeons of England (RCSE 2011) category of high risk surgery, it is clearly important therefore to formulate tailored nutritional regimes for each patient undergoing such major procedures.

One such method of determining nutritional status is Bioelectrical Impedance Analysis (BIA). This is a non-invasive, easily reproducible and inexpensive means of accurately measuring body composition parameters including fat free mass, percentage body fat, percentage lean muscle mass, and intracellular and extracellular water volume. Furthermore, the phase angle (PhA), as measured by BIA, is a reflection of cell membrane resistance and reactance and has been used to determine malnutrition at the cellular level. BIA has previously been used as a prognostic marker to predict survival in colorectal and pancreatic cancer (Gupta et al. 2004), but its prognostic role in UGI cancer has not yet been investigated.

1.9 Surgical Treatment

1.9.1 Oesophagectomy

The aim of curative oesophagectomy is excision of the primary tumour with adequate longitudinal and radial resection margins, appropriate lymphadenectomy, and an uncomplicated anastomosis with low morbidity. Tumour location, histological type, proposed extent of lymphadenectomy and patient co-morbidity determine the operative approach.

There are two standard surgical approaches for oesophagectomy; transhiatal and transthoracic. A transhiatal approach involves abdominal and left-sided neck incisions and is most appropriate for early stage node negative disease (T1-4, N0), HGD, or patients with associated significant co-morbidity who would not withstand a thoracotomy. The two-phase transthoracic, or Ivor Lewis approach, is used for middle or upper third tumours and is the standard practice in Europe and the United States. Additional neck lymphadenectomy is performed in areas where SCC is prevalent. The procedure involves a laparotomy and right thoracic approach with the anastomosis high in the chest, some surgeons also perform a cervical incision to create the anastomosis at this level. This approach facilitates good mediastinal and para-oesophageal lymphadenectomy, thereby enabling a large yield of lymph nodes for histological assessment.

Minimally invasive oesophagectomy (MIO) is the most recently described technique and involves laparoscopic access to the abdomen and thoracoscopic access to the chest. The technique is associated with a quicker recuperation period and can potentially harvest an adequate lymph node yield to discern the presence of metastatic disease (Luketich et al. 2003; Noble et al. 2013). Each approach has its

proponents and there is no level 1 evidence to suggest that any one approach is associated with a survival benefit (Rubenstein et al. 2015). Randomised studies have however associated a transhiatal approach with less post-operative morbidity (Hulscher et al. 2002).

1.9.2 Gastrectomy

Gastrectomy with curative intent should be undertaken only after discussion at an UGI multi-disciplinary meeting taking into account all staging information, patient co-morbidity, nutritional status and patient preference. The type of resection is based on the position and staging of the tumour and the extent of the intended lymphadenectomy.

British Society of Gastroenterology and British Association of Surgical Oncology guidelines recommend proximal tumours be removed by total gastrectomy, distal (antral) tumours be removed by subtotal gastrectomy, and type II oesophago-gastric junctional tumours, cardiac and subcardiac tumours be treated by transhiatal extended total gastrectomy or oesophago-gastrectomy (Allum et al. 2011). The extent of lymphadenectomy is determined by the location and stage of the cancer, in a D1 lymphadenectomy the perigastric nodes closest to the primary tumour are removed en bloc with the stomach, whereas a D2 lymphadenectomy involves the removal of the perigastric and distant nodes along the main arteries supplying the stomach (first 2 tiers of lymph nodes, N1 and N2). For patients with stage II and III cancers a D2 lymphadenectomy is recommended if performance status allows (Allum et al. 2011). A previous Dutch study with long-term follow-up showed better cancer-related survival after D2 lymphadenectomy (Songun et al. 2010). A minimum

of 15 lymph nodes should be resected for histological examination to ensure accurate reliable staging (Sobin et al. 2002).

Limited gastric resections should be reserved for palliation or very elderly patients only. Furthermore, the spleen and splenic hilar nodes should only be resected in cases of tumours on the greater curvature or posterior wall of the stomach in close proximity to the splenic hilum, and the distal pancreas should only be resected when there is direct invasion but the intent of procedure is curative and the tumour is in the proximal stomach.

1.10 Enhanced Recovery after Surgery

The concept of Enhanced Recovery after Surgery (ERAS) was first pioneered by Kehlet in Copenhagen in patients undergoing colorectal surgery and challenged many of the traditional dogmatic aspects of peri-operative care (Basse et al. 2000). Conventional peri-operative care surrounding gastrointestinal resection and anastomosis was based on prolonged periods of fasting and gastrointestinal tract rest until the return of normal gut function, routinely requiring patients to remain in hospital for up to 3 weeks, even in the absence of any major complications (Karl et al. 2000; Hofstetter et al. 2002).

ERAS described an evidence-based multi-disciplinary package of care for patients undergoing colorectal surgery aiming to reduce the stress response to surgery and promote the return of normal gut and body function (Fearon et al. 2005). The package includes pre-admission patient education, avoidance of pre-operative bowel preparation, reduced pre-operative fasting, carbohydrate loading, anti-thrombotic and antibiotic prophylaxis, goal-directed anaesthesia and fluid resuscitation, and early post-operative enteral nutrition and mobilisation (Basse et al. 2000). The efficacy of ERAS has subsequently been demonstrated in large meta-analyses which have shown significantly reduced morbidity rates and shortened hospital stay following colorectal resection (Gouvas et al. 2009; Varadhan et al. 2010), and now represents a mainstay of contemporary colorectal surgical practice. The role of ERAS in upper gastrointestinal surgery however is less well established. A recent systematic review concluded that experience of ERAS for oesophagectomy tentatively suggests that it is feasible and associated with improved levels of

morbidity and mortality but the evidence is poor, sparse, and with a dearth of evidence for individual components (Findlay et al. 2014; Karran et al. 2016).

1.11 Neoadjuvant Therapy

The treatment of oesophago-gastric cancer has become more complex due to increasing evidence of improved outcomes associated with multimodal therapy, rapidly changing patterns of disease, improved staging capability and an increasingly elderly and co-morbid population. Surgery with curative intent is restricted to only those patients with early stage disease due to the high recurrence rates in advanced tumours. The rationale behind neo-adjuvant therapy is to shrink and downstage a tumour prior to surgery, thereby increasing the chances of resection and also to treat occult metastatic disease and minimise potential for local recurrence. Furthermore, by reducing tumour volume a patient may regain the ability to swallow and thereby gain weight and improve both their nutritional and performance status.

The three most recent large trials investigating pre-operative chemotherapy plus surgery versus surgery alone have produced conflicting results. The Rotterdam Esophageal Tumour Study Group randomised 160 SCC patients to chemotherapy plus surgery versus surgery alone. The study showed a significant difference ($p=0.002$) in the median survival between chemotherapy plus surgery and surgery alone groups (18.5 months vs. 11 months) respectively (Kok et al. 1997). The American Intergroup Trial (INT 0113) randomised 440 patients to chemotherapy plus surgery versus surgery alone and found no difference in median survival between the groups (16.1 months vs. 14.9 months) respectively, and no difference in 1, 2 and 3-year survival respectively (Kelsen et al. 1998). However, the UK Medical Research Council (MRC) OEO2 study, potentially the largest and arguably the most influential trial in the field, randomised over 800 patients to chemotherapy plus surgery versus surgery alone. The study reported that overall survival was significantly improved

following pre-operative chemotherapy plus surgery ($p=0.004$), with 5 year survival of 23% compared with 17% after surgery alone. Furthermore there was no evidence that the effect of chemotherapy was influenced by histology (MRC Oesophageal Cancer Working Party 2002). Pre-operative chemotherapy is therefore the accepted standard of care in the UK as opposed to the US where chemoradiotherapy is the standard treatment (Malthaner et al. 2010).

The recently completed MRC OEO5 trial, comparing OEO2 chemotherapy with four cycles of ECX (epirubicin-cisplatin-capecitabine), may alter practice if this regimen is found to further improve survival (Allum et al. 2009). Pre-operative chemoradiation and pre-operative chemotherapy have not been directly compared in the context of a phase III randomised controlled trial and pre-operative radiotherapy is not recommended for potentially resectable oesophageal SCC or adenocarcinoma (Allum et al. 2011). The advantages associated with pre-operative chemotherapy should however be weighed up against potential delay in proceeding to resection due to excess toxicity or non-response to chemotherapy (Shapiro et al. 2015).

1.12 Definitive Chemoradiotherapy

Chemotherapy or chemoradiation is a definitive treatment for patients with unresectable, metastatic or recurrent disease. For patients with localised oesophageal adenocarcinoma unsuitable for surgery, definitive chemoradiation (dCRT) is a valid treatment option (Anderson et al. 2007). For localised squamous cell carcinoma of the oesophagus dCRT is the current recommended standard of care after the 2010 UK National Oesophago-Gastric Cancer Audit (NOGCA) showed the disease could be treated by either dCRT or surgery (NOGCA 2010). Indeed in upper SCC, dCRT can achieve local control in up to 70% of patients and surgery is only reserved as a salvage option (Denham et al. 2003).

For oesophageal tumours, palliative chemotherapy provides symptom relief and improves health-related quality of life (HRQL) in inoperable or metastatic disease, and palliative combination chemotherapy improves survival compared with best supportive care (Allum et al. 2011). Palliative external beam radiotherapy can relieve the dysphagia and pain associated with unresectable oesophageal cancer with minimal toxicity, albeit more slowly compared with stent insertion (Caspers et al. 1988; Cwikiel et al. 1996). Palliative brachytherapy has been shown to improve HRQL in cases where a patient is expected to survive for greater than 3 months. For patients with HER2-positive oesophago-gastric junctional adenocarcinoma trastuzumab in combination with cisplatin and fluoropyrimidine improves disease-free survival and overall survival (van Cutsem et al. 2009). Chemoradiation is associated with better disease control and improved survival when compared with radiation alone, but is associated with greater toxicity (Wong et al. 2006). While the aim of

dCRT is prolongation of survival, overall 5 year survival remains less than 15% (Rubenstein et al. 2015).

For locally advanced and/or metastatic gastric cancer palliative combination chemotherapy provides HRQL and survival benefit, increasing survival from 7 to 10 months compared with 3 to 4 months when treated with best supportive care (Allum et al. 2011). Furthermore, combination therapy is superior to single-agent therapy, but no international consensus has yet been reached regarding which combination regimen should be used first-line. In the UK ECF (epirubicin, cisplatin and infused 5-FU) has been the preferred regimen to date.

1.13 Non-Surgical Treatment

In Barrett's oesophagus radiofrequency ablation (RFA) has been reported to eradicate oesophageal metaplasia in up to 80% of cases and dysplasia in over 85% of cases (Shaheen et al. 2009). Regular endoscopic surveillance is however recommended for patients who have undergone RFA for a superficial tumour (Orman et al. 2013). Endoscopic cryotherapy and photodynamic therapy have also been associated with positive outcomes for patients with early adenocarcinoma but data remains limited (Yachimski et al. 2009; Greenwald et al. 2010).

Endoscopic mucosal resection (EMR) and submucosal dissection (SMD) are also used in treating Barrett's oesophagus with high-grade dysplasia or T1a adenocarcinoma. Once the tumour invades the submucosa (T1b) however, the risk of lymph node metastasis rises by up to 60% (Gockel et al. 2011). As EMR and SMD do not treat regional lymph nodes, their use is therefore limited to T1a tumours. Furthermore, SCC of the oesophagus is reputed to be more aggressive than adenocarcinoma, patients with T1a adenocarcinoma have a 0% risk of nodal metastases vs 18% risk for those patients with SCC tumours (Eguchi et al. 2006; Griffin et al. 2011). EMR and SMD are not therefore used to treat SCC. Patients with T1b tumours should undergo oesophagectomy with curative intent.

Endoscopic management of superficial tumours have reported rates of local control greater than 95% (Pech et al. 2014), and several observational studies have suggested cure and survival rates are equivalent to those achieved with surgical resection (Ngamruengphing et al. 2013). However, endoscopic eradication therapy is recommended after complete EMR as over 30% of patients who undergo EMR without adjuvant eradication therapy develop recurrent disease (Pech et al. 2014).

Additionally, after removing high-risk lesions with EMR or SMD, the mucosa will also need to be ablated, most frequently with RFA.

Obstructive tumours not amenable to resection can be palliated by endoscopic placement of covered self-expanding metal stents (SEMS), and their use is associated with marked improvement in dysphagia symptoms (Battersby et al. 2012; Stewart et al. 2013). In randomised controlled trials SEMS have been found to confer greater symptomatic relief with fewer complications requiring re-intervention, and are now the first-line palliative option for dysphagia (Zhu et al. 2014).

1.14 Deprivation

Deprivation is a broad concept which includes limited access to the opportunities and resources which society might expect such as good health, a clean and safe living environment, and protection from crime (Welsh Assembly Government 2011). Eight types of deprivation, or domains, have been described including; employment, income, education, health, community, geographical access to services, housing, and physical environment. Multiple deprivation refers to the different types that might occur, and represents a far more profound notion than poverty alone. Deprivation varies geographically, and Wales is recognised as having relatively high levels when compared with England and several other European countries. Indeed, when compared with the UK as a whole, the general health of the population of Wales is significantly poorer with more emergency hospital admissions per capita, and an overall life expectancy one year shorter when compared with England (National Audit Office 2012).

Linear relationships between levels of deprivation and survival have been reported for no fewer than 44 of 47 specific anatomical cancer sites, including oesophageal, colon and rectal cancer (Coleman et al. 1999). Deprivation is also associated with an increased incidence of upper gastrointestinal cancer (McKinney et al. 1995; Gossage et al. 2009) and several reports have highlighted a survival benefit for patients residing in less deprived geographical areas when compared with more deprived areas (Auvinen et al. 1995; Kogevinas et al. 1997; Stephens et al. 2005). Discrepancies in cancer-related survival cannot be explained entirely by differences in the stage at diagnosis (Thomson et al. 2001; Hole et al. 2002) or by higher co-morbidity among patients from deprived backgrounds (Wrigley et al. 2003).

Moreover, a widening of survival inequality with time has been reported, whereby the improved outcomes experienced by patients living in less deprived geographical areas over the past 25 years have not been shared by patients from more deprived areas (Coleman et al. 2004). The NHS Cancer Plan of September 2000 (Dept of Health 2000), and subsequent government targets introduced in 2003, were aimed at reducing such inequalities across the socio-economic divide, and specific and demanding NHS targets were set (Dept of Health 2003).

1.15 Service Reconfiguration

Implementation of the Improving Outcomes Guidance (IOG) by the UK Dept of Health in 2001, and subsequent NHS re-configuration, has resulted in the establishment of 41 specialist centres providing oesophageal and gastric cancer care in England and Wales. Centralisation of UGI cancer services has however been an issue of ongoing contentious debate since its inception, and was only introduced in South East Wales at the University Hospital of Wales in August 2010 following a period of protracted negotiation between politicians, managers and clinicians.

Historically the provision of UGI cancer resectional surgery was poorly organised and fragmented, undertaken by individual surgeons operating on very small numbers of patients. It was associated with a 30 day mortality rate of between 10 to 20% (Bachmann et al. 1999; Northern and Yorkshire Cancer Registry and Information Service 1999). The rationale behind a centralised service was that UGI cancer surgery, amongst the most complex surgical procedures, benefits when performed in specialist high-volume centres of excellence (Birkmeyer et al. 2003, Brusselaars et al. 2014). The IOG document recommended that these specialist cancer units should aim to perform at least 40 oesophagectomies and 60 gastrectomies each year, drawing patients from catchment areas with populations of one to two million (Dept of Health 2001). More recently the Association of Surgeons of Great Britain and Ireland (AUGIS) suggested the ideal unit would have four to six dedicated UGI surgeons each performing a minimum of 15 to 20 resections per year (AUGIS 2010).

The potential disadvantages include increased distance from home for patients, greater social isolation, and increased expenses incurred by visiting families. From a clinical perspective local district general hospitals are downgraded and lose their

cancer workload, waiting times for benign operations potentially increase, and there are significant costs associated with implementing a centralised service in a hospital. Furthermore, despite having been shown to significantly improve in-hospital and 30 day mortality, the data regarding long-term survival remains limited and even contradictory in some individual studies (Gruen et al. 2009; Lauder et al. 2010; Markar et al. 2012; Tol et al. 2012; Wouters et al. 2012, Lagergren et al. 2013; Chan et al. 2013).

