APPLIED PHYSIOLOGY IN UPPER GASTROINTESTINAL CANCER SURGERY: PERIOPERATIVE RISK STRATIFICATION AND MANAGEMENT.

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A thesis submitted to Cardiff University for the degree of Doctor of

Medicine

August 2014

"The vicissitudes that afflict the individual have their source in society."

"The great discoveries in medicine that have revolutionised surgery and the treatment of disease were made by dedicated men and women whose work was inspired by values that have nothing to do with the rapacious bustle of the stock exchange: Pasteur, Simpson, Jenner, Lister, Semelweiss, Fleming, Domagk, Röentgen – the list is endless."

Aneurin Bevan

(1897 - 1960, died of gastric cancer)

DEDICATION

For my Mother and Father and my fiancée, Jessica.

Thank you for your unwavering belief and support.

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ACKNOWLEDGEMENTS

input.

I also acknowledge the support of all members of the Upper GI Surgery Unit not mentioned above, including the specialist nurses, surgical care practitioner, secretaries and junior doctors. The friendly, welcoming and supportive environment, toward which each of you contributed, was important in making my time in the unit such a pleasure.

I offer special thanks to my family, and in particular my fiancée Jessica, whose unwavering and unconditional support and tolerance throughout this period of research has made this work possible.

LIST OF ABBREVIATIONS

3SO	- Three-stage oesophagectomy
AC	- Adenocarcinoma
AJCC	- American Joint Committee on Cancer
ASA	- American Society of Anesthesiologists
AT	- Anaerobic threshold
AUC	- Area under the curve
BAPEN	- British Association for Parenteral and Enteral Nutrition
BIA	- Bioelectrical impedence analysis
BMI	- Body mass index
CC LOS	- Critical care length of stay in days
CD	- Clavien-Dindo grade
CI	- Confidence interval
CPX	- Cardiopulmonary exercise testing
CRP	- C-reactive protein
CT	- Computed tomography
CT-PET	- CT-positron emission tomography
EMR	- Endoscopic mucosal resection
ERAS	- Enhanced recovery after surgery
ERP	- Enhanced recovery programme
EUS	- Endoluminal ultrasonography
FFM	- Fat free mass
GCA	- Gastric cancer
GORD	- Gastro-oesophageal reflux disease

HDU LOS	- High dependency length of stay (HDU LOS)
HR	- Hazard ratio
HU	- Hounsfield Units
ICTRP	- World Health Organization International Clinical Trials Registry Platform
IL-1, IL-6	- Interleukin 1 and 6
IQR	- Interquartile range
ITU	- Intensive therapy unit
ITU LOS	- Intensive therapy unit length of stay
IVI	- Intravenous infusion
JJC	- Japanese Joint Committee
Lap	- Laparoscopic
LMF	- Lipid metabolising factor (LMF)
LOHS	- Length of hospital stay
MAG	- Malnutrition Advisory Group
Max PMD	- Maximum psoas muscle density (from left and right measurements)
MD	- Mean difference
MDT	- Multidisciplinary Team
MeSH	- Medical subject headings
M-H	- Mantel-Haenszel statistic
MM	- Muscle mass
MUST	- Malnutrition Universal Screening Tool
MWU	- Mann-Whitney U-test
NeoAdj	- Neoadjuvant therapy

NICE	- National Institute for Health and Clinical Excellence
NHS	- National Health Service
NPY	- Neuropeptide Y
O&C	- Open and close (no resection performed)
OCA	- Oesophageal cancer
OR	- Odds ratio
OG	- Oesophagogastric
Path Stage	- Histopathological stage according to TNM7 classification
PC	- Prospective cohort study
PhA	- Phase angle
PIF	- Proteolysis inducing factor
PM	- Psoas muscle
PMD	- Psoas muscle density
POSSUM	- Physiological and Operative Severity Score for the enumeration of Mortality and morbidity
PRISMA	- Preferred Reporting Items for Systematic Review and Meta-Analyses
PVS	- Plummer-Vinson syndrome
Rad Stage	- Rad stage, radiological stage according to TNM7 classification
RC	- Retrospective cohort study
RCRI	- Revised Cardiac Risk Index
RCT	- Randomised controlled trial
ROC -	- Receiver Operator Characteristic
RNA	- Ribonucleic acid

RT   - Randomised trial

SCC   - Squamous cell carcinoma

SMD   - Standardised mean difference

SPSS®   - Statistical Programme for the Social Sciences

STG   - Subtotal gastrectomy

TG   - Total gastrectomy

THO   - Trans-hiatal oesophagectomy

TNFα   - Tumour necrosis factor alpha

TNM   - Tumour, nodal, metastasis staging classification

TTO   - Trans-thoracic oesophagectomy

UCP   - Mitochondrial uncoupling proteins

UGI   - Upper gastrointestinal

UICC   - International Union Against Cancer

UK   - United Kingdom

USA   - United States of America

VAS   - Visual analogue scale

VE/VCO$_2$ - Ventilatory equivalent for carbon dioxide

VO$_2$ peak   - Peak oxygen uptake

WAASP   - Weight, Appetite, Ability to eat, Stress factors, Pressure

                      sores/wounds screening tool

WIMD   - Welsh Index of Multiple Deprivation

SUMMARY

This thesis examines methods of perioperative risk stratification and outcome in patients receiving multidisciplinary stage-directed treatment for oesophagogastric cancer.

The hypotheses tested were: Suboptimal bioelectrical impedance analysis (BIA) body composition variables predict poor outcomes in oesophagogastric cancer (OGC) surgery; low CT-measured psoas muscle density (PMD) predicts poor outcomes in OGC surgery; suboptimal cardiopulmonary exercise (CPX) performance predicts poor outcomes following OGC surgery; the literature offers evidence in support of enhanced recovery programmes in OGC surgery; the use of an enhanced recovery programme in OGC surgery is feasible, safe and not associated with adverse outcomes.

High values for BIA-derived measures of fat-free mass and muscle mass respectively predicted longer survival (p=0.047, p=0.011), but were not associated with reduced 30-day mortality, major morbidity or length of stay.

CT-measured psoas muscle density greater than the median of 48.7 Hounsfield Units predicted longer survival (p=0.046), but was not associated with reduced 30-day mortality, major morbidity or length of stay (LOHS). Multivariable analysis demonstrated radiological TNM stage (p=0.015), and both left (p=0.046) and right PMD (p=0.047), as significant and independent predictors of survival.

Cardiopulmonary exercise testing results materially altered the management plan in 6.8% patients. Major morbidity (p=0.049) and poor

survival (p=0.048) were associated with a high ventilatory equivalent for carbon dioxide (VE/VCO$_2$), but not with the anaerobic threshold (AT) or peak oxygen uptake (VO$_{2peak}$). VE/VCO$_2$ also emerged on multivariable analysis as an independent and significant predictor of LOHS (p=0.001). Systematic review and meta-analysis revealed enhanced recovery programmes (ERPs) in OGC surgery to be feasible, safe and cost-effective, significantly shortening length of stay (LOHS, p<0.0001). In our unit, the introduction of ERPs in gastric and oesophageal cancer surgery respectively, significantly reduced LOHS (p=0.004; p=0.032), critical care stay (p<0.0001; p<0.0001) and overall cost (p=0.001; p<0.0001).

CHAPTER 1

Introduction and a review of the literature

1.1 Epidemiology

1.1.1 Oesophageal cancer

Oesophageal carcinoma is the eighth commonest cancer worldwide, with almost 500,000 cases diagnosed in 2008, and the thirteenth commonest cancer in the UK, where it accounted for more than 8,000 new diagnoses and more than 7,600 deaths in 2011 (CRUK, 2014). The age-standardised incidence is 9.5 per 100,000, 14.2 and 8.5 per 100,000 for men and women respectively in the UK (CRUK, 2014).

The reported incidence in Wales is lower than other UK countries in males at 12.3 per 100,000, compared with 12.5 to 16.5 per 100,000, but higher than all UK countries except for Scotland in females at 6.3 per 100,000, compared with 4.6 to 6.5 per 100,000 (CRUK, 2014).

The almost threefold male predominance in England (2.7:1) is much more pronounced in adenocarcinomas (AC, 5.2:1) and almost equal between men and women among squamous cell carcinomas (SCC, 1.1:1) (CRUK, 2014).

It remains predominantly a disease of old age, with >80% of cases diagnosed in people over the age of 60 (CRUK, 2014).

The last 30 years have seen a marked overall increase in the UK incidence of oesophageal cancer, particularly for males, in whom the incidence has increased by 65% between 1975 and 2011. In females, a more modest increase of 26% was observed to 2001, followed by a 10% decrease (CRUK, 2014).

Rates of incidence as much as 74% higher have also been observed in

deprived populations, seemingly mostly concerning SCC, rather than AC (CRUK, 2014).

Epidemiological variation is seen according to histological subtype in oesophageal cancer. Worldwide, SCC is the dominant type, with the highest incidences reported in less developed regions, where >80% of cases occur. The highest incidence rates are seen in Southern Africa, with over 20 cases per 100,000 population, and the lowest rates in Western Africa (men) and Southern Europe (women), at around 1 per 100,000 (CRUK, 2014).

Adenocarcinoma is the most common histological subtype for Caucasian men in the UK, in whom reported rates of adenocarcinoma are the highest in the world (Bollschweiler et al., 2001, Wild and Hardie, 2003). An increasing incidence of adenocarcinoma of the gastric cardia has mirrored this oesophageal AC rise across the same time period, and now accounts for more than 50% of gastric cancers, suggesting the possibility of simliar aetiology (CRUK, 2014).

1.1.2 Gastric cancer

Gastric cancer is the 15th most common malignancy in the UK with a decreasing incidence reported at 7.6 per 100,000 population in 2011 (CRUK, 2014), down from 8.4 per 100,000 population in 2008 (Newnham A, 2003, CRUK, 2012). It accounted for over 7,000 new cases and 4,800 deaths in 2011 (CRUK, 2014).

The incidence in men is more than twice that in women (11.2 vs. 4.7 per 100,000). In Wales, the incidence in men is higher than in other countries

within the UK at 14.6 per 100,000, compared with 10.8-14.2 per 100,000 in the remaining UK nations (CRUK, 2014). Gastric cancer is predominantly a disease of advanced age, with more than half of all cases between 2009 and 2011 diagnosed in over 75 year-olds (CRUK, 2014). An estimated almost one million cases were diagnosed worldwide in 2008. The highest incidence rates were seen in Eastern Asia, at up to 42 per 100,000 for males and 18 per 100,000 for females.

Most (95%) cases are adenocarcinomas, the remainder predominantly comprising lymphomas and leiomyosarcomas. Adenocarcinomas are further classified as either intestinal or diffuse type. Intestinal type is associated with atrophic gastritis and confers a preferable survival when compared with diffuse type, which is more common in the elderly, women and people with blood group A (CRUK, 2014).

1.2 Aetiology

The aetiology of oesophageal and gastric cancer differs according histological cell type.

1.2.1 Squamous cell carcinoma

The predominant risk factors for oesophageal squamous cell carcinoma in western countries are smoking and alcohol consumption. A synergistic effect has been observed, with the risk ranging from 20 to 130- fold higher according to certain combinations of excessive drinking and smoking (Castellsague et al., 1999, Freedman et al., 2007, Zambon et

al., 2000). The effect of alcohol on risk varies according to the volume consumed. Risk increases have been reported ranging from 18% for men and 35% for women per 10g/day alcohol consumption (Weikert et al., 2009), to 5-fold with more than three daily drinks (Freedman et al., 2007), and even up to an almost 25-fold risk in men drinking 84 or more drinks per week (Zambon et al., 2000). The mechanism of action for alcohol is unclear and may be related to a combination of direct mucosal damage, increased susceptibility to other carcinogens, or secondary associated dietary deficiencies. A diet deficient in fruit and vegetables has been identified as the third main risk factor for oesophageal SCC in the developed world, with associated reductions in risk demonstrated with increased consumption of both fruit and vegetables (Key, 2011).

Additional dietary and lifestyle factors affecting the risk of oesophageal SCC include childhood nutritional deficiencies, in particular riboflavin and vitamins A and C, as well as the high intake of nitrosamines and the consumption of very hot drinks (Group, 1979, Mosavi-Jarrahi and Mohagheghi, 2006, Pourshams et al., 2005). It is suggested that these factors may result in a chronic asymptomatic oesophagitis, different from gastro-oesophageal reflux disease, and possibly representing a precursor to SCC. These aetiological factors are most important in less developed countries, where poverty and malnutrition are prevalent.

Traumatic oesophageal strictures following the ingestion of corrosive agents, particularly in childhood, are associated with a 1000-fold increase in the risk of carcinoma. Achalasia also confers an increase in risk,

estimated at 140 times greater than the general population (Brucher et al., 2001). Plummer-Vinson syndrome (PVS) is described as dysphagia, iron-deficiency anaemia, koilonychia and oropharyngeal mucosal atrophy. An associated increased risk of cervical oesophageal cancer has been reported in PVS (Ribeiro et al., 1996). Finally the rare autosomal dominant condition tylosis palmarum is associated with a very high incidence of squamous cell carcinoma (Varela et al., 2011).

1.2.2 Adenocarcinoma

The predominant risk factors for oesophageal adenocarcinoma are gastro-oesophageal reflux disease (GORD) and obesity. In gastric cancer, Helicobacter pylori is a recognised risk factor for gastric cancer, conferring a lifetime risk of 0.1% in infected individuals (Compare et al., 2010), although it probably represents a minority cause of gastric cancer in the Western World (Kelley and Duggan, 2003).

An estimated 4-9% of the population experience heartburn on a daily basis, and up to 20% weekly (Cameron, 1997). Symptomatic reflux is associated with a risk of oesophageal cancer almost eight times greater than the asymptomatic individual. With the most severe, frequent and enduring symptoms, a risk of up to 44-fold has been shown (Lagergen J, 1999), although it has been argued that the presence of GORD may not itself represent a genuine risk factor for oesophageal cancer (Solaymani-Dodaran et al., 2004). Rather, the resultant Barrett's metaplasia has been held culpable, arising as a result of chronic reflux and potentially leading to a spectrum of subsequent changes through increasing grades of

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epithelial dysplasia to invasive adenocarcinoma (Fitzgerald, 2006).

Described over 60 years ago, Barrett's oesophagus is the replacement of

normal squamous epithelium of the distal oesophagus by a columnar-

lined mucosa (Barrett, 1950). The true prevalence of Barrett's

oesophagus is not clear, owing to its asymptomatic nature in most

patients; indeed estimates from post-mortem studies suggesting levels as

high as 5% (Cameron et al., 1990), while levels of 1% were found in

unselected endoscopy patients (Cameron and Lomboy, 1992) and 12%

of patients with reflux (Winters et al., 1987).

The more clinically important minority, whose Barrett's transforms into

adenocarcinoma, are not well quantified. The various estimates of

malignant transformation risk have ranged from 1 in 56, to 1 in 315 cases

per patient year (Robertson et al., 1988, Miros et al., 1991, Katz et al.,

1998, Oberg et al., 2005). Segment length represents the most important

risk factor for malignant transformation (Menke-Pluymers et al., 1993),

with additional factors including male sex, age over 45 years, Caucasian

ethnicity, severe reflux symptoms, obesity and heavy smoking (Watson

A, 2005).

Oesophageal adenocarcinoma is three to six times more common in the

overweight (Cheng et al., 2000), the mechanism likely related to the

increase in the incidence of gastro-oesophageal reflux and hiatus hernia

observed in the overweight. There is emerging evidence that there are

obesity effects independent of reflux (Lindblad et al., 2005). A gender

difference in the obesity effect has also been observed, particular risk

associated with the abdominal pattern of fat distribution that is

characteristically seen in males (Vaughan et al., 2002).

Additional factors that have been associated with gastric cancer include previous gastric surgery, peptic ulcer disease, low fruit and vegetable intake, high salt, nitrite or nitrate intake, ionising radiation, and pernicious anaemia, although evidence has not been consistent (Kelley and Duggan, 2003).

While socio-economic deprivation has been linked to adenocarcinoma risk, this link is far less pronounced than for squamous cell carcinoma. It may be that confounding factors prevalent in social deprivation and those already discussed herein, including obesity, smoking and alcohol, are actually responsible for the differences observed according to socioeconomic status. Interestingly, the rising incidence of cardia cancer has been predominantly observed in the professional classes (Powell and McConkey, 1992).

1.3 Stage classifications

The TNM staging classification system was introduced in 1986, as a result of an agreement between the American Joint Committee on Cancer (AJCC), the Japanese Joint Committee (JJC) and the International Union Against Cancer (UICC). The TNM system is used globally as the gold standard staging system. It informs the treatment planning, assists in determining prognosis and allows outcome comparison between centres. The most up-to-date version is the 7th edition (Sobin LH, 2009a), which came into effect in 2010.

1.3.1 Anatomical site

The TNM classification of the anatomical site of the primary tumour is derived from the original description by the Japanese Society for Esophageal Diseases (Japanese Society for Oesophageal *Diseases*, 1976). It divides the oesophagus into four parts:

The cervical oesophagus begins at the lower border of the cricoid cartilage and reaches the thoracic inlet at the suprasternal notch. The upper thoracic portion originates at the thoracic inlet and reaches as far as the tracheal bifurcation. The mid thoracic portion is the proximal half of the length of oesophagus between the tracheal bifurcation and the oesophagogastric junction, and the lower thoracic portion is the distal half (Sobin LH, 2009a).

1.3.2 Tumour stage

The T stage describes the depth of the tumour's invasion through the layers of the oesophageal wall. T-stage begins with in-situ disease, classified as either high grade dysplasia or carcinoma in situ. Stage T1 describes tumour invading lamina propria or submucosa and is further subdivided into T1a when confined to the mucosa, or T1b when extending into the submucosa. Stage T2 describes tumour invading into but not through the muscularis propria. In T3 disease the tumour invades the adventitia, and in T4 disease the tumour invades adjacent structures. T4 is subdivided into T4a, when structures can be surgically removed, and T4b when structures are irresectable.

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1.3.3 Nodal stage

The N stage describes the presence and degree of pathological lymph node involvement. Nodes are identified according to their anatomical site in relation to the primary tumour.

Lymph node status represents one of the most important prognostic markers (Khan et al., 2003, Lozac'h et al., 1997, Paraf et al., 1995). When lymph node status is positive, the number of lymph node metastases is widely recognised as an important prognostic indicator (Ide et al., 1994, Lieberman et al., 1995, Kawahara et al., 1998, Zafirellis et al., 2002, Kunisaki et al., 2005, Mariette et al., 2003). For this reason, TNM7 incorporated additional N stage sub classifications of N1 (1-2 nodes), N2 (3-6 nodes), or N3 (>6 nodes), which were absent in the preceding version, TNM6 (Sobin LH, 2002).

1.3.4 Metastasis stage

The M stage describes the presence of distant metastases. The sub classifications M1a and M1b were used in the 6th edition of TNM, according to the position of the primary tumour and the location of metastases (Sobin LH, 2002). These were simplified to M0 and M1 in TNM7, denoting the presence or absence of metastatic disease respectively.

1.3.5.1 TNM classification for gastric cancer

(Edge et al., 2007, p120)

TX	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
Tis	Carcinoma *in situ*: intraepithelial tumour without invasion of the lamina propria[a].
T1	Tumour invades lamina propria, muscularis mucosae, or submucosa.
T1a	Tumour invades lamina propria or muscularis mucosae.
T1b	Tumour invades submucosa.
T2	Tumour invades muscularis propria.
T3	Tumour penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures.
T4	Tumour invades serosa (visceral peritoneum) or adjacent structures.
T4a	Tumour invades serosa (visceral peritoneum).
T4b	Tumour invades adjacent structures.

NX	Regional lymph node(s) cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastases in 1–2 regional lymph nodes.
N2	Metastases in 3–6 regional lymph nodes.
N3	Metastases in ≥7 regional lymph nodes.
N3a	Metastases in 7–15 regional lymph nodes.
N3b	Metastases in ≥16 regional lymph nodes.

M0	No distant metastasis.
M1	Distant metastasis.

[a]High-grade dysplasia includes all noninvasive neoplastic epithelia that was formerly called carcinoma *in situ*, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.

1.3.5.2 TNM anatomic stage/prognostic groups for gastric cancer

(Edge et al., 2007, p120)

0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
	T1	N1	M0
IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
IV	Any T	Any N	M1

1.3.5.3 TNM classification for oesophageal cancer

(Edge et al., 2007, p103)

TX	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
Tis	High-grade dysplasia.[a]
T1	Tumour invades lamina propria, muscularis mucosae, or submucosa.
T1a	Tumour invades lamina propria or muscularis mucosae.
T1b	Tumour invades submucosa.
T2	Tumour invades muscularis propria.
T3	Tumour invades adventitia.
T4	Tumour invades adjacent structures.
T4a	Resectable tumour invading pleura, pericardium, or diaphragm.
T4b	Unresectable tumour invading other adjacent structures, such as aorta, vertebral body, trachea, etc.

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastases in 1–2 regional lymph nodes.
N2	Metastases in 3–6 regional lymph nodes.
N3	Metastases in ≥7 regional lymph nodes.

M0	No distant metastasis.
M1	Distant metastasis.

[a]High-grade dysplasia includes all noninvasive neoplastic epithelia that was formerly called carcinoma *in situ*, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.

1.3.5.4 TNM anatomic stage/prognostic groups for oesophageal cancer

(Edge et al., 2007, p103)

Adenocarcinoma

Stage	T	N	M	Grade
0	Tis (HGD)	N0	M0	1, X
IA	T1	N0	M0	1–2, X
IB	T1	N0	M0	3
	T2	N0	M0	1–2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1–2	N1	M0	Any
IIIA	T1–2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1–2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

Squamous Cell Carcinoma[a]

Stage	T	N	M	Grade	Tumor Location[b]
0	Tis (HGD)	N0	M0	1, X	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2–3	Any
	T2–3	N0	M0	1, X	Lower, X
IIA	T2–3	N0	M0	1, X	Upper, middle
	T2–3	N0	M0	2–3	Lower, X
IIB	T2–3	N0	M0	2–3	Upper, middle
	T1–2	N1	M0	Any	Any
IIIA	T1–2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1–2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

[a]Or mixed histology, including a squamous component or not otherwise specified.
[b]Location of the primary cancer site is defined by the proximal tumour edge.

1.4 Preoperative staging

The accuracy of radiological staging is critical in determining appropriate treatment options. All treatment of oesophagogastric cancer is stage-directed and accurate staging permits identification of those patients whose disease is potentially curable. Equally, identifying those patients with incurable disease can prevent them from being subjected to inappropriate treatment, associated with significant potential for morbidity. Staging follows the TNM classification and first identifies those patients with metastatic disease, in whom curative treatment is not possible. Subsequently, more precise assessment of the local and regional disease is made, determining accurate T and N stages, as well as precise disease margins. A multimodal approach is adopted, utilising computed tomography (CT), endoluminal ultrasonography (EUS), endoscopic mucosal resection (EMR), CT-positron emission tomography (CT-PET) and diagnostic laparoscopy.

1.5 Preoperative physiological assessment

Oesophagogastric resectional surgery carries a significant physiological burden and high risk of morbidity and mortality (Centre, 2010). Various assessment modalities are used to measure the capacity of an individual to cope with such physiological insults. The information gathered using these assessments informs the multidisciplinary team decision on appropriate treatment modalities for individual patients, permitting interventions in the perioperative period to ensure optimisation of

performance status, and thereby minimise operative risk.

1.5.1 ASA grade

The American Society of Anesthesiologists' (ASA) classification of preoperative physical status is widely used across the globe. Its main limitation is its broad non-specificity. However, it is easily applied and correlates with outcomes across a wide range of settings.