1.16 Aims and Hypotheses

In light of the above, this thesis aims to address the following:

1. To determine the influence of the Index of Multiple Deprivation (IMD) and Health Deprivation (HD) on Upper GI cancer treatment outcome.
2. To examine the time taken to diagnose Upper GI cancer, identify sources of delay, and assess the prognostic significance of delay.
3. To determine the prognostic value of Bioelectrical Impedance Analysis and sarcopenia in Upper GI cancer surgery.
4. To determine the impact of centralisation on Upper GI cancer outcomes and survival at two years.

The hypotheses tested are:

1. Socio-economic and health deprivation adversely influence outcome in patients undergoing surgery for oesophageal and gastric cancer.
2. Patient delay accounts for the majority of delay in the diagnosis of Upper GI cancer, deprivation is an important factor in patient delay, and delay adversely influences outcome.
3. Body composition and sarcopenia as measured by BIA are important prognostic indicators in patients undergoing Upper GI surgery.
4. Centralisation of oesophago-gastric cancer services improves post-operative morbidity, decreases length of hospital stay and improves survival.

Chapter 2

Prognostic significance of deprivation in upper gastrointestinal cancer

2.1 Summary

The aim of this study was to determine the influence of the Index of Multiple Deprivation (IMD) and Health Deprivation (HD) on upper gastrointestinal (UGI) cancer outcome.

Consecutive 1185 patients (697 oesophageal, 488 gastric cancer) were studied prospectively. Deprivation scores were calculated using the IMD of the Welsh Government. Mortality data were obtained from the Office for National Statistics (ONS) and this data, as well as survival data, were independently verified by the Welsh Cancer Intelligence and Surveillance Unit. Primary outcome measure was survival from diagnosis.

Median survival for gastric cancer patients was 8 months (0.25 to 64) compared with 10 months (0.25 to 62) for oesophageal cancer patients. Open and close laparotomy for all surgical patients was commoner in patients residing in deprived geographical areas with a 6.5% open and close rate in the least deprived IMD quintile versus 13.5% in the most deprived quintile ($P=0.006$). On post-operative histopathology, IMD was associated with pT ($r=-0.146$, $P=0.043$), pN ($r=-0.158$, $P=0.029$), and pM stage ($r=-0.189$, $P=0.016$). On univariate analysis survival was associated with oesophageal versus gastric tumour site ($P=0.028$), histopathological cell type ($P<0.0001$), age ($P<0.0001$), radiological (r) TNM stage ($P<0.0001$), radical treatment intent ($P<0.0001$), IMD ($P<0.0001$) and HD ($P<0.0001$). On multivariate

analysis of all patients, age (HR 1.021, 95% CI, 1.014-1.028, $P<0.0001$), rTNM stage (HR 1.559, 95% CI, 1.427-1.704 $P<0.0001$), radical treatment intent (HR 0.338, 95% CI, 0.274-0.418, $P<0.0001$), and IMD rank (HR 1.000, 95% CI, 1.000-1.000, $P=0.084$) were associated with duration of survival.

In conclusion deprivation is an important prognostic indicator in UGI cancer.

2.2 Introduction

Deprivation is a broad concept which describes limited access to the opportunities and resources which society might expect such as good health, a clean and safe living environment, and protection from crime (Welsh Assembly Government 2011). Eight types of deprivation, or domains, have been described, including; employment, income, education, health, community, geographical access to services, housing, and physical environment. Multiple deprivation refers to the different types that might occur, and represents a far more profound notion than poverty alone. Deprivation varies geographically, and Wales is recognised as having relatively high levels when compared with England and several other European countries. Indeed, when compared with the UK as a whole, the general health of the population of Wales is significantly poorer with more emergency hospital admissions per capita, and an overall life expectancy one year shorter when compared with England (National Audit Office 2012).

Linear relationships between levels of deprivation and survival have been reported for no fewer than 44 of 47 specific anatomical cancer sites, including oesophageal, colon and rectal cancer (Coleman et al. 1999). Deprivation is also associated with an increased incidence of upper gastrointestinal cancer (McKinney et al. 1995; Gossage et al. 2009), and several reports have highlighted a survival benefit for patients residing in less deprived geographical areas when compared with more deprived areas (Auvinen et al. 1995; Kogevinas et al. 1997; Stephens et al. 2005). Discrepancies in cancer related survival cannot be explained entirely by differences in the stage at diagnosis (Thomson et al. 2001; Hole et al. 2002) or by higher co-morbidity among patients from deprived backgrounds (Wrigley et al. 2003). Moreover, a widening of survival inequality with time has been reported, whereby the

improved outcomes experienced by patients living in less deprived geographical areas over the past 25 years have not been shared by patients from the more deprived areas (Coleman et al. 2004). The NHS Cancer Plan of September 2000 (Dept of Health 2000), and subsequent government targets introduced in 2003, were aimed at reducing such inequalities across the socio-economic divide, and specific and demanding NHS targets were set (Dept of Health 2003). It remains to be established whether deprivation per se directly influences outcome in UGI cancer, and if so, whether the effect may be analogue or digital in nature. As prognosis for patients diagnosed with UGI cancer is often poor, the potential benefit from understanding and addressing reversible factors is substantial. The aims of this study were to determine the influence of deprivation on outcomes for patients with UGI cancer, with particular emphasis on survival following potentially curative therapy. The setting was a UK cancer network serving a population of 1.4 million people.

2.3 Material and Methods

Between 1st August 2008 and 31st July 2012, a total of 1185 patients were diagnosed with UGI cancer and managed by the South East Wales UGI multidisciplinary team [median age 72 (22-97) years, 783 male, 402 female, 697 oesophageal, 488 gastric cancer, 903 adenocarcinoma (ACA), 206 squamous cell carcinoma (SCC)]. The details of these patients were collected prospectively and data was cross-referenced with the oncology (CANISC) database. Mortality data were obtained from the Office for National Statistics (ONS) and this data, as well as survival data, were independently verified by the Welsh Cancer Intelligence and Surveillance Unit. Deprivation rankings were designated for each patient using the Welsh Index of Multiple Deprivation (IMD) 2011, as determined by the National Assembly for Wales (Welsh Assembly Government 2011). This index gives the official measure of multiple deprivation for every postcode in Wales and is based on the eight previously described forms of deprivation. The country is divided into 1,896 areas each having about 1,500 people with the most deprived geographical area ranked 1 and the least deprived area ranked 1,896. The IMD for all areas was sub-classified into equally sized socio-economic quintiles; the most deprived group was labelled quintile 1, and the least deprived quintile 5. These cut-off points allowed subgroup analysis of patients from similarly deprived areas while facilitating comparison across the spectrum. Health deprivation (HD) was also examined, the indicators for which are cancer incidence, all-cause death rate, percentage of live single births <2.5kg, and the number of inhabitants with limiting long-term illness per 100,000 of the population. HD was similarly sub-classified into equally sized quintiles.

2.3.1 Staging investigations

Patients deemed to have potentially curable tumours underwent diagnostic gastroscopy with histopathological confirmation of oesophageal or gastric cancer and computed tomography (CT) of the thorax and upper abdomen. Patients selected for radical treatment also underwent endoluminal ultrasound (EUS), CT Positron Emission Tomography (PET/CT) and laparoscopy, if appropriate. Tumours were staged according to the unified TNM classification of UGI cancer edition 6 (Sobin et al. 2002) until 2010 and edition 7 (Edge et al. 2010) thereafter.

2.3.2 Multidisciplinary management

Patients were initially discussed at one of three local multi-disciplinary team (MDT) meetings and if deemed potentially curative they were then referred to and discussed at the regional South East Wales UGI MDT meeting. The MDT consists of seven specialist upper GI surgeons, oncologists, palliative care physicians, radiologists, pathologists, specialist nurses and dieticians. Patients were selected for appropriate radical treatment based on histopathological stage, co-morbidity, the technical feasibility of surgery and patient choice according to an algorithm described previously (Stephens et al. 2006). Those not suitable or in favour of radical therapy were offered palliative care by specialist palliative care physicians.

2.3.3 American Society of Anaesthesiologists grade

The ASA grade was calculated for surgical patients as a measure of co-morbidity. The system has five grades: normal healthy individual; mild systemic disease that does not limit activity; severe systemic disease that limits activity but is not incapacitating; incapacitating systemic disease which is constantly life-threatening; moribund, not expected to survive 24 hours.

2.3.4 Surgical treatment

Surgery was performed by one or a combination of seven upper gastrointestinal surgeons working within the parameters of the MDT. For patients with oesophageal cancer a transhiatal resection as described by Orringer was performed in those with T1-2, N0 tumours (Orringer 1984). It was also employed selectively for patients with adenocarcinomas of the lower third of the oesophagus which were more advanced (T3 N1) and for patients with associated significant co-morbidity (ASA grade III). The remaining oesophageal cancer patients underwent standard subtotal oesophagectomy as described by Lewis or Tanner (Lewis 1946; Tanner 1947). For those with gastric cancers it was the policy to perform a modified radical D2 resection with extended lymphadenectomy but preserving the pancreas and spleen where possible (Lewis et al. 2002; Edwards et al. 2004). The definition of a potentially curative resection was that all visible tumours were removed and that both proximal and distal resection margins were free of tumour on histological examination. Morbidity and mortality included all in-hospital complications and deaths. Morbidities were recorded against a specific list agreed by all the surgeons involved and graded using the Clavien-Dindo Classification of surgical complications (Dindo et al. 2004).

2.3.5 Definitive chemoradiotherapy (dCRT)

Patients undergoing dCRT received a treatment protocol which involved four 3-weekly cycles of cisplatin (dose 60mg/m²) and infusional 5-fluorouracil (5-FU, 300mg/m²/day). Cycles three and four were given concurrently with five weeks of radiotherapy (50Gy in 25F), during which time the 5-FU was reduced to 225mg/m²/day. If during the course of treatment the glomerular filtration rate (GFR) was less than 40ml/min or the patients experienced significant neuro- or nephrotoxicity, cisplatin was discontinued and replaced with carboplatin.

2.3.6 Follow-up

Patients undergoing surgery were reviewed every three months for the first year and every six months thereafter. Definitive chemoradiation patients were followed up by the oncologists at equivalent periods. Endoscopy and CT were performed if recurrent disease was suspected. Patients treated with palliative intent were followed up by both oncology and palliative care physicians. All patients were followed up for a minimum of 6 months or until death, and no patients were lost to follow-up. Dates of death were obtained from the Office for National Statistics thus ensuring accurate survival times and dates of death for all patients. Nine hundred and eighty five patients (83.1%) were followed up for two years (n=157) or until death (n=828).

2.3.7 Statistical Analysis

Statistical analysis appropriate for non-parametric data was used. Grouped data were presented as median (range), and quintiles were grouped to allow accurate Cox regression analysis. Bivariate correlations were calculated using Spearman's correlation test. Differences were deemed statistically significant when $P < 0.05$.

Cumulative overall survival was calculated by the life-table method of Kaplan and Meier (Kaplan et al. 1958). Differences in survival between groups of patients were analysed using the log-rank method (Altman 1991). Factors found to be significantly associated with duration of survival on univariate analysis and with P -value <0.10 were entered into a multivariate analysis using Cox's proportional hazards model. To identify any potential confounding factors, a separate stepwise regression was also performed using the univariate effect of deprivation as the first step. Data analysis was carried out with the Statistical Package for Social Sciences (SPSS) version 20 package (IBM Corporation, New York).

2.4 Results

Demographic details of the patients related to quintile are presented in Table 1.

2.4.1 Age at presentation

There was a direct correlation between age at diagnosis and IMD rank. Median age in the most deprived quintile (1) was 72 years (range 22-94) compared with 74 years (42-97) for patients in quintile 5 ($r = 0.058$, $P=0.046$). There was also a significant correlation between age at diagnosis and anatomical site of the tumour whereby the median age of patients presenting with oesophageal cancers (including type 1 and type 2 junctional tumours) was 71 (24-97) years, compared with 75 (22-97) years for patients presenting with gastric cancer, including type 3 junctional tumours ($r=0.146$, $P<0.0001$).

2.4.2 Anatomical site of tumour

There was no significant correlation between the anatomical site of the tumour and the IMD ($r=-0.003$, $P=0.905$) or HD ($r=-0.017$, $P=0.562$).

2.4.3 Histopathology and stage of cancer at presentation

Details of patient's histopathology related to IMD quintile are presented in Table 1. There were 903 (76.2%) adenocarcinomas (ACA), 206 (17.5%) squamous cell carcinomas (SCC), and the remaining 6.3% comprised of high grade dysplasia (HGD), neuroendocrine tumours, or undifferentiated carcinomas. There was a significant association between a diagnosis of SCC and lower IMD quintiles ($r=-0.059$, $P=0.044$), and HD quintiles ($r=-0.063$, $P=0.030$). Females accounted for 121 (59%) of the 206 SCC cancers, with males making up the remaining 85 (41%, $r=0.241$, $P<0.0001$). Radiological staging investigations revealed a strong correlation

between EUS defined tumour length and both IMD and HD rank ($r=-0.165$, $P=0.025$ and 0.026 respectively). No correlation was found between the perceived rTNM stage at presentation and either IMD ($r = -0.054$, $P=0.089$), or HD ($r=-0.048$, $P=0.126$).

2.4.4 Details of the surgery

A total of 229 patients (19.3%) were suitable for radical surgical treatment and their details are shown in Table 2. One hundred and nine patients had neoadjuvant therapy followed by surgery, and 120 patients had surgery alone. No correlation was found between IMD and perceived fitness for surgery as defined by the American Society of Anaesthesiology (ASA) grade ($r = 0.016$, $P=0.863$). Open and close laparotomy for all surgical patients was commoner in patients residing in deprived geographical areas with a 6.5% open and close rate in the least deprived IMD quintile versus 13.5% in the most deprived quintile ($P=0.006$). No correlation was found between IMD and operative morbidity (41.4% in quintile 1 versus 39.4% in quintile 5, $r=0.016$, $P=0.841$), or HD and operative morbidity (51.7% in quintile 1 versus 48.4% in quintile 5, $r=0.041$, $P=0.594$) respectively. Furthermore, there was no correlation between IMD or HD and operative mortality within 30 days of surgery (3.3% in quintile 1 versus 0% in quintile 5, $r = -0.077$, $P=0.318$, $r=-0.016$, $P=0.834$ respectively). On post-operative histopathology, IMD was associated with pT ($r=-0.146$, $P=0.043$), pN ($r=-0.158$, $P=0.029$), and pM stage ($r=-0.189$, $P=0.016$).

2.4.5 Palliative treatment

A total of 857 patients were considered to be of too poor performance status, or were diagnosed with tumours of such advanced stage that radical treatment was not possible. These patients received palliative chemotherapy, radiotherapy, stent insertion or best supportive care in keeping with the patients' wishes.

2.4.6 Survival

Median survival from diagnosis for all 1185 patients was 9 (range 0.25 to 64) months. Regarding the 229 patients who underwent surgery with curative intent median survival was 20 (range 1 to 64) months, and 21 (range 3 to 57) months for the 81 patients receiving definitive chemoradiotherapy.

The duration of survival from diagnosis was significantly associated with both IMD ($P < 0.0001$), and HD ($P < 0.0001$). There was a strong correlation between duration of survival and IMD for Siewert type I and II oesophago-gastric junctional cancers (log-rank 480.930, γ 304, $P < 0.0001$). The median survival for patients diagnosed with oesophageal cancer was 9 months (range 0.25-55), and this increased to 18 months (range 3-55) for patients undergoing oesophagectomy. For patients who underwent oesophagectomy, there was a correlation between greater deprivation and shorter median survival (log-rank 325.504, γ 97, $P < 0.0001$). When analysed by quintile, the median survival after oesophagectomy for patients in the three most deprived quintiles (1-3) was 16 months (range 3-46) compared with 23 months (range 5-55) for patients in the two least deprived quintiles (4-5).

For the 81 patients with oesophageal cancer treated with dCRT the median duration of survival was 18 months, and again there was a strong correlation between

residing in a deprived geographical area and shorter duration of survival (log-rank 241.828, χ^2 69, $P < 0.0001$).