1.5.1.1 Table of ASA grades

ASA Category	Preoperative Health Status	Comments, Examples
ASA 1	Normal healthy patient	No organic, physiologic, or psychiatric disturbance; excludes the very young and very old; healthy with good exercise tolerance
ASA 2	Patients with mild systemic disease	No functional limitations; has a well-controlled disease of one body system; controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease (COPD); mild obesity, pregnancy
ASA 3	Patients with severe systemic disease	Some functional limitation; has a controlled disease of more than one body system or one major system; no immediate danger of death; controlled congestive heart failure (CHF), stable angina, old heart attack, poorly controlled hypertension, morbid obesity, chronic renal failure; bronchospastic disease with intermittent symptoms
ASA 4	Patients with severe systemic disease that is a constant threat to life	Has at least one severe disease that is poorly controlled or at end stage; possible risk of death; unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure
ASA 5	Moribund patients who are not expected to survive without the operation	Not expected to survive > 24 hours without surgery; imminent risk of death; multiorgan failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy
ASA 6	A declared brain-dead patient who organs are being removed for donor purposes	

1.5.2 POSSUM score

The Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (POSSUM) has emerged as a useful risk prediction tool across many fields of surgery (Copeland et al., 1991). POSSUM encompasses an assessment of the patient's physiological status (physiology score) across twelve variables (Table 1.5.2.1), combining it with a measure of the surgical burden of the operation (operative severity score) across six variables (Table 1.5.2.2). However, POSSUM has been demonstrated to have a poor predictive accuracy in oesophagectomy (Zafirellis et al., 2002). A modified version, developed in response to over-estimations of mortality, yielded more accurate predictions (Prytherch et al., 1998), and later, O-POSSUM was devised, specific to oesophagogastric surgery (Tekkis et al., 2004). Controversy persists regarding the predictive value of the various POSSUM scores with conflicting reports highlighting P-POSSUM (Nagabhushan et al., 2007, Dutta et al., 2010) and O-POSSUM (Bosch et al., 2011) as most accurate.

1.5.2.1 POSSUM score - physiological parameters

Age	<61 years
	61-70 years
	>70 years
Cardiac	No cardiac failure
	Diuretic, digoxin, treatment for angina or hypertension
	Peripheral oedema, warfarin, borderline cardiomyopathy
	Raised JVP, cardiomegaly
Respiratory	No dyspnoea
	Dyspnoea on exertion, mild COAD
	Limiting dyspnoea, moderate COAD
	Dyspnoea at rest, pulmonary fibrosis/consolidation on x-ray
ECG	ECG normal
	ECG = AF, rate 60-90
	ECG = other abnormal rhythm, >4 ectopics, Q waves, ST/T changes
Systolic BP	110-130 mmHg
	100 - 109 or 131 - 170 mmHG
	>170, or 90 - 99 mmHg
	<90 mmHg
Pulse Rate	50-80 bpm
	40 - 49, or 81 - 100 bpm
	101 - 120 bpm
	<40, or >120 bpm
Haemoglobin	13 - 16 g/dL
	11.5 - 12.9, or 16.1 - 17 g/dL
	10 - 11.4, or 17.1 - 18 g/dL
	<10, or >18 g/dL
WBC	4 - 10
	10.1 - 20, or 3.1 - 4
	>20 or <3
Urea	<7.6
	7.6 - 10
	10.1 - 15
	>15
Sodium	>135 mmol/L
	131 - 135 mmol/L
	126 - 130 mmol/L
	>126 mmol/L
Potassium	3.5 - 5 mmol/L
	3.2 - 3.4, or 5.1 - 5.3 mmol/L
	2.9 - 3.1, or 5.4 - 5.9 mmol/L
	<2.9, or >5.9 mmol/L
GCS	15
	12 - 14
	9 - 11
	<9

1.5.2.2 POSSUM score – surgical parameters

Operation Type	Minor
	Moderate
	Major
	Complex major
Number of procedures	One
	Two
	more than two
Operative Blood Loss	<100 ml
	101 - 499 ml
	500 - 999
	>1000
Peritoneal Contamination	No soiling
	Minor soiling
	Local pus
	Free bowel content, pus or blood
Malignancy Status	Not malignant
	Primary malignancy only
	Primary plus nodal mets
	Primary plus distant mets
CEPOD	Elective
	Urgent / 'emergency'
	Emergency (within 2hrs)

1.5.3 Bioelectrical impedance analysis (BIA)

BIA measures body resistance and reactance to an alternating electrical current and specific validated equations are applied to derive measures including fat-free mass and muscle mass (Kyle et al., 2004). Based on electrical properties described since 1871 (L., 1871), subcutaneous (Thomasset, 1962) and later surface electrode (Hoffer et al., 1969, Nyboer, 1970) techniques were developed, transforming the concept into a non-invasive, rapid and reproducible method of estimating body composition. However, little attention has been paid to these simple

bioelectrical measures in the surgical literature and specifically oesophagogastric cancer surgery.

1.5.4 Cardiopulmonary exercise testing (CPX)

CPX combines an incremental exercise stress test with direct measurement of exercise respiratory gas exchange as well as electrocardiography and, as such, represents a simulation of the neurohumoral stress response to surgery. Invoking this stress response allows an assessment to be made of the patient's physiological capacity to tolerate the major surgical insult involved in oesophagogastric resection.

Energy supply to respiring tissues relies principally upon aerobic respiration. When this supply is exhausted, anaerobic respiration occurs to supplement the tissues' energy supply. The anaerobic threshold (AT) represents the rate of oxygen consumption at the point when a patient's tissue oxygen demand exceeds supply, and AT has received much attention in the literature. Two additional CPX variables of interest are the peak oxygen uptake (VO_2 peak) and the ventilatory equivalent for carbon dioxide (V_E/VCO_2).

The role of CPX in pulmonary thoracic surgery has been studied extensively (Benzo et al., 2007), and published UK guidelines have been available for over a decade (Society, 2001). Moreover, in major abdominal surgery measurements of anaerobic threshold (AT), and peak oxygen uptake (VO_2 peak) have been reported to predict short-term (Epstein et al., 2004, Wilson et al., 2010) and mid-term mortality (Carlisle

and Swart, 2007, Wilson et al., 2010), cardio-pulmonary related mortality (Older et al., 1993, Older et al., 1999), and length of hospital stay (Snowden et al., 2010).

An AT of less than 11 ml/kg/min was shown to be associated with an operative mortality rate of 18% compared with a mortality rate of 0.8% in patients with an AT greater than 11ml/kg/min ($p<0.001$) in a study of 187 elderly patients undergoing major abdominal surgery, such as abdominal aortic aneurysm resection or anterior resection of the rectum (Older et al., 1993, Older et al., 1999). These data, however, were published during the 1990s and both anaesthetic and surgical practice have since progressed.

More recently, ATs below 10.9 ml/kg/min have been associated with an increased risk of mortality within 90 days, (RR 6.8%, 95% CI 1.6-29.5), an increased likelihood of high dependency care (457 patients with an AT of ≤10.9 ml/kg/min vs. 390 with an AT of ≥10.9 ml/kg/min, $p<0.001$) and an increased median length of hospital stay (9 vs. 8 days, $p<0.001$) following major abdominal surgery such as elective colorectal resection, radical nephrectomy or cystectomy (Wilson et al., 2010). Similarly, in a study of patients undergoing major elective procedures such as open aortic aneurysm repair, liver resections and pancreatic sarcoma surgery, AT was found to be higher (11.9 vs. 9.1 mL/kg/min, $p=0.001$) in patients who developed one or less post-operative complication and subsequent LOHS was also shorter (10 vs. 26 days, $p<0.001$) (Snowden et al., 2010).

Data regarding CPX in UGI cancer surgery, however, are thin by

comparison, and existing reports were, until recently, confined to oesophageal surgery (Nagamatsu et al., 1994, Nagamatsu et al., 2001, Forshaw et al., 2008). One recent study reported outcomes among 180 patients with oesophagogastric cancer assessed using CPX, with 108 (60%) ultimately receiving surgical treatment. The operated cohort comprised 43 (40%) patients with gastric cancer and 65 (60%) patients with oesophageal cancer. Patients with cardiopulmonary operative morbidity were reported to have a significantly lower AT than those without such morbidity (9.9 vs. 11.2 ml/kg/min, p=0.04). An AT below 9 ml/kg/min was associated with operative cardiopulmonary morbidity using ROC analysis (sensitivity=74%, specificity=57%, p=0.04).

In recent years a small body of literature has emerged examining the effect of intervention to improve cardiopulmonary capacity. This work has been founded upon the hypothesis that, to some degree, the benefits observed in patients with good exercise capacity may be achieved by training. In 2007, Lee and colleagues intervened using just such a programme in 25 patients with lung cancer in advance of surgery. Patients were provided access to attended exercise classes of progressively increasing frequency and intensity. Patients averaged 30 sessions before surgery and managed to improve their VO_2peak by 2.4 ml/kg, with the best attenders improving the most (≥80% attendance, 3.3ml/kg). However, the researchers investigation this very small sample do not report any exploration of the surgical outcomes of the 20 patients who eventually underwent surgical resection and it remains to be seen whether the observed improvement holds any genuine clinical relevance.

It would be interesting to see a group randomised to an exercise intervention or control group, with robust follow-up of short and long term outcomes, including mortality, morbidity, length of stay and, of course, survival.

1.6 Nutrition

In recent years, the importance of malnutrition in surgical patients has received significant attention. It has been demonstrated for almost three decades that weight loss is associated with poor outcomes after surgery (Windsor and Hill, 1988).

1.6.1 Cachexia

Cachexia is a complex condition characterised by abnormally low weight, weakness and general bodily decline. It occurs as the clinical consequence of a complex chronic systemic response to inflammation (Wigmore et al., 1997) and is present in up to 50% of patients with cancer (Gould et al., 2013).

The complexities leading to the summative and profound weight losses in cancer have been associated with a myriad of theoretical pathological alterations in circulating hormones and their signaling axes. These can be broadly categorised as affecting appetite, protein metabolism and the chronic inflammatory state.

The capacity to ingest nutrients is restricted in many patients with oesophagogastric cancer by mechanical obstruction. Psychological barriers may arise with the learnt behaviour of consuming small and easily swallowed meals as dysphagia arises and progresses. Treatment toxicity can also diminish appetite and cause symptoms such as nausea, vomiting and diarrhoea (Martignoni et al., 2003). Further diminution of the appetite has been attributed to alterations in the feedback loop regulating the release of leptin from adipocytes. High levels of leptin inhibit the release of the potent feeding-stimulatory hormone neuropeptide Y (NPY) (Martignoni et al., 2003), leading to inhibition of food intake, in the face of increased energy requirements.

Tumour-derived factors put forward as promoters of the cachectic syndrome include proteolysis inducing factor (PIF) (Tisdale, 2009), lipid metabolising factor (LMF) (Islam-Ali and Tisdale, 2001), mitochondrial uncoupling proteins (UCPs) (Kotler, 2000).

The association of cachexia with a chronic systemic inflammatory response has been evidenced by high serum levels of IL-1, IL-6 and gamma interferon, each shown to correlate with tumour progression and further inhibit food intake via disruption of the NPY and leptin pathway described above (Martignoni et al., 2003). Tumour necrosis factor alpha (TNFα) is also implicated, altering messenger RNA activity for repair of damaged muscle tissue (Guttridge et al., 2000).

Patients with upper gastrointestinal cancer are especially likely to suffer from substantial weight loss associated with cancer cachexia (Martignoni

et al., 2003). Indeed, patients with gastric cancer may suffer extreme weight loss of up to 30% of premorbid body weight (Martignoni et al., 2003).

1.6.2 Malnutrition and surgical outcomes

Malnutrition has been defined as "a state in which a deficiency of energy, protein and/or other nutrients causes measurable adverse effects on tissue/body for, composition, function or clinical outcome" (MCaE, 2003). The National Institute for Health and Care Excellence (NICE) highlighted problems associated with the healthcare profession's poor understanding of issues surrounding nutrition (NICE, 2005).

Provision of nutritional support is poorly aligned with clinical need (NICE, 2005), indeed 30-40% of those in whom nutritional intervention is indicated do not receive it, and up to a quarter of nutritional care provided is either not needed, or even has the potential to do harm (Heyland et al., 2004).

Malnourished patients are more likely to experience complications following elective surgery. This has been recognised since as far back as the 1930s (Studley, 2001, Shils, 2000) and has been reported following major surgery in the modern era (Sungurtekin et al., 2004). Nutritional indices have been shown to demonstrate increasing rates of malnutrition in a surgical population across their stay in hospital (Sungurtekin et al., 2004). In addition, the ground-breaking work of Professor Henrik Kehlet and colleagues has brought focus onto the surgical stress response and

its impact on organ function, increasing oxygen demand and energy consumption (Kehlet, 1997). The wealth of multimodal approaches that have emerged following Kehlet's work, optimising peri-operative care in virtually all surgical disciplines, seek to minimise these end-organ effects. However, data are few reporting nutritional measures in oesophagogastric ERAS programmes (Jiang et al., 2007, Liu et al., 2010) and direct assessment of the influence on outcomes of reliable, reproducible measures of skeletal muscle mass or specific risk indices is lacking in the literature.

1.6.3 Skeletal muscle mass

An increasing body of work has emerged focusing on skeletal muscle mass and outcomes in surgery in recent years.

Studies have demonstrated clear relationships between CT measures of psoas muscle and surgical outcomes. A cohort of 163 patients undergoing liver transplant were examined according to the combined cross-sectional area of their psoas muscles at the level of the fourth lumbar vertebra, mortality was significantly higher and survival shorter at one and three years in the lowest quartile for psoas area, compared with the highest quartile (Englesbe et al., 2010). Sarcopaenic patients from a cohort of 196 patients undergoing colorectal hepatic metastatectomy, had a lower survival rate than those with higher skeletal muscle mass on CT analysis (van Vledder et al., 2012).

In 262 patients undergoing elective abdominal aortic aneurysm repair, psoas muscle size reduced over time during follow-up and psoas area

showed a significant association with postoperative mortality (Lee et al., 2011a).

Indeed, CT measures of skeletal muscle mass have been built into a risk prediction algorithm to determine the "morphometric age" according to various factors observed on their CT scan (Englesbe et al., 2013). Applied to a cohort of 1,370 patients who underwent major abdominal surgery in the USA, morphometric age was a stronger predictor of operative mortality than chronological age and more than half of the patients in the morphometrically 'oldest' 10% were neither comorbid nor advanced in chronological age (Englesbe et al., 2013). This suggests that morphometric age can contribute novel predictive value that extends beyond factors traditionally assessed by the parameters age and comorbidity.

The complex use of novel, simple risk predictors in this way exemplifies how future risk stratification may utilise readily available radiological imaging to new levels, with objective and precise measurements permitting the development of risk algorithms and perhaps leading to a more specific risk profile for the individual patient.

1.6.4 Attenuation of muscle mass loss

While it appears the depletion of skeletal muscle mass in upper gastrointestinal surgery may be attenuated by administration of pre-operative oral carbohydrate-containing fluid or eicosapentaenoic acid enriched enteral nutrition, the implications of this on clinical factors, such as function and rehabilitation time, remain unknown (Yuill et al., 2005,

Ryan et al., 2009).

An American group compared the weight and fat free mass (FFM) of patients with stage IV solid organ cancers over 24 weeks. Administration of an experimental treatment containing β-hydroxy-β-methylbutyrate (3 g/d), L-arginine (14 g/d), and L-glutamine (14 g/d [HMB/Arg/Gln]) was shown to be superior to an isonitrogenous control mixture of nonessential amino acids, with differences in weight change (+0.95 vs. -0.24kg) explained by significant differences observed in FFM between groups (1.34 +/-0.78kg vs. 1.12 +/-0.68kg, p=0.02) without any treatment-related complications (May et al., 2002).

1.6.5 Obesity

Obesity and underweight are defined as a BMI of 30 kg / m^2 or over, and 18.5 kg / m^2 or below. Both have been shown to be associated with greater risk of recurrence or death following adjuvant chemotherapy for colon cancer, compared with patients of normal weight (Dignam et al., 2006). Overweight and obesity have also been shown to be associated with reduced survival in patients with pancreatic cancer in the USA, regardless of disease stage or resectional status (overweight patients: hazard ratio, 1.26 [95% CI, 0.94-1.69], P = .04; obese patients: hazard ratio, 1.86 [95% CI, 1.35-2.56], P < .001) (Li et al., 2009). Within oesophagogastric surgery, there is limited evidence of an association between both anterior-posterior abdominal diameter and BMI with post-operative complications following gastrectomy for gastric cancer, but this association was only observed in female patients (Lee et al., 2007). Other

researchers have failed to identify significant association between obesity (BMI) and post-operative mortality or complications after gastrectomy or oesophagectomy (Mullen et al., 2008). In addition, it has been demonstrated that BMI does not affect survival after oesophagectomy (Melis et al., 2011).

1.6.6 Nutritional Risk Assessment Tools

It is clear that malnutrition is both a cause and a consequence of ill-health. It can increase susceptibility to infection, delayed wound healing, impaired cardiac and pulmonary function, reduced muscle strength and depression (NICE, 2005). Despite its far-reaching and significant implications a widely accepted definition for malnutrition remains elusive (NICE, 2005). The Malnutrition Advisory Group (MAG) is a standing committee of the BAPEN (formerly known as the British Association for Parenteral and Enteral Nutrition). MAG produced the Malnutrition Universal Screening Tool (MUST) (Elia Marinos, 2012) as a tool to identify those adults who are malnourished or at risk of malnutrition. It also incorporates management guidelines, which can be used by a wide range of healthcare workers to develop a patient care plan (Stratton et al., 2004, BAPEN, 2012). Similarly, WAASP (Weight, Appetite, Ability to eat, Stress factors, Pressure sores/wounds) is a screening tool with a similar objective, developed in South Wales for the assessment of nutrition (WAASP, 2005).

1.7 Enhanced recovery after surgery

Enhanced recovery programmes (ERPs) employing holistic multimodal perioperative strategies have long been embedded within colorectal cancer surgical care and have been beneficial in reducing post-operative morbidity and length of hospital stay (LOHS) (Varadhan et al., 2010). Such improvements are achieved in the modern ERP through aggregation of the benefits of a number of interventions to optimise physiological, psychological and healthcare system factors surrounding major gastrointestinal surgery. Interventions are combined within a standardised pathway incorporating clear goals for patients and staff members alike. In contrast, ERPs in upper gastrointestinal (UGI) cancer surgery are less established.

Reports regarding ERPs in gastric cancer surgery are few, with modest sample sizes and widely variable quality (He, 2010, Jeong et al., 2011, Jiang et al., 2007, Kiyama et al., 2003, Liu et al., 2010, So et al., 2008, Tang, 2013, Wang et al., 2010, Yamada et al., 2012, Feng et al., 2013, Chen Hu et al., 2012, Kim et al., 2012). Two existing meta-analyses of multimodal peri-gastrectomy ERPs have failed to include all available data from the literature, one pooling data from six studies (n=400) (Yu et al., 2014) and the other pooling data from just four studies (n=218) (Chen Hu et al., 2012) for meta-analysis.

In oesophageal cancer surgery, one randomised trial (Zhao et al., 2014) and seven cohort studies have examined ERAS (Munitiz et al., 2010, Tang, 2013, Brodner et al., 1998, Tomaszek et al., 2010, Li et al., 2012,

Cao et al., 2012, You et al., 2012). No systematic review or meta-analysis of the implementation of a multimodal pathway in oesophagectomy for cancer exists.

Within this thesis the literature is systematically reviewed and meta-analysed for each of gastric and oesophageal cancer ERAS. Within theses meta-analyses, significant attention is paid to the populations studied, which were predominantly based in Eastern Asian countries such as China, and Japan. Few studies exist examining Western populations.

1.8 Neoadjuvant and adjuvant therapy

The poor prognosis associated with oesophagogastric cancer reflects the late onset of symptoms and consequent late presentation, with advanced disease. Most patients present with stage III or IV disease and therefore rates of curability are low. Indeed, survival rates at five years have been quoted as 16% for oesophageal cancer and 24% for gastric cancer in the United States of America (Jemal et al., 2008). While surgery remains the mainstay of curative treatment, in recent years chemoradiotherapeutic options have emerged as effective additional treatments, prolonging survival after major oesophagogastric resectional surgery for cancer (Cunningham et al., 2006, Macdonald et al., 2001, Sjoquist et al., 2011, van Hagen et al., 2012).

Adjuvant chemotherapeutic approaches are based upon the concept that the systemic administration of agents can target systemic or distant

disease, where surgery alone cannot. However, with various available regimens, conflict exists regarding the most effective combination. Modern Western clinical practice in oesophageal cancer surgery has been guided by two important randomised trials of neoadjuvant therapy versus surgery alone. However, these two large trials provided conflicting evidence, exemplifying the need for ongoing work. The InterGroup Trial was conducted in the USA and failed to demonstrate a survival difference (Kelson, 1998). The similar OEO2 trial was conducted in the UK and reported a 2-year survival benefit of 9% (Allum, 1995).

More recently, meta-analysis has concluded that survival benefits result from both chemotherapy (HR 0.87, 95% CI 0.79 - 0.96, p=0.005) and chemoradiotherapy (HR 0.78, 95% CI 0.70-0.88, p<0.0001) in comparison to surgery alone.

1.9 Operative morbidity

1.9.1 Clavien-Dindo Classification

In 2004, the Swiss transplant surgeons Pierre-Alain Clavien and Daniel Dindo proposed a classification of operative morbidity that was simple to apply and broad enough to be transferrable to the majority of operative procedures (Dindo *et al.*, 2004). It remains widely used and has been incorporated into the outcome analysis of a number of the chapters in this thesis.

Major morbidity is classed as that of Clavien-Dindo (CD) grade three or higher, representing any morbidity requiring invasive intervention.

1.9.2 Clavien-Dindo classification of operative morbidity.

(Dindo *et al.*, 2004)

Clavien-Dindo Grade		Definition
0		No deviation from the normal post-operative course
I		Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
		Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II		Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	IIIa	Requiring surgical, endoscopic or radiological intervention intervention not under general anesthesia
	IIIb	Above intervention under general anesthesia
IV	IVa	Life-threatening complication (including CNS complications) +/- requiring IC/ICU-management with single organ dysfunction (including dialysis)
	IVb	Above complication, with multi-organ dysfunction
V		Operative death

1.10 Aims and hypotheses

In light of the areas of uncertainty highlighted above, this thesis aims to:

1. Determine the prognostic value of bioelectrical impedance analysis body composition variables in oesophagogastric cancer surgery.

2. Determine the prognostic value of CT-measured psoas muscle density in oesophagogastric cancer surgery.

3. Determine the prognostic value of cardiopulmonary exercise testing in oesophagogastric cancer surgery.

4. Systematically review and meta-analyse the literature on enhanced recovery programmes in gastric and oesophageal cancer surgery respectively.

5. Assess outcomes following oesophagogastric cancer surgery following the introduction of an enhanced recovery programme.

The hypotheses tested are:

1. Suboptimal bioelectrical impedance analysis body composition variables predict poor outcomes following oesophagogastric cancer surgery.

2. A low CT-measured psoas muscle density predicts poor outcomes following oesophagogastric cancer surgery.

3. Suboptimal performance on cardiopulmonary exercise testing predicts poor outcomes following oesophagogastric cancer surgery.

4. Systematic review and meta-analysis of the literature on enhanced recovery programmes in gastric and oesophageal cancer surgery will show evidence in support of their use.

5. The introduction of an enhanced recovery programme in oesophagogastric cancer surgery is feasible, safe and not associated with adverse outcomes.

CHAPTER 2

A pilot study of bioelectrical impedance analysis as a prognostic indicator in oesophagogastric cancer surgery.

2.1 SUMMARY

The aim of this study was to determine the predictive value of bioelectrical impedance analysis (BIA)-derived body composition measures of muscle mass and fat-free mass (FFM) and muscle mass (MM) in oesophagogastric cancer resectional surgery.

A total of 83 patients (33 GCA: 50 OCA, 62m), aged 66 (24-86) years, were assessed in the South East Wales Cancer Network using BIA during pre-operative assessment of patients with oesophago-gastric cancer undergoing surgical resection between August 2011 and October 2013.

FFM and MM correlated with existing nutritional risk assessment tools: WAASP (FFM, p=0.026; MM, p=0.027) and MUST (FFM, p=0.023; MM, p=0.040).

No significant association between FFM or MM and operative morbidity or mortality was identified. Multivariable analysis demonstrated FFM (p=0.004) and MM (p=0.010) as independent and significantly predictors of length of hospital stay.

Cumulative survival was more favourable in those with high FFM (X^2=3.955, p=0.047) and MM (X^2=6.403, p=0.011).

BIA-derived measures of body composition have emerged as novel predictive measures of outcome in oesophagogastric surgery. Low values for fat-free mass and muscle mass were associated with poor outcomes.

2.2 INTRODUCTION

Oesophagogastric cancer is associated with a poor prognosis, owing to late onset of symptoms and consequent late presentation with advanced disease (Centre, 2010). With rates of operative morbidity quoted at 30% and 19%, mortality rates at 4.5% and 6% respectively, oesophagectomy and gastrectomy are associated with considerable operative risk (Centre, 2010). Furthermore, survival rates at five years have been quoted at just 16% for oesophageal cancer and 24% for gastric cancer (Jemal et al., 2008). Even among patients treated with curative intent, survival at one year is reported at 76% and 78% respectively (Centre, 2010).