The median survival for patients diagnosed with gastric cancer was 7 months (range 0.25-58), and this increased to 22 months (range 1-58) for patients undergoing gastrectomy. There was a strong correlation between duration of survival and IMD for all patients diagnosed with gastric cancer (log-rank 449.383, χ^2 247, $P < 0.0001$). For patients who underwent gastrectomy, there was a correlation between greater deprivation and shorter median survival (log-rank 344.364, χ^2 89, $P < 0.0001$). When analysed by quintile, the median survival after sub- or total-gastrectomy for patients in the three most deprived quintiles (1-3) was 24 months (range 1-64) compared with 27 months (range 3-57) for patients in the two least deprived quintiles (4-5).

2.4.7 Univariate analysis

A univariate analysis of the factors influencing survival is shown in Table 3.

2.4.8 Multivariate analysis

Factors found to be associated with survival at the $P < 0.10$ level on univariate analysis (age, IMD rank, HD rank, pre-operative rTNM stage, histopathology and radical treatment intent) were entered into a multivariate analysis using Cox's proportional hazards model, Table 4.

2.5 Discussion

This is the largest study of the effect of deprivation on outcomes in patients diagnosed with UGI cancer including almost 1200 patients over a four-year period. The principal findings were that both IMD and HD were associated with adverse outcomes for patients diagnosed with UGI cancer, and overall deprivation was associated with duration of survival. Despite developing disease at a younger age, being of similar stage of disease at diagnosis, and being offered similar treatment protocols, patients residing in the most deprived geographical areas were more likely to have significantly shorter median duration of survival than patients in the least deprived geographical areas. No differences were found in the proportion of patients receiving treatment with curative intent related to deprivation quintile, and similar proportions of patients from each quintile were offered surgery, definitive chemoradiotherapy and palliative care. Despite equal proportions of patients from more deprived backgrounds meeting mandatory performance status criteria for surgery, survival was significantly shorter than for patients from less deprived backgrounds.

This study has a number of limitations. Deprivation exists in a number of forms and this multimodal complexity makes quantification challenging. Important discrepancies in outcome and duration of survival between UGI cancer patients from different socio-economic backgrounds were identified, but no explanation emerged as to why this should be so. This study used deprivation scores measured at the area level, i.e. each individual was given a score based on the degree of deprivation of their local community. The use of such area-based deprivation scores, as opposed to individual-based scores, calculated on individuals' incomes or occupations, does introduce potential bias, given that it is unlikely that all residents of a specific

postcode will have the attributes of that community (the ecological fallacy) (Morgan et al. 2007). There is however a clear distinction between poverty (insufficient financial resources) and deprivation (insufficient multiple resources, including financial). IMDs are an accurate measure of true deprivation, taking into account poverty, housing, access to services, health and physical environment. Survival was calculated using all-cause mortality and it is likely that some patients will have died of causes other than progressive or recurrent oesophageal or gastric cancer. This is of particular relevance when considering deprivation, as it is acknowledged that patients from more deprived areas have a higher proportion of many chronic diseases, and their mortality is therefore higher than that of patients from more socio-economically advantaged areas. This latter point is, however, controversial as it has previously been reported that disease-specific mortality provides the most accurate measure of survival when no information regarding co-morbidity is available (Kravdal 2002). Certainly other investigators have reported that the assignment of cancer as a cause of death may be influenced by deprivation (Brewster et al. 2000), and it is therefore probable that the true oesophago-gastric cancer survival rate lies somewhere midway between these two extremes. This was a comparative study, and the definition and analysis of subgroups within a study may lead to bias, while comparisons of groups may prove to be not statistically significant simply because the study has insufficient power to demonstrate real differences. The use of quintiles (as opposed to quartiles or deciles, for example) was arbitrary, and it is not clear from the results presented here whether there is an analogue correlation between deprivation and outcome or whether the effect is binary, with a critical level of deprivation above which adverse outcomes become more likely.

The strengths of the study are that prospectively collected data for unselected consecutive patients from a well-defined geographical area were used, a significant proportion of whom reside in areas shown to be amongst the most deprived in the United Kingdom. Access to the IMDs for over 99.5% of all the patients adds further strength. The prognostic data are especially robust, with over 83% of patients followed up for at least 24 months or until death. All patients were managed by a specialist MDT whose results are well audited and can stand up to international scrutiny (Stephens et al. 2006). Furthermore, the accuracy of the survival data is especially robust, as the dates for death were confirmed by the Office for National Statistics and outcomes have also correlated with independent formal analysis by Welsh Assembly Government healthcare statisticians.

The most important prognostic factor in patients diagnosed with oesophageal or gastric cancer has, by tradition, been the stage of disease at diagnosis (Allum et al. 2002). This study however, failed to demonstrate any correlation between deprivation and the perceived radiological tumour stage at diagnosis. The study did find that for all patients treated, and particularly those who had undergone surgery, those from least deprived geographic areas had longer median durations of survival. Similar proportions of the more deprived patients progressed to surgery and this could potentially be explained by a more focused input from allied healthcare professionals, dieticians and physiotherapists in particular, to optimise pre-operative performance in patients from more deprived geographical areas who tend to have poorer health and increased rates of cardio-respiratory related diseases (Carstairs 1995; Brown et al. 2001). The findings contrast with a previous study which reported no association between duration of survival after oesophagectomy for cancer and deprivation (Morgan et al. 2007), but were in keeping with Stephens *et al* who

reported deprivation was associated with shorter duration of survival following gastrectomy for cancer (Stephens et al. 2005). Both of these reports utilised an earlier more embryonic version of the Wales IMD.

2.6 Conclusion

In conclusion, the Acheson report highlighted the need for action across the whole of society to address the deep-seated inequalities in our health (Dept of Health 1998). The UK Government responded by pledging a commitment to this end, inviting the independent Scientific Reference Group on Health Inequalities to oversee implementation and assess outcomes (Dept of Health 2007). In the subsequent decade, life expectancy for males and females living in the 70 local authority areas with the worst health and deprivation indicators in England have increased by 2.9 and 1.9 years respectively, compared with 3.1 and 2.1 years for the population as a whole. This highlights the point that although the health of society's most deprived has improved, the gap between society's most and least deprived has failed to narrow (Dept of Health 2007; Dept of Health 2009) and further research and effort to address these health care and deprivation related inequalities is warranted.

Table 2.1 Demographic details of patients related to deprivation quintile

Deprivation Quintile	1	2	3	4	5
Median IMD Rank	135	407	763	1274	1744
Range	2-264	265-577	553-972	978-1558	1489-1896
Median HD Rank	134	400	747	1134	1712
Range	1-283	286-561	563-911	911-1431	1431-1895
Median Age	72 (22-94)	72 (36-95)	73 (24-94)	71 (31-94)	74 (42-97)
Gender (M:F)	148:88	159:77	169:67	151:85	152:84
Histology					
ACA	182	185	179	179	175
SCC	32	38	41	50	45
Undifferentiated	11	10	12	3	10
HGD	11	3	4	4	6
Tumour Site					
Oesophageal	138	136	145	131	145
Gastric	98	100	91	105	91
Surgery	37	50	46	50	46
dCRT	21	12	20	15	13
EMR	2	3	2	7	4
Palliative	176	171	168	164	173

Figures are numbers of patients

Table 2.2 Details of the patients undergoing surgery

Deprivation Quintile	1	2	3	4	5
No. of pts (%)	37 (16)	50 (21)	46(19)	50 (21)	46(19)
Median age	67	64	65	67	66
Gender M:F	24:13	41:9	36:10	38:12	35:11
Histopathology					
ACA	34	49	41	45	44
SCC	1	1	4	5	2
HGD	2	0	1	0	0
Site of Tumour					
Oesophageal	15	22	19	23	19
Junctional	5	8	8	9	14
Gastric	17	20	19	18	13
Overall Stage					
HGD	2	0	0	0	1
I	6	16	9	14	14
II	10	9	21	10	16
III	15	19	14	25	14
IV	2	5	1	1	1
Operation					
TTO	6	3	8	13	12
THO	6	12	8	8	12
Gastrectomy	10	6	11	7	7
Subtotal Gastrx	6	13	9	12	9
Oes-Gastrx	1	3	2	2	2
Emergency Op	3	4	3	2	1
Open & Close	5	9	5	6	3
CRM +ve (%)	5 (13)	6 (12)	7 (15)	11 (22)	13 (28)
Complications					
Morbidity CD≥3	6 (16)	2 (4)	10 (21)	8 (16)	3(7)
Mortality	1	0	3	0	0

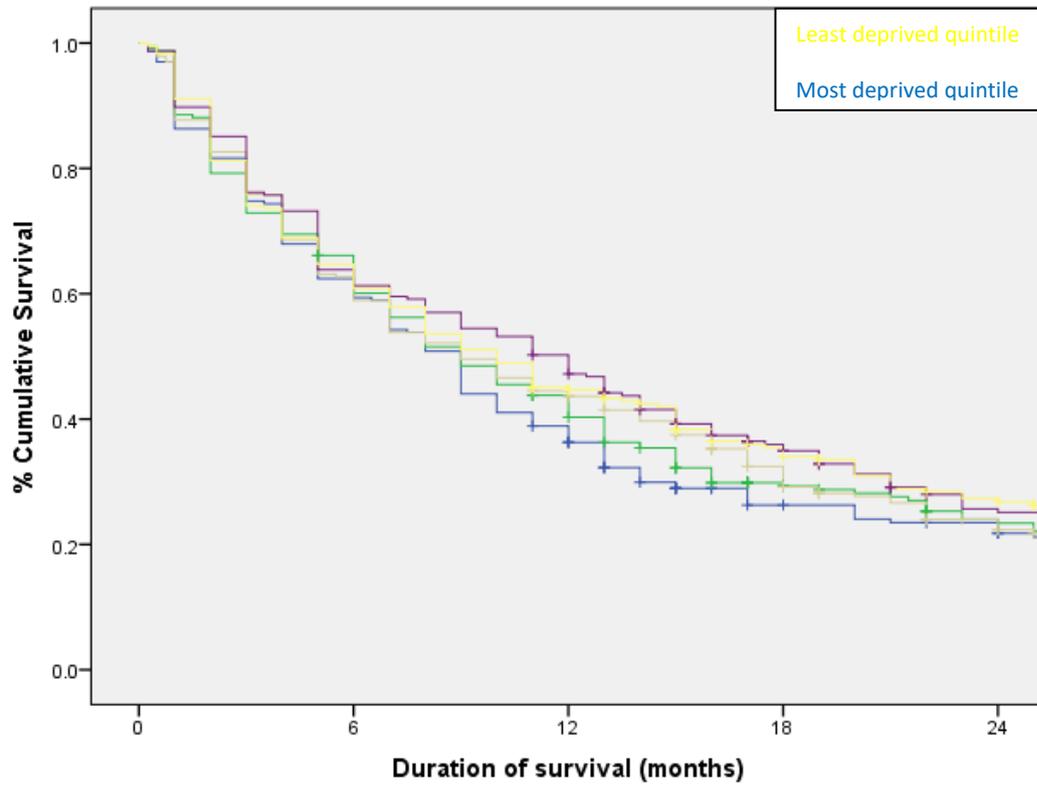
Table 2.3 Univariate analysis of factors associated with duration of survival

Factor	Log rank	DF	p-value
Cancer site	4.852	1	p=0.028
Age	178.628	67	p<0.0001
rTNM	315.129	4	p<0.0001
Histology	44.186	3	p<0.0001
Radical Rx Intent	367.524	1	p<0.0001
SED Rank	1586.772	616	p<0.0001
HD Rank	1586.772	616	p<0.0001

Table 2.4 Multivariate analysis of factors associated with duration of survival

Factor	HR	CI (95%)	p-value
Age	1.021	1.014-1.028	p<0.0001
Curative Rx intent	0.338	0.274-0.418	p<0.0001
rTNM Stage	1.559	1.427-1.704	p<0.0001
IMD	1.000	1.000-1.000	p=0.084

Figure 2.1 2 year survival related to IMD quintile



Log Rank 1586.772, γ 616, $P < 0.0001$

Chapter 3

Prognostic significance of diagnostic delay and deprivation in the management of upper gastrointestinal cancer

3.1 Summary

The aim of this study was to examine the time taken to diagnose upper gastrointestinal (UGI) cancer, identify sources of delay, and assess its prognostic significance.

This was a prospective study of 150 consecutive upper GI cancer patients (median age 70 years, 96 males, 102 oesophageal and 48 gastric cancers respectively) presenting to a UK cancer network. Outcome measures were times from onset of symptoms to histological diagnosis, radiological-staging steps, decision to treatment, and whether potentially curative therapy was possible. Deprivation scores were obtained from the Welsh Indices of Multiple Deprivation (WIMD).

Total delay consisted of the following components: patient delay [median 12 (1-104) weeks, 76%]; practitioner delay [median 1 day (range 1 day to 78 weeks), 1%] and hospital delay [median 25 days (1-262), 23%]. Overall median delay from onset of symptoms to diagnosis was 15.5 (1-142) weeks, and to decision to treat 18 (3-143) weeks. On multivariate analysis the factors influencing patient delay were gender (HR 1.463, 95% CI 1.038-2.063, $p=0.030$) and overall deprivation rank (HR 1.000, 95% CI 1.000-1.001, $p=0.005$). Urgent Suspected Cancer (USC) referrals (open access endoscopy) consisted of 94 patients (63%) and were more likely to receive curative treatment (43%) than the 56 patients (37%) referred via Non Urgent Suspected Cancer (NUSC) pathways (25%, $p=0.017$). For USC patients the median

delay from receipt of GP referral to the date treatment started was 85 (1-526) days, with 36% of patients starting treatment within 62 days (median delay 15 days). In contrast, for non-USC patients the median delay from decision to treat to treatment commencing was 1 (1-253) day, with 91% (51/56) within 31 days. Regarding USC patients, 18 (24.7%) started treatment within the recommended 62 day guideline from time of receipt of referral, and for non-USC patients 51 (91.1%) had commenced treatment within 31 days. Survival was significantly related to overall delay ($R=0.210$, $p=0.010$), whereby patients with the shortest delays survived for a median 6 (0.25 to 30) months compared with patients with the longest delays who survived for a median 12.5 (0.5 to 32) months.

In conclusion patient delay accounted for over three quarters of total delay, and deprivation was an important and independent factor in this regard. Improved public awareness and doctor education, lower thresholds for referral in deprived geographical areas, and streamlined diagnostic pathways are required if earlier diagnosis of UGI cancer is to be achieved.

3.2 Introduction

The most important prognostic factor in patients diagnosed with oesophageal or gastric cancer is the stage of disease at presentation, yet despite advances in information technology and therapies incurable metastatic disease is still diagnosed in as many as 50% of patients at first presentation (Allum et al. 2002). In the absence of a national UK screening programme, and given that tumour doubling time can be as little as 2 months for advanced gastric cancer (Kohli et al. 1981; Haruma et al. 1988) and less than 7 months for oesophageal cancer (Nabeya et al. 1990), avoidable delay may potentially allow tumours to upstage significantly.

British Society of Gastroenterology (BSG) guidelines recommend that all patients over 55 years of age with recent onset dyspepsia, and all patients with alarm symptoms suggestive of UGI cancer irrespective of age, should be referred for rapid access endoscopy and biopsy (Allum et al. 2011). Moreover, the UK Department of Health has specified that these urgent investigations be performed within two weeks of referral (HMSO 2011). Nevertheless, the potential for delay along the patient's journey are many, and delay may arise at any of three junctures from the initial onset of symptoms to diagnosis; the interval between first noticing symptoms and first consulting a doctor (patient delay); the interval between primary consultation and the subsequent time taken for referral for further investigations (practitioner delay); and finally the time between receipt of referral and diagnosis (hospital delay) (Nichols et al. 1981).

Deprivation is a broad concept which includes limited access to the opportunities and resources which society might expect such as good health, a clean and safe living environment, and protection from crime. Eight types of deprivation, or domains, have

been described, including; employment, income, education, health, community, geographical access to services, housing, and physical environment (Welsh Assembly Government 2011). Multiple deprivation refers to the different types that might occur, and represents a far more profound notion than poverty alone. According to the Welsh Government Cancer Delivery Plan Annual Report (2014) considerable differences remain in cancer incidence, mortality and survival between the least and most deprived geographical areas of the country whereby there is a 21% higher incidence in the most deprived areas compared with the least. Furthermore, one year survival rate is 17% lower in the most deprived areas compared with the least deprived areas, and five year survival difference is even greater, with 28% fewer patients in the most deprived areas surviving to 5 years compared with patients in the least deprived areas (Welsh Assembly Government 2014).

Staging protocols for oesophageal cancer are now complex including endoscopy, CT, PET/CT and Endoscopic Ultrasonography (EUS), all of which carry their own potential for further delay. As prognosis for patients diagnosed with UGI cancer is often poor, the potential benefit from understanding and addressing reversible factors is substantial. The aim of this study is to identify the source and magnitude of such delays, determine the prognostic significance, and examine whether delays are related to deprivation.

3.3 Material and Methods

Data was collected on 150 consecutive patients [median age 70 years (range 26 to 95), 96 male, 54 female, 102 oesophageal, 48 gastric cancer, 125 adenocarcinoma (ACA), 25 squamous cell carcinoma (SCC)], diagnosed between 1st August 2012 and 31st July 2013 within 2 South East Wales Health Boards (Aneurin Bevan and Cardiff and Vale) . All patients were managed by the South East Wales UGI Cancer network multidisciplinary team (MDT).

3.3.1 Time Intervals

The time interval (weeks) between the patient first noticing symptoms and presenting to their general practitioner (GP) was recorded according to the patient's personal recollection of events and cross-referenced with the GP urgent suspected cancer (USC) referral letter. For emergency admissions the delay between first noticing a symptom and presentation to hospital was recorded. Practitioner delays (days) were recorded from the Welsh National Cancer Network Information System (CANISC) database and patient notes. Hospital delays were also recorded contemporaneously from CANISC. For hospital delays, intervals were recorded between date of GP referral to the date of upper gastrointestinal endoscopy (OGD), to date of CT (days), from date of OGD to CT (days), from CT to EUS (weeks), from CT to PET/CT (weeks), from referral to diagnosis (days), from referral to the decision to treat date at the regional MDT (weeks), and from the decision to treat date to the commencement of treatment (weeks). The overall delay between initial onset of symptoms and the date a decision to treat was made was also recorded. Date of diagnosis was the day on which a histological diagnosis of malignancy was

confirmed. In the case of patients who did not undergo OGD date of diagnosis was recorded as the day the patient underwent radiological imaging.

3.3.2 Deprivation rankings

Deprivation rankings were designated for each patient using the Welsh Index of Multiple Deprivation (WIMD) 2011, (Welsh Assembly Government 2011). This index gives the official measure of multiple deprivation for every postcode in Wales and is based on the eight aforementioned forms of deprivation including employment, income, education, health, community, geographical access to services, housing, and physical environment. The country is divided into 1,896 areas of approximately 1,500 people with the most deprived geographical area ranked 1 and the least deprived area ranked 1,896. The WIMD for all areas was also sub-classified into equally sized socio-economic quintiles; the most deprived group was labelled quintile 1, and the least deprived quintile 5. Health deprivation (HD) was also examined, the indicators for which are cancer incidence, all-cause death rate, percentage of live single births <2.5kg, and the number of inhabitants with limiting long-term illness per 100,000 of the population (Welsh Assembly Government 2011). HD was similarly sub-classified into equally sized quintiles.

3.3.3 Staging Investigations

Patients deemed to have potentially curable tumours underwent diagnostic gastroscopy with histopathological confirmation of oesophageal or gastric cancer and computed tomography (CT) of the thorax and upper abdomen. Patients selected for radical treatment also underwent EUS, CT Positron Emission Tomography (PET/CT) and laparoscopy, if appropriate. Tumours were staged according to the unified TNM classification of UGI cancer, edition 7 (Edge et al. 2010).

3.3.4 Multidisciplinary management

Patients were initially discussed at one of three local multi-disciplinary team (MDT) meetings and if deemed potentially curative they were then discussed at the regional South East Wales UGI MDT meeting. Patients were selected for appropriate radical treatment based on histopathological stage, co-morbidity, the technical feasibility of surgery and patient choice according to an algorithm described previously (Stephens et al. 2006). Patients unsuitable or who declined radical therapy were offered specialist palliative care.

3.3.5 Statistical Analysis

Statistical analysis appropriate for non-parametric data was used. Grouped data were presented as median (range), and quintiles were grouped to allow Cox regression analysis. Bivariate correlations were calculated using Spearman's correlation test. Differences were deemed statistically significant when $p < 0.05$. Data analysis was carried out with the Statistical Package for Social Sciences (SPSS) version 20 package (IBM Corporation, New York).

3.4 Results

3.4.1 Patient Delay

The median time interval between patients first experiencing symptoms and initial presentation to a medical practitioner was 12 (1-104) weeks and accounted for 76% of the delay from initial onset of symptoms until the decision to treat date. Patient delay correlated with gender [females 13 (2-104) weeks compared with males 8 (1-78) weeks ($R=-0.179$, $p=0.030$)], level of overall deprivation ($R=-0.214$, $p=0.009$), and health deprivation ($R=-0.214$, $p=0.009$). When analysed by quintile, the median delay for patients in the most deprived quintile was 13 (2-78) weeks compared with 8 (1-26) weeks for those in the least deprived quintile ($R=-0.210$, $p=0.010$). With regard to HD, the median delay for patients in the most deprived HD quintile was 15 (4-78) weeks compared with 8 (1-26) weeks for those in the least deprived quintile ($R=-0.210$, $p=0.010$).

Patients with oesophageal cancer had a median delay of 9 (1-78) weeks and patients with gastric cancer 13 (1-104) weeks ($R=0.041$, $p=0.620$). No correlation was found between longer patient delays and advanced radiological (r)TNM staging ($R=-0.063$, $p=0.477$) or with radiologically defined metastatic disease ($R=0.058$, $p=0.509$). For patients who underwent radiological staging, stage I disease was diagnosed in 11%, stage II in 17%, stage III in 27% and stage IV in 45%.

3.4.2 Univariate analysis of factors associated with length of patient delay

The factors associated with patient delay are shown in Table 2.

3.4.3 Multivariate analysis of factors associated with length of patient delay

Factors found to be associated with patient delay ($p < 0.10$) on univariate analysis were entered into a multivariate analysis using Cox's proportional hazards model shown in Table 3. Gender (HR 1.463, 95% CI 1.038-2.063, $p = 0.030$) and overall deprivation rank (HR 1.000, 95% CI 1.000-1.001, $p = 0.005$) were found to be independently associated with patient delay.

3.4.4 Practitioner Delay

The median delay between a patient consulting their GP and referral for further investigation was 1 day (range 1 day to 18 months) and accounted for 1.25% of the total delay from the onset of symptoms to the decision to treat date.

Ninety four patients (63%) were referred via the Urgent Suspected Cancer (USC) pathway or open access gastroscopy pathway, with the remaining 56 patients (37%) admitted to hospital with emergency complications of their tumours. Patients referred via USC pathways had a median 27 day delay (1-262) between the time of GP referral and diagnosis. There was an inverse correlation between age and USC referral ($R = -0.233$, $p = 0.004$), whereby all patients younger than 50 years were referred via the USC route compared with 11 patients (39.3%) aged 80 years or older ($R = -.225$, $p = 0.006$). Forty-four percent of the younger cohort were offered curative treatment compared with 14.3% of the older cohort ($R = -0.277$, $p = 0.001$). There was a strong correlation between referral via USC pathway and the likelihood of potentially curative treatment ($R = 0.194$, $p = 0.017$), with 43% of USC patients offered treatment with curative intent compared with 25% of patients referred via non-USC routes. There was no correlation between gender and USC endoscopy referrals with 72.3% of female and 60% of male patients referred by their GPs via

this route ($R=-0.091$, $p=0.269$). For USC patients median delay from receipt of GP referral to date treatment started was 85 (1-526) days. Thirty four patients (36.2%) started treatment within 62 days and the median delay for this cohort was 15 (1-59) days. For the remaining 60 patients (63.8%), the median delay was 119 (64-526) days. Among non-USC patients ($n=56$), median delay from the decision to treat date was made to treatment was 1 (1-253) days, and 51 patients (91.1%) were treated within 31 days. For the remaining 5 patients median delay was 176 (53-253) days.

3.4.5 Hospital Delay

Median delay between GP referral and histological diagnosis was 25 (1-262) days and accounted for 23% of the total delay experienced by the patient.

For patients undergoing surgery the median delay between diagnosis and surgery was 23 (2-46) weeks. Oesophageal cancer patients waited a median 25 (8-46) weeks compared with gastric cancer patients who had a median delay of 8 (4-29) weeks ($R=-0.537$, $p=0.003$). A positive correlation was observed between HD and delay to surgery with patients in the most deprived quintile waiting a median 25 (8-46) weeks compared with patients in the least deprived quintile who waited 13 (4.0-31) weeks ($R=-0.401$, $p=0.038$). No correlation was observed between the duration of patient delay and subsequent operability (open and close surgery, $R=0.088$, $p=0.684$), post-operative morbidity ($R=0.180$, $p=0.474$), post-operative mortality ($R=0.051$, $p=0.840$), length of hospital stay ($R=0.157$, $p=0.535$), pT ($R=-0.089$, $p=0.724$), pN ($R=-0.012$, $p=0.963$) or pM stage ($R=-0.393$, $p=0.441$).

3.4.6 Univariate analysis of factors associated with length of total delay

The factors associated with length of total delay are shown in Table 4

3.4.7 Multivariate analysis of factors associated with length of total delay

Factors found to be associated with length of total delay ($p < 0.10$) on univariate analysis were also entered into a multivariate analysis using Cox's proportional hazards model shown in Table 5. Length of patient delay (HR 0.924, 95% CI 0.896-0.953, $p < 0.0001$) and urgent suspected cancer (USC) referrals (HR 0.374, 95% CI 0.165-0.849, $p = 0.019$) were found to be independently associated with total delay.

3.4.8 Survival

Median survival for all patients was 10 (0.25 to 32) months. There was no correlation between survival and length of patient delay ($R = 0.094$, $p = 0.251$), with survival similar irrespective of the delay (quintiles 1 and 5) at 9.5 (0.25 to 30) and 9.5 (1 to 32) months respectively. Survival did however correlate with overall delay ($R = 0.210$, $p = 0.010$), whereby patients with the shortest overall delay (quintile 1) survived for a median 6 (0.25 to 30) months compared with patients with the longest overall delay who survived for a median 12.5 (0.5 to 32) months.

3.5 Discussion

The principal findings of this study were that delays in the diagnosis and treatment of UGI cancer remain common, on average approaching four months, little better than the 17 weeks described in a similar study in Leeds, UK some 20 years ago (Martin et al. 1997). In contrast to the above report however, where practitioner and hospital delay accounted for the majority, delay on the part of the patient was responsible for over 75% of the time interval between initial onset of symptoms and diagnosis. Deprivation and female gender were significantly and independently associated with longer patient delays, with females and patients residing in the most deprived geographical areas waiting a median of 5 weeks longer before seeking medical advice when compared with males and patients residing in the least deprived areas. Almost two thirds of patients were referred via the open access urgent suspected cancer (USC) endoscopy route, which was associated with younger age, and a higher likelihood of potentially curative treatment. The study also found that those patients with the shortest overall delay time subsequently had the shortest survival time, and on review these patients were, for the majority, emergency admissions with previously undiagnosed stage IV disease.

Several factors have been implicated and reported to be associated with UGI cancer diagnostic delay. Traditionally, with regard to patient delay, the perceived significance of symptoms, the presence of pain or bleeding, and multiple symptoms all influence delay (MacDonald et al. 2006). Pain has been equivocally reported to be associated with both an apparent decreased (Grannell et al. 2001; Mariscal et al. 2001) and increased delay (Look et al. 2003), and weight loss has also been reported to be associated with increased delay (Haugstvedt et al. 1991). Factors influencing practitioner delay include initial misdiagnosis of common symptoms and

the blind prescription of treatments such as acid suppression for presumed benign conditions in patients subsequently diagnosed with UGI cancer (MacDonald et al. 2006). The influence of deprivation is controversial, with a report by Porta suggesting that lower socio-economic status was associated with increased delay (Porta et al. 1996), yet Mikulin reported that patients from lower socio-economic groups, once having presented to their GPs, experienced shorter referral times (Mikulin et al. 1987). Other factors found to reduce practitioner delay include availability of a rapid access endoscopy service (Martin et al. 1997; Manes et al. 2002), the introduction of Department of Health cancer referral guidelines (Irving et al. 2002), male gender (Zilling et al. 1990), and older age (Mikulin et al. 1987).

The study has a number of potential limitations. The length of patient delay was a subjective recollection on the part of the patient or their relatives without objective corroboration. Deprivation scores were measured at the area level, i.e. each individual was given a score based on the degree of deprivation of their local community. Area-based deprivation scores, as opposed to individual-based scores, calculated on individuals' incomes or occupations, risks the introduction of potential bias, given that it is unlikely that all residents of a specific postcode will have the attributes of that community (the ecological fallacy) (Morgan et al. 2007). This was a comparative study, and the definition and analysis of sub-groups within a study may lead to bias, while comparisons of groups may prove to be not statistically significant simply because the study has insufficient power to demonstrate real differences. The use of quintiles was arbitrary. In contrast the study has several strengths in that data was prospectively and consecutively collected for unselected patients from a well-defined geographical area, a large proportion of whom reside in areas shown to be amongst the most deprived in the United Kingdom. All patients were managed by a

specialist MDT whose clinical outcomes and results are well audited and can stand up to international scrutiny (Stephens et al. 2006). All dates were initially recorded according to the patient's recollection but were then cross referenced and verified with the patient's notes, the electronic clinical portal and CANISC. This is the first study to correlate diagnostic delay with government designed socio-economic (SED) and health deprivation (HD) ranking systems, and access to the SED and HD rank for all patients adds further strength. The findings of an association between greater level of deprivation and increased patient delay are in keeping with those of Porta (Porta et al. 1996). Regarding other patient demographic factors, the findings are in keeping with previous reports which did not find any association between patient delay and age (Mariscal et al. 2001), but contradict further studies which reported little evidence of any association between time to presentation and gender (Macdonald et al. 2006). The principal factor influencing contemporary practitioner delay in South East Wales appeared to be initial misdiagnosis on first presentation, a finding supported by Rothwell who reported delays in referral particularly for young female patients who were instead being blindly treated with acid suppression for a presumed benign condition (Rothwell et al. 1987). This finding was further supported by a report by Bramble (Bramble et al. 2000). Furthermore this study supports the findings of Manes who reported patients experienced less delay in referral where a rapid access service was available (Manes et al. 2002). The median delay between GP referral and OGD was 25 days (1 day- 37 weeks), falling short of the UK Department of Health recommendation that urgent OGD be performed within 2 weeks of referral (Dept of Health 2011). Indeed only a quarter of USC referrals (25.7%) underwent OGD within the 14 day Department of Health cancer referral guidelines. Previous work has reported deprived patients were less likely to accept

an invitation to be screened for colorectal cancer (Whynes et al. 2003), but this was not apparent in the current study in that no reluctance was evident on the part of the most deprived patients to undergo OGD. This study found that patient delay did not influence survival, patients with the shortest and longest patient delay times had similar median survival times of 9 and 9.5 months respectively. Overall delay time was however significantly associated with duration of survival, patients with the shortest overall delay survived a median 6 months compared with 12.5 months for patients with longest overall delay. The former patients were however, mostly emergency admissions with complications of their tumours who were treated palliatively and did not undergo extensive radiological investigation involving EUS and PET/CT scans or staging laparoscopies.

Previous reports have suggested that patient referral and hospital assessment be expedited in an attempt to reduce delays in diagnosis and treatment in UGI cancer (Martin et al. 1997). This is of particular clinical significance in UGI cancer given a potentially short tumour doubling time and associated poorer prognosis. There has been significant research performed in this arena and specific guidelines issued recommending that primary healthcare professionals should take part in education, peer review and other activities to improve the quality of clinical consulting, reasoning and diagnostic skills (The Royal College of Physicians 1997). Yet the findings of this study suggest that the majority of diagnostic delay was accounted for by the patients rather than individual practitioners or hospital services. Indeed, previous UK population surveys have shown widespread lack of awareness of cancer symptoms (Linsell et al. 2008; Robb et al. 2009), and such awareness is poorer among lower socio-economic strata (Robb et al. 2009). A further Office for National Statistics survey reported respondents were able to name just two cancer

symptoms or signs with the commonest perceived sign of mischief being the presence of an abnormal lump, but fewer than 32% could name any other symptom and 9% knew of none (Cancer Research UK 2010).