It is well-known that body composition can be rapidly and significantly altered by cancer, and patients with oesophagogastric cancer are especially likely to experience substantial weight loss (Martignoni et al., 2003). Factors contributing to weight loss are numerous, including hormonal changes within a chronic inflammatory response, leading to inhibition of food intake in the face of increased nutritional requirements (Martignoni et al., 2003). The observed sequelae have been incorporated into definitions of malnutrition syndromes of cachexia and sarcopaenia. Clear parallels exist between these definitions, cachexia characterised by abnormally low weight, weakness and general bodily decline (Wigmore et al., 1997), while sarcopaenia implies a functional impairment related to suboptimal skeletal muscle mass (Janssen et al., 2002).

For many years, weight loss and poor skeletal muscle function have been shown to be relevant to surgery, associated with increased risk of adverse outcomes including operative morbidity and prolonged stay in hospital (Windsor and Hill, 1988). Up to 50% of patients with cancer can be classified as cachectic (Wigmore et al., 1997) and, in resectional oesophagogastric cancer surgery, with implicit periods of reduced or absent nutritional intake, malnutrition may be compounded.

There is limited evidence of an association between gross measures of body composition, such as abdominal diameter and BMI, with post-operative complications following gastrectomy (Lee et al., 2007). However, other researchers have failed to identify significant associations between BMI and post-operative mortality or complications after gastrectomy or oesophagectomy (Mullen et al., 2008). In addition, it has been demonstrated that BMI does not reduce survival after oesophagectomy (Melis et al., 2011).

More specific measures of body composition using computerised tomography have emerged as predictive of outcomes in colorectal metastasis resection (Peng et al., 2011), but little evidence exists investigating the predictive value of such specific measures of body composition for outcomes after OG surgery. Novel derived measures of body composition have emerged with the advent of Bioelectrical Impedance Analysis (BIA).

In addition to simple resistance, the body exerts a second force of resistance to an alternating current passed through it, known as reactance. This is the resistance resulting from the storage of some

charge between cell membranes. BIA measures both resistance and reactance and specific validated equations are applied to derive a wide range of measures including the commonly used phase angle (see 2.2.1) and body composition measures including fat-free mass (FFM) and muscle mass (MM) (Kyle et al., 2004). Based on electrical properties described since 1871 (L., 1871), subcutaneous (Thomasset, 1962) and more recently surface electrode (Hoffer et al., 1969, Nyboer, 1970) techniques were developed, transforming the concept into a non-invasive, rapid and reproducible method of estimating body composition.

Little attention has been paid to these simple measures in the surgical literature and specifically OG cancer surgery.

The aim of this study, therefore, was to determine the predictive value of BIA-derived body composition measures of muscle mass and fat-free mass in oesophagogastric cancer resectional surgery.

2.2.1. Graph to illustrate manipulation of resistance and reactance in phase angle derivation (Adapted from Kyle et al. Clin Nutr (2004) 23, 1226-1243)
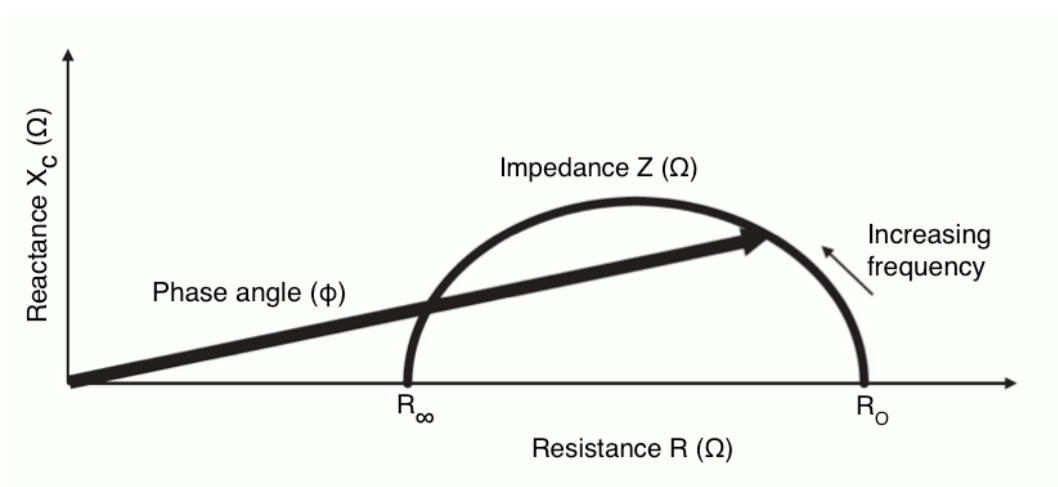
2.3. METHODS

A total of 83 patients in the South East Wales Cancer Network consented and were assessed using bioelectrical impedance analysis during pre-operative assessment of patients with oesophago-gastric cancer undergoing surgical resection between August 2011 and October 2013.

2.3.1 Exclusion criteria

Exclusion criteria were non-operative management and the absence of fully informed consent. No patient refused to participate.

Analysis was performed on all 83 patients (table 1), with a median (range) age of 66 (24-84) years. There were 62 (75%) males, 50 (60%) oesophageal and 33 (40%) gastric cancers. Treatment intent was curative in all patients. Data relating to the pre-operative status, operative procedure and outcome were collected prospectively for all patients.

2.3.2 Variables

Pre-operative assessment was performed on all patients in the standard manner for the unit. This involved the clinical history and examination, together with risk assessment indicators including cardiopulmonary exercise testing and Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) scores (Copeland et al., 1991). Nutritional data was collected including the WAASP score (Weight, Appetite, Ability to eat, Stress factors, Pressure sores/wounds)

(Cardiff and Vale NHS Trust, 2005) and MUST score (Malnutrition Universal Screening Tool) (Elia Marinos, 2012).

Other data collected included age, gender, American Society of Anesthesiologists (ASA) grade (Anesthesiologists, 1963), Welsh Index of Multiple Deprivation overall (WIMD) (2008), radiological and histopathological stage of disease (TNM7) (Sobin LH, 2009b), anatomical site of surgery, surgical procedure performed, 30-day mortality, 30-day morbidity related to the Clavien-Dindo grade (CD) (Dindo et al., 2004), intensive therapy unit (ITU) length of stay (ITU LOS), high dependency length of stay (HDU LOS), critical care length of stay in days (CC LOS) and total length of hospital stay (LOHS) in days.

2.3.3 BIA measurement

BIA variables were measured using the Maltron Bioscan 920 bioelectrical impedance analyser (Maltron International Ltd., Rayleigh, Essex, UK). Patients were fasted for two hours prior to assessment and the bladder voided within the 30 minutes preceding measurement. The height (to nearest 0.1cm) and weight (to nearest 0.1kg) were measured using a calibrated stadiometer and a balance-beam scale. These measurements were made in duplicate and averaged. The body mass index was calculated as the weight (kg) divided by height (m) squared (kg/m^2).

BIA measurements were made following 10 minutes of inactivity with the patient supine upon a non-conducting surface as follows: The skin on the dorsum of the right hand and foot was prepared with 70% alcohol cleanser and allowed to dry. An electrical current of 50kHz and 0.8mA

was applied to the skin via four adhesive electrodes and the whole body

resistance and reactance were measured as shown in the schematic

below (2.3.3.1). The phase angle was calculated using the equation arc

tangent resistance/reactance x $(180^{o}/\pi)$.

Figure 2.3.3.1. BIA test schematic
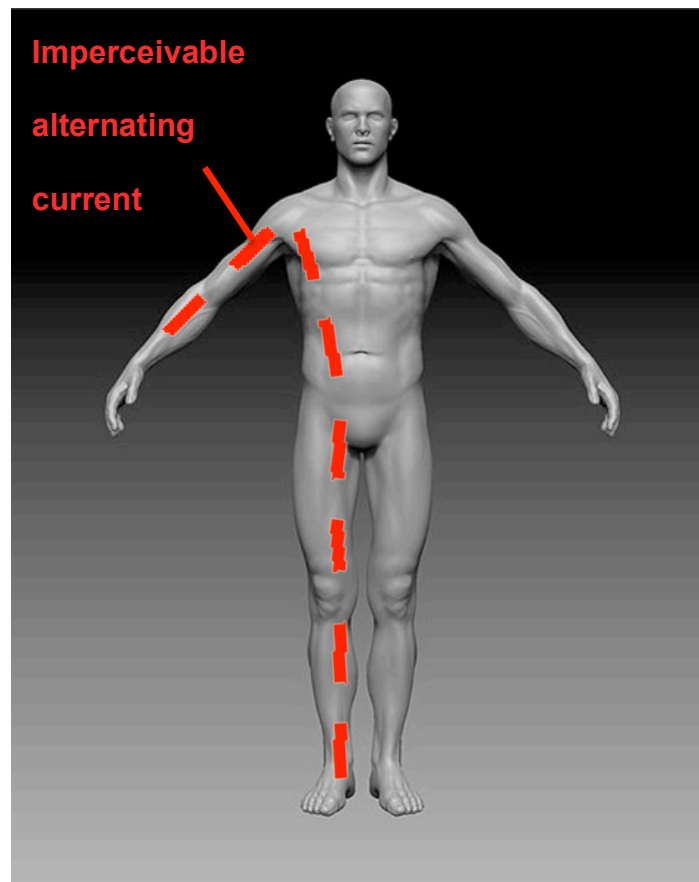
2.3.4 Outcome measures

The primary outcome measure was survival in months from diagnosis.

Additional outcome measures included morbidity related to Clavien-Dindo

grade (Dindo et al., 2004), LOHS, HDU LOS, ITU LOS, CC LOS and

correlation with two existing nutritional risk measures (WAASP and

MUST). A Clavien-Dindo grade of ≥III represents morbidity requiring therapeutic intervention beyond pharmacological treatment or superficial wound opening and was considered to represent major morbidity in this study.

2.3.5 Statistical analysis

Statistical analysis was performed using the Statistical Programme for the Social Sciences (SPSS v20.0.2, IBM Corporation, Armonk, New York, USA). Grouped data were expressed as median (range) and non-parametric analyses were used throughout. Statistical significance was determined as $p<0.05$. Categorical data were compared using the χ^2 test, except where groups contained counts of fewer than five, when Fisher's exact test (Fisher, 1922) was used. Grouped continuous data were compared using the Mann-Whitney U-test (Mann and Whitney, 1947). Spearman's rank correlation coefficient (Spearman, 1904) was used to determine correlation. BIA-derived variables were grouped into quintiles for assessment and the upper two quintiles were compared with the lower three. Univariable analysis of the predictive value of pre-operative factors for LOHS was performed using the Mantel-Cox log rank method of Kaplan and Meier model (Kaplan and Meier, 1958). This incorporated LOHS into the model in place of survival, using discharge from hospital as the event and resulting in the construction of LOHS plots. Multivariable analysis of factors significantly influencing LOHS was performed using the Cox regression analysis model (Cox, 1972). Kaplan-Meier plots were

created to demonstrate survival in the manner originally described (Kaplan and Meier, 1958).

2.3.6 Power

A power calculation was performed for the primary outcome measure of survival using the Altman method (Whitley and Ball, 2002). This was based on a sample of existing data from the same unit with a standard deviation of 7.5 months. With alpha set at 0.05 and powered at 80%, a total of 70 patients were required in order to detect a 5-month survival difference at two years.

2.4 RESULTS

2.4.1 Details of the patients

Details of the 83 patients studied are shown in Table 1. The surgical procedures performed are shown in Table 2.

2.4.2 Correlation with existing nutritional risk tools

Significant correlation was identified between BIA body composition variables and established nutritional risk assessment tools, with a low MM correlating with poor WAASP (Rho -0.354, p=0.027) and MUST (Rho -0.331, p=0.040) scores. Similarly, a low FFM correlated with poor WAASP (Rho -0.357, p=0.026) and MUST (Rho -0.364, p=0.023) scores.

2.4.3 Operative morbidity and mortality

No significant association was identified according to grouped quintiles (upper 2 vs. lower 3) between FFM and operative morbidity (41% vs. 43%, p=0.562), CD class ≥II (29% vs. 36%, p=0.488) or CD class ≥III (12% vs. 20%, p=0.301). Neither was a significant association identified between MM and operative morbidity (45% vs. 39%, p=0.643), CD class ≥II (39% vs. 35%, p=0.725) or CD class ≥III (19% vs. 17%, p=0.827). Using the same groups, although neither FFM nor MM was significantly associated with operative mortality, non-significant higher incidences of operative death were seen in the groups with lower FFM and MM (0% vs. 9%, p=0.092).

2.4.4 Length of stay

Analysis of lengths of stay is shown in Table 3. While median LOHS did not differ significantly between groups spilt by FFM (13.5 vs. 13 kg, p=0.609) or MM (15 vs. 13 kg, p=0.228) quintiles, a longer stay in HDU was observed among those patients who recorded a high MM (1 vs. 0 day, p=0.007).

Despite the absence of a significant difference in median LOHS between these grouped quintiles, univariable analysis identified FFM and MM among a number of variables significantly predicting LOHS (Table 4). Indeed, multivariable analysis demonstrated both FFM and MM to be significant and independent predictors of LOHS (Table 5).

2.4.5 Survival

Median follow up (or time to death) was 25 months (range 2-37 months), with a 2-year survival of 68.9% (31/45) and a median survival of 18 months. Survival analysis demonstrated significant differences between the upper two and lower three quintiles for FFM (median 18 vs. 18 months, p= 0.047, Figure 1) and MM (median 21 vs. 16 months, p=0.011, Figure 2) respectively.

2.5 DISCUSSION

This is the first study to investigate the predictive value of BIA-derived measures of body composition in oesophagogastric surgery, related to outcomes.

The principal findings were that BIA-derived measures of fat-free mass and muscle mass were significant predictors of outcome after oesophagogastric resection for cancer in this cohort. A low FFM and MM was associated with poor survival and both FFM and MM emerged as independent and significant predictors of length of hospital stay.

It is well known that patients presenting with upper gastrointestinal cancer are especially likely to suffer substantial weight loss associated with cancer cachexia (Martignoni et al., 2003). This gross weight loss is recognised as multifactorial and, in addition to mechanical factors causing obstruction of the gastrointestinal tract, tumour-derived factors have been shown to promote proteolysis (Tisdale, 2009) and lipid

metabolism (Islam-Ali and Tisdale, 2001). A chronic systemic inflammatory state is observed as cancer progresses, associated with significant disruption of hormonal satiety pathways, including those involving leptin and neuropeptide Y, leading to inhibition of food intake (Martignoni et al., 2003). Furthermore, iatrogenic factors, such as chemotherapeutic toxicity can compound patients' difficulty in maintaining satisfactory nutrition (Martignoni et al., 2003). And whilst patients are in this vulnerable catabolic state, tumour necrosis factor alpha (TNFα) alters muscle repair, impairing effective muscle regeneration in the event that nutritional intake can be achieved (Guttridge et al., 2000).

It follows then, that measures of body composition may afford insight into a patient's potential outcomes both on grounds of disease progression and an individual's premorbid capacity to cope with the multifactorial assault on the body's composition.

As the first study to examine BIA-derived measures of FFM and MM in relation to outcomes following oesophagogastric surgery for cancer, this represents a novel area of investigation. Other strengths include prospective data collection of a consecutive series of patients through an established and experienced MDT, whose results are well audited and stand up to international comparison (Centre, 2010), all surgery performed by specialist surgeons. A large consecutive series minimised the risk of selection bias.

In contrast, there are several potential limitations to this study. The dataset includes oesophagogastric cancer resections ranging from subtotal gastrectomy to three-stage oesophagectomy. The physiological burden of surgery was therefore variable according to the extent of the procedure required. However, this is representative of the workload within this large centralised unit with good throughput. Further analysis of subgroups will be feasible in future and may yield more specific data according to procedure type and other variables.

Values for FFM and MM were unadjusted. This may allow for the influence of confounders such as gender. However, gender was formally assessed in analyses and no association the reported outcomes emerged. Furthermore, BMI was included in univariable and multivariable analyses, and along with FFM and MM, it emerged as independent predictors of LOHS.

Measures of FFM and MM in this study correlated with existing nutritional risk measures, which supported their utility in assessing risk in this vulnerable group.

Patients in the upper two quintiles for MM were observed to stay significantly longer at level II than those in the lower three quintiles. It is not clear why this occurred. I interrogated the data further to seek an explanation for this and identified a non-significant disparity in mean level III stay between groups, patients with lower MM staying longer at level III. In this unit, fit patients often require only level II care and those in level III beds often return to level I directly from level III. Therefore it is possible

that a type II statistical error has prevented a reciprocal picture of longer level III stay in patients with low MM from emerging. This possible explanation fits with the findings for CC LOS (levels II and III combined), for which no significant difference was identified between groups.

Similarly, since the study was powered to detect a difference in survival, it is possible that a type II statistical error was responsible for the absence of a statistical difference in LOHS between FFM and MM groups, while more detailed statistical analysis suggested the existence of a significant influence in this cohort.

Further work is warranted to investigate the relationship between emerging measures of nutritional assessment, nutritional risk measures and to explore interventions to modify such identifiable nutritional risk factors in oesophagogastric cancer surgery.

Some exploration of pre-operative exercise exists in the literature. In the elderly, physical activity does not seem to prevent the loss of skeletal muscle (Raguso *et al.*, 2006), but some review evidence suggests that pre-operative exercise therapy prior to abdominal surgery can lead to improved clinical outcomes, including shorter hospital stay and reduced postoperative complication rates (Valkenet, 2011). However, the literature surrounding this is both thin and relatively contradictory. Two recent systematic reviews of the effects on cardiopulmonary function, outcome and recovery after abdominal surgery yield inconclusive findings (Lemanu et al., 2013, Pouwels, 2014). They did suggest that there may be potential for improvement in complication rates, particularly pulmonary

complications, but further research is necessary and consensus regarding intervention choice is, so far, lacking (Valkenet, 2011, Lemanu et al., 2013, Pouwels, 2014). Allied to ERAS, upon which several chapters later in this thesis focus, this area of research may ultimately yield further benefit to patients by adding potential further pre-operative interventions to improve the post-operative course following major abdominal surgery such as oesophagogastric resection.

2.6 CONCLUSION

BIA-derived measures of fat-free mass and muscle mass were significant predictors of outcome after oesophagogastric resection for cancer. A low FFM and MM was associated with poor survival and both FFM and MM emerged as independent and significant predictors of length of hospital stay.

2.7 TABLES AND FIGURES

2.7.1 Table 1. Details of the patients

Variable	Total
n	83
Site (gast:oes)	33:50
Histology (ACA:SCC:HGD)	76:6:1
Gender (m:f)	62:21
Age (years)	66 (24-86)
BMI (kg/m^2)	26 (15-44)
ASA (I-II:III-IV)	57:26
FFM (kg)	58.4 (33.0-97.4)
Muscle mass (kg)	27.7 (8.0-94.0)
PhA (degrees)	7.80 (4.53-15.13)
WAASP score	14 (7-22)
MUST score	1 (0-3)
P-POSSUM morb (%)	41.58 (17.00-86.99)
P-POSSUM mort (%)	2.36 (0.80-43.05)
O-POSSUM mort (%)	7.09 (1.04-41.75)
WIMD	853 (2-1886)
LOHS (days)	13 (4-52)
CCLOS (days)	1 (0-17)
HDU LOS (days)	1 (0-13)

ITU LOS (days)	0 (0-17)
Operative morbidity	35 (42%)
CD ≥2	28 (33.7%)
CD ≥3	14 (16.9%)
30-day mortality	4 (4.8%)
Survival (months)	18 (2-37)
Median follow up (months)	25 (9-45)

Figures are given as median (range) unless stated. n, number; Site, disease site (gastric:oesophageal); histology, histopathological cell type; ACA, adenocarcinoma; SCC, squamous cell carcinoma; HGD, high grade dysplasia; m:f, male to female ratio; BMI, body mass index; ASA, American Society of Anesthesiologists score; FFM, fat-free mass; MM, muscle mass; PhA, phase angle; POSSUM, physiological and operative severity score for the enumeration of mortality and morbidity (P – generic score; O – oesophageal score; Mort, mortality; morb – morbidity); WIMD, Welsh index of multiple deprivation rank; WAASP, Weight, Appetite, Ability to eat, Stress factors, Pressure sores/wounds; MUST, Malnutrition Universal Screening Tool; LOHS, length of hospital stay; CC LOS, critical care stay; ITU LOS, intensive therapy unit stay; HDU LOS, high dependency unit stay; CD class, Clavien-Dindo classification of operative morbidity.

2.7.2 Table 2. Details of the procedures

Procedure	n (%)
TG	14 (16.9)
STG	14 (16.9)
3SO	2 (2.4)
TTO	7 (8.4)
THO	34 (41.0)
O&C	12 (14.5)
TOTAL	**83**

N, number; TG, total gastrectomy; STG, subtotal gastrectomy; 3SO, three-stage oesophagectomy; TTO, trans-thoracic oesophagectomy; THO, trans-hiatal oesophagectomy; O&C, Open and close procedure (inoperable cancer).

2.7.3 Table 3. Influence of FFM and MM on lengths of stay.

Variable	Fat Free Mass		p-value	Muscle Mass		p-value
	Upper 2 Quintiles	Lower 3 Quintiles		Upper 2 Quintiles	Lower 3 Quintiles	
LOHS (days)	13.5 (4-41)	13 (4-52)	0.609	15 (4-52)	13 (3-35)	0.228
CC LOS (days)	1 (0-2)	1 (0-17)	0.680	1 (0-15)	1 (0-17)	0.097
ITU LOS (days)	0 (0-1)	0 (0-17)	0.537	0 (0-2)	0 (0-17)	0.691
HDU LOS (days)	1 (0-2)	0 (0-13)	0.232	1 (0-13)	0 (0-5)	0.007

2.7.4 Table 4. Univariable analysis to determine factors influencing LOHS using the Mantel-Cox log rank method of Kaplan and Meier.

Variable	χ^2	df	p value
FFM	234.683	68	<0.0001
WIMD	231.946	66	<0.0001
PhA	230.909	65	<0.0001
MM	212.471	61	<0.0001
BMI	185.835	57	<0.0001
O Possum mortality	125.146	49	<0.0001
P POSSUM morbidity	85.935	41	<0.0001
P POSSUM mortality	83.129	40	<0.0001
Age	49.856	34	<0.0001
pT stage	36.872	4	<0.0001
CD class	27.597	6	<0.0001
pN stage	7.727	3	0.052
WAASP score	21.488	13	0.064
pM stage	4.905	2	0.086
Rad stage	5.491	3	0.139
ASA	3.051	2	0.217
MUST score	1.929	3	0.587
Site	0.212	1	0.645
Histology	0.092	1	0.762
Gender	0.026	1	0.872

χ^2, chi square value; df, degrees of freedom; FFM, fat-free mass; WIMD, Welsh index of multiple deprivation rank; PhA, phase angle; MM, muscle mass; BMI, body mass index; POSSUM, physiological and operative severity score for the enumeration of mortality and morbidity (P – generic score; O – oesophageal score; Mort, mortality; morb – morbidity); pT, pN and pM stage, tumour, nodal and metastasis histopathological stage of disease according to TNM7 classification; CD class, Clavien-Dindo classification of operative morbidity; WAASP, Weight, Appetite, Ability to eat, Stress factors, Pressure sores/wounds; MUST, Malnutrition Universal Screening Tool; ASA, American Society of Anesthesiologists score; Site, disease site (oesophagus, stomach); Histology, histopathological cell type.

2.7.5 Table 5. Multivariable analysis of factors influencing length of hospital stay. Backward Log Rank Cox Regression

Variable	HR	95% CI	p value
CD class	0.342	0.179-0.654	0.001
BMI	0.580	0.425-0.792	0.001
PhA	0.357	0.182-0.701	0.003
FFM	1.420	1.119-1.801	0.004
O POSSUM mort	0.658	0.493-0.879	0.005
P POSSUM mort	3.070	1.390-6.779	0.006
P POSSUM morb	0.882	0.805-0.879	0.007
MM	0.672	0.497-0.909	0.010
WAASP	1.219	1.038-1.430	0.016
pN stage	0.534	0.272-1.045	0.067
Age	1.072	0.994-1.156	0.071
WIMD	1.001	1.000-1.003	0.124

HR, hazard ratio; CI, confidence interval; CD class, Clavien-Dindo classification of operative morbidity; BMI, body mass index; PhA, phase angle; FFM, fat-free mass; POSSUM, physiological and operative severity score for the enumeration of mortality and morbidity (P – generic score; O – oesophageal score); MM, muscle mass; WAASP, Weight, Appetite, Ability to eat, Stress factors, Pressure sores/wounds; pN stage, nodal histopathological stage of disease according to TNM7 classification; WIMD, Welsh index of multiple deprivation rank.