3.6 Conclusion

In conclusion, this study has shown that long delays remain common in the diagnosis and treatment of upper GI cancer, and these delays are strongly associated with deprivation and are therefore likely associated with lack of awareness and poor education. In order to address this lack of understanding, the Cancer Reform Strategy, published in 2007, launched the National Awareness and Early Diagnosis Initiative (NAEDI), a partnership between the Department of Health and Cancer Research UK. The role of NAEDI is to help raise public awareness of cancer signs and symptoms, and reverse the trend towards the later diagnosis seen in Great Britain than in other countries with comparable health care systems. Previous campaigns to raise public awareness of cancer such as the UK National Bowel Cancer Awareness Campaign, the US National Breast Cancer Awareness Month and the UK National Lung Cancer Awareness campaign each significantly raised the profile of these specific conditions and led to increased public awareness of the respective red-flag signs and symptoms (Pande et al. 2014; Jacobsen et al. 2011; Baird 2003). The next challenge for the Department of Health, organisations such as Cancer Research UK, and frontline clinicians is to raise public awareness of the potential significance of dysphagia, dyspepsia and weight loss, often the harbingers of UGI cancer, through efforts such as the UK Northern Oesophago Gastric Unit's "Oesophagoose" annual awareness campaign.

Improved patient awareness and doctor education, with lower thresholds for referral in deprived geographical areas, allied to streamlined diagnostic pathways are required if earlier diagnosis of UGI cancer is to be achieved and treatment outcomes optimised.

Table 3.1 Details of diagnostic delay

Delay Intervals	Oesophagus	Gastric	All
Symptoms to GP (weeks)	9 (1-78)	13 (1-104)	12 (1-104)
GP to referral (days)	1 (1-5)	1 (1-546)	1 (1-546)
Referral to OGD (days)	25 (1-201)	25.5 (1-262)	25 (1-262)
Referral to CT (days)	33.5 (1-212)	35.5 (1-268)	34 (1-268)
Symptoms to diagnosis (weeks)	13 (1-64)	17 (2-142)	15.5(1-142)
CT to EUS (weeks)	4 (2-10)	3 (2-4)	4 (2-10)
CT to PET/CT (weeks)	3 (0.5-11.5)	2.5 (1.5-3.5)	3 (0.5-11.5)
Referral to decision to treat (weeks)	6 (1-33)	5.5 (0.5-39)	6 (0.5-39)
Total delay from symptom onset to decision to treat (weeks)	16 (3-69)	20 (3-143)	18 (3-143)

Numbers are median (range)

Table 3.2 Univariate analysis of factors associated with length of patient delay

Factor	Log Rank	DF	p-value
Age	57.513	45	p=0.100
Age (per decade)	8.883	4	p=0.064
Gender	4.822	1	p=0.028
IMD Rank	416.390	136	p<0.0001
HD Rank	416.390	136	p<0.0001

Table 3.3 Multivariate analysis of factors associated with length of patient delay

Factor	HR	CI (95%)	p-value
Gender	1.463	1.038-2.063	p=0.030
IMD Rank	1.000	1.000-1.001	p=0.005

Table 3.4 Univariate analysis of factors associated with length of total delay

Factor	Log Rank	DF	p-value
Age	93.935	45	p<0.0001
IMD Rank	519.419	136	p<0.0001
HD Rank	519.410	136	p<0.0001
Length patient delay	131.871	20	p<0.0001
Practitioner delay	28.656	3	p<0.0001
Delay referral to OGD	135.650	54	p<0.0001
Delay referral to diagnosis	133.625	56	p<0.0001
Delay symptoms diagnosis	217.472	51	p<0.0001
USC Referral	10.626	1	p=0.001

Table 3.5 Multivariate analysis of factors associated with length of total delay

Factor	HR	CI (95%)	p-value
Patient Delay	0.924	0.896-0.953	p<0.0001
USC Referral	0.374	0.165-0.849	p=0.019

Chapter 4

Prognostic significance of body composition determined by Bioelectrical Impedance Analysis (BIA) in upper gastrointestinal cancer surgery

4.1 Summary

Malnutrition and sarcopenia are associated with higher rates of operative morbidity and therefore represent potentially reversible prognostic risk factors. Bioelectrical Impedance Analysis (BIA) is a non-invasive, easily reproducible and inexpensive means of accurately measuring body composition, and the aim of this study was to determine the prognostic value of BIA and sarcopenia in UGI cancer surgery.

Consecutive 125 patients [median age 66 years (24-86), 94 males, 73 oesophageal and 52 gastric cancers] underwent pre-operative BIA (Maltron Bioscan 920) assessment to measure percentage Free Fat Mass (FFM%), percentage Body Fat (BF%), percentage Lean Muscle Mass (LMM%), Total Body Water (TBW%), Intracellular and Extracellular Fluid Volume (ICV, ECV, %), and Phase Angle (PhA). Furthermore, the lean muscle mass for each patient was divided by their total body weight, the results were then split into quartiles and the quartile with the lowest lean muscle mass to total body weight ratio was used as a surrogate for sarcopenia. Primary outcome measures were operative morbidity and length of hospital stay.

Pre-operatively anaerobic threshold (AT) correlated with ICV% ($R=0.370$, $p=0.001$), LMM% ($R=0.236$, $p=0.042$), and PhA ($R=0.289$, $p=0.010$). Surgery mortality risk (O-POSSUM score) correlated with FFM% ($R=0.247$, $p=0.020$) and BF% ($R=0.259$,

p=0.015). Sarcopenia was associated with AT (R=0.277, p=0.017), operative severity (R=0.330, p=0.003), P-POSSUM morbidity (R=0.306, p=0.005), and P-POSSUM mortality (R=0.239, p=0.031). Sarcopenia was also associated with female gender (R=-0.705, p<0.001), and tumours located in the distal oesophagus (R=-0.319, p=0.033). Open and close laparotomy was associated with FFM% (R=0.200, p=0.027), and BF% (R=-0.197, p=0.030). Post-operative morbidity (Clavien-Dindo ≥ 3) was associated with ICV (R=0.265, p=0.018), TBW (R=0.269, p=0.019), and sarcopenia (R=0.232, p=0.045), the quartile most affected by sarcopenia showed almost twice the rate of Clavien-Dindo ≥ 3 complications compared with the quartile least affected (24.1% vs 13.8%). Critical care length of stay was associated with ICV (R=0.279, p=0.009), LMM (R=0.302, p=0.006), PhA (R=0.239, p=0.025) and sarcopenia (R=0.236, p=0.011).

In conclusion BIA defined body composition is an important and independent prognostic indicator in UGI cancer. Further research is warranted to determine critical body composition values so that enhanced recovery programmes containing bespoke nutritional strategies may be developed to improve surgical outcomes.

4.2 Introduction

Cachexia affects up to two-thirds of patients with cancer, and the extent of malnutrition is related to the site, stage and type of the tumour. It is especially pronounced in oesophageal and gastric cancers (Bozetti et al. 1982). It is a multifactorial syndrome characterised by weight loss, altered metabolism of lipids, protein and carbohydrates, loss of both skeletal muscle and white adipose tissue, and anaemia (Argiles et al. 1997). Indeed, it has been reported that cachexia is responsible for at least 20% of cancer-related deaths rather than the underlying tumour itself, and decreases the quality of life in many more patients (Ottery 1994). A decline in food and energy intake, coupled with elevated resting energy expenditure, is the fundamental physiologic derangement leading to cancer-associated weight loss (Kern et al. 1988). Furthermore, after a point it may not be possible to reverse the process even with intensive nutritional support, including total parenteral nutrition (Costa et al. 1980). Finally, sarcopenia describes a syndrome characterised by progressive generalised loss of skeletal muscle mass and strength. In 2010 the European Working Group on Sarcopenia published consensus guidelines on the definition and diagnosis of sarcopenia. Known risk factors for sarcopenia include increasing age and inadequate nutrition, and it can be diagnosed by low muscle mass measured, for example, by bioimpedence (Cruz-Jentoft et al. 2010)

Malnutrition alters the relative fluid distribution between intra- and extracellular compartments whereby there is a characteristic increase in extracellular volume (ECV) and resultant decrease in intracellular volume (ICV). An increase in cancer-related tumour necrosis factor (TNF) lowers both transmembrane Na⁺ gradients and muscle cell membrane potential. These changes, in combination with an increase in inflammatory cytokines, oxygen radicals and altered hormone homeostasis induce

extracellular expansion and cellular shrinkage. The resultant intracellular dehydration triggers proteolysis and catabolism. Previous authors report there is evidence that the catabolism causing these fluid shifts also governs the degree of protein wasting and ultimately survival (Davis et al. 2009).

Upper gastrointestinal (UGI) cancer resection falls within the category of high risk surgery as defined by the Royal College of Surgeons of England (RCSE 2011). Pre-operative malnutrition is associated with higher rates of post-operative sepsis and morbidity (Deans et al. 2007), and is therefore a potentially reversible prognostic risk factor of particular relevance to patients with resectable UGI tumours. Current risk assessment tools for patients undergoing UGI cancer resection include the American Society of Anaesthesiologists (ASA) physical status classification system, Cardio-Pulmonary Exercise (CPEX) testing and the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) scoring.

Bioelectrical Impedance Analysis (BIA) is a non-invasive, easily reproducible and inexpensive means of accurately measuring total body water (TBW), ICV, ECV, fat-free mass (FFM) and changes in the distribution between these media. Single frequency BIA at 50 kHz measures body resistance and reactance to an alternating electrical current and can also quantify body fat and lean body mass, and is therefore indicative of nutritional status. The Phase Angle (PhA), a further parameter measured by BIA, is the ratio of resistance and reactance, where resistance is a reflection of the intracellular fluid and electrolyte volume and reactance is a measure of cellular membrane integrity. A low PhA implies decreased cellular integrity or cell

death, a high PhA is a sign of intact and healthy cellular membranes. From these measurements PhA can also be considered a reliable indicator of malnutrition.

More recently BIA, and in particular the PhA, has been used as a prognostic marker to predict survival in colorectal and pancreatic cancer (Gupta et al. 2004; Gupta et al. 2004). The disruption to cellular membrane integrity, altered fluid balance and electrolyte disturbances seen in UGI cancer however has not yet been investigated. The aim of this study was to determine the prognostic value of BIA-derived body composition in UGI cancer surgery. Outcome measures were post-operative morbidity and length of hospital stay, particularly critical care length of stay.

4.3 Material and Methods

This was a prospective study of 125 consecutive patients [median age 66 (24-86) years, 94 males, 73 oesophageal and 52 gastric cancers] undergoing surgery for histologically confirmed upper gastrointestinal cancer. Patients were treated within an Enhanced Recovery after Surgery (ERAS) programme by the South East Wales UGI cancer multi-disciplinary team from August 2011 to April 2014. Patient details were collected prospectively and data was cross-referenced with the oncology (CANISC) database. Informed consent was obtained from all patients and ethical approval was sought from the regional ethics committee.

4.3.1 Bioelectrical Impedance Analysis

Patients underwent multi-frequency (0.5 kHz, 50 kHz and 100 kHz) BIA assessment using a Maltron Bioscan 920 (Maltron International Ltd, Essex, UK). BIA was measured by the same clinician pre-operatively on the day of surgery and again on pre-planned days post-operatively. Demographic data (age, gender, ethnicity) and clinical data (height, weight, renal function and dependence on dialysis) were recorded on the Bioscan software prior to assessment. The patient was supine and motionless throughout the test and the right arm was held equidistant from the torso on each testing. Measurements taken included TBW%, ICF%, ECF%, FFM%, BF%, and PhA, calculated using the formula: $PhA = [(\text{arc tangent resistance} / \text{reactance}) \times (180^\circ/\pi)]$. Furthermore, the lean muscle mass percentage for each patient was divided by their total body weight, the results were then split into quartiles and the quartile with the lowest LMM% to total body weight ratio was used as a surrogate for sarcopenia. CPEX testing was routinely performed by specialist anaesthetic colleagues as part of the pre-surgery work-up, and all patients had ASA, P-POSSUM

and O-POSSUM scores calculated. BIA parameters were also sub-divided into equally sized quintiles to facilitate subgroup analysis of patients and allow comparison across the spectrum.

4.3.2 Details of Surgery

Surgery was performed by one or a combination of seven UGI surgeons. For early stage oesophageal tumours (T1-2, N0), a transhiatal resection as described by Orringer was performed (Orringer 1984). It was also employed selectively for patients with more advanced adenocarcinomas of the lower third of the oesophagus (T3 N1), and for patients with significant associated co-morbidity (ASA grade \geq III). The remaining oesophageal cancer patients underwent standard subtotal oesophagectomy as described by Lewis and Tanner (Lewis 1946; Tanner 1947). Patients with gastric cancer underwent a modified radical D2 resection with extended lymphadenectomy but preserving the pancreas and spleen where possible. Morbidity included all complications occurring up to 30 days post-operatively, and complications were graded using the Clavien-Dindo Classification of surgical complications (Dindo et al. 2004).

4.3.3 Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for Social Sciences (SPSS) Statistics 20 package (IBM Corporation, New York). Grouped data were presented as median (range). Bivariate correlations were calculated using Spearman's correlation test. Differences were deemed statistically significant when $p < 0.05$. Lengths of critical care and ITU stay were plotted on the life-table method of Kaplan and Meier (Kaplan et al. 1958).

4.4 Results

One hundred and twenty five consecutive patients newly diagnosed with histologically confirmed UGI cancer were recruited to the study. There were 94 males and 31 females, 73 patients had oesophageal cancer and 52 gastric cancer. Median age was 66 (24-86) years. Radiological TNM (rTNM) staging at presentation was as follows: stage I (n=36, 29%), stage II (n=37, 30%), stage III (n=49, 39%) and stage IV (n=3, 2%).

4.4.1 Pre-Operative

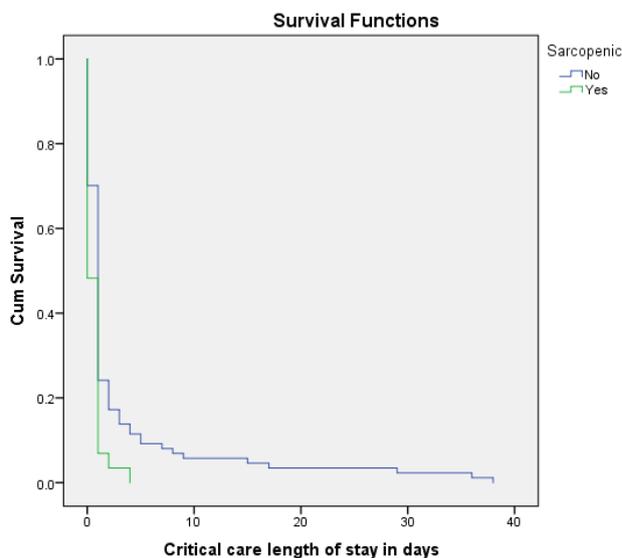
Anaerobic threshold (AT) correlated with ICV% (R=0.370, p=0.001), LMM% (R=0.236, p=0.042), and PhA (R=0.289, p=0.010). Surgery mortality risk (O-POSSUM score) correlated with both FFM% (R=-0.247, p=0.020) and BF% (R=0.259, p=0.015). Staging CT N stage correlated with FFM% (R=0.260, p=0.011), BF% (R=-0.245, p=0.016) and TBW% (R=0.358, p=0.001), while CT M stage correlated with FFM% (R=0.341, p=0.001), BF% (R=-0.330, p=0.001), and TBW% (R=0.459, p<0.0001). Sarcopenia was associated with AT (R=0.277, p=0.017), operative severity (R=0.330, p=0.003), P-POSSUM morbidity (R=0.306, p=0.005), and P-POSSUM mortality (R=0.239, p=0.031). Sarcopenia was also associated with female gender (R=-0.705, p<0.001), and tumours located in the distal oesophagus (R=-0.319, p=0.033).

4.4.2 Peri-operative

Open and close laparotomy was significantly associated with FFM% (R=0.200, p=0.027), and BF% (R=-0.197, p=0.030). Positive circumferential margins were associated with BF% (R=0.212, p=0.050), and the ratio of positive resected lymph

nodes was associated with ECV% (R=0.205, p=0.041). Post-operative morbidity (Clavien-Dindo ≥ 3) was associated with ICV (R=0.265, p=0.018), TBW (R=0.269, p=0.019), and sarcopenia (R=0.232, p=0.045). Critical care length of stay (CCLOS) was associated with ICV (R=0.279, p=0.009), LMM (R=0.302, p=0.006), PhA (R=0.239, p=0.025) and sarcopenia (R=0.236, p=0.011), while ITU LOS in particular was associated with ICV (R=0.227, p=0.034), PhA (R=0.268, p=0.012) and again sarcopenia (R=0.236, p=0.011).

Figure 4.1 Critical care length of stay related to sarcopenia

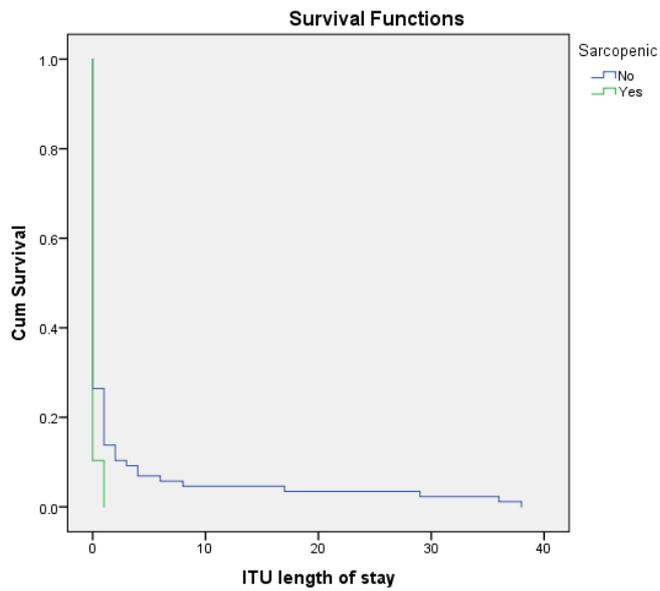


Chi² 7.835 DF 1 p=0.005

Table 4.1 Post-operative complications related to sarcopenia quartiles

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Clavien-Dindo≥ 3	24.1%	13.8%	17.2%	13.8%

Figure 4.2 ITU length of stay related to sarcopenia



Chi² 5.301 DF 1 p=0.021

Table 4.2 Median (range) lengths of stay related to sarcopenia quartiles

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
LOHS	13 (4-52)	14 (4-30)	14 (5-95)	13 (3-41)
CCLOS	1 (0-38)	1 (0-9)	1 (0-28)	1 (0-17)
ITU LOS	0 (0-38)	0 (0-6)	0 (0-28)	0 (0-17)
HDU LOS	0 (0-28)	1(0-5)	1 (0-13)	0 (0-3)

4.5 Discussion

This study is the first to employ Bioelectrical Impedance Analysis to determine the prognostic significance of body composition in upper gastrointestinal cancer surgery patients. The principal findings are significant correlations between certain body composition measurements as determined by BIA and the rate of open and close laparotomy, post-operative morbidity, and critical care length of stay. Pre-operatively PhA, ICV, LMM and sarcopenia correlated significantly with anaerobic threshold levels, while FFM and BF correlated with O-POSSUM scores. Sarcopenia correlated with operative severity, P-POSSUM morbidity, and P-POSSUM mortality. Surgical complications scoring Clavien-Dindo grade 3 or above i.e. requiring surgical, endoscopic or radiological intervention at a minimum were strongly associated with ICV, TBW and sarcopenia. The PhA, ICV, LMM and sarcopenia correlated strongly with critical care length of stay, the two former measurements being particularly strongly associated with ITU length of stay.

The strengths of the study are that data was collected prospectively from one hundred and twenty five unselected consecutive patients undergoing surgery for histologically confirmed upper gastrointestinal cancer. These details were also cross-referenced with the national oncology (CANISC) database. All patients were managed by a specialist MDT whose results are well audited and can stand up to international scrutiny (Stephens et al. 2006). BIA measurements were taken by one of two operators in the same manner and using the same protocol at fixed pre-operative times. The study used multi-frequency BIA which is a more accurate means of estimating the TBW (Martinoli et al. 2003). Furthermore, none of the patients were lost to follow-up.

The study has a number of limitations. The study population was a combination of both oesophageal and gastric cancer patients and analyses were conducted on the group as a whole with no comparisons made across the groups. With continued recruitment over time further testing will be undertaken to identify any potential differences or particular trends in the two groups. Analyses were only performed on those patients who were deemed potentially suitable and fit enough for surgery. Further investigation will also be undertaken in those patients who present with non-resectable tumours to determine baseline measurements and thereby initiate specialist dietetic input tailored to their individual needs. A surrogate measurement of sarcopenia was used in the study but the objective assessment of sarcopenia using CT-measured psoas muscle density has now begun and will be incorporated into future studies. Finally we were unable to compare our findings to other similar studies involving oesophageal and gastric cancer.

The study found that significant post-operative complications requiring surgical, radiological or endoscopic intervention were associated with sarcopenia and this was in keeping with Naber et al who found the risk of complications after admission to hospital was higher in malnourished patients (Naber et al. 1997). The study also found that critical care length of stay was associated with lean muscle mass and this is in keeping with Pichard et al who reported that fat-free mass was significantly associated with an increased length of hospital stay (Pichard et al. 2004).

4.6 Conclusion

Upper GI cancer patients undergoing major resections must be assessed and provided with tailored goal-directed nutritional support in order to reduce the operative morbidity and mortality associated with complications, in particular anastomotic leak, wound dehiscence or infection. This study shows BIA defined body composition is an important and independent prognostic indicator in UGI cancer. Further research is warranted to determine critical body composition values so that enhanced recovery programmes containing bespoke nutritional strategies may be developed to improve outcomes and survival.

Chapter 5

Centralisation of upper gastrointestinal cancer: does a regionalised service model influence patient safety, quality of care and survival?

5.1 Summary

The aim of this study was to determine the influence of a centralised upper gastrointestinal (UGI) cancer service model on post-operative morbidity and survival.

Prospective and contemporaneous details of 1177 consecutive UGI cancer patients were collected before (n=566) and after (n=611) centralisation of care. Primary outcome measure was survival, secondary outcome measures were rates of curative intent, operative morbidity, and length of hospital stay.

Treatment with curative intent was offered to 122 (21.6%) and 181 (29.6%) patients before and after centralisation respectively ($\chi^2 = 10.007$, DF=1, $p= 0.002$), with resectional surgery performed in 78 (81.3%) and 99 (81.1%) patients ($p =0.985$) pre- and post-centralisation. The incidence of serious post-operative morbidity (Dindo-Clavien ≥ 3) decreased from 19 (22.3%) to 15 (12.5%) patients before and after centralisation ($\chi^2 =1.690$, DF = 1, $p= 0.194$). There were significant reductions in ITU ($p<0.0001$) and critical care unit ($p<0.0001$) lengths of stay, with overall length of hospital stay reduced by 2.5 days ($p= 0.008$). Rate of re-admission to critical care decreased from 10 (29.4%) to 6 (6.3%) ($\chi^2 = 12.480$, DF = 1, $p<0.0001$). There were 5 (5.9%) operative deaths before and 1 (0.8%) operative death after the introduction of a centralised service ($\chi^2 = 3.977$, DF=1, $p= 0.046$). Median survival pre-centralisation was 9 (0.25-73) months compared with 10 (0.25-49) months post-centralisation ($\chi^2 = 175.293$, DF = 87, $p<0.0001$). On univariate analysis of factors

influencing two-year survival centralisation was statistically significant ($p=0.001$). On multivariate analysis radiological TNM (rTNM) stage and open and close procedures were independently associated with two-year survival.

The study demonstrated an increased proportion of patients receiving potentially curative treatment, fewer cancelled operations, reduced operative morbidity requiring intervention, reduced total length of hospital stay, and improved survival, many by significant margins. The study thereby clearly supports the centralisation of surgery for upper gastrointestinal cancer.

5.2 Introduction

Centralisation of upper gastrointestinal (UGI) cancer surgery was first proposed in the Calman-Hine Report which recommended limiting oesophago-gastric cancer surgery to specialised, designated high-volume sites in order to improve peri-operative mortality and long-term survival (Dept of Health 1995). Furthermore, in 2001 the Improving Outcomes Guidance document recommended that these specialist cancer units should aim to perform at least 40 oesophagectomies and 60 gastrectomies each year drawing patients from catchment areas with populations of one to two million (Dept of Health 2001). More recently the Association of Surgeons of Great Britain and Ireland (AUGIS) suggested the ideal unit would have four to six dedicated UGI surgeons each performing a minimum of 15 to 20 resections per year (AUGIS 2010). The process of centralisation began in 2001 and by 2013 there were 41 specialist centres established across England and Wales.

The rationale underpinning the introduction of a centralised service was that oesophageal cancer surgery, amongst the most complex surgical procedures, would benefit if performed in specialist high-volume centres of excellence. Historically the provision of UGI cancer resectional surgery was poorly organised and fragmented, undertaken by individual surgeons operating on very small numbers of patients, and was associated with a 30 day mortality rate of between 10 to 20% (Bachmann et al. 1999; Northern and Yorkshire Cancer Registry and Information Service 1999). Indeed a previous report published in 2007 stated “any given surgeon would see relatively few cases per year, resect even fewer and outcomes were notoriously poor” (Siriwardena 2007). A centralised multi-disciplinary service would improve patient care via explicit referral protocols, appointed lead clinicians, dedicated radiological services, clinical nurse specialists and intensive care units with specialist

post-operative support. Surgery, widely regarded as the only intervention that can offer a cure for UGI cancer, would only be undertaken by designated members of specialist teams in centres performing approximately one hundred resections per year (Dept of Health 2001). The emphasis on a concentrated workload followed a seminal study in the US which reported a patient's chances of survival increase substantially if operated on by a surgeon who performs the operation on a frequent basis (Birkmeyer et al. 2003). This finding was further supported by a meta-analysis which reported a survival benefit after oesophagectomy in favour of high-volume surgeons (Brusselaars et al. 2014). Additionally, operating on a difficult case within a centralised specialist unit offers the benefit of an immediate second opinion and an experienced consultant assistant if and when required (Morgan et al 2008).

Since its inception however, centralisation has remained controversial and continues to polarise opinion. Despite having been shown to significantly improve in-hospital and 30 day mortality, the data regarding long-term survival remains limited and even contradictory in some individual studies (Gruen et al. 2009; Lagergren et al. 2013; Lauder et al. 2010; Markar et al. 2012; Tol et al. 2012; Wouters et al. 2012). The disadvantages of a centralised service can be seen from both a patient and a service provision perspective. For patients there is the increased distance from home and greater social isolation, in addition to the expenses incurred by visiting families. From an NHS perspective local district general hospitals are downgraded and lose their cancer workload with subsequent loss of surgical skills. Also, the hospitals appointed to provide a centralised service have to address the initial costs and increased infrastructure required to establish a high-volume centralised centre (Siriwardena 2007).

The aim of this study was to determine the influence of a re-configured centralised service, allied to an enhanced recovery after surgery (ERAS) programme, when compared with the historical control outcomes of three local hospital trusts in the two years preceding centralisation. The setting was a UK regional cancer network serving a population of 1.4 million.

5.3 Material and Methods

The South East Wales cancer network encompasses three National Health Service Health Boards; Cardiff and Vale University Health Board (C&V UHB, catchment population 450,000), Aneurin Bevan Local Health Board (AB LHB, catchment population 600,000) and Cwm Taf Local Health Board (CT LHB, catchment population 325,000). Together these LHBs are responsible for six acute hospitals: four district general hospitals and two teaching hospitals. Before August 2010, the surgical care of patients with oesophago-gastric cancer was delivered by eight surgeons operating at four different hospital sites. An agreement was reached in December 2009 to re-configure and centralise the UGI surgical service on a single site at the University Hospital of Wales, Cardiff, with an agreed start date of 1st August 2010.

The new model was based on five specialist UGI surgeons carrying out all the resectional surgery; three of the surgeons were based at the surgical centre and the other two were to operate on an in-reach basis, with a facility for joint consultant operating where necessary. Diagnosis and staging continued to be undertaken locally within each health board, co-ordinated via three local MDT meetings, and all cases deemed suitable for curative treatment were subsequently discussed at a weekly South East Wales MDT meeting. Specific additional changes at the Royal

Gwent Hospital, Newport, included a two-fold increased frequency of local MDT meetings from fortnightly to weekly and the establishment of a dedicated UGI cancer out-patient clinic, serviced by one of the Cardiff-based surgeons. Integral to the new surgical model was the establishment of an enhanced recovery after surgery (ERAS) programme based on the established principles introduced in colorectal surgery (Basse et al. 2000).

The oesophageal and gastric cancer caseload referred to the MDTs during the two years preceding the introduction of centralisation (August 2008 to July 2010) was compared with the following two years (August 2010 to July 2012). Pre-centralisation data across the three health boards was collected using a combination of a prospectively maintained database combined with MDT records and a retrospective review of all hospital records. Measures of outcome included post-operative morbidity and mortality, length of hospital stay and survival rate 2 years from diagnosis. All patients were followed up for at least 2 years or until death and no patients were lost to follow-up. Dates and causes of death were obtained by the Wales Cancer Intelligence and Surveillance Unit from the Office for National Statistics (ONS) thus ensuring accurate survival times for all patients.

All patients had management plans individually tailored according to factors relating to both the patient and their disease. Staging was by means of computed tomography (CT), endoscopic ultrasound (EUS), computed tomography positron emission tomography (PET/CT), and staging laparoscopy as appropriate. The South East Wales MDT treatment algorithms for oesophageal and gastric cancer have been described previously (Lewis et al. 2002; Morgan et al. 2009). Operative morbidity was graded in accordance with the Clavien-Dindo classification system (Dindo et al. 2004). Particular emphasis was placed on the incidence of morbidity of

Clavien-Dindo grade III or higher, as this represented a complication requiring any combination of endoscopic, radiological or surgical intervention, in contrast with morbidity of lower grade requiring only pharmacological treatment. Definitive chemoradiotherapy was offered to patients with localised squamous cell carcinoma and patients with adenocarcinoma deemed unsuitable for surgery because of disease extent and/or medical co-morbidity.

Grouped data were expressed as the median (range) and non-parametric statistical methods were used. Bivariate correlations were calculated using Spearman's correlation test. Continuous data were compared using the Mann-Whitney test and categorical data using the chi-squared test. A non-parametric two-sample test on the equality of medians was carried out. This tested the null hypothesis that pre-centralisation and post-centralisation patients were drawn from populations with the same median. Cumulative overall survival was calculated by the life-table method of Kaplan and Meier. Differences in survival between groups of patients were analysed using the log-rank method. Differences were deemed to be statistically significant when the p -value was less than 0.05. Factors found to be significantly associated with duration of survival on univariate analysis and with p -value <0.10 were entered into a multivariate analysis using Cox's proportional hazards model.

5.4 Results

A total of 1177 UGI cancer patients presented to the regional MDTs over the four-year period, 566 (48.1%) pre- and 611 (51.9%) post-centralisation. There were 779 males (66.2%), median age was 73 (22-97) years and 692 patients (59%) had oesophageal cancer (Table 1 shows demographic and treatment details).

5.4.1 Details of Patient Treatment

Pre-operatively there was a statistically significant increase in the proportion of rTNM stage IV tumours detected post-centralisation compared with pre-centralisation (37% vs 46%, $p=0.008$). Potentially curative treatment however, was still offered to 182 (29.8%) patients after centralisation compared with 129 (22.8%) before ($\chi^2 = 7.396$, $DF = 1$, $p= 0.007$). The rate of surgery with curative intent was similar before and after centralisation with 78 (81.25%) and 99 (81.2%) cases respectively ($p =0.985$). Of those patients treated surgically, 33 and 50 underwent oesophagectomy and 35 and 49 underwent gastrectomy pre- and post-centralisation respectively. Cancellation rates decreased from 9 (8.7%) to 6 (5.1%) after centralisation ($p=0.253$). The rate of open and close laparotomy remained comparable at 12 (14.1%) and 16 (13.3%) respectively ($\chi^2 = 0.314$, $DF = 1$, $p=0.575$). The number of patients undergoing curative EMR increased from 2 to 20 before and after centralisation respectively ($\chi^2 = 10.309$, $DF = 1$, $p= 0.001$).