2.7.6 Table 6. Univariable analysis to determine factors influencing survival using the Mantel-Cox log rank method of Kaplan and Meier.

Variable	x^2	df	p value
FFM	224.177	8	<0.0001
WIMD	211.964	80	<0.0001
PhA	220.981	79	<0.0001
MM	204.312	74	<0.0001
BMI	169.368	65	<0.0001
O Possum Mort	121.978	49	<0.0001
P POSSUM morb	111.261	41	<0.0001
P POSSUM mort	104.563	40	<0.0001
CD class	94.303	6	<0.0001
LOHS	67.002	24	<0.0001
ITU LOS	53.926	4	<0.0001
CC LOS	50.339	8	<0.0001
WAASP score	46.441	13	<0.0001
pM stage	16.510	2	<0.0001
pT stage	17.663	4	0.001
Age	56.701	37	0.020
MUST score	8.737	3	0.033
ASA	5.335	2	0.069
Rad stage	4.588	3	0.205
pN stage	4.305	3	0.230
Histology	2.351	2	0.309

HDU LOS	6.837	6	0.336
Site	0.345	1	0.557
Gender	0.015	1	0.902

χ^2, chi square value; df, degrees of freedom; FFM, fat-free mass; WIMD, Welsh index of multiple deprivation rank; PhA, phase angle; MM, muscle mass; BMI, body mass index; POSSUM, physiological and operative severity score for the enumeration of mortality and morbidity (P – generic score; O – oesophageal score; Mort, mortality; morb – morbidity); CD class, Clavien-Dindo classification of operative morbidity; LOHS, length of hospital stay; ITU LOS, intensive therapy unit stay; CC LOS, critical care stay; WAASP, Weight, Appetite, Ability to eat, Stress factors, Pressure sores/wounds; pT, pN and pM stage, tumour, nodal and metastasis histopathological stage of disease according to TNM7 classification; MUST, Malnutrition Universal Screening Tool; ASA, American Society of Anesthesiologists score; Rad stage, radiological stage; Histology, histopathological cell type; HDU LOS, high dependency unit stay; Site, disease site (oesophagus, stomach).

2.7.7 Table 7. Multivariable analysis of factors influencing survival.

Backward Log Rank Cox Regression

Variable	HR	95% CI	p value
pT stage	5.276	1.414-19.685	0.013
ASA	0.112	0.015-0.854	0.035
ITU LOS	1.639	1.023-2.625	0.040

HR, hazard ratio; CI, confidence interval; pT stage, tumour histopathological stage of disease according to TNM7 classification; ASA, American Society of Anesthesiologists score; ITU LOS, intensive therapy unit stay.

2.7.8 Figure 1. Kaplan-Meier plot to demonstrate cumulative survival according to fat-free mass.
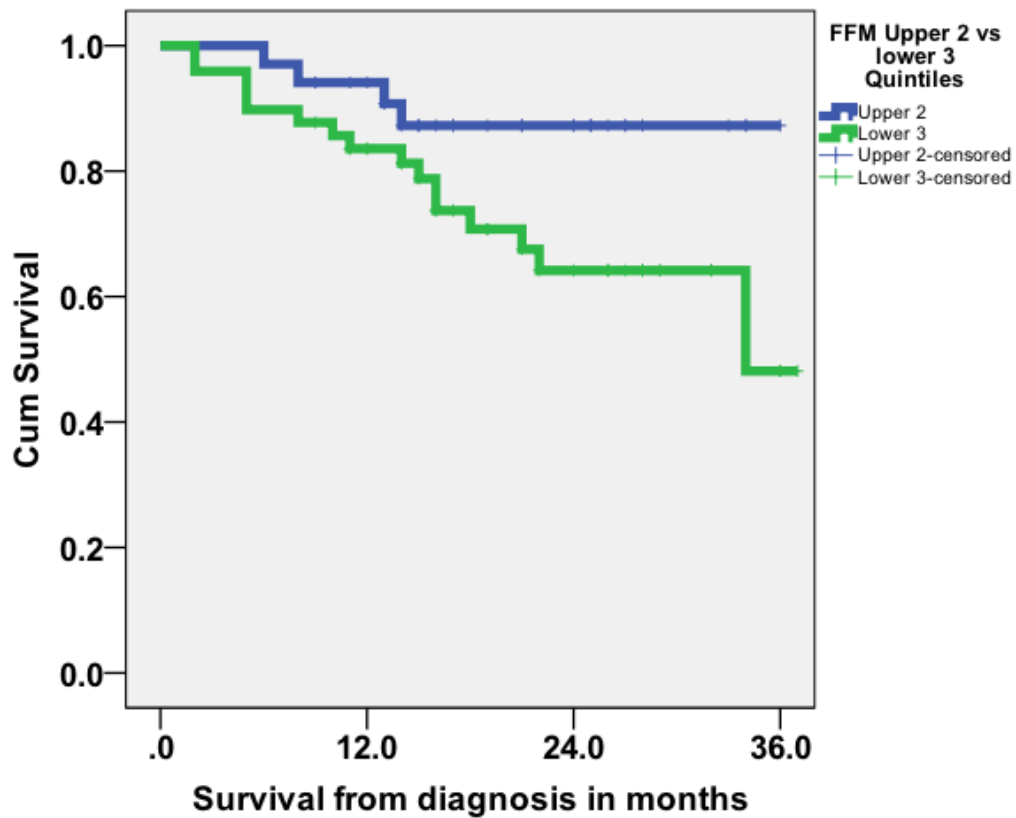
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	3.955	1	.047

Test of equality of survival distributions for the different levels of FFM Upper 2 vs lower 3 Quintiles.

2.7.9 Figure 2. Kaplan-Meier plot to demonstrate cumulative survival according to muscle mass.
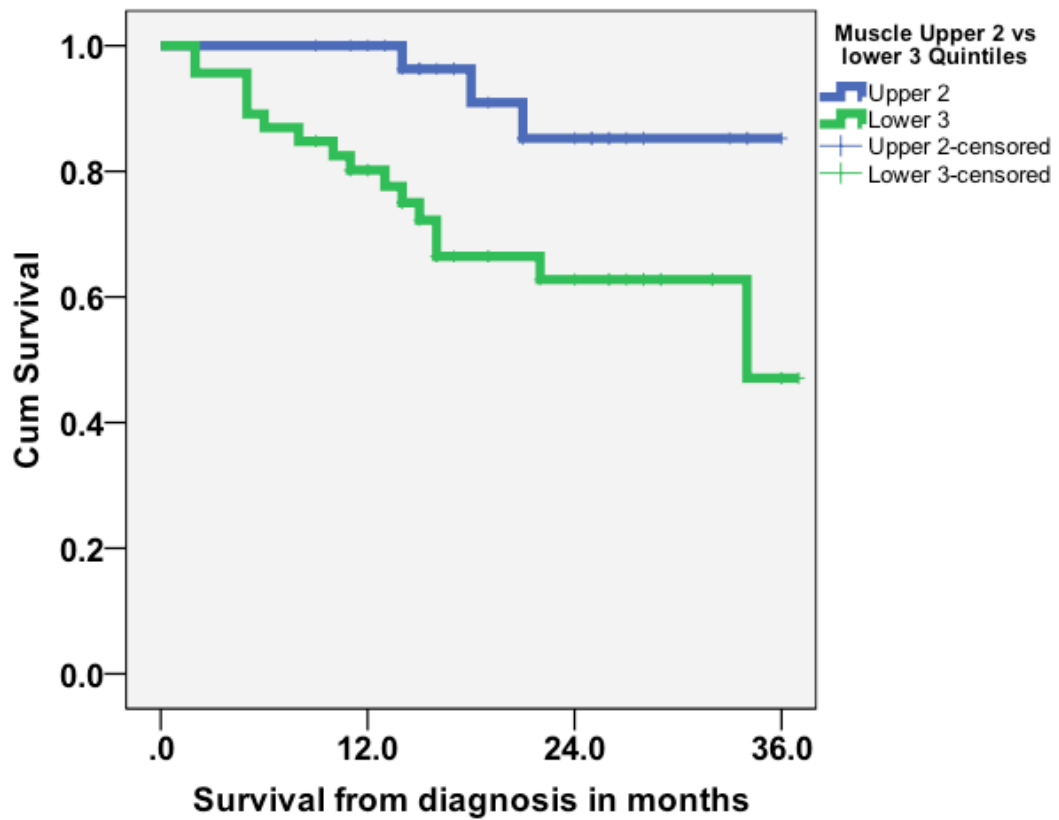
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	6.403	1	.011

Test of equality of survival distributions for the different levels of Muscle Upper 2 vs lower 3 Quintiles.

CHAPTER 3

CT-measured sarcopaenia predicts survival in upper gastrointestinal cancer

3.1 SUMMARY

The aim of this study was to determine the predictive value of computerised tomography (CT)-derived average psoas muscle density (PMD) with regard to outcomes following in oesophagogastric cancer resectional surgery.

The pre-operative staging CTs of 100 patients with oesophago-gastric cancer (49 GCA: 51 OCA, 74m), aged 66 (36-85) years, were assessed for left, right and max (the greater of the two) PMD in Hounsfield units (HU). Patients underwent surgical resection within the South East Wales Cancer Network between May 2009 and June 2011. The primary outcome measure was survival and secondary outcomes included major morbidity (Clavien-Dindo class ≥3), mortality and length of hospital stay (LOHS).

No statistically significant difference was identified in major morbidity (22% vs. 18%, p=0.617), 30-day mortality (4% vs. 2%, p=0.558) or LOHS (14 vs. 14 days, p=0.781) according to PMD (<median vs. ≥median). Multivariable analysis demonstrated maximum PMD (HR 1.897, 95% CI 1.175-3.062, p=0.009) and pathology TNM stage (HR 1.467, 95% CI 1.076-2.000, p=0.015) as significant and independent predictors of survival.

CT measures of PMD have emerged as novel, simple and readily available predictors of outcome in oesophagogastric surgery. Risk assessment for oesophagogastric cancer surgery may benefit from

incorporation of muscle density measures and further work should seek to determine whether specific predictive cut-off values exist.

3.2 INTRODUCTION

Oesophagogastric cancer is associated with a poor prognosis, owing to late onset of symptoms and consequent late presentation with advanced disease. Survival rates at five years have been quoted as 16% for oesophageal cancer and 24% for gastric cancer (Jemal et al., 2008). Surgery remains the mainstay of curative treatment, with chemoradiotherapeutic options having emerged as effective adjuncts, prolonging survival after major resectional surgery for oesophagogastric cancer (Cunningham et al., 2006, Macdonald et al., 2001, Sjoquist et al., 2011, van Hagen et al., 2012).

It has been clear for many decades that malnutrition is associated with poor outcomes after surgery (Studley, 2001, Shils, 2000). Patients with upper gastrointestinal cancer are especially likely to suffer from substantial weight loss (Martignoni et al., 2003) associated with cancer cachexia, with mechanical obstructive factors contributing to difficulties in maintaining adequate nutritional intake in many of these patients.

Malnutrition has been known to correlate positively with postoperative complications for over three decades (Smale et al., 1981, Meguid and Meguid, 1985) and in the modern era, the importance of nutrition in surgical patients has received rejuvenated attention (Sungurtekin et al.,

2004) alongside extensive work on multimodal optimisation of surgical care, pioneered by Henrik Kehlet (Kehlet, 1997). However, reports containing data on nutritional measures in oesophagogastric ERAS programmes are few (Jiang et al., 2007, Liu et al., 2010) and direct assessment of the influence on outcomes of reliable, reproducible measures of skeletal muscle mass or specific risk indices in this disease is lacking in the literature.

The TNM staging process (Sobin LH, 2009b) involves computerised tomographic (CT) imaging, including the abdomen. Numerous studies have utilised the psoas muscles in such imaging to determine skeletal muscle parameters (Englesbe et al., 2010, Englesbe et al., 2013, Englesbe et al., 2012, Sabel et al., 2011, Harbaugh et al., 2013, Lee et al., 2011b), demonstrating poor surgical outcomes in those deemed sarcopaenic. The density of psoas muscles is easily and precisely measured from CT images, using standard radiology programmes (Mourtzakis et al., 2008, MacDonald et al., 2011, Baracos et al., 2012).

The aim of this study, therefore, was to assess the clinical prognostic value of pre-operative CT-measured psoas muscle density in the management of patients diagnosed with potentially curable oesophagogastric cancer. The primary outcome measure was and cumulative survival in months from diagnosis. Secondary outcome measures included 30-day mortality and 30-day operative morbidity. A secondary study aim was to determine whether a statistically significant difference in PMD exists between genders. The setting was a UK regional cancer network serving a population of 1.4 million.

3.3 METHODS

Approval of the local ethics committee was obtained to prospectively collect and analyse data on the medical and surgical outcome and results of investigations of all patients considered for surgery for UGI cancer. The ethics committee did not require written informed consent from participating subjects.

3.3.1 Details of the patients

One hundred consecutive patients diagnosed with oesophagogastric cancer by the South East Wales Cancer Network Multi Disciplinary Team and undergoing surgical resection with curative intent were assessed for psoas muscle density.

3.3.2 CT analysis

Patients were diagnosed between May 2009 and June 2011 and underwent computerised tomography (CT) of the abdomen as part of their pre-operative staging. We employed a previously described technique (Lee et al., 2011a) for analysis of psoas muscle density, which has been widely used over recent years (Sabel et al., 2011, Englesbe et al., 2010, Harbaugh et al., 2013, Lee et al., 2011a, Englesbe et al., 2012, Lee et al., 2011b). In short, a single axial CT image at the upper border of the 4th lumbar vertebra was isolated for examination. This study differed from previous reports in that semi-automation, the process by which

software delineates the borders of the muscle, was not available. Each psoas muscle was delineated manually using IMPAX system (AGFA Healthcare, Belgium). The cross sectional area, perimeter and mean density of each delineated area were automatically calculated by the imaging package.

Where restaging CT was performed after chemoradiotherapy, the post-treatment scan was used. Data relating to the pre-operative status, operative procedure and outcome were collected prospectively.

3.3.3 Data collected

Data collected included age, gender, American Society of Anesthesiologists grade (ASA) (Anesthesiologists, 1963), Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) scores (Copeland et al., 1991), Welsh Index of Multiple Deprivation overall (WIMD) and health (H-WIMD) deprivation scores (2008), radiological and histopathological stage of disease (TNM7) (Sobin LH, 2009b), cancer site (oesophageal or gastric), 30-day mortality, operative morbidity related to the Clavien-Dindo grade (CD) (Dindo et al., 2004), length of hospital stay (LOHS) and cumulative survival.

3.3.4 Outcome measures

The primary outcome measure was cumulative survival in months from diagnosis. This was expressed in months, with the significance expressed using the log rank statistic. Secondary outcome measures included

LOHS, operative morbidity using the Clavien-Dindo classification (Dindo et al., 2004) and 30-day mortality.

3.3.5 Statistical analysis

Statistical analysis was performed using SPSS® (IBM® SPSS® Statistics v20.0.0.2, IBM Corporation, Armonk, New York, USA). Grouped data were expressed as median (range) and non-parametric analyses were used throughout. Two-tailed tests were used and statistical significance was determined as $p<0.05$. Categorical data were compared using the χ^2 test, except where groups contained counts of fewer than five, when Fisher's exact test (Fisher, 1922) was used. Grouped continuous data were compared using the Mann-Whitney U-test (Mann and Whitney, 1947). Univariable analysis of the predictive value of pre-operative factors for survival was performed using the Mantel-Cox log rank method (Kaplan and Meier, 1958). Multivariable analysis of factors significantly influencing LOHS was performed using the Cox regression analysis model (Cox, 1972).

3.3.6 Power

The size of the dataset was powered to detect a survival difference of 8 months, between groups split about the median PMD. This was calculated using the Altman method (Whitley and Ball, 2002), using the standard deviation from an earlier consecutive sample of 100 patients from the same unit. Alpha was set at 0.05 and a power of 80% was used and a group size of 90 was suggested.

3.4 RESULTS

3.4.1 Details of the patients

The median (range) maximum psoas muscle density was 48.7 (-5.5-72.1 Hounsfield Units) and additional psoas muscle measurements are shown in Table 1. Remaining details of the patients are shown in Table 2. Forty-nine patients were treated for gastric cancer and fifty-one for oesophageal cancer. Details of the surgery performed are shown in Table 3.

3.4.2 Survival

Cumulative survival at two years was 70% overall (70/100), 64% (32/50) in patients with PMD <median and 76% (38/50) in patients with PMD ≥median (X^2=1.714, p=0.190). By three years of follow-up cumulative survival was 38% (26/69) overall, 18% (6/33) in patients with PMD <median and 56% (20/36) in patients with PMD ≥median (X^2=10.241, p=0.001). Median follow-up (or time to death) overall was 37.5 (range 3-59) months; in patients with PMD <median, 30 months (range 3-55); and in patients with PMD ≥median, 42 months (range 5-59). Kaplan-Meier analysis demonstrated survival to be significantly longer in patients with PMD ≥median (X^2=0.046, p=0.046, Figure 1).

Univariable analysis demonstrated the maximum psoas measurement (max PMD), radiological TNM stage and pathological TNM stage to be significantly associated with cumulative survival (Table 4).

Multivariable analysis revealed max PMD as the strongest predictor of survival in this cohort, a greater psoas density predicting a longer survival (Table 5; HR 1.897, 95% CI 1.175-3.062, p=0.009). Pathology TNM stage also emerged as a significant and independent predictor of survival, more advanced disease predicting shorter survival (Table 5; p=0.032).

3.4.3 Operative Morbidity and Mortality

Major operative morbidity (CD ≥III) occurred in 20 patients (20%), including three deaths (3%). No statistically significant difference was observed in CD ≥III (11 vs. 9, p=0.617) or mortality (2 vs. 1, p=0.558) according to PMD < median or ≥median, respectively.

3.4.4 Length of Hospital Stay

The median (range) LOHS was 14 (2-72) days overall. No statistically significant differences were observed between PMD groups in LOHS, CC LOS, ITU LOS, or HDU LOS (p>0.05, Table 2).

3.4.5 Influence of gender on PMD

Gender did not significantly influence PMD within this cohort (p=0.418). However, statistically significant differences in both PM area and PM perimeter were identified between males and females (p<0.0001).

3.5 DISCUSSION:

This is the first study to report surgical outcomes of a contemporary cohort of oesophagogastric cancer patients in relation to radiological skeletal muscle density.

The principle finding was that max PMD was a significant and independent predictor of survival in patients undergoing oesophagogastric surgery for cancer, a high PMD associated with longer survival.

This study's strengths include prospective data collection for the maintenance of an accurate database for a consecutive series of patients through an established and experienced MDT, whose results are well audited and stand up to international comparison (Centre, 2010), all surgery performed by specialist surgeons. All psoas measurements were performed manually by a single author (AJB) and checked by a Consultant Radiologist co-author (SAR). This allowed confirmation of accuracy of methods and prevented inter-rater inconsistency of psoas delineation or axial slice level.

In contrast, there are several potential limitations to this study. No adjustment was applied to account for differences in stature or gender. However, the hypothesis that gender would not influence PMD was upheld within this cohort (p=0.418), while hypotheses that gender would not influence PM area or PM perimeter were rejected upon statistical

analysis (p<0.0001). This suggested that it was appropriate to use unadjusted PMD values, but not area or perimeter values.

This study explored just a single dimension of skeletal muscle, without a concurrent objective assessment of function. It may be useful to combine CT measured psoas muscle measurements with functional parameters such as hand-grip strength.

Cachexia is a complex condition associated with myriad pathological alterations in hormonal and other signaling axes, promoting a characteristic chronic systemic inflammatory response (Wigmore et al., 1997). Cachexia implicitly confers a pathological cause for the weight loss, weakness and general decline observed (Wigmore et al., 1997). In efforts to assess skeletal muscle aspects of malnutrition, the concept of sarcopaenia has been used. Definitions of sarcopaenia vary, but have in common their inherent reliance upon quantification of skeletal muscle parameters (Cherin, P., 2009, Janssen et al., Baumgartner et al., 1998), yet reference ranges for these measures of skeletal muscle have been slow to emerge.

Previous studies have shown a relationship between CT measures of psoas muscle and surgical outcomes. In a cohort of 163 patients undergoing liver transplant, mortality was significantly higher and survival shorter at one and three years in those with the smallest psoas area (Englesbe et al., 2010). In 262 patients undergoing elective abdominal aortic aneurysm repair, psoas muscle size reduced over time during follow-up and psoas area showed a significant association with

postoperative mortality (Lee et al., 2011a). Sarcopaenic patients from a cohort of 196 patients undergoing colorectal hepatic metastatectomy, had a lower survival rate than those with higher skeletal muscle mass on CT analysis (van Vledder et al., 2012).

Indeed, CT measures of skeletal muscle mass have been built into a risk prediction algorithm to determine the "morphometric age" according to various factors observed on their CT scan (Englesbe et al., 2013). Applied to a cohort of 1,370 patients who underwent major abdominal surgery in the USA, morphometric age was a stronger predictor of operative mortality than chronological age and more than half of the patients in the morphometrically 'oldest' 10% were neither comorbid nor advanced in chronological age (Englesbe et al., 2013). This suggests that morphometric age could contribute novel predictive value that extends beyond factors traditionally assessed by the parameters age and comorbidity.

The complex use of novel, simple risk predictors in this way exemplifies how future risk stratification may utilise readily available radiological imaging to new levels, with objective and precise measurements permitting the development of risk algorithms and perhaps leading to a more specific risk profile for the individual patient.

Further research should seek to provide useful reference ranges for, and examine the influence on outcomes of indices of sarcopaenia including those examined herein and various other CT, anthropometric and functional measures. With mounting evidence that muscle mass

influences outcomes following surgery, randomised clinical trials should be considered in order to determine the most appropriate treatment modality in patients identified as being sarcopaenic. Additionally, further work should seek to determine whether more specific predictive cut-off values exist.

3.5 CONCLUSION:

The findings of this study suggest that CT measured max PMD represents a novel, simple and readily available, independent predictor of survival following oesophagogastric surgery. Incorporation of muscle density measures in risk assessment may assist patients and clinicians in decision-making regarding therapeutic options in oesophagogastric cancer.

3.7 TABLES AND FIGURES

3.7.1 Table 1. Psoas muscle parameters

Variable	Left	Right	Maximum value
PMD (HU)	45.2 (-5.6-72.1)	47.3 (-16.4-67.4)	48.7 (-5.5-72.1)
PM area (mm^2)	1109.0 (434.7-1915)	1091.5 (527.2-1750)	1166.5 (527.2-1915.0)
PM perimeter (mm)	146.8 (96.9-202.0)	32.0 (106.5-183.3)	148.3 (106.5-202.0)

Values given as median (range). Maximum value = greater value from left and right psoas muscle measurements. PMD, psoas muscle density; HU, Hounsfield units; PM, psoas muscle.

3.7.2 Table 2. Details of the patients

Variable		All patients	Max PMD <median	>median	p-value
Operated (n)		100	50	50	-
Site (Oes:Gast)		51:49	25:25	26:24	0.841
Age (years)		65.5 (36-85)	67 (47-82)	64 (36-85)	0.158
Gender (male:female)		74:26	38:12	36:14	0.648
BMI (kg/m^2)		27 (15-50)	27 (20-37)	25 (15-30)	0.251
ASA	I	1	2	2	0.596§
	II	37	19	18	
	III	23	13	10	
	IV	2	2	0	
POSSUM	P morb	41.9 (14.6-81.0)	44.3 (19.5-81)	29.7 (14.6-75.6)	0.333
	P mort	2.1 (0.6-11.8)	2.2 (0.8-11.8)	1.9 (0.6-8.7)	0.357
	O mort	6.5 (0.7-27.7)	10.4 (3.6-23.2)	6.9 (0.7-27.7)	0.072
WIMD rank		878 (18-1890)	845 (18-1860)	948 (37-1890)	0.368
Health WIMD		735 (10-1885)	731 (10-1881)	764 (14-1885)	0.807
Rad stage	HGD	2	0	2	0.335§
	I	25	11	14	
	II	26	13	13	
	III	45	24	21	
	IVa	2	2	0	
pTNM stage	HGD	3	1	2	0.348§
	I	23	10	13	
	II	24	14	10	
	III	25	9	16	
	IV	7	5	2	
	No resection	18	11	7	
Operative morbidity (Clavien-Dindo class)	0	48	26	22	0.423
	I	5	3	2	
	II	22	12	10	
	III	6	3	3	
	IV	11	6	5	
(30-day mortality)	V	3	2	1	0.558
LOHS (days)	Total	14 (2-72)	14 (4-72)	14 (2-62)	0.781
	CC LOS	1 (0-70)	1 (0-70)	1 (0-36)	0.714
	ITU LOS	0 (0-70)	0 (0-70)	0 (0-32)	0.580
	HDU LOS	1 (0-13)	1 (0-13)	1 (0-11)	0.779

Legend for 3.7.2

Figures in parentheses are range. §, X^2 test across all groups within variable; ± some data unavailable for ASA grade; n, number; Oes, oesophagus; Gast, gastrectomy; BMI, body mass index; ASA, American Society of Anesthesiologists grade; POSSUM, physiological and operative severity score for the enumeration of mortality and morbidity (P – generic score; O – oesophageal score; Mort – mortality; morb - morbidity); WIMD, Welsh index of multiple deprivation rank; Health WIMD, health related WIMD rank; Rad stage, radiological stage according to TNM7 classification; HGD, high grade dysplasia; pTNM stage, TNM7 tumour, nodal, metastasis stage; LOHS, length of hospital stay; LOS, length of stay (CC, critical care unit; ITU, intensive therapy unit; HDU, high dependency unit).