5.4.2 Operative Morbidity and Mortality

Data regarding short-term surgical outcomes and duration of hospital stay are presented in Table 2. There were 5 (5.9%) operative deaths before and 1 (0.8%) operative death after centralisation ($\chi^2 = 3.977$, DF = 1, $p = 0.046$). The causes of the five pre-centralisation in-hospital deaths were two natural deaths 10 and 30 days after open and close attempted Ivor Lewis oesophagectomies, one myocardial infarction 2 days after a total gastrectomy, intra-abdominal sepsis after a total gastrectomy and a case of multi-organ failure secondary to conduit necrosis after trans-thoracic oesophagectomy. The death after centralisation was due to intra-abdominal sepsis after sub-total gastrectomy. The incidence of post-operative morbidity (Clavien-Dindo ≥ 3) decreased from 19 (22.3%) to 15 (12.5%) patients before and after centralisation ($\chi^2 = 1.690$, DF = 1, $p = 0.094$). Anastomotic leaks occurred in 9 (10.5%) and 8 (6.7%) patients before and after respectively ($\chi^2 = 0.389$, DF = 1, $p = 0.533$).

5.4.3 Duration of Hospital Stay

Centralisation was associated with a significant reduction in ITU ($p < 0.0001$) and critical care ($p < 0.0001$) length of stay for all surgical patients. The overall length of hospital stay for surgical patients decreased by 2.5 days ($p = 0.008$). The rate of re-admission to critical care significantly decreased from 10 (29.4%) to 6 (6.3%) before and after centralisation ($\chi^2 = 12.480$, DF = 1, $p < 0.0001$), while 30 day hospital re-admission rates remained similar at 8 (12.7%) and 13 (11.2%) respectively ($\chi^2 = 0.088$, DF = 1, $p = 0.767$). Regarding the 13 patients re-admitted post-centralisation (pneumonia=3, dysphagia=2, intra-abdominal collection=2, incisional hernia=1, wound infection=2, chyle leak =1, pancreatitis=1, urinary retention=1), one patient

required radiological drainage of a sub-phrenic abscess and the remaining patients were treated conservatively, for the most part in their referring local district general hospital.

5.4.4 Survival

The median survival for all patients was 9 (0.25-73) months, increasing to 34 (3-73) months for patients who underwent surgery with curative intent. For all patients median survival pre-centralisation was 9 (0.25-73) months compared with 10 (0.25-49) months post-centralisation ($p < 0.0001$). Two year survival for all patients before centralisation was 23% and 26% after centralisation ($p = 0.277$). The percentage of patients who survived for one year after curative resectional surgery increased from 88% pre-centralisation to 92% after centralisation ($p = 0.438$), and the two year survival rate was similar at 73% for both groups respectively ($p = 0.959$). Regarding patients who underwent oesophagectomy with curative intent, one year survival rate pre-centralisation was 90% compared with 95% post-centralisation ($p = 0.512$).

5.4.5 Factors Influencing Two Year Survival

A univariate analysis of factors influencing two-year survival is shown in Table 3, centralisation being a statistically significant factor, ($p = 0.001$). All factors found to be significant on univariate analysis were included in a multivariate analysis. A backward elimination stepwise regression was carried out whereupon rTNM and open and close procedures were found to be independently associated with two-year survival.

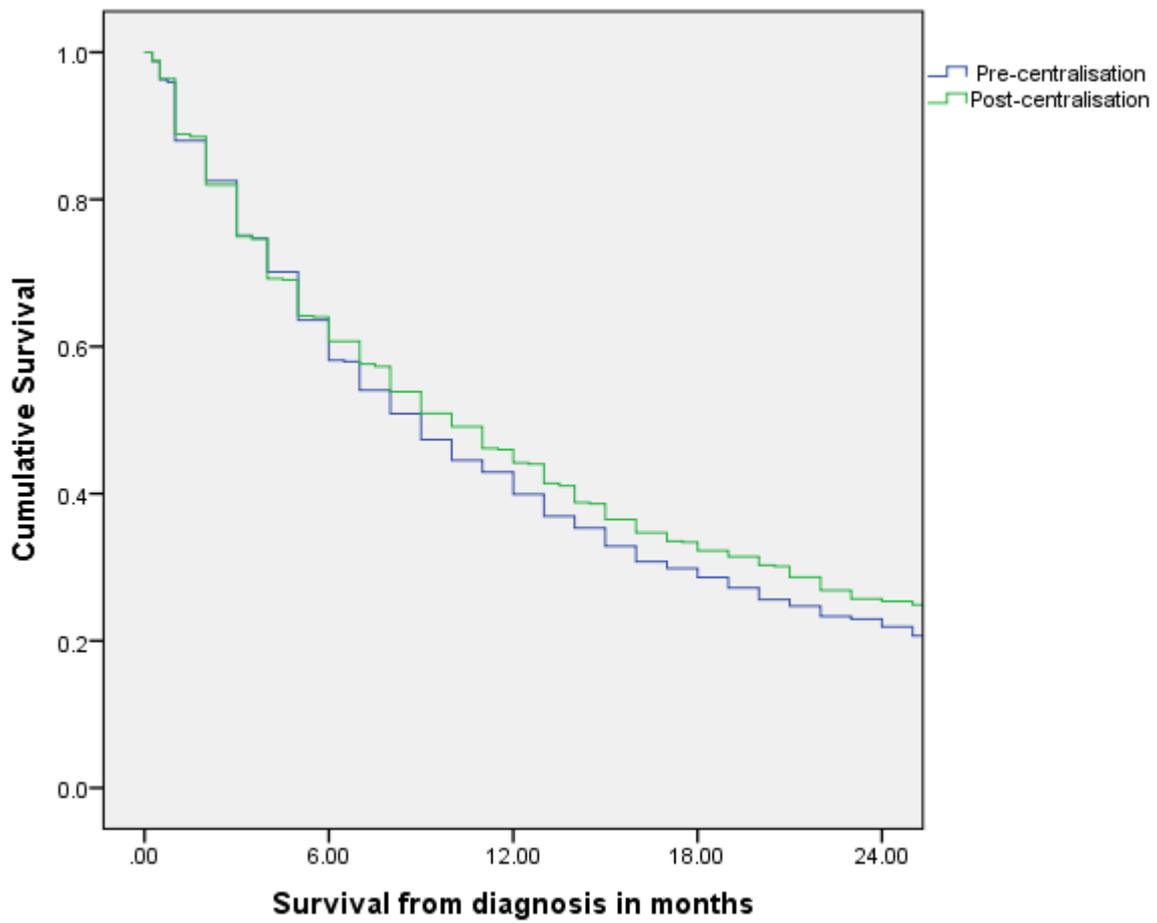


Figure 5.1 Kaplan-Meier survival plot related to centralisation for all patients

5.5 Discussion

Since its inception the centralisation of UGI cancer care has remained a controversial topic of debate in several countries (Brusselaars et al. 2014). This study however, showed that a centralised service was able to provide potentially curative treatment to a significantly greater number of patients and with a reduced number of cancelled operations. Furthermore, for those patients who underwent surgery, centralisation was associated with shorter critical care and total hospital lengths of stay, reduced post-operative morbidity, decreased number of re-admissions to ITU, less operative deaths and increased one year survival rate.

The strengths of the current study are that with a study population approaching nearly 1,200 consecutive patients presenting to a single UK regional cancer network, this represents a large UK report regarding UGI cancer service centralisation. Data were contemporaneously and prospectively collected at all local and regional MDT meetings over a 4 year period before, during and after centralisation was introduced. Survival data are especially robust as no patients were lost to follow-up, while death certification was obtained from the Office of National Statistics and data on re-admissions to critical care and hospital were complete. The significant increase in the number of patients to whom potentially curative treatment was offered after centralisation is in keeping with findings by Forshaw et al and Boddy et al, but contrasts with the findings of Branagan and Davies who reported a similar number of patients undergoing resection before and after centralisation (Forshaw et al. 2006; Boddy et al. 2012; Branagan et al. 2004). Forshaw et al also reported a reduction in cancelled operations due to pressure on ITU beds, similar to our experience. This study found the rate of open and close laparotomy procedures decreased slightly after centralisation, in keeping with Branagan and Davies (Branagan et al. 2004).

The current study also shows length of hospital stay was reduced by a median 2.5 days, with a significant reduction in ITU length of stay, a similar finding to that reported by Chan et al (Chan et al. 2013). Post-operative morbidity (Clavien-Dindo ≥ 3) decreased from 23% to 12% post-centralisation, but this was not statistically significant. Thirty day post-operative mortality decreased significantly in accordance with the findings of Boddy et al who reported 30-day mortality fell from 10.3% to 3.6%, and with Branagan and Davies who reported operative mortality decreased significantly from 15.2% to 0% ($p=0.022$). These results also resonate with findings by Anderson et al who reported high hospital volume significantly and independently correlated with improved 30-day post-operative mortality (Anderson et al. 2011). Median survival for all patients increased by 11% (9 months vs 10 months, $p<0.0001$) post-centralisation while two year survival rate increased from 23% before centralisation to 26% after ($p=0.277$). The increase in survival reported in this study is again in keeping with the findings of Boddy et al who reported after introducing centralisation within a UK unit in 2006, and with a systematic review and meta-analysis performed by Brusselaers et al which looked at sixteen international studies and reported a survival benefit in favour of high-volume surgeons (Boddy et al. 2012; Brusselaers et al. 2014). The increase in length of survival seen in this study is however shorter than that reported elsewhere where median survival times of 2.1 and 1.5 years were reported for oesophageal and gastric cancers respectively (Boddy et al. 2012). Our study population however, included patients from amongst the most deprived areas of Wales, with Wales as a whole recognised as having relatively high levels of deprivation and an overall life expectancy one year shorter when compared with England (National Audit Office 2012).

The study does have a number of potential limitations. The data collected from one hospital site concerning post-operative surgical outcomes was collected retrospectively and may not therefore be as robust as that collected from the other two hospital sites. This is mitigated however by the fact that computerised digital records recorded all radiological and pathological test results. Furthermore, operation notes and discharge summary documentation for these patients, and all data from the remaining two hospital sites, was collected contemporaneously by a dedicated clinical research fellow present at all local and regional MDT meetings. Also, the direct impact of a contemporaneous ERAS programme could not be quantified. Despite showing shorter critical care and total hospital lengths of stay, decreased number of re-admissions to ITU, less operative deaths and increased survival rates at two years, the study was unable to identify an explicit reason to account for these improvements. This was not a randomised controlled trial aimed at investigating any single factor or cause and the answer most probably lies in a combination of small incremental steps. Allied to better patient selection after rigorous radiological investigation and MDT discussion, the cornerstone of such improvements could simply be practice – the clinical judgement and technical skill achieved only by surgeons frequently performing a specific operation. The combined experience and expertise of dedicated radiologists, oncologists, anaesthetists, and allied health professionals working within an ERAS programme must also be considered. In our experience the median number of operations carried out by the individual surgeons increased five-fold, with over 50% carried out by two consultants working together. In addition, the study did not examine the impact of co-existing co-morbidity when considering post-operative morbidity, mortality and length of stay.

5.6 Conclusion

In conclusion, this study involving nearly 1200 consecutive UGI cancer patients clearly shows an increased proportion of patients receiving potentially curative treatment, fewer cancelled operations, reduced serious post-operative morbidity, shortened total length of hospital stay and improved survival, many by significant margins. Albeit not a randomised control trial, the results of the study unequivocally demonstrate what can be achieved by a UK regional cancer network serving some of the most deprived people in the country, The improved morbidity and mortality outcomes seen clearly support the centralisation of surgery for upper gastrointestinal cancer, and it is the network's intention to continue follow-up for 5 years in order to appreciate the full impact on patient safety and survival bestowed by the introduction of a centralised service.

Table 5.1**Demographic details and treatment pre- and post-centralisation (%)**

	<u>Pre-centralisation</u>	<u>Post-centralisation</u>	<i>p</i> value
Total	566	611	
Median age (range), years	73 (22-97)	72 (24-97)	0.412
Gender Male:Female	379:187 (67:33)	400:211 (65.5:34.5)	0.588
Oesophageal:Gastric	345:221 (61:39)	347:264 (57:43)	0.147
Radiological Stage I	44 (8)	66 (11)	0.075
II	81 (14)	86 (14)	0.908
III	157 (28)	133 (22)	0.018
IV	209 (37)	272 (46)	0.008
Unstaged	74 (13)	37(7)	<0.0001
Treatment			
Curative:Palliative			
Total	129:437 (23:77)	182:429 (30:70)	0.002
Oesophageal	83:262 (24:76)	118:229 (34:66)	0.004
Gastric	46:175 (21:79)	63:201 (24:76)	0.424
Definitive Chemoradiotherapy	36 (6)	46 (8)	0.432
Surgery	96 (17)	122 (20)	0.037
EMR	2 (1.6)	20 (11)	0.001

Table 5.2 Surgical outcomes pre- and post-centralisation

[Figures are in numbers (%), lengths of stay are the median in days (range)]

	Pre (n=85)	Post (n=120)	<i>p</i> value
Clavien-Dindo grade \geq 3	19 (20%)	15 (13%)	0.094
All morbidity	32 (33%)	51 (45%)	0.078
Operative (30 day) mortality	5 (5.2%)	1 (0.9%)	0.046
Total hospital stay	15 (2-72)	12 (3-53)	0.008
High dependency unit stay	1 (0-11)	1 (0-13)	0.001
Intensive therapy unit stay	0 (0-70)	0 (0-12)	<0.0001
Critical care stay	1 (0-70)	1 (0-20)	<0.0001

Table 5.3 Univariate analysis of factors associated with 2 year survival

Factor	Log Rank	DF	p value
O-POSSUM Mortality	153.124	120	0.022
Age	105.091	67	0.002
Open and Close	9.470	1	0.002
Centralisation	10.756	1	0.001
Curative Treatment	403.255	1	<0.0001
rTNM	248.104	4	<0.0001
Histology	47.276	7	<0.0001

DF = Degrees of Freedom

Table 5.4 Multivariate analysis of factors associated with 2 year survival

Factor	HR	95% CI	p value
rTNM	1.333	1.022-1.739	0.034
Open and Close	2.460	1.367-4.430	0.003

HR = Hazard ratio

95% CI = 95% Confidence Interval

Chapter 6

General Discussion and Prospect

The management of oesophago-gastric cancer has evolved significantly in the last decade, underpinned by The National Oesophago-Gastric Cancer Audit (NOGCA), a collaborative project involving the British Society of Gastroenterology, the Association of Upper Gastrointestinal Surgeons, the Royal College of Surgeons of England Clinical Effectiveness Unit and the Department of Health. Their collective aim is to establish standardised benchmarks for the treatment of UGI cancer and identify areas for future improvement. However, despite such a multi-disciplinary and stage-directed approach, outcomes remain poor when compared with many other malignancies and incurable metastatic disease is still diagnosed in as many as 50% of patients at first presentation. For those patients to whom treatment with curative intent can be offered, chemotherapy and radiotherapy are associated with significant toxicity and morbidity, and radical surgery for oesophageal and gastric tumours are among the most physiologically stressful procedures performed.

By enhancing our understanding of the prognostic factors influencing outcome and survival it is hoped further improvements can be achieved. In the current climate of the “aggregation of marginal gains” it is clear that improvement will most likely be in the form of incremental advances. This study follows the patient’s journey from the time of first noticing significant symptoms through to radiological investigations, diagnosis, MDT discussion, treatment, and duration of survival. The idea of undertaking this thesis was first considered when recurring trends and observations were noted while seeing patients suspected of having, or recently confirmed as having, oesophageal or gastric cancer. It was perceived the majority were from more

socio-economically deprived areas, who had allowed significant time-lapses before first presenting to a medical practitioner by which stage many had incurable disease, and many appeared cachectic. It examines a range of demographic, physiological and organisational elements influencing a patient's outcome, and aims to identify where amendments can be made and improvements implemented. More specifically it addresses the influence of socio-economic and health deprivation, the influence of diagnostic delay, the significance of malnutrition, and the impact of centralisation on outcome and survival.