3.7.3 Table 3. Surgical treatment

Operation	Intention to treat	Actual
STG	23	20
TG	26	17
THO	25	22
TTO	23	20
3SO	3	3
Open & close	-	16
Palliative bypass	-	2

STG, subtotal gastrectomy; TG, total gastrectomy; THO, trans-hiatal oesophagectomy; TTO, trans-thoracic oesophagectomy; TSO, three-stage oesophagectomy; Open & close, irresectable disease with no bypass; Palliative bypass, irresectable disease with bypass.

3.7.4 Table 4. Univariable analysis to determine factors influencing survival using the Mantel-Cox log rank method of Kaplan and Meier.

Variable	χ2	df	p value
Rad stage	14.807	2	0.001
Path stage	14.826	2	0.001
Max PMD median	3.979	1	0.046
Max PM perimeter median	2.619	1	0.106
Morbidity	2.049	1	0.152
P POSSUM morb quint	6.358	4	0.174
Right PMD median	1.611	1	0.204
Histology	2.189	2	0.335
ASA	0.855	1	0.355
P POSSUM mort quint	4.280	4	0.369
O Possum Mort quint	3.510	4	0.476
Site	0.478	1	0.490
Max PM area median	0.329	1	0.566
WIMD	2.464	4	0.651
Age	2.370	4	0.668
LOHS quintile	1.788	4	0.775
Left PMD median	0.036	1	0.850
Gender	0.019	1	0.889

χ^2, chi square value; df, degrees of freedom; Rad stage, radiological stage according to TNM7 classification; Path stage, histopathological stage of disease according to TNM7 classification; PMD, psoas muscle density (right, left or maximum from both right and left measurements); max PM perimeter, maximum psoas muscle perimeter; POSSUM, physiological and operative severity score for the enumeration of mortality and morbidity (P – generic score; O – oesophageal score; Mort, mortality; morb – morbidity); Histology, histopathological cell type (HGD, adenocarcinoma, squamous cell carcinoma); ASA, American Society of Anesthesiologists score; Site, disease site (oesophagus, stomach); WIMD, Welsh index of multiple deprivation rank; max PM area, maximum psoas muscle area; LOHS, length of hospital stay.

3.7.5 Table 5. Multivariable analysis of factors influencing cumulative survival.

Variable	Category	n	Mean survival	HR	95% CI	p value
Max PMD	>median	43	36.1 +/- 15.2	Reference group		0.009
	<median	39	28.6 +/-14.1	1.897	1.175-3.062	
Path Stage	III-IV	32	31.0 +/- 14.4	Reference group		0.032
	II	24	31.2 +/- 16.2	0.746	0.424-1.315	
	I	26	44.0 +/- 7.4	0.494	0.292-0.837	

HR – Hazard Ratio; 95% confidence interval; PMD, psoas muscle density (left or right measurements).

3.7.6 Figure 1. Kaplan-Meier plot demonstrating cumulative survival according to maximum PMD in patients undergoing surgery for oesophagogastric cancer.
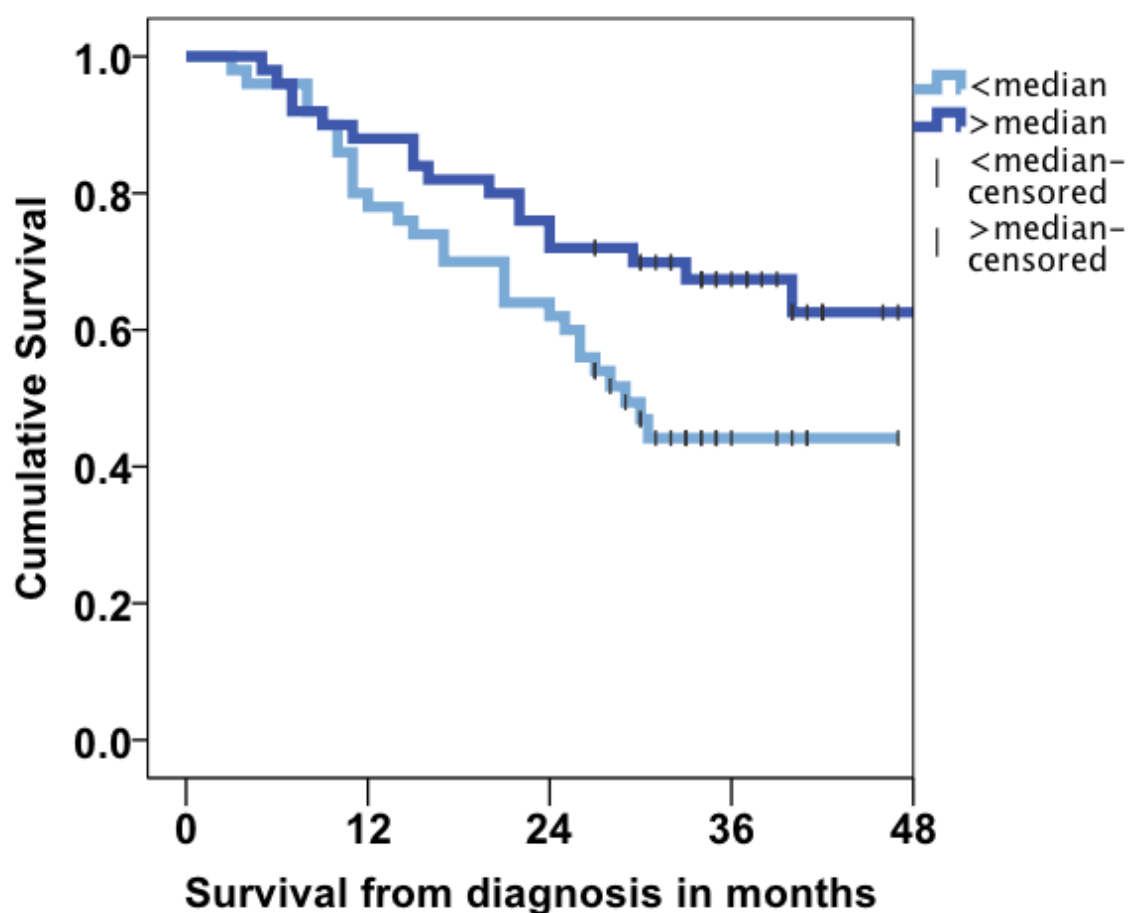
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	3.979	1	.046

Test of equality of survival distributions for the different levels of >median MaxAvHU.

CHAPTER 4

Prognostic value of cardiopulmonary exercise testing in gastric cancer surgery

4.1 SUMMARY

The aim of this study was to assess the predictive value of CPX in patients with gastric cancer related to outcome.

Seventy-four consecutive were assessed using CPX (median age 72 years; 55 male). Primary outcome measures were operative morbidity, length of hospital stay (LOHS) and survival.

Median (range) anaerobic threshold (AT), VO_{2peak} and VE/VCO_2 were 10.3ml/kg/min (5.5-15.5), 15.0ml/kg/min (7.6-27.3) and 32.0 (20.0-51.0) respectively. Five patients' treatment (6.8%) was altered because of CPX findings (mean AT = 7.0 ml/kg/min). Major operative morbidity (Clavien-Dindo ≥III) was associated with a greater VE/VCO_2 (median 37.0 vs. 32.0, p=0.049), but was unrelated to AT (p=0.116) and VCO_2 (p=0.627). Survival was significantly longer in patients with a VE/VCO_2 less than 34 (24 vs. 17 months, p=0.048).

CPX assessment of UGI cancer patients provided risk stratification, which predicted operative morbidity and survival. A number of patients' management was materially altered as a result of the CPX assessment. Further research to determine critical CPX predictive values is justified.

4.2 INTRODUCTION

4.2.1 Risk stratification

Risk stratification is an important component of contemporary anaesthetic and surgical practice, nowhere more so than in the arena of upper gastrointestinal (UGI) cancer surgery, which by its very nature carries significant inherent risk. Gastric cancer is the 15th most common malignancy in the UK with a decreasing incidence reported at 7.6 per 100,000 population in 2011 (CRUK, 2014), down from 8.4 per 100,000 population in 2008 (Newnham A, 2003, CRUK, 2012) and patients frequently present with advanced disease allied to significant cardiopulmonary operative morbidity.

4.2.2 Surgical risk

The Royal College of Surgeons of England has defined patients with a predicted hospital mortality of ≥5% as high-risk (Health., 2011) and UK National Audit figures report hospital mortality of 6.0% (95%CI 4.8-7.4) after gastrectomy (Centre, 2010). Subjective assessment underestimates operative risk (Findlay, 2011), and objective assessment of pre-operative physiological cardiopulmonary reserve by means of CPX can provide additional information in this regard (Simpson, 2009, Ridgway and Howell, 2010, Hennis et al., 2011, Moyes et al., 2013).

4.2.3 CPX testing

CPX combines an incremental exercise stress test with direct measurement of exercise respiratory gas exchange as well as electrocardiography and, as such, represents a simulation of the neurohumoral stress response to surgery. Figure 4.2.3 shows a patient undergoing CPX testing.

Figure 4.2.3. CPX testing equipment in use

The role of CPX in pulmonary thoracic surgery has been studied extensively (Benzo et al., 2007), and published UK guidelines have been available for over a decade (Society, 2001). Moreover, in major

abdominal surgery measurements of anaerobic threshold (AT), and peak oxygen uptake (VO_2 peak) have been reported to predict short (Epstein et al., 2004, Wilson et al., 2010) and mid-term mortality (Carlisle and Swart, 2007, Wilson et al., 2010), cardio-pulmonary related mortality (Older et al., 1993, Older et al., 1999), and length of hospital stay (LOHS) (Snowden et al., 2010).

Data regarding CPX in UGI cancer surgery, however, are scant by comparison, and existing reports are predominantly confined to oesophageal surgery (Nagamatsu et al., 1994, Nagamatsu et al., 2001, Forshaw et al., 2008). One recent study included gastric resections and reported a correlation between AT and the development of cardiopulmonary complications (Moyes et al., 2013).

4.2.4 Aims

The aim of this study, therefore, was to assess the clinical prognostic value of CPX in the risk stratification of patients diagnosed with potentially curable gastric cancer within the framework of an Enhanced Recovery After Surgery (ERAS) programme. The primary outcome measures were operative morbidity, LOHS in days, and survival in months from diagnosis. The setting was a UK regional cancer network serving a population of 1.4 million.

4.3 METHODS

Approval of the local ethics committee was obtained to prospectively collect and analyse data on the medical and surgical outcome and results of investigations of all patients considered for surgery for UGI cancer. The ethics committee did not require written informed consent from participating subjects.

4.3.1 Patient testing

Seventy-four consecutive patients diagnosed with gastric cancer by the South East Wales Cancer Network Multi Disciplinary Team and with initial curative intent to treat were referred for CPX testing between April 2009 and August 2013 as a component of pre-operative assessment. Analysis was performed on these 74 patients (table 1). The median (range) age was 72 (47-87) years and 55 (74%) were male.

4.3.2 Treatment

Treatment intent was curative in all patients at the time of referral for CPX and eventual treatment modality was surgical in 61 (82.4%), definitive chemoradiotherapy in 4 (5.4%) and palliative in 9 (12.2%) patients. Data relating to the pre-operative status, operative procedure and outcome were collected prospectively.

4.3.3 Data collected

The pre-operative assessment process was defined in this study as the process from diagnosis to either the time of anaesthesia for definitive surgery or a decision not to operate. This period included the completion of the radiological staging process. Data collected included age, gender, smoking history, American Society of Anesthesiologists grade (ASA) (Anesthesiologists, 1963), Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) scores (Copeland et al., 1991), Detsky score (Detsky et al., 1986), Revised Cardiac Risk Index (RCRI) (Lee et al., 1999), Welsh Index of Multiple Deprivation overall (WIMD) and health (H-WIMD) deprivation scores (2008), radiological and histopathological stage of disease (TNM7) (Sobin LH, 2009b), cancer site, 30-day mortality, operative morbidity related to the Clavien-Dindo grade (CD) (Dindo et al., 2004), critical care length of stay in days (CC LOS), LOHS and survival.

4.3.4 CPX testing

CPX fitness was measured at a single centre using the Medgraphics CPX Ultima^{TM} (Medical Graphics, St Paul, Minnesota, USA), with Breezesuite^{TM} and Welch Allyn® (*Welch Allyn,* Inc., NY, USA) software. Measurements of the ventilatory minute volume, oxygen consumption and carbon dioxide production were taken during standard cycle ergometry. Wasserman nine-panel plots (Wasserman, 2005) were used to derive AT, VO_2 peak, the ventilatory equivalent for carbon dioxide (VE/VCO_2).

4.3.5 Pre-operative planning

Multidisciplinary discussion and stratification of individual patient risk informed decisions regarding the planned post-operative level of care and invasive monitoring.

4.3.6 Outcome measures

Primary outcome measures were operative morbidity, related to Clavien-Dindo grade (Dindo et al., 2004), operative mortality, length of hospital stay (LOHS) in days and survival in months from date of diagnosis. A Clavien-Dindo grade of III or greater (CD ≥III) represents operative morbidity requiring therapeutic intervention beyond pharmacological treatment or superficial wound opening and was considered to represent major operative morbidity in this study. Secondary outcome measures included change in treatment modality as a result of CPX performance, change in post-operative level of care requirement prediction as a result of CPX performance, critical care related cancellation rates and critical care length of stay (CC LOS).

4.3.7 Statistical analysis

Statistical analysis was performed using SPSS® (IBM® SPSS® Statistics v20.0.0.2, IBM Corporation, Armonk, New York, USA). Grouped data were expressed as median (range) and non-parametric analyses were used throughout. Statistical significance was determined as p<0.05. Categorical data were compared using the χ^2 test, except where groups

contained counts of fewer than five, when Fisher's exact test (Fisher, 1922) was used. Grouped continuous data were compared using the Mann-Whitney U-test (Mann and Whitney, 1947). Spearman's rank correlation coefficient (Spearman, 1904) was used to determine correlation. Univariable analysis of the predictive value of pre-operative factors for LOHS was performed using the Mantel-Cox log rank method of Kaplan and Meier (Kaplan and Meier, 1958). This incorporated LOHS into the model in place of survival, using discharge from hospital as the event and resulting in the construction of LOHS plots. Multivariable analysis of factors significantly influencing LOHS was performed using the Cox regression analysis model (Cox, 1972). Survival analysis was conducted using the conventional method described by Kaplan and Meier (Kaplan and Meier, 1958).

4.4 RESULTS

4.4.1 CPX variables

Median (range) values for CPX variables are shown in Table 2. One patient was unable to record results because of intolerance of the exercise test.

4.4.2 Overall morbidity and LOHS

Of the 61 patients managed surgically, major operative morbidity (CD ≥III) occurred in 7 patients (11.5%), including two deaths (3.3%), and the median (range) LOHS was 11.0 (4-52) days.

4.4.3 Anaerobic threshold

Suboptimal AT (<11ml/kg/min), recorded in 49 (66.2%) patients, was associated with high ASA grade (≥III, 63% vs. 36%, p=0.026), but not operative morbidity, LOHS, CC LOS, age, BMI, other measured risk stratification scores (including POSSUM, Detsky, RCRI), cancer radiological stage or histopathological stage.

4.4.4 ASA grade

Poor AT (determined as <9ml/kg/min) was recorded in 22 (29.7%) patients and was associated with high ASA grade (≥III, 73% vs. 46%, p=0.036) alone.

ASA grade ≥III patients' CPX variables were suboptimal when compared with ASA grade I and II patients; lower AT (median 9.5 vs. 10.7 ml/kg/min, p=0.023) and lower VO_2peak (median 13.3 vs. 17.3 ml/kg/min, p=0.005). LOHS (median 14.0 vs. 11 days, p=0.018), but not CC LOS (median 1 vs. 1 days, p=0.083), was significantly longer in this comorbid group. Higher risk scores were also observed in patients with ASA ≥III: P-POSSUM morbidity (median 50.2 vs. 40.9%, p=0.002), P-POSSUM mortality (2.8 vs. 2.1%, p=0.003), and Detsky (5 vs. 5, p<0.0001).

4.4.5 Correlation with risk assessment tools

Significant correlation was identified between CPX variables and established risk assessment tools, with poor performance correlating with higher risk scores in each case. AT correlated with ASA (Rho -0.278, p=0.017). VO_2peak correlated with ASA (Rho -0.335, p= 0.004) and Detsky score (Rho -0.247, p=0.038). No correlation with POSSUM scores was identified.

4.4.6 Changes in treatment modality

Treatment modality was changed in the course of pre-operative assessment in 13 patients (17.6%), and directly as a result of CPX in 5 patients (6.8%). Within this subgroup of 5 patients, mean (range) AT was 7.0 (5.5-9.2) ml/kg/min, VO_2peak 9.9 (8.7-12.4) ml/kg/min and VE/VCO_2 36.8 (28.0-48.0). The eventual treatment modality was palliative in four patients and outpatient monitoring of high-grade dysplasia in the fifth patient.

4.4.7 Operative morbidity and mortality

Operative morbidity of CD grade ≥III was associated with a higher ASA grade (Rho=0.275, p=0.032) and greater VE/VCO_2 (median 37.0 vs 32.0, p=0.049), but not AT and VO_2 peak (p=0.116 and p=0.627 respectively). This was demonstrated by Receiver Operator Characteristic (ROC) analysis, performed for CPX variables (Figure 1).

Operative mortality did not correlate with any CPX variables: AT (rho=-0.084, p=0.518), VO_2 peak (rho=-0.177, p=0.179) or VE/VCO_2 (rho=0.209, p=0.113).

4.4.8 Length of hospital stay

Univariable analysis of factors influencing LOHS is shown in Table 5. Upon multivariable analysis, ASA grade and the operation type emerged as a significant and independent predictor of LOHS, but none of the examined CPX variables emerged as such.

4.4.9 Survival

Cumulative survival at two years was 63.6% (n=28/44) overall, 87.0% (20/23) in patients with VE/VCO_2 <34 and 38.1% (8/21) in patients with VE/VCO_2 ≥34 (p=0.001). Median follow-up (or time to death) overall was 28 months (range 0-46); in patients with VE/VCO_2 <34, 33 months (range 15-40); and in patients with VE/VCO_2 ≥34, 19 months (range 0-46). Cumulative survival was significantly longer in patients with a VE/VCO_2 <34 (24 vs. 17 months, p=0.048, Figure 2).

4.5 DISCUSSION

This study represents the largest contemporary cohort of gastric cancer patients undergoing CPX assessment and surgery, related to outcomes.

The principal findings were that a low VE/VCO_2 was predictive of major morbidity and associated with poor survival with a cut-off of 34. AT and VO_2 peak were not significantly associated with operative morbidity, mortality or survival. CPX variables also correlated significantly with established risk assessment tools including ASA grade and Detsky score. For over a decade a high VE/VCO_2 has been associated with poor outcome. As long as fifteen years ago, Older and colleagues reported using a VE/VCO_2 of >35 in criteria for admission to HDU following major abdominal surgery (Older et al., 1999). In 2002, a VE/VCO_2 of ≥34 was reported to be associated with a five-fold increase in risk of death in non-surgical patients with heart failure (Gitt et al., 2002). Since then, studies in surgery have specifically examined VE/VCO_2 as a predictor of operative morbidity and mortality, LOHS and survival.

In major abdominal surgical patients, Wilson and colleagues found that a VE/VCO_2 of ≥34 had 88% sensitivity and 47% specificity for in-hospital mortality (Wilson et al., 2010). In 108 patients undergoing major hepatic resection, Junejo and colleagues reported 47% sensitivity and 84% specificity for operative morbidity at a VE/VCO_2 of ≥34.5 (Junejo et al., 2012). A recent paper from West and colleagues demonstrated a higher ratio to be associated with increased risk of operative morbidity in colorectal cancer surgery, with a cut-off of 32.9 providing most predictive value. West and colleagues also reported VE/VCO_2 to be associated with prolonged LOHS (West et al., 2014). However, Hennis and colleagues reported that outcomes in 106 patients undergoing Roux-en-Y gastric bypass surgery for obesity were not predicted by VE/VCO_2 (Hennis et al.,

2012) and in upper GI cancer, previous studies have not reported outcomes related to VE/VCO_2 (Forshaw et al., 2008, Moyes et al., 2013, Nagamatsu et al., 2001).

Regarding AT, previous reports have identified critical prognostic values of 9 ml/kg/min in UGI cancer resection (Moyes et al., 2013), and 11 (Older et al., 1993, Older et al., 1999), 10.9 (Wilson et al., 2010) and 10.1 ml/kg/min (Snowden et al., 2010) in major abdominal surgery. In contrast, no critical prognostic value for AT was identified in the present study. An AT of less than 11 ml/kg/min has been shown to be associated with an operative mortality rate of 18% compared with a mortality rate of 0.8% in patients with an AT greater than 11ml/kg/min ($p<0.001$) in a study of 187 elderly patients undergoing major abdominal surgery such as abdominal aortic aneurysm resection or anterior resection of the rectum (Older et al., 1993, Older et al., 1999). These data were, however, published in 1993 and 1999 respectively and anaesthetic and surgical practice have since advanced. More recently, ATs below 10.9 ml/kg/min have been associated with an increased risk of mortality within 90 days, (RR 6.8%, 95% CI 1.6-29.5), an increased likelihood of high dependency care (457 patients with an AT of ≤10.9 ml/kg/min vs. 390 with an AT of ≥10.9 ml/kg/min, $p<0.001$) and an increased median length of hospital stay (9 vs. 8 days, $p<0.001$) following major abdominal surgery such as elective colorectal resection, radical nephrectomy or cystectomy (Wilson et al., 2010). Similarly, in a study of patients undergoing major elective procedures such as open aortic aneurysm repair, liver resections and pancreatic sarcoma surgery, AT was found to be higher (11.9 vs. 9.1

mL/kg/min, *p*=0.001) in patients who developed one or less post-operative complication and subsequent LOHS was also shorter (10 vs. 26 days, p<0.001) (Snowden et al., 2010). Recently, and within the context of UGI cancer resection, patients with cardiopulmonary operative morbidity were reported to have a significantly lower AT than those without cardiopulmonary operative morbidity (9.9 vs. 11.2 ml/kg/min, p=0.04) (Moyes et al., 2013). The authors reported that an AT below 9 ml/kg/min was associated with operative cardiopulmonary morbidity using ROC analysis (sensitivity=74%, specificity=57%, p=0.04). This paper reported outcomes on 180 patients assessed using CPX, 108 (60%) ultimately receiving surgical treatment, including 43 (40%) patients with gastric cancer (39 resected). The mean AT was greater than in the present study (10.8 vs. 10.3 ml/kg/min), arguably because of the absence of oesophageal patients herein.

The overall complication rate in the present study's cohort was comparable with that reported by Moyes et al. [15/39 (38.5%) vs. 19/61 (31.1%), p=0.451], as was the cardiopulmonary complication rate [5/39 (12.8%) vs. 9/61 (14.8%), p=0.786]. ROC analysis did not identify a critical predictive threshold for CPX variables for cardiopulmonary or all operative morbidity in our cohort, which was not explained by a significant difference in operative morbidity in comparison to the dataset reported by Moyes et al.

Early studies such as Older's (Older et al., 1999) used CPX to stratify post-operative care requirement, and it is this type of use that has proved of most interest to our Anaesthetic colleagues. Those patients whose

overall performance was suboptimal were highlighted as an 'at risk' group and provision made for a higher level of care in the immediate postoperative period. This was not necessarily reliant upon specific numeric values from the CPX tests, but based on the overall impression of the experienced clinician, acting as Anaesthetist and Exercise Physiologist, and was often a team decision. By introducing this method of risk stratification, those patients whose performance was satisfactory could be reasonable spared the requirement for a confirmed critical care bed to be available prior to surgery taking place, since they were unlikely to require higher level of care than level 1, which would take place on the specialist upper gastrointestinal surgical ward. In a climate of extreme critical care bed pressure, this offered an important solution to some of the psychologically, financially and potentially oncologically detrimental effects of cancelling of operations because of bed unavailability. The development of a reliable risk calculation tool or the incorporation of existing tools may help to formalize this process in future.

This study's strengths include prospective data collection of a consecutive series of patients through an established and experienced MDT whose results are well audited and stand up to international comparison (Centre, 2010), with all surgery performed by specialist surgeons. Moreover, the dataset consisted of a large consecutive series, minimising the risk of selection bias.

In contrast, there are several potential limitations to this study. Clearly this was not a randomised control trial and so no comparison group exists to confirm the impact of CPX on patient care. Although this study represents

the largest cohort of patients with gastric cancer undergoing CPX assessment to date, the numbers remain relatively small when sub-analysed. The possibility exists, therefore, that some critical CPX values have failed to emerge owing to the influence of selection bias, type II statistical error, or both.

4.6 CONCLUSION

In conclusion, CPX remains a relatively rare clinical commodity. Indeed, only 17% of NHS Trusts reported access to CPX testing as a risk assessment tool in 2008 (Simpson, 2009). The findings of this study suggest that significant thresholds of AT and VO_2 peak for prediction of outcomes may not exist. VE/VCO_2 was found to be of greater predictive value than other CPX variables in terms of major morbidity and survival. A VE/VCO_2 cut-off of 34 emerged as a significant predictor of survival a lower figure predicting longer survival. Furthermore, allied to other risk assessment tools in a multidisciplinary team environment, CPX provided benefits in risk stratification, informing and influencing decisions relating to the appropriate treatment modality and the optimum level of post-operative critical care required. A number of patients' management was materially altered as a result of the CPX assessment. Further research to determine additional critical predictive values and potential thresholds of specific individual CPX derived variables in patients diagnosed with upper GI cancer is justified.

4.7 TABLES AND FIGURES

4.7.1 Table 1. Details of the patients

Variable		n
n		74
Operated		61 (82%)
Age (range) in years		72.0 (47-87)
Gender (male:female)		55:19 (74:26%)
BMI (range)		27.0 (18-50)
ASA	I	1 (1%)
	II	33 (45%)
	III	39 (53%)
	IV	1 (1%)
POSSUM	P morbidity	45.5 (14.6-85.8)
	P mortality	2.4 (0.6-15.9)
	O mortality	13.6 (1.4-41.8)
Destky score		5 (0-30)
Lee RCRI		1 (1-3)
WIMD rank		860 (103-1893)
Health WIMD		764 (46-1880)
Rad stage	I	16 (22%)
	II	20 (27%)
	III	35 (47%)
	IVa	3 (4%)
Opertion type	TG	23 (43%)
	STG	20 (33%)
	THO	4 (7%)
	Open & close	14 (23%)

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Variable		**n**
pTNM stage	**HGD**	4 (7%)
	I	11 (18%)
	II	10 (16%)
	III	14 (23%)
	IV	8 (13%)
	No specimen resected	27 (44%)
Cardiopulmonary operative morbidity		9 (15%)
Operative morbidity (Clavien-Dindo score)	**0**	41 (67%)
	I	6 (10%)
	II	7 (11%)
	III	4 (7%)
	IV	1 (2%)
(30-day mortality)	**V**	2 (3%)

Percentages refer to the proportion of the whole cohort of 74 patients except for surgery, pTNM stage and morbidity classes. Figures are given as median (range) or number (percentage). n – number; BMI – body mass index; ASA – American Society of Anesthesiologists score; POSSUM - physiological and operative severity score for the enumeration of mortality and morbidity (P – generic score; O – oesophageal score; Mort – mortality; morb – morbidity); RCRI – revised cardiac risk index; WIMD – Welsh index of multiple deprivation score; Health WIMD – health related WIMD score; Rad stage – radiological stage; TG – total gastrectomy; STG – subtotal gastrectomy; THO – total hiatal oesophagectomy (oesophagogastrectomy); Open & Close – irresectable disease; pTNM stage – TNM7 tumour, nodal, metastasis stage; CPR – complete pathological response.

4.7.2 Table 2. CPX variables

Variable

AT (ml/min/kg)	10.3 (5.5-15.5)
VO$_2$peak (ml/min/kg)	15.0 (7.6-27.3)
VE/VCO$_2$	32.0 (20.0-51.0)

Values given as median (range). AT – anaerobic threshold; VO$_2$peak – peak oxygen uptake; VE/VCO$_2$ – ventilatory equivalent for carbon dioxide.

4.7.3 Table 3. Changes in treatment modality.

Primary reason for change	Eventual treatment	n (%)
CPX performance	Palliation	5 (6.8)
	All	*5 (6.8)*
Upstaged by laparoscopy or biopsy	dCRT	2 (2.7)
	Palliation	4 (5.4)
	All	*6 (8.1)*
Upstaged on CT	dCRT	2 (2.7)
	All	*2 (2.7)*
TOTAL		13 (17.6)

Percentages in parentheses refer to the proportion of the whole cohort of 74 patients. n – number; CPX – cardiopulmonary exercise testing; dCRT – definitive chemo-radiation therapy; CT – computerised tomography.

4.7.4 Table 4. Performance details of patients whose management was changed by CPX.

Patient	Rad stage	Age (years)	AT (ml/min/kg)	VO$_2$ peak (ml/min/kg)	VE/VCO$_2$
1	II	54	5.5	12.4	28.0
2	I	82	6.6	9.2	41.0
3	III	82	6.8	8.7	48.0
4	I	81	9.2	9.2	30.0
5	III	72	§	§	§
Mean		74	7.0	9.9	36.8

Rad stage – radiological stage; AT – anaerobic threshold; VO$_2$peak – peak oxygen uptake; VE/VCO$_2$ – ventilatory equivalent for carbon dioxide; § - performance so poor values unrecordable.

4.7.5 Table 5. Univariable analysis to determine influence of pre-operative assessment factors on length of hospital stay using the Mantel-Cox log rank method of Kaplan and Meier.

Variable	$\chi 2$	df	p-value
Radiology stage	19.436	3	<0.0001
Operation type	12.800	2	0.002
ASA	9.723	1	0.002
pT Stage	11.283	5	0.046
Detsky score	8.077	4	0.089
AT quartile	5.692	3	0.128
Health WIMD quintile	6.828	4	0.145
pM Stage	5.125	3	0.163
pN Stage	5.588	4	0.232
VE/VCO2 quartile	3.986	3	0.263
WIMD quintile	4.946	4	0.293
Gender	0.808	1	0.369
Age	2.863	4	0.581
POSSUM physiology score quartile	0815	3	0.846
VO2 peak quartile	0.655	3	0.884
Lee RCRI	0.231	2	0.891
P POSSUM morbidity quartile	0.577	3	0.902
O POSSUM mortality quartile	0.422	3	0.936
P POSSUM mortality quartile	0.229	3	0.973

χ^2 - chi square value; df – degrees of freedom; Rad stage – radiological TNM7 stage; Operation type – resection type according to anatomy; ASA – American Society of Anesthesiologists score; pT / pN / pM stage – TNM7 tumour / nodal / metastasis stage; Detsky - Detsky score; AT – anaerobic threshold; Health WIMD, health related depreivation score; VE/VCO$_2$ – ventilatory equivalent for carbon dioxide; WIMD – Welsh index of multiple deprivation rank; POSSUM - physiological and operative severity score for the enumeration of mortality and morbidity (P – generic score; O – oesophageal score; Mort – mortality; morb – morbidity); VO$_2$peak – peak oxygen uptake; Lee RCRI – revised cardiac risk index.

4.7.6 Table 6. Multivariable analysis of factors influencing length of hospital stay.

Variable	Category	n	Mean LOHS	HR	95% CI	p value
ASA	III-IV	19	15.9	Reference group		<0.0001
	I-II	28	10.5	4.414	1.982-9.832	
Operation type	TG	23	17.3	Reference group		<0.0001
	STG	19	10.0	0.210	0.102-0.434	

HR – Hazard Ratio; 95% confidence interval; ASA – American Society of Anesthesiologists score; Operation type – resection type according to anatomy; TG, total gastrectomy; STG, subtotal gastrectomy; Oes, oesophagogastric resection; Open & close, unresectable tumour - resection not completed.

4.7.7 FIGURE 1. Receiver Operator Characteristic (ROC) curves for CPX variables as predictors of operative morbidity.

The diagonal reference line indicates no discrimination. Probability values are shown for ROC analysis and Mann Whitney U (MWU) tests.
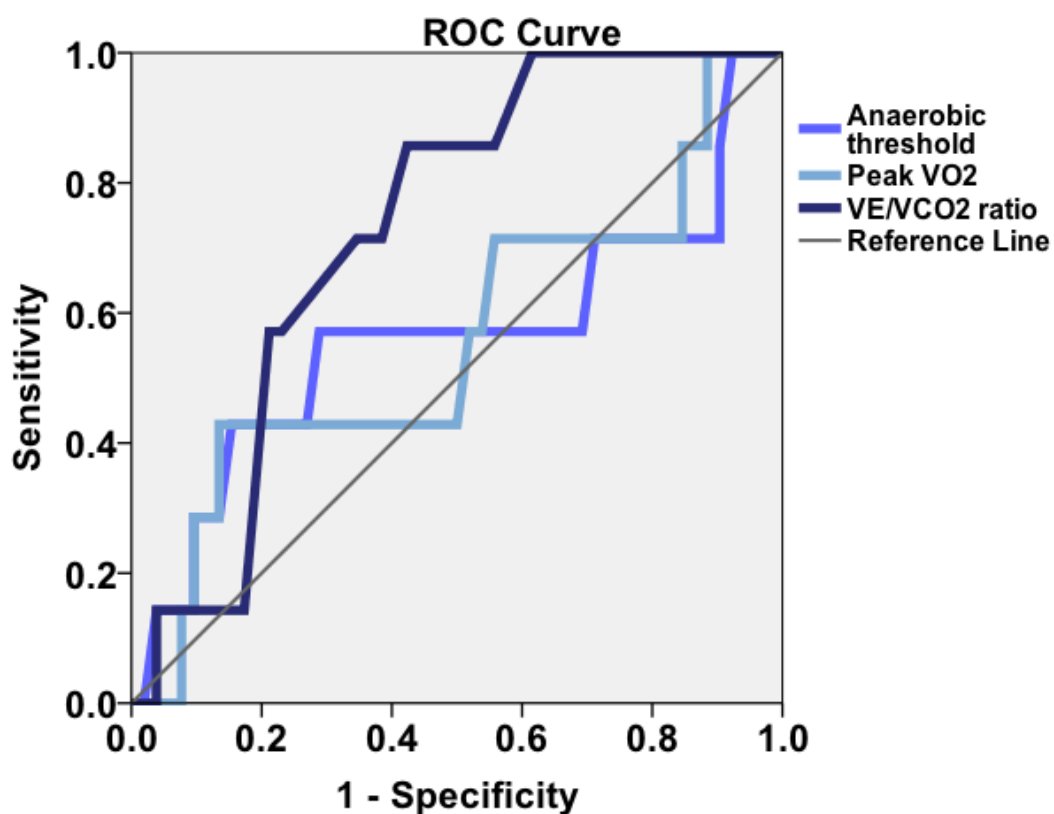
Diagonal segments are produced by ties.

Variable	AUC	95% CI	p value (ROC)	(MWU)
AT	0.562	0.287-0.837	0.598	0.587
VO$_2$ peak	0.558	0.308-0.808	0.623	0.638
VE/VCO$_2$	0.729	0.576-0.883	0.050	0.049

AUC, area under curve; 95% CI, 95% confidence interval; ROC, receiver operator characteristic; MWU, Mann-Whitney U statistic; AT, anaerobic threshold; VO$_2$peak – peak oxygen uptake; VE/VCO$_2$ – ventilatory equivalent for carbon dioxide.

4.7.8 FIGURE 2. Kaplan-Meier plot demonstrating cumulative survival according to VE/VCO$_2$ in patients undergoing CPX assessment for gastric cancer.
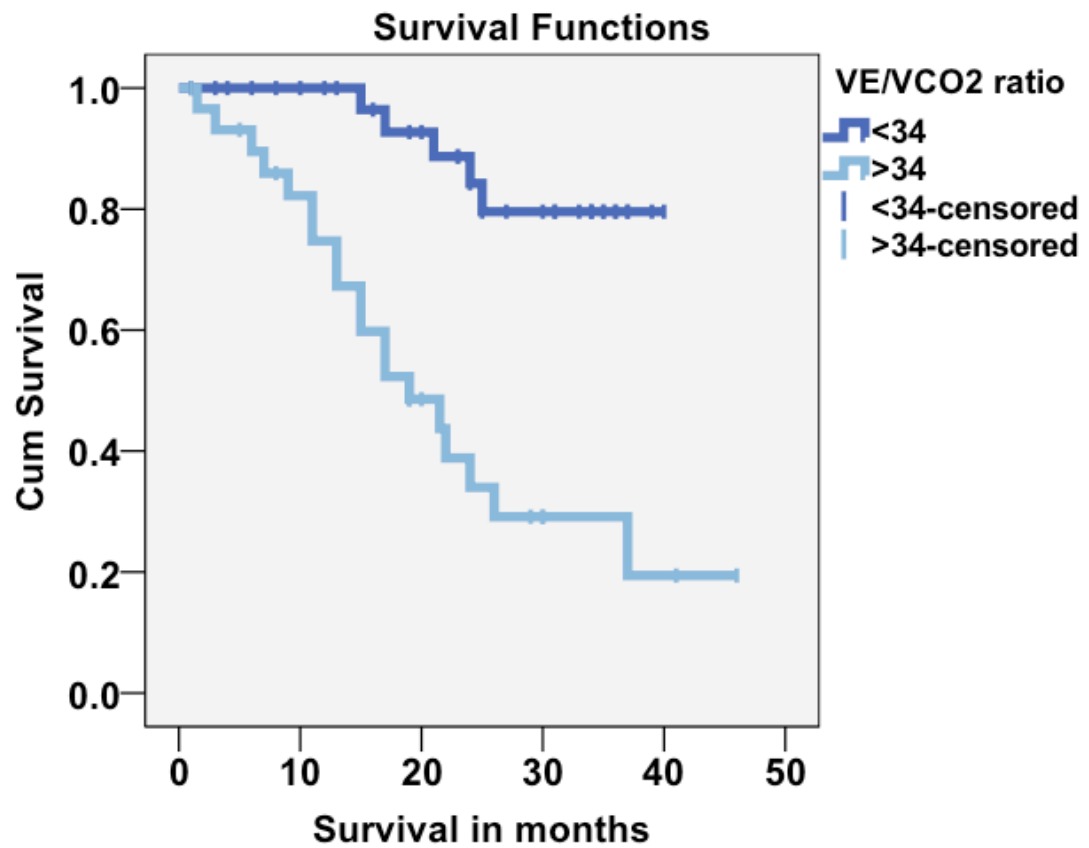
VE/VCO$_2$ – ventilatory equivalent for carbon dioxide.

p=0.047

CHAPTER 5

Prognostic value of cardiopulmonary exercise testing in oesophageal cancer surgery

5.1 SUMMARY

The aim of this chapter was to assess the predictive value of CPX in patients with oesophageal cancer related to outcome.

One hundred and twenty-three consecutive patients were assessed using CPX (median age 65 years; 101 male). Primary outcome measures were operative morbidity, length of hospital stay (LOHS) and survival.

Median (range) anaerobic threshold (AT), VO_2 peak and VE/VCO_2 were 11.2ml/kg/min (6.8-22.3), 18.8ml/kg/min (8.5-43.0) and 30.0 (11.0-48.0) respectively. Thirteen patients' treatment (10.6%) was altered because of CPX findings (median AT = 9.3 ml/kg/min). Major operative morbidity (Clavien-Dindo ≥III) was associated with a greater VE/VCO_2 (median 32.0 vs. 27.0, p=0.027) and lower VO_2 peak (median 17.1 vs. 20.1, p=0.012), but no significant difference in AT (11.1 vs. 11.2, p=0.437). ROC analysis confirmed this significant relationship for VE/VCO_2 (AUC 0.689, p=0.027) and VO_2 peak (AUC 0.271, p=0.012). Multivariate analysis revealed VO_2 peak to be an independent and significant predictor of LOHS (p=0.028) and survival was significantly longer in patients with a VO_2 peak greater than 22 ml/kg/min (18 vs. 16 months, p=0.037). Cumulative survival was significantly longer in patients with a VO_2 peak greater than 22 ml/kg/min. CPX assessment of patients with oesophageal cancer provided risk stratification, which predicted operative morbidity and survival. A number of patients' management was materially altered as a result of the CPX

assessment. Further research to determine critical CPX predictive values is justified.

5.2 INTRODUCTION

5.2.1 Risk stratification

Risk stratification is an important component of contemporary anaesthetic and surgical practice, nowhere more so than in the arena of upper gastrointestinal (UGI) cancer surgery, which by its very nature carries significant inherent risk. Oesophageal cancer is the 13th most common malignancy in the UK with an increasing incidence reported at 9.5 per 100,000 population (Newnham A, 2003, CRUK, 2012), and patients frequently present with advanced disease allied to significant cardiopulmonary operative morbidity.

5.2.2 Surgical risk

UK National Audit figures report hospital mortality at 3.8% (95%CI 3.1-4.7) after gastrectomy (Centre, 2010), approaching the Royal College of Surgeons of England definition of high-risk surgery ≥5% (Health., 2011). It has been shown that subjective assessment underestimates operative risk (Findlay, 2011), and that pre-operative objective assessment of physiological cardiopulmonary reserve using CPX can provide additional information in this regard (Simpson, 2009, Ridgway and Howell, 2010, Hennis et al., 2011, Moyes et al., 2013).

5.2.3 CPX testing

CPX provides direct measurement of exercise respiratory gas exchange with concurrent electrocardiography, during an incremental exercise stress test. As such, it represents a simulation of the neurohumoral stress response to surgery.

Following extensive study of the role of CPX in pulmonary thoracic surgery (Benzo et al., 2007), published UK guidelines have been available for over a decade (Society, 2001). Reports in major abdominal surgery have shown anaerobic threshold (AT), and peak oxygen uptake (VO_2 peak) measurements to predict short (Epstein et al., 2004, Wilson et al., 2010) and mid-term mortality (Carlisle and Swart, 2007, Wilson et al., 2010), cardio-pulmonary related mortality (Older et al., 1993, Older et al., 1999), and length of hospital stay (LOHS) (Snowden et al., 2010).

Studies examining CPX in oesophageal cancer surgery, however, are few in number. These have demonstrated significantly higher incidences of cardiopulmonary complications in patients with a poor VO_2 peak (Nagamatsu et al., 2001, Nagamatsu et al., 1994, Forshaw et al., 2008) and AT (Nagamatsu et al., 1994, Moyes et al., 2013).

5.2.4 Aims

The aim of this study, therefore, was to assess the clinical prognostic value of CPX in the risk stratification of patients diagnosed with potentially curable oesophageal cancer within the framework of an enhanced recovery after surgery (ERAS) programme. The primary

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outcome measures were operative morbidity, LOHS in days, and survival in months from diagnosis. The setting was a UK regional cancer network serving a population of 1.4 million.

5.3 METHODS

Approval of the local ethics committee was obtained to prospectively collect and analyse data on the medical and surgical outcome and results of investigations of all patients considered for surgery for UGI cancer. The ethics committee did not require written informed consent from participating subjects.

5.3.1 Patient testing

One hundred and twenty-three consecutive patients diagnosed with oesophageal cancer by the South East Wales Cancer Network Multi Disciplinary Team and referred for CPX testing with initial curative intent to treat between April 2008 and November 2013 were studied. Analysis was performed on these 123 patients (table 1). The median (range) age was 65 (35-86) years and 101 (82.1%) were male.

5.3.2 Treatment

Treatment intent was curative in all patients at the time of referral for CPX and eventual treatment modality was surgical in 78 (63.4%), definitive

chemoradiotherapy in 18 (14.6%), palliative in 24 (19.5%) and endoscopic mucosal resection in 3 (2.4%) patients. Data relating to the pre-operative status, operative procedure and outcome were collected prospectively.

5.3.3 Data collected

The pre-operative assessment process was defined in this study as the process from diagnosis to either the time of anaesthesia for definitive surgery or a decision not to operate. This period included the completion of the radiological staging process. Data collected included age, gender, smoking history, American Society of Anesthesiologists grade (ASA) (Anesthesiologists, 1963), Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) scores (Copeland et al., 1991), Welsh Index of Multiple Deprivation overall (WIMD) and health (H-WIMD) deprivation scores (2008), radiological and histopathological stage of disease (TNM7) (Sobin LH, 2009b), cancer site, 30-day mortality, operative morbidity related to the Clavien-Dindo grade (CD) (Dindo et al., 2004), critical care length of stay in days (CC LOS), LOHS and survival.

5.3.4 CPX testing

CPX fitness was measured at a single centre using the Medgraphics CPX Ultima™ (Medical Graphics, St Paul, Minnesota, USA), with Breezesuite™ and Welch Allyn® (Welch Allyn, Inc., NY, USA) software. Measurements of the ventilatory minute volume, oxygen consumption

and carbon dioxide production were taken during standard cycle ergometry. Wasserman nine-panel plots (Wasserman, 2005) were used to derive AT, VO_2 peak and the ventilatory equivalent for carbon dioxide (VE/VCO_2).

5.3.5 Pre-operative planning

Multidisciplinary discussion and stratification of individual patient risk informed decisions regarding the planned post-operative level of care and invasive monitoring.

5.3.6 Outcome measures

Primary outcome measures were operative morbidity, related to Clavien-Dindo grade (Dindo et al., 2004), operative mortality, length of hospital stay (LOHS) in days and survival in months from date of diagnosis. A Clavien-Dindo grade of III or greater (CD ≥III) represents operative morbidity requiring therapeutic intervention beyond pharmacological treatment or superficial wound opening and was considered to represent major operative morbidity in this study. Secondary outcome measures included change in treatment modality as a result of CPX performance, change in post-operative level of care requirement prediction as a result of CPX performance, critical care related cancellation rates and critical care length of stay (CC LOS).

5.3.7 Statistical analysis

Statistical analysis was performed using SPSS® (IBM® SPSS® Statistics v20.0.0.2, IBM Corporation, Armonk, New York, USA). Grouped data were expressed as median (range) and non-parametric analyses were used throughout. Statistical significance was determined as $p<0.05$. Categorical data were compared using the χ^2 test, except where groups contained counts of fewer than five, when Fisher's exact test (Fisher, 1922) was used. Grouped continuous data were compared using the Mann-Whitney U-test (Mann and Whitney, 1947). Spearman's rank correlation coefficient (Spearman, 1904) was used to determine correlation. Univariable analysis of the predictive value of pre-operative factors for LOHS was performed using the Mantel-Cox log rank method of Kaplan and Meier (Kaplan and Meier, 1958). This incorporated LOHS into the model in place of survival, using discharge from hospital as the event and resulting in the construction of LOHS plots. Multivariable analysis of factors significantly influencing LOHS was performed using the Cox regression analysis model (Cox, 1972). Survival analysis was conducted using the conventional method described by Kaplan and Meier (Kaplan and Meier, 1958).

5.4 RESULTS

5.4.1 CPX variables

Median (range) values for CPX variables are shown in Table 2. Two patients were unable to record results because of intolerance of the exercise test.

5.4.2 Overall morbidity and LOHS

Of the 78 patients managed surgically, major operative morbidity (CD ≥III) occurred in 13 patients (16.7%), including two deaths (2.6%), and the median (range) LOHS was 15.0 (4-62) days.

5.4.3 Anaerobic threshold

Suboptimal AT (<11ml/kg/min), recorded in 34 (44%) operated patients, was not associated with operative morbidity (p=0.751), LOHS (p=0.728), CC LOS (p=0.859), age (p=0.232), ASA grade (p=0.650), cancer radiological stage (p=0.742), or histopathological stage (p=0.188).