6.1 Prognostic significance of deprivation

The South East Wales Upper GI cancer MDT manages patients within an area encompassing 1.4 million people, many of whom are recognised as living within some of the most socio-economically deprived areas of the UK. Deprivation is associated with an increased incidence of upper gastrointestinal cancer (McKinney et al. 1995; Gossage et al. 2009), and linear relationships between levels of deprivation and survival have previously been reported for oesophageal cancer (Coleman et al. 1999). Furthermore, a widening of survival inequality with time has been reported whereby the improved outcomes experienced by patients living in less deprived geographical areas have not been shared by patients from more deprived areas (Coleman et al. 2004). In response the NHS Cancer Plan of September 2000, and subsequent government targets introduced in 2003, were aimed at reducing such inequalities across the socio-economic divide.

The study supported previous findings indicating that level of socio-economic deprivation was strongly associated with adverse outcomes in patients diagnosed with UGI cancer, and overall deprivation was associated with duration of survival.

Furthermore, despite developing disease at a younger age, being of similar stage of disease at diagnosis, and being offered similar treatment protocols, including radical surgery, the most deprived patients had significantly shorter median duration of survival than the least deprived cohort of patients, notwithstanding these patients were offered a more focused input from allied healthcare professionals including dieticians and physiotherapists in particular to optimise pre-operative performance. The study was unable to identify any particular reason or cause to explain these findings, but previously reported increased rates of alcohol and cigarette consumption among lower socio-economic classes could be an attributing factor.

It is of course beyond the realms of this study to solve or provide any easy solutions to the perennial problem of deprivation. At present, whilst the health of society's most deprived population has improved, the gap between the most and least deprived has failed to narrow (Dept. of Health 2007, 2009). Previous studies have shown that lower socio-economic status is associated with greater delay before first presentation (Porta et al. 1996), and this could certainly be a factor explaining the decreased survival seen amongst the most deprived. On the understanding that it is perhaps an economic impossibility to lift the entire population of a country out of deprivation, and particularly in the current climate of economic austerity, the focus should therefore be on greater education directed specifically at those residing in more deprived geographical areas. This education should focus on topics including lifestyle choices, in particular the harm associated with smoking and alcohol excess, and on improving early symptom awareness, encouraging prompt visits to one's General Practitioner, and also supporting GPs to appropriately refer patients with worrying signs and symptoms as Urgent Suspected Cancers for endoscopy within 14 days.

6.2 Prognostic significance of diagnostic delay

The timely diagnosis and subsequent treatment of cancer is an increasingly common topic for health improvement quality initiatives, and also a frequent theme in the media. Indeed, the UK Health Secretary has recently proposed ranking all general practices on the NHS Choices website according to how promptly patients subsequently diagnosed with cancer were initially referred to specialist services for suspected cancer (Malnick 2014). Approximately 80% of patients diagnosed with cancer are referred to a hospital specialist after one (50%) or two (30%) GP consultations (Lyrtzopoulos et al. 2012; Lyrtzopoulos et al. 2013), but a substantial minority of up to 20% of patients with cancer visit a primary care doctor with relevant symptoms three or more times before referral. The European Cancer Registry EUROCare-4 survey showed that the UK ranked 9th and 22nd for male and female cancer mortality rates respectively compared with 27 other European countries (de Angelis et al. 2009), and late or missed diagnosis has been suggested as a major contributor to the UK's ranking (Dept of Health 2007).

Patient delay, whereby an individual with symptoms does not seek healthcare advice as they attribute vague or non-specific symptoms to everyday explanations such as indigestion, or indeed do not identify symptoms such as worsening dysphagia as potentially cancer, is thereby prolonged. To address these delays The NHS Cancer Plan for England (2000) set out a comprehensive 10 year strategy to improve prevention, screening, early diagnosis and treatment for cancer. The Cancer Reform Strategy was published in 2007 and set the direction for the next five years, with early diagnosis highlighted as one of the most significant challenges to be addressed (Dept of Health 2007). Furthermore, The National Awareness and Early Diagnosis Initiative (NAEDI) was launched in 2008 with the specific aim of addressing public

awareness of cancer, promoting earlier presentation, and reducing primary care delay.

The main findings of this study were that delays in the diagnosis on average approached four months, with little improvement having been made when compared with a similar study performed in Leeds 20 years ago (Martin et al. 1997). In contrast to that study however where practitioner and hospital delay accounted for the majority, this study found patient delay was responsible for over 75% of the time interval between initial onset of symptoms and diagnosis. Furthermore, deprivation and female gender were significantly and independently associated with longer patient delays.

A review of the literature suggests that one of the most important reasons for patient delay is symptom misattribution: people who do not identify their symptoms as possible indicators of cancer are more likely to delay going to their doctor. Also, fear regarding a potential diagnosis of cancer delays people seeking help, with older people in particular affected in this regard. Encouraging early presentation is essential to tackling patient delay, so initiatives such as NAEDI are therefore key to promoting awareness of the early signs and symptoms of cancer among the general public and medical practitioners, and particularly those patients living in more deprived areas. Patient empowerment is also key, and patients should be encouraged to take more control of their care, to ensure they are kept informed, ask questions, and seek second opinions if they feel this is warranted.

6.3 Prognostic significance of Bioelectrical Impedance Analysis

A review of the literature would indicate that this is the first known study to investigate the prognostic significance of BIA-derived body composition parameters in oesophago-gastric cancer patients undergoing resection with curative intent. The South-East Wales Upper GI Cancer Network serves a population residing in some of the most socio-economically deprived areas in the UK, with many patients presenting after significant delays (Chapter 3) and with severe consequent malnourishment. These patients therefore need particular pre-operative optimisation of nutritional status to withstand such surgery and avoid poor outcome.

The study showed cancer-related malnutrition and catabolism, particularly prevalent in UGI cancer, correlated with established pre-, intra-, and post-operative prognostic indicators of morbidity and mortality, in keeping with Gupta's findings in colorectal and pancreatic cancer (Gupta et al. 2004). Although a surrogate measurement of sarcopenia was used, sarcopenia in particular correlated significantly with surgical complications requiring further intervention, and on multivariate analysis was independently associated with survival.

As the prognosis for patients diagnosed with UGI cancer is so often poor, the potential benefit from understanding and addressing all reversible factors is substantial. With continued patient recruitment over time further research will be conducted to investigate oesophageal and gastric cancer patients separately and thereby determine whether any particular trends develop when analysed as distinct entities. Objective assessments of sarcopenia with CT-measured psoas muscle density and body composition will further contribute to the understanding of how nutritional status and weight loss can be addressed to improve outcomes. Further

research is also warranted to determine allied critical body composition parameters such as the phase angle so that enhanced recovery programmes containing bespoke nutritional strategies may be developed to improve outcomes and survival. This knowledge will guide health policy makers to prioritise funding and provide further dietetic support and research into this challenging but ultimately achievable goal.

6.4 Centralisation of Upper GI Cancer Services

Since first introduced in 2001 the centralisation of oesophageal and gastric cancer resection has remained a topic of ongoing debate in contemporary medical literature. Centralisation is based on the hypothesis that high volume centres produce better short and long term outcomes after research reported a patient's chances of survival increase substantially if operated on by a surgeon performing a specific operation on a frequent basis (Birkmeyer et al. 2003). This finding was further supported in a subsequent meta-analysis which reported such a survival benefit specifically after oesophagectomy (Brusellaars et al. 2014). To date there are 41 specialist centres providing UGI cancer care in England and Wales, but despite having been shown to significantly improve in-hospital and 30 day mortality, the data regarding long-term survival remains limited. A previous report from Wales has shown that centralisation resulted in lower morbidity, mortality and length of hospital stay in patients undergoing surgery and moreover, one year survival increased in all patients (Chan et al. 2013).

Historically there has been little consensus regarding the possible benefits of either centralisation or operative volume on the outcomes of UGI cancer surgery in the UK, with particular debate centred on long-term survival. This study, and similar findings

by Derogar demonstrate that annual and cumulative surgeon volume are predictors of longer term survival and thereby recommend that surgeons should maintain a high yearly volume to further optimise prognosis (Derogar et al. 2013). The reasons for these documented improvements are multi-factorial; explicit referral protocols, more frequent MDT meetings, improved radiological staging and patient selection, and improved peri-operative care. A further factor which has received little acknowledgement or clinical interest to date however is the benefit of an immediate second opinion and an experienced consultant colleague if and when required in theatre. In this study in excess of fifty percent of operations were carried out by two consultants working together as an operative Consultant team.

Further to previous findings, this study demonstrated an increased proportion of patients receiving potentially curative treatment, fewer cancelled operations, reduced post-operative morbidity, shortened total length of hospital stay, and improved survival rates, many by significant margins. Furthermore, most of the patients in this study reside in areas of significant socio-economic deprivation which could adversely influence outcomes. The study thereby clearly supports the centralisation of surgery for upper gastrointestinal cancer with strategic national implications for the re-configuration of similar services in other specialties.

The 2014 UK National Oesophageal and Gastric Cancer Audit (NOGCA) reported an ever-improving service for UGI cancer patients, in particular improved mortality rates, improved outcomes after surgery, and other quality indicators of surgery such as decreased positive resection margins, thereby further endorsing the centralisation of services (NOGCA 2014). Further high quality studies, including the publication of 5 and 10-year survival rates, identifying which specific aspects of centralisation improve outcome, and the cost-effectiveness in terms of quality-adjusted life years,

are needed in order to appreciate the full impact on patient safety and survival bestowed by the introduction of a centralised service. This data will also inform policy decision makers in the future re-organisation of cancer services.

6.5 Conclusion

A diagnosis of oesophago-gastric cancer is still thought of as the sounding of the death knell by many patients and clinicians alike, indeed gastric cancer was commonly described as one of the “captains of men of death”. This thesis set out to identify potential prognostic indicators for people diagnosed with these cancers, and furthermore identify whether these factors are reversible. While demographic factors such as one’s level of socio-economic deprivation are not amenable to any rapid amelioration, enhanced public awareness of the signs and symptoms associated with UGI cancer are however more feasible, as are systemic changes such as further funding for general public and clinician education programmes, more expedient diagnosis procedures, further centralisation of cancer care, and greater support for patients undergoing surgery in particular addressing nutritional deficiencies. A recent innovation in Cardiff is the ‘Fit for List’ health screen which includes an array of simple tests and interventions to be used by GPs and specialist nurses to facilitate the early detection of problems such as high blood pressure or anaemia at the time of initial referral and thereby optimise the patient before they undergo their cancer treatment and prevent any potential delays. To date there has been significant improvement in the fate of patients diagnosed with UGI cancer, and the focus at present is centred on incremental improvements but there are still hard yards to be fought and won. The hypotheses and results generated in this thesis should be further built upon to improve treatment algorithms and outcome for patients diagnosed with oesophago-gastric cancer.

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APPENDIX A

Publications derived from work in this thesis

Published Papers

Blake PA, Karran A, Chan DSY, Roberts SA and Lewis WG. Prognostic significance of deprivation in upper gastrointestinal cancer. *Gastrointestinal Cancer: Research & Therapy* 2017 Accepted for publication.

Blake PA, Karran A, Chan DSY, Roberts SA and Lewis WG. Prognostic significance of diagnostic delay and deprivation in upper gastrointestinal cancer. *Gastrointestinal Cancer: Research & Therapy* 2017 Accepted for publication.

Published abstracts

Blake PA, Karran A, Chan DSY, Reid TD, and Lewis WG Influence of a regional centralised upper gastrointestinal cancer service model on patient safety, quality of care and survival *British Journal of Surgery* 2013;100

Blake PA, Beamish AJ, Karran A, Chan DSY, and Lewis WG Prognostic significance of the Phase Angle (PhA) determined by Bioelectrical Impedance Analysis in upper gastrointestinal cancer surgery *British Journal of Surgery* 2013;144(5):9-10

Blake PA, Karran A, Beamish AJ, Karran A, Chan DSY, Howells G, Barlow R, and Lewis WG Prognostic significance of body composition in upper gastrointestinal (UGI) cancer surgery *British Journal of Surgery* 2014;101

Blake PA, Thomas CE, Karran A, Chan DSY, Blackshaw G, Clark GW, Havard T, Escofet X, Roberts SA, and Lewis WG Prognostic significance of deprivation in upper gastrointestinal cancer *Gastroenterology* 2014;146(5):568

Blake PA, Davies LI, Beamish AJ, Karran A and Lewis WG Prognostic significance of body composition determined by Bioelectrical Impedance Analysis in Upper Gastrointestinal cancer surgery *British Journal of Surgery* 2015;102

Blake PA, Karran A, Thomas CE, Hill S and Lewis WG Prognostic significance of diagnostic delays in Upper Gastrointestinal (UGI) cancer management *British Journal of Surgery* 2015;102

APPENDIX B

Oral Presentations to Learned Societies

Blake PA, Karran A, Chan DSY, Reid T and Lewis WG Influence of a regional centralised upper gastrointestinal cancer service model on patient safety, quality of care and survival. Association of Surgeons of Great Britain and Ireland, Glasgow, May 2013

Blake PA, Karran A, Beamish AJ, Chan DSY and Lewis WG. Propensity score matched analysis of the influence of an Enhanced Recovery Programme (ERP) in Upper Gastrointestinal (UGI) cancer surgery. Association of Surgeons of Great Britain and Ireland, Glasgow, May 2013

Blake PA, Davies L, Beamish AJ, Karran A and Lewis WG Prognostic significance of body composition determined by Bioelectrical Impedance Analysis in upper gastrointestinal cancer surgery Association of Surgeons of Great Britain and Ireland, Harrogate, May 2014

Blake PA, Karran A, Thomas CE, Hill S and Lewis WG Prognostic significance of diagnostic delays in upper GI cancer management. Association of Surgeons of Great Britain and Ireland, Harrogate, May 2014

APPENDIX C

Poster presentations to learned societies

Blake PA, Beamish AJ, Karran A, Chan DSY and Lewis WG. Prognostic significance of the Phase Angle (PhA) determined by Bioelectrical Impedance Analysis in Upper Gastrointestinal Surgery *Digestive Diseases Week, Orlando, May 2013*

Blake PA, Karran A, Chan DSY, Beamish AJ and Lewis WG. Influence of socio-economic deprivation on outcomes for patients diagnosed with gastric cancer *International Gastric Cancer Congress, Verona, June 2013*

Blake PA, Beamish AJ, Karran A, Chan DSY and Lewis WG. Prognostic significance of the Phase Angle (PhA) determined by Bioelectrical Impedance Analysis in Upper Gastrointestinal Surgery *Association of Surgeons of Great Britain and Ireland, Glasgow, May 2013*

Blake PA, Thomas CE, Karran A, Chan DSY, Blackshaw GR, Clark GWB, Havard T, Escofet X, Roberts SA and Lewis WG. Prognostic significance of deprivation in upper gastrointestinal cancer. *Digestive Diseases Week, Chicago, May 2014*

Blake PA, Davies LD, Beamish AJ, Karran A, Thomas CE, Witherspoon J, Howell G, Barlow RC and Lewis WG. Prognostic significance of Bioelectrical Impedance Analysis defined body composition in upper gastrointestinal Surgery. *Digestive Diseases Week, Chicago, May 2014*

Blake PA, Thomas C, Karran A, Chan DSY, Lewis WG. Prognostic significance of deprivation in upper gastrointestinal cancer. *Association of Surgeons of Great Britain and Ireland, Harrogate, May 2014*

Blake PA, Karran A, Beamish A, Chan D, Howells G, Barlow R and Lewis WG. Prognostic significance of body composition in upper gastrointestinal (UGI) cancer surgery *Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, Brighton September 2014*

**Cardiff and Vale University Health Board, Dept. of Upper Gastrointestinal
Surgery**

CONSENT FORM

Bioelectrical Impedance Analysis (BIA) in Surgical Patients

Name of Researcher: Prof W G Lewis

Px ID:

Please tick after each statement

1. I confirm that I have read and understand the information sheet dated April 2014, version 3 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records
4. I agree to my GP being informed of my participation in the study
5. I agree to take part in the above study

_____/_____/20____ Signature

Name of patient Date

_____/_____/20____ Signature

Name of person taking consent Date