5.4.4 Changes in treatment modality

Treatment modality was changed in the course of pre-operative assessment in 45 patients (36.6%), and directly as a result of CPX in 13 patients (10.6%). Within this subgroup of 13 patients, median (range) AT was 9.3 (6.8-12.2) ml/kg/min, VO_2peak 11.8 (8.5-15.6) ml/kg/min and VE/VCO_2 36.0 (28.0-48.0). The reasons for changes and the eventual treatment modality are shown in Table 3.

5.4.5 Operative morbidity and mortality

Operative morbidity of CD grade ≥III was associated with a higher ASA grade (X^2=17.216, p=0.001), greater VE/VCO_2 (median 32.0 vs. 27.0, p=0.027) and lower VO_2 peak (median 17.1 vs. 20.1, p=0.012), but no significant difference in AT (11.1 vs. 11.2, p=0.437). This was demonstrated by Receiver Operator Characteristic (ROC) analysis, performed for CPX variables (Figure 1).

Operative mortality did not correlate with any CPX variable: AT (rho=-0.022, p=0.851), VO_2 peak (rho=-0.004, p=0.975) or VE/VCO_2 (rho=0.191, p=0.093).

5.4.6 Length of hospital stay

Univariable analysis of factors influencing LOHS is shown in Table 5. Upon multivariable analysis, VO_2 peak emerged as a significant and independent predictor of LOHS (Table 6, p=0.032).

5.4.7 Survival

Cumulative survival at one year was 87.8% (n=86/98) overall, 96.3% (26/27) in patients with VO_2 peak ≥22 ml/kg/min and 84.5% (60/71) in patients with VO_2 peak <22 ml/kg/min (p=0.101). Median follow-up (or time to death) overall was 17 months (range 1-63), 18 (5-40) months in patients with VO_2 peak ≥22 ml/kg/min and 16 (1-63) months in patients with VO_2 peak <22 ml/kg/min. Cumulative survival was significantly

longer in patients with a VO_2 peak ≥ 22 ml/kg/min (18 vs. 16 months, p=0.021, Figure 2).

5.5 DISCUSSION

This study represents the largest contemporary cohort of oesophageal cancer patients undergoing CPX assessment and surgery, related to outcomes. The principal findings were that a low VO_2 peak and a high VE/VCO_2 were associated with operative morbidity, and VO_2 peak was an independent and significant predictor of LOHS and predicted survival with a cut-off of 22 ml/kg/min. AT was not significantly associated with operative morbidity.

For over a decade a high VE/VCO_2 has been associated with poor outcome. As long as fifteen years ago, Older and colleagues reported using a VE/VCO_2 of >35 in criteria for admission to HDU following major abdominal surgery (Older et al., 1999). In 2002, a VE/VCO_2 of ≥ 34 was reported to be associated with a five-fold increase in risk of death in non-surgical patients with heart failure (Gitt et al., 2002). Since then, studies in surgery have specifically examined VE/VCO_2 as a predictor of operative morbidity and mortality, LOHS and survival.

In major abdominal surgical patients, Wilson and colleagues found that a VE/VCO_2 of ≥ 34 had 88% sensitivity and 47% specificity for in-hospital mortality (Wilson et al., 2010). In 108 patients undergoing major hepatic

resection, Junejo and colleagues reported 47% sensitivity and 84% specificity for operative morbidity at a VE/VCO_2 of ≥34.5. A recent paper from West and colleagues demonstrated a higher ratio to be associated with increased risk of operative morbidity in colorectal cancer surgery, with a cut-off of 32.9 providing most predictive value. This paper also reported VE/VCO_2 to be associated with prolonged LOHS (West et al., 2014). However, Hennis and colleagues reported that outcomes in 106 patients undergoing gastric bypass surgery were not predicted by VE/VCO_2 (Hennis et al., 2012) and in upper GI cancer, previous studies have not reported significant differences in outcomes related to VE/VCO_2 (Forshaw et al., 2008, Moyes et al., 2013, Nagamatsu et al., 2001, Nagamatsu et al., 1994).

Few studies have found a significant difference in outcome according to VO_2 peak. Groups in Japan and England have demonstrated a significantly lower VO_2 peak in patients with cardiopulmonary complications following oesophagectomy (Nagamatsu et al., 2001, Nagamatsu et al., 1994, Forshaw et al., 2008), but a more recent study, from an author of the English paper, did not replicate this finding in patients undergoing oesophagectomy in Glasgow (Moyes et al., 2013).

Regarding AT, previous reports have identified critical prognostic values of 9 ml/kg/min in UGI cancer resection (Moyes et al., 2013), and 11 (Older et al., 1993, Older et al., 1999), 10.9 (Wilson et al., 2010) and 10.1 ml/kg/min (Snowden et al., 2010) in major abdominal surgery. In contrast, no critical prognostic value for AT was identified in the present study. An AT of less than 11 ml/kg/min has been shown to be associated with an

operative mortality rate of 18% compared with a mortality rate of 0.8% in patients with an AT greater than 11ml/kg/min ($p<0.001$) in a study of 187 elderly patients undergoing major abdominal surgery such as abdominal aortic aneurysm resection or anterior resection of the rectum (Older et al., 1993, Older et al., 1999). These data were, however, published in 1993 and 1999 respectively and anaesthetic and surgical practice have since advanced. More recently, ATs below 10.9 ml/kg/min have been associated with an increased risk of mortality within 90 days, (RR 6.8%, 95% CI 1.6-29.5), an increased likelihood of high dependency care (457 patients with an AT of ≤10.9 ml/kg/min vs. 390 with an AT of ≥10.9 ml/kg/min, $p<0.001$) and an increased median length of hospital stay (9 vs. 8 days, $p<0.001$) following major abdominal surgery such as elective colorectal resection, radical nephrectomy or cystectomy (Wilson et al., 2010). Similarly, in a study of patients undergoing major elective procedures such as open aortic aneurysm repair, liver resections and pancreatic sarcoma surgery, AT was found to be higher (11.9 vs. 9.1 mL/kg/min, $p=0.001$) in patients who developed one or less post-operative complication and subsequent LOHS was also shorter (10 vs. 26 days, p<0.001) (Snowden et al., 2010). Recently, and within the context of UGI cancer resection, patients with cardiopulmonary operative morbidity were reported to have a significantly lower AT than those without cardiopulmonary operative morbidity (9.9 vs. 11.2 ml/kg/min, p=0.04) (Moyes et al., 2013). The authors reported that an AT below 9 ml/kg/min was associated with operative cardiopulmonary morbidity using ROC analysis (sensitivity=74%, specificity=57%, p=0.04). This paper

reported outcomes on 180 patients assessed using CPX, 108 (60%) ultimately receiving surgical treatment, including 65 (60%) patients with oesophageal cancer (64 resected). The mean AT was marginally lower than in the present study (10.8 vs. 11.2 ml/kg/min), arguably because of the absence of patients with gastric cancer herein.

The overall complication rate in the present study's cohort was slightly lower than that reported in this recent study (44/78 (56.4%) vs. 56/64 (87.5%), p=0.001), as was the cardiopulmonary complication rate (26/78 (33.3%) vs. 36/64 (56.3%), p=0.007).

Early studies such as Older's (Older et al., 1999) used CPX to stratify care requirement in the peri-operative period. Indeed this type of use has proved of particular interest to the medical team comprising surgical and anaesthetic specialists. Using the large volume of information yielded by the CPX test, as opposed to simply focusing on individual numeric values, allows the team to make overall judgements regarding anaesthetic approaches, monitoring requirements, goal-direction for fluid therapy, timing of extubation, and postoperative destination (ITU / HDU).

Those patients whose overall performance was suboptimal were highlighted as an 'at risk' group and provision made for a level three care (ITU), whereas those patients whose CPX performance was satisfactory could be given level two care (HDU) postoperativel and could often be extubated earlier and discharged from critical care directly to the specialist upper gastrointestinal surgical ward. Without relying upon specific numeric values from the CPX tests, this was based on the overall impression of the experienced clinician, acting as Anaesthetist and

Exercise Physiologist, and was often a team decision. In a climate of extreme critical care bed pressure, this offered an important solution to some of the psychologically, financially and potentially oncologically detrimental effects of cancelling of operations because of bed unavailability. The development of a reliable risk calculation tool or the incorporation of existing tools may help to formalize this process in future.

This study's strengths include prospective data collection of a consecutive series of patients through an established and experienced MDT whose results are well audited and stand up to international comparison (Centre, 2010), all surgery performed by specialist surgeons. Moreover, the dataset consisted of a large consecutive series, minimising the risk of selection bias.

In contrast, there are several potential limitations to this study. Clearly this was not a randomised control trial and so no comparison group exists to confirm the impact of CPX on patient care. Although this study represents the largest cohort of patients with oesophageal cancer undergoing CPX assessment to date, the numbers remain relatively small when sub-analysed. The possibility exists, therefore, that critical CPX values for some outcomes have failed to emerge owing to the influence of selection bias, type II statistical error, or both.

5.6 CONCLUSION

In conclusion, CPX remains a relatively rare clinical commodity. Indeed, only 17% of NHS Trusts reported access to CPX testing as a risk assessment tool in 2008 (Simpson, 2009). The findings of this study suggest that significant thresholds of AT for prediction of outcomes may not exist. VO_2 peak was found to be of greater predictive value than other CPX variables for operative morbidity, LOHS and survival. Multivariable analysis demonstrated VO_2 peak to be an independent, significant predictor of LOHS, and a cut-off of 22 ml/kg/min emerged as a significant predictor of survival. Furthermore, allied to other risk assessment tools in a multidisciplinary team environment, CPX provided benefits in risk stratification, informing and influencing decisions relating to the appropriate treatment modality and the optimum level of post-operative critical care required. A number of patients' management was materially altered as a result of the CPX assessment. Further research to determine additional critical predictive values and potential thresholds of specific individual CPX derived variables in patients diagnosed with oesophageal cancer is justified.

5.7 TABLES AND FIGURES

5.7.1 Table 1. Details of the patients

Variable		n
n		123
Operated		78 (63%)
Age (range) in years		65.0 (35-86)
Gender (male:female)		101:22 (82:18%)
ASA	**I**	5 (4%)
	II	35 (28%)
	III	18 (15%)
	IV	2 (2%)
	Unknown	63 (51%)
POSSUM	**P morbidity**	41.6 (20.9-74.8)
	P mortality	2.0 (0.8-7.3)
	O mortality	7.3 (1.6-23.5)
WIMD rank		1057 (5-1886)
Health WIMD		915 (4-1551)
Rad stage	**HGD**	4 (3%)
	I	39 (32%)
	II	31 (25%)
	III	37 (30%)
	IVa	12 (10%)
Operation type	**THO**	49 (63%)
	TTH	16 (21%)
	TSO	3 (38%)
	Salvage	1 (1%)
	Open & close	9 (12%)

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pTNM stage	HGD	2	(3%)
	I	20	(26%)
	II	21	(27%)
	III	22	(78%)
	IV	4	(5%)
	No specimen resected	9	(12%)
Cardiopulmonary operative morbidity (%)		26	(33%)
Operative morbidity (Clavien-Dindo score) (%)	**0**	34	(44%)
	I	5	(6%)
	II	26	(33%)
	III	7	(9%)
	IV	4	(5%)
(30-day mortality)	**V**	2	(2%)

Percentages refer to the proportion of the whole cohort of 74 patients except for surgery, pTNM stage and morbidity classes. Figures are given as median (range) or number (percentage). n – number; ASA – American Society of Anesthesiologists score; POSSUM - physiological and operative severity score for the enumeration of mortality and morbidity (P – generic score; O – oesophageal score; Mort – mortality; morb – morbidity); WIMD – Welsh index of multiple deprivation score; Health WIMD – health related WIMD score; Rad stage – radiological stage; THO – trans-hiatal oesophagectomy; TTO – trans-thoracic oesophagectomy; TSO – three-stage oesophagectomy; Salvage – salvage oesophagectomy; Open & close – irresectable disease; pTNM stage – TNM7 tumour, nodal, metastasis stage; CPR – complete pathological response.

5.7.2 Table 2. CPX variables

Variable

AT (ml/min/kg)	11.2 (6.8-22.3)
VO$_2$peak (ml/min/kg)	18.8 (8.5-43.0)
VE/VCO$_2$	30.0 (11.0-48.0)

Values given as median (range). AT – anaerobic threshold; VO$_2$peak – peak oxygen uptake; VE/VCO$_2$ – ventilatory equivalent for carbon dioxide; OUES – oxygen uptake efficiency slope.

5.7.3 Table 3. Changes in treatment modality.

Primary reason for change	Eventual treatment	n (%)
CPX performance	EMR	1 (0.8)
	dCRT	6 (4.9)
	Palliation	6 (4.9)
	All	*13 (10.6)*
Upstaged on CT	dCRT	5 (4.1)
	Palliation	5 (4.1)
	All	*10 (8.2)*
Upstaged on PET-CT	Palliation	6 (4.9)
	All	*6 (4.9)*
Upstaged on EUS	Palliation	1 (0.8)
	All	*1 (0.8)*
Upstaged by laparoscopy	Palliation	2 (1.6)
	All	*2 (1.6)*
Upstaged after NeoAdj	dCRT	2 (1.6)
	Palliation	1 (0.8)
	All	*3 (2.4)*
Suitable for EMR	EMR	2 (1.6)
	All	*2 (1.6)*
Patient choice	dCRT	5 (4.0)
	Palliation	3 (2.4)
	All	*8 (6.4)*
TOTAL		45 (36.6)

Percentages given as a proportion of all tested 123 individuals. n – number; CPX – cardiopulmonary exercise testing; EMR – endoscopic mucosal resection; dCRT – definitive chemo-radiation therapy; CT – computerised tomography.

5.7.4 Table 4. Performance details of patients whose management was changed by CPX.

Patient	Rad stage	Age (years)	AT (ml/min/kg)	VO$_2$ peak (ml/min/kg)	VE/VCO$_2$
1	4	74	6.8	8.5	41.0
2	1	79	7.0	11.0	29.0
3	1	79	8.3	10.5	35.0
4	3	60	8.8	11.0	45.0
5	3	51	8.8	12.4	28.0
6	2	73	9.1	10.5	34.0
7	2	69	9.5	13.4	36.0
8	2	67	9.7	11.8	30.0
9	1	73	10.8	14.2	48.0
10	2	71	10.8	§	§
11	2	71	11.7	15.6	38.0
12	3	59	12.2	14.9	36.0
13	2	86	§	§	§
Median	**2**	**71**	**9.3**	**11.8**	**36.0**

Rad stage – radiological stage; AT – anaerobic threshold; VO$_2$peak – peak oxygen uptake; VE/VCO$_2$ – ventilatory equivalent for carbon dioxide; § - performance so poor values unrecordable.

5.7.5 Table 5. Univariable analysis to determine influence of pre-operative assessment factors on length of hospital stay using the Mantel-Cox log rank method of Kaplan and Meier.

Variable	$\chi 2$	df	p value
Operation type	25.126	2	<0.0001
VO2 peak quartile	6.331	3	0.097
Age group	6.740	4	0.150
VE/VCO2 quartile	5.117	3	0.163
AT quartile	4.648	3	0.199
Radiology Stage	4.621	3	0.202
ASA	1.577	1	0.209
P POSSUM morbidity quartile	4.194	3	0.241
P POSSUM mortality quartile	3.059	3	0.383
Gender	0.462	1	0.497
WIMD quintile	3.298	4	0.509
O POSSUM mort quartile	1.608	3	0.658
Physiology score quartile	1.283	3	0.733
Health WIMD quintile	1.365	4	0.850

χ^2 - chi square value; df – degrees of freedom; VO_2peak – peak oxygen uptake; VE/VCO_2 – ventilatory equivalent for carbon dioxide; AT – anaerobic threshold; ASA – American Society of Anesthesiologists score; POSSUM - physiological and operative severity score for the enumeration of mortality and morbidity (P – generic score; O – oesophageal score; Mort – mortality; morb – morbidity); WIMD – Welsh index of multiple deprivation rank;

5.7.6 Table 6. Multivariable analysis of factors influencing length of hospital stay.

Variable	Category	n	Mean LOHS	HR	95% CI	p value
VO$_2$peak	Lower	9	28.7	Reference group		0.032
(Quartile)	Lower middle	24	17.6	2.236	0.925-5.407	
	Upper middle	19	16.2	3.752	1.504-9.359	
	Upper	24	16.9	2.957	1.202-7.278	
Operation type	Transhiatal	49	19.2	Reference group		<0.0001
(Oesophagectomy)	TTO / 3SO	19	18.9	0.912	0.515-1.646	
	Open & close	8	9.5	6.711	2.902-15.518	

HR – Hazard Ratio; 95% confidence interval; VO$_2$peak, peak oxygen uptake; TTO, transthoracic oesophagectomy; 3SO, three-stage oesophagectomy; Open & close, no resection performed.

5.7.7 Figure 1. Receiver Operator Characteristic (ROC) curves for CPX variables as predictors of major morbidity.

The diagonal reference line indicates no discrimination. Probability values are shown for ROC analysis and Mann Whitney U (MWU) tests.

Diagonal segments are produced by ties.
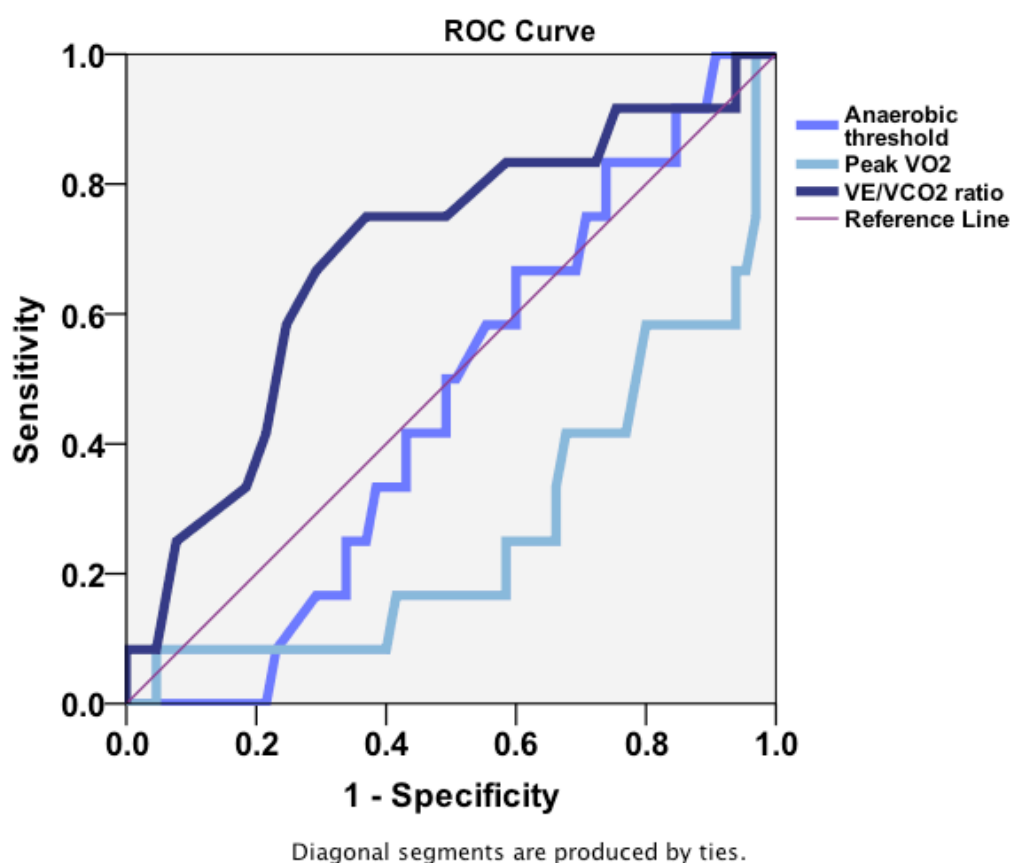
Variable	AUC	95% CI	p value (ROC)	(MWU)
AT	0.689	0.313-0.614	0.463	0.437
VO₂ peak	0.271	0.107-0.436	0.012	0.012
VE/VCO₂	0.689	0.520-0.858	0.038	0.027

AUC, area under curve; 95% CI, 95% confidence interval; AT, anaerobic threshold; VO$_2$peak – peak oxygen uptake; VE/VCO$_2$ – ventilatory equivalent for carbon dioxide.

5.7.8 Figure 2. Kaplan-Meier plot demonstrating cumulative survival according to VO$_2$peak in patients undergoing CPX assessment for oesophageal cancer.
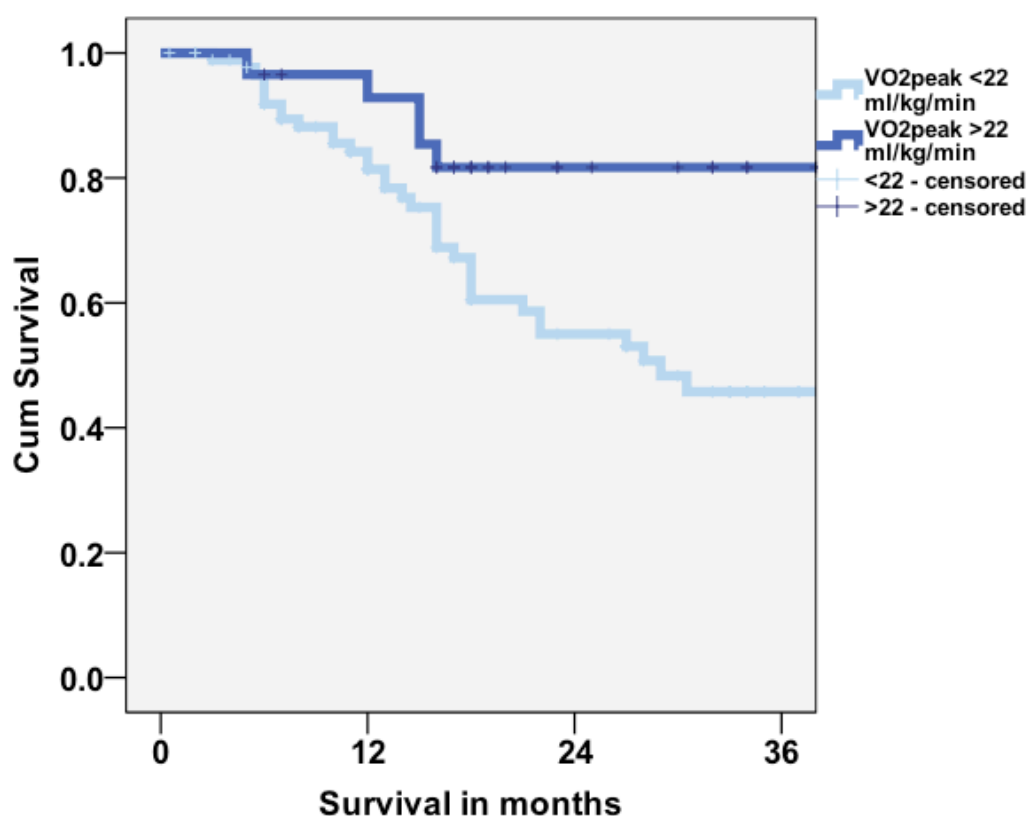
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	5.298	1	.021

Test of equality of survival distributions for the different levels of VO2 >22.

CHAPTER 6

Systematic review and meta-analysis of enhanced recovery programmes in gastric cancer surgery

6.1 SUMMARY

This chapter constitutes a systematic review and meta-analysis, performed to determine the influence of enhanced recovery programmes (ERPs) on outcomes after gastric cancer surgery. Medline, Embase, the Cochrane library and ClinicalTrials.gov were searched for studies on outcomes of gastrectomy in enhanced recovery or fast-track programmes. The primary outcome measure was post-operative length of hospital stay (LOHS), and secondary outcome measures were selected based on inclusion in two or more studies. Statistical analysis was performed using standardised mean difference (SMD) and odds ratio (OR) as the summary statistics.

Thirteen studies, including nine randomised trials, totaling 1629 patients with gastric cancer were analysed. LOHS was significantly shorter after ERP when compared with control patients (CON, SMD -1.02, 95% confidence interval -1.47 to -0.56, p<0.001), but with significant heterogeneity between studies (I^2=93%, p<0.001). ERP was also associated with reduced serum inflammatory response (CRP: SMD -0.56, 95% CI -1.09 to -0.03, p=0.04; IL-6: SMD -0.62, 95% CI -0.94 to -0.29, p<0.001), less weight loss (SMD -0.79, 95% CI -1.11 to -0.46, p<0.001), and lower cost (SMD -1.02, 95% CI -1.59 to -0.45, p<0.001), as well as a trend toward shorter duration of intravenous infusion (SMD -2.70, 95% CI -5.35 to -0.05, p=0.05). Inclusion in an ERP was not associated with increased post-operative morbidity (OR 0.82, 95% CI 0.64 to 1.05,

p=0.12) or hospital readmission (OR 1.61, 95% CI 0.83 to 3.12, p=0.16). In conclusion, multimodal, standardised perioperative gastrectomy care appears feasible, safe and cost effective.

6.2 INTRODUCTION

Enhanced recovery programmes (ERPs) have long been embedded within colorectal cancer surgical care and have been beneficial in reducing post-operative morbidity and lengths of hospital stay (LOHS) (Varadhan et al., 2010). In contrast, ERPs in upper gastrointestinal (UGI) cancer surgery are less developed. Reports regarding ERPs in gastric cancer surgery are few, with modest sample sizes and widely variable quality (He, 2010, Jeong et al., 2011, Jiang et al., 2007, Kiyama et al., 2003, Liu et al., 2010, So et al., 2008, Tang, 2013, Wang et al., 2010, Yamada et al., 2012, Feng et al., 2013, Chen Hu et al., 2012, Kim et al., 2012). Two existing meta-analyses of multimodal peri-gastrectomy ERPs have failed to include all available data from the literature, one pooling data from six studies (n=400) (Yu et al., 2014) and the other pooling data from just four studies (n=218) (Chen Hu et al., 2012) for meta-analysis. The populations studied in these previous meta-analyses have been predominantly Eastern Asian, most arising from China and Japan.

Gastric cancer surgery is pervaded by several controversies including the relative benefit of neoadjuvant and adjuvant chemotherapy, operative

approach (laparoscopic vs. open), the level of the lymphadenectomy and the benefit of early enteral nutrition, all of which may materially influence outcome (Nygren et al., 2003, Weimann et al., 2006, Centre, 2010, Liberati et al., 2009). Gastric cancer surgery in particular, is frequently performed in malnourished patients (Nygren et al., 2009), which, if severe, may be associated with a higher incidence of post-operative complications, which can in turn impede recovery (Weimann et al., 2006). Indeed, the UK National Audit reported post-operative morbidity of 19.4 per cent and in-hospital mortality of 6.0 per cent (95% CI 4.8-7.4) in patients undergoing gastrectomy for cancer (Centre, 2010). Consequently there may have been a relative reluctance to introduce an UGI specific ERP, certainly in the West, because of perceived risks related to the potential for adverse early post-operative outcomes.

The aim of this systematic review and meta-analysis was, therefore, to evaluate all existing available evidence regarding the implementation of an ERP in surgery for gastric cancer.

6.3 METHODS

6.3.1 Data sources, search methods and selection criteria.

A systematic review of published work was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (*Fig. 1).* (Liberati et al., 2009) Sources searched

were: MEDLINE via Ovid (January 1966 to April 2014), Embase (no date restriction), the Cochrane Library database (Cochrane Central Register of Controlled Trials; no date restriction) and World Health Organization International Clinical Trials Registry Platform (ICTRP; no date restriction) for studies reporting outcomes after gastrectomy in an enhanced recovery programme.

No limitation was placed on language or publication type, but non-English language studies without extractable data were excluded. Relevant studies were identified using the MeSH subject headings gastric cancer and surgery. These results were combined with MeSH terms; perioperative care, multimodal treatment, early ambulation, length of stay, morbidity, mortality, hospital readmission, and the additional non-MeSH terms enhanced recovery, ERAS and fast-track. Variants such as stomach and gastrectomy were also accommodated in the literature search. The ClinicalTrials.gov website was also searched for randomised controlled trials (RCTs) involving enhanced recovery in gastric cancer surgery. Further articles were identified by hand searching of references and using the PubMed related articles function. The related article results were cross-referenced with full results from previous searches. The last search date was April 1st, 2014. Outcome events were identified for inclusion if they were reported in an extractable form in two or more studies. The review search algorithm is shown in Table 6.

6.3.2 Data extraction

Data were extracted independently by two authors (AJB and DSYC). The

following details were extracted from each study: first author, year of publication, study design (randomised, comparison, case series, prospective or retrospective), number of participants in each group (ERP and Control), inclusion criteria, details of pathways, quality of study and outcome events.

6.3.3 Inclusion and exclusion criteria

Studies reporting outcomes in patients undergoing gastrectomy for cancer within a multimodal pathway or enhanced recovery programme were included. Studies from which it was not possible to extract data from the published reports available from the British Library, and studies reporting outcomes of single interventions were excluded.

6.3.4 Outcome measures

The primary outcome was defined as LOHS in days. Secondary outcome measures were incidence of post-operative morbidity and mortality, rates of readmission to hospital, inflammatory response [day 1 serum C-reactive protein (CRP), interleukin 6 (IL-6), tumour necrosis factor alpha (TNFα)], maximum post-operative pain score using a visual analogue scale (VAS), time to return of gut function, duration of intravenous fluid therapy (IVI), total cost, and post-operative weight loss. The construction of the ERP and the evidence underpinning individual elements therein were outside the remit of this study and were not addressed in this review.

6.3.5 Statistical analysis

The meta-analysis was performed in line with the recommendations of the Cochrane Collaboration (Higgins, 2010) and the PRISMA guidelines (Liberati et al., 2009). Analysis was performed using Review Manager 5.1.7 (The Nordic Cochrane Centre, Copenhagen, Denmark). Statistical analysis was performed using standardized mean difference (SMD) as the summary statistic for continuous variables and odds ratio (OR) for dichotomous variables. The SMD is the number of standard deviations' difference of the intervention, as a dimensionless form of the actual findings (Higgins, 2010). A random effects model was used when the I^2 value was greater than 50 per cent and a fixed effects model was used when it was less than 50 per cent. Results were reported with 95 per cent confidence intervals (95% CI). Where values for mean and standard deviation were not available, these were imputed from the median and range using methods described by Hozo *et al*., (2005) as appropriate to sample size. This involved using the median as a surrogate for mean. Where sample size was greater than 70, SD was imputed as range/6 and where sample size was 15-69, SD was calculated as range/4. Where the interquartile range (IQR) was given, ranges were estimated as the median +/- IQR.

6.3.6. Assessment of bias

Randomised studies were examined for quality according to risk-of bias tables from the Cochrane Handbook (Higgins, 2010), across domains of selection, performance, detection, attrition, reporting, and other bias.

Studies achieving a score of four or more from a maximum of seven were considered to be of higher quality. Non-randomised studies were examined for quality using the Newcastle–Ottawa scale (Higgins, 2010) across domains of patient selection methods, comparability of study groups and assessment of outcome. Studies achieving seven or more stars from a maximum of nine were considered to be of higher quality. Sensitivity analysis was performed for outcomes combining five or more studies. This was performed on two subgroups: i. studies assessed as higher quality; ii. randomised studies alone. The I^2 test was reported for each analysis. Bias was assessed using funnel plots (Egger and Smith, 1998), with asymmetry implying that results were subject to reporting or publication bias between studies and symmetry implying non-bias. Studies containing zero events in both arms were excluded from meta-analysis.

6.4 RESULTS

6.4.1 Included studies

Thirteen studies, published between 2004 and 2014, were analysed (*Table 1*) (He, 2010, Jeong et al., 2011, Jiang et al., 2007, Kiyama et al., 2003, Liu et al., 2010, So et al., 2008, Tang, 2013, Wang et al., 2010, Yamada et al., 2012, Feng et al., 2013, Chen Hu et al., 2012, Kim et al., 2012) comprising a total of 1,629 (726 ERP and 903 control) patients.

One report (Chen Hu et al., 2012) incorporated four arms to the trial and reported data on laparoscopic and open procedures separately and so is considered in this meta-analysis as two separate studies. Another report, (He, 2010) for which only an abstract was available, was deemed by the authors to contain sufficient data for inclusion, although the study quality could not be assessed formally and so was assumed to be poor. Where data was unavailable or means and standard deviations were not stated, further data was sought from corresponding authors by e-mail. Three corresponding authors supplied supplementary data for analysis (Jeong et al., 2011, Jiang et al., 2007, Yamada et al., 2012).

6.4.2 Characteristics of the included studies

The characteristics of the included studies are shown in *Table 1,* and the details of the main features of the pathways are given in *Table 4*. Nine studies were randomised trials (He, 2010, Jiang et al., 2007, Kiyama et al., 2003, Liu et al., 2010, Wang et al., 2010, Feng et al., 2013, Chen Hu et al., 2012, Kim et al., 2012), and the remaining four were cohort studies (Jeong et al., 2011, So et al., 2008, Tang, 2013, Yamada et al., 2012), of which three compared prospectively collected ERP and control data (So et al., 2008, Tang, 2013, Yamada et al., 2012), and the fourth compared prospectively collected ERP data with retrospectively collected control data (Jeong et al., 2011).

6.4.3 Study Quality

Using the Newcastle-Ottawa scale (Higgins, 2010), cohort studies were assessed for potential bias (*Table 2*). From a maximum of nine stars, two studies achieved 7 stars and were deemed high quality (Tang, 2013, Yamada et al., 2012). The remaining two studies scored 5 and 6 stars respectively (Jeong et al., 2011, So et al., 2008). Risk of bias assessment for randomised trials is shown in *Table 3*. Blinding was the most consistent risk of bias among randomised trials and, since this type of surgical study is not readily amenable to blinding, it was predictable that none of the trials were double blinded. The unavailability of full and/or English language manuscripts was another potential source of bias, reflected by the low scores of three studies (He, 2010, Jiang et al., 2007, Kiyama et al., 2003).

6.4.4 Primary outcome measure

Twelve studies reported LOHS (He, 2010, Jeong et al., 2011, Jiang et al., 2007, Kiyama et al., 2003, Liu et al., 2010, Tang, 2013, Wang et al., 2010, Yamada et al., 2012, Feng et al., 2013, Chen Hu et al., 2012, Kim et al., 2012). Nine of these reported significantly lower LOHS in the ERP patients (He, 2010, Jiang et al., 2007, Kiyama et al., 2003, Liu et al., 2010, Tang, 2013, Wang et al., 2010, Feng et al., 2013, Kim et al., 2012) and three reported no significant difference (Yamada et al., 2012, Jeong et al., 2011, Chen Hu et al., 2012). A significantly shorter LOHS was demonstrated in ERP patients in the overall analysis [SMD -1.02, (-1.47 to -0.56), p<0.001, *Fig. 2, Table 1*]. There was significant heterogeneity

between the studies (I^2= 93 per cent, p<0.001). Sensitivity analysis also demonstrated a significant difference in LOHS between the nine randomised trials (He, 2010, Jiang et al., 2007, Kiyama et al., 2003, Liu et al., 2010, Wang et al., 2010, Feng et al., 2013, Chen Hu et al., 2012, Kim et al., 2012), which showed a significantly shorter LOHS in ERP patients [SMD -1.27 (-1.77 to -0.77), p<0.001, *Fig. 2, Table 2*]. Heterogeneity, while slightly lower than that of the overall analysis, remained high between these studies (I^2= 88 per cent, p<0.001). The six high-quality studies (Liu et al., 2010, Wang et al., 2010, Yamada et al., 2012, Feng et al., 2013, Kim et al., 2012, Tang, 2013) showed similar findings [SMD -1.20 (-2.06 to -0.33), p=0.007], with a slightly greater heterogeneity observed between studies (I^2= 95 per cent, p<0.001, *Fig. 2, Table 3*). Funnel plots for LOHS including all studies, only randomised trials, and only higher-quality studies all lacked symmetry, which reflects the heterogeneity observed for this outcome (*Fig. 2*), potentially representing publication bias.

6.4.5 Secondary outcome measures

6.4.5.1 Post-operative morbidity

No significant difference was demonstrated between ERP and control patients in the twelve studies (He, 2010, Jeong et al., 2011, Kiyama et al., 2003, Liu et al., 2010, So et al., 2008, Tang, 2013, Wang et al., 2010, Yamada et al., 2012, Feng et al., 2013, Chen Hu et al., 2012, Kim et al., 2012) reporting incidence of post-operative morbidity [OR 0.82 (0.64 to 1.05), p=0.12, *Fig. 3, Table 1*]. There was no significant heterogeneity

between the studies (I^2= 36 per cent, p=0.10). Sensitivity analysis also demonstrated no significant difference in morbidity, without significant heterogeneity between studies (*Fig. 3, Tables 2-3*). Eight randomised trials (He, 2010, Kiyama et al., 2003, Liu et al., 2010, Wang et al., 2010, Feng et al., 2013, Chen Hu et al., 2012, Kim et al., 2012) reported morbidity, with no significant difference in post-operative morbidity between groups [OR 0.76 (0.49 to 1.16), p=0.20]. Heterogeneity was borderline significant between these studies (I^2= 50 per cent, p=0.05). However, analysis of data from the six higher-quality studies (Liu et al., 2010, Tang, 2013, Wang et al., 2010, Yamada et al., 2012) showed a significantly lower incidence of complications in the ERP group [OR 0.56 (0.37 to 0.84), p=0.005], without heterogeneity between studies (I^2= 0 per cent, p=0.60, *Fig. 3, Table 3*).

Only three deaths within 30 days of surgery were reported and these were limited to the control arm of a single study (So et al., 2008). Meta-analysis was therefore not possible for this outcome, but no significant difference between ERP and control cohorts was demonstrated in the study in question.

6.4.5.2 Readmission rate

No significant difference was demonstrated in readmission rates between ERP and control groups [OR 1.61 (0.83 to 3.12), p=0.16, *Fig. 4, Table 1*]. There was no significant heterogeneity between the studies (I^2= 0 per cent, p=0.82). Sensitivity analysis also failed to demonstrate a significant difference in readmission rate, without significant heterogeneity between

studies (*Fig. 4, Table* 2). Four randomised trials (Liu et al., 2010, Wang et al., 2010, Feng et al., 2013, Kim et al., 2012) reported readmission rate, with no significant difference between cohorts [OR 2.01 (0.36 to 11.29), p=0.43, *Fig. 4, Table* 2]. Heterogeneity remained insignificant between these studies (I^2= 0 per cent, p=0.85). Analysis of the six higher-quality studies (Liu et al., 2010, Wang et al., 2010, Feng et al., 2013, Kim et al., 2012, Tang, 2013, Yamada et al., 2012) showed similar findings [OR 2.45 (0.89 to 6.74), p=0.08], but with a non-significant trend toward higher readmission rate in the ERP group. There was no heterogeneity between studies (I^2= 0 per cent, p=0.92), (*Fig. 4, Table* 3).

6.4.5.3 Additional outcomes

A lesser acute-phase reaction was observed in ERP patients when compared with control patients on post-operative day one, as a lower serum CRP [SMD -0.56 (-1.09 to -0.03), p=0.04, *Table 5]* and IL-6 [SMD -0.62 (-0.94 to -0.29), p<0.001, *Table 5*]. However, no significant difference was observed in serum TNFα level on post-operative day one [SMD -0.19 (-1.35 to 0.97), p=0.74, *Table 5*] or the maximum post-operative pain score [SMD -1.78 (-4.07 to -0.51), p=0.13, *Table 5*], although a trend toward lower pain scores was observed in ERP patients. Gut function returned earlier in ERP patients, as demonstrated by shorter time to first passage of flatus [SMD -0.95 (-1.42 to -0.51), p<0.001, *Table 5*]. A shorter duration of IVI, seen in ERP patients, was borderline significant [SMD -2.70 (-5.35 to -0.05), p=0.05, *Table 5*], and post-operative weight loss was significantly less in ERP groups [SMD -0.79 (-

1.11 to -0.46), p<0.001, *Table 5*]. Finally, total associated costs were also significantly lower in ERP cohorts [SMD -1.02 (-1.59 to -0.45), p<0.001, *Table 5*].

6.5 DISCUSSION

This study represents the most comprehensive systematic review and meta-analysis to examine the effects of ERPs in patients undergoing surgery for gastric cancer to date. An exhaustive search was performed for relevant studies, and almost forty per cent of the data was obtained from randomised trials. The principal findings were that ERPs were associated with significantly shorter LOHS and reduced cost, without increasing post-operative morbidity or hospital readmission rates. Other significant benefits included a blunting of the inflammatory response (CRP and IL-6), less reliance on intravenous hydration, faster return of gut function, and less weight loss.

Several potential limitations were identified. Full text was unavailable for one randomised trial (He, 2010) and, while sufficient data was available for inclusion, complete and accurate assessment of the quality of this study, including assessment of the risk of bias, was precluded. Two randomised trials were only available in their original format, using the Japanese (Kiyama et al., 2003) and Mandarin (Jiang et al., 2007) languages. Although some detail was available from the published

abstract and figures, complete and accurate assessment of quality and bias was not completed, which may have resulted in an underestimation of quality (*Table 3*). However, inclusion of such studies reduced concern regarding bias toward more mainstream publications. Nine of the thirteen studies were randomised trials, but all included fewer than 200 patients, which may introduce unreliability (Rerkasem and Rothwell, 2010). While the majority of studies were randomised trials, these accounted for only 40 per cent of patients; the remaining 60 per cent of patients were contained within the four non-randomised studies. Systematic reviews of retrospective observational studies are known to be confounding-sensitive (Higgins, 2010). Assessment of potential bias using funnel plots must be interpreted with caution where fewer than ten studies were included and, in anticipation of similar difficulties, meta-regression was not performed (Higgins, 2010). Assessment of study quality included measures of potential for bias, in both randomised and non-randomised studies. Studies deemed to be of higher quality included 554 patients (34 per cent), and when analysed in isolation, demonstrated findings were wholly comparable to both the dataset as a whole and the randomised studies alone. This allowed concerns regarding inclusion of poor quality studies to be allayed, while ensuring all available data was assessed herein. Operative mortality could not be meta-analysed effectively because of the small number of events.

The interventions that comprised individual ERPs were heterogeneous (*,* Online Resource). While there was overlap between reported programmes, there was also much variation. With no contemporary

consensus regarding which interventions should be included in an ERP encompassing gastric cancer surgery, programmes were developed based upon principles from related work in other surgical arenas. While it is possible that consistency between programmes may develop with further research, the colorectal experience has been that such variation persists (Wind et al., 2006).

Most studies did not state whether patients received neoadjuvant chemotherapy (He, 2010, Jeong et al., 2011, Jiang et al., 2007, Kiyama et al., 2003, So et al., 2008, Tang, 2013, Yamada et al., 2012, Chen Hu et al., 2012, Kim et al., 2012). Patients receiving such therapy have been shown to deteriorate nutritionally (Awad et al., 2012) and some evidence suggests an increased risk of post-operative complications (Voelter et al., 2004, Schuhmacher et al., 2010) including mortality (Makary et al., 2003). This raised the potential for bias in favour of studies excluding patients receiving neoadjuvant chemotherapy.

In several studies it was not possible to determine whether surgery was performed by laparoscopic or open techniques (He, 2010, Jiang et al., 2007, Kiyama et al., 2003, So et al., 2008, Tang, 2013, Wang et al., 2010). One study described inclusion of both laparoscopic and open procedures (Yamada et al., 2012) and reported no significant related difference. Four studies excluded laparoscopic procedures (Jeong et al., 2011, Liu et al., 2010, Chen Hu et al., 2012, Kim et al., 2012). This inconsistency and uncertainty was a potential source of bias, particularly if both approaches were used and imbalance existed between cohorts.

It was also unclear in most studies whether a D1 or D2 lymphadenectomy

was performed (He, 2010, Kiyama et al., 2003, Liu et al., 2010, So et al., 2008, Tang, 2013, Wang et al., 2010, Chen Hu et al., 2012, Kim et al., 2012). This was a potential source of bias since the incidence of post-operative morbidity and mortality has been shown in randomised clinical trials to be greater following D2 than D1 gastrectomy (Dent et al., 1988, Robertson et al., 1994, Bonenkamp et al., 1999, Bonenkamp et al., 1995, Cuschieri et al., 1999, McCulloch et al., 2005).

The studies included were predominantly from Eastern Asia and it is clear that there is a paucity of work in this arena emerging from the Western world. Care must be taken, therefore, when interpreting the results with a view to application in other geographical locations.

No significant heterogeneity was observed between studies in relation to the incidence of complications, incidence of readmission, day 1 serum IL-6 level, and post-operative weight loss. However, significant heterogeneity (I^2 = 88-95 per cent) was observed between the twelve studies reporting LOHS. This was likely a consequence of the heterogeneity between control programmes of individual studies, with wide variation in reported conventional practice and mean LOHS ranging from 7 to 28 days in control groups. Programmes with a relatively short LOHS prior to introduction of an ERP would find it challenging to reduce LOHS further. Similar reasons may explain the heterogeneity observed between the six studies reporting cost, since LOHS represented a major cost component. Heterogeneity was also observed between studies examining inflammatory response markers (CRP and TNFα), pain scores, intravenous fluid therapy and passage of flatus.

6.6 CONCLUSION

In conclusion, this meta-analysis supports the development and use of ERPs in the arena of gastric cancer surgery. The implementation of such multimodal approaches to perioperative management appears feasible, and safe, conferring benefits to health care providers and patients alike.

6.7 TABLES AND FIGURES

6.7.1 Table 1. Study characteristics

Authors	Year	Study design	ERP patients	Control patients	Outcomes of interest	Study quality*	Neoadjuvant Rx	Open or laparoscopic	D1 or D2
Feng et al.	2013	RT	59	60	1, 2, 3, 4, 7, 9	6/7	No	Open	D2
He et al.	2010	RT	41	41	1, 2, 7, 9	2/7	?	?	?
Hu et al. LAP	2012	RT	19	22	1, 2, 7, 9	3/7	?	Lap	?
Hu et al. OPEN	2012	RT	21	20	1, 2, 7, 9	3/7	?	Open	?
Jeong et al.	2011	RC	228	403	1, 2, 3, 4, 9	5/9	?	Open	D2
Jiang et al.	2007	RT	40	40	1, 7, 8, 9, 10	0/7	?	?	D2
Kim et al.	2012	RT	22	22	1, 5, 7, 9	4/7	?	Lap	?
Kiyama et al.	2004	RT	47	38	1, 2, 8, 9	3/7	?	?	?
Liu et al.	2010	RT	33	30	1, 2, 3, 4, 5, 7, 10	5/7	No	Open	?
So et al.	2008	PC	61	54	2, 3, 4	6/9	?	?	?
Tang et al	2013	RC	19	26	1, 2, 4	7/9	?	?	?
Wang et al.	2010	RT	45	47	1, 2, 3, 4, 5, 6, 7, 9	4/7	No	?	?
Yamada et al.	2012	PC	91	100	1, 2, 3, 4, 6, 7,	7/9	?	Both	D2

ERP, enhanced recovery programme. *According to data available. Outcomes of interest: 1, length of hospital stay; 2, operative morbidity; 3, operative mortality; 4, readmission rate; 5, inflammatory response (day 1 CRP, IL-6 and TNFα); 6, maximum post-operative pain score; 7, time to passage of flatus; 8, duration of intravenous fluid therapy; 9, total cost; 10, post-operative body weight loss. RT, randomised trial; PC, prospective cohort study; RC, retrospective cohort study; ?, unclear from paper.

6.7.2 Table 2. Assessment of bias for cohort studies

	Jeong et al.	So et al.	Tang et al.	Yamada et al.
Representativeness of the exposed cohort (selection bias)	+	+	+	+
Selection of the non exposed cohort (selection bias)	-	+	+	+
Ascertainment of exposure (selection bias)	+	+	+	+
Demonstration that outcome of interest was not present at start of study (selection bias)	-	-	+	+
Comparability of cohorts on the basis of the design or analysis (performance bias)	- -	- -	- -	- -
Assessment of outcome (reporting bias)	+	+	+	+
Was follow-up long enough for outcomes to occur (detection bias)	+	+	+	+
Adequacy of follow up of cohorts (detection bias)	+	+	+	+
Score /9 (stars)	5	6	7	7

+, Low risk of bias; -, high risk of bias; two stars available for comparability.

6.7.3 Table 3. Assessment of bias for randomised trials

	Feng et al.	He et al.	Hu et al.*	Jiang et al.	Kim et al.	Kiyama et al.	Liu et al.	Wang et al.
Random sequence generation (selection bias)	+	+	?	?	+	?	+	+
Allocation concealment (selection bias)	+	+	?	?	+	?	+	+
Blinding of participants and personnel (performance bias)	-	?	-	-	-	-	-	-
Blinding of outcome assessment (detection bias)	+	?	-	-	-	-	-	-
Incomplete outcome data (attrition bias)	+	?	+	?	-	+	+	+
Selective reporting (reporting bias)	+	?	+	?	+	+	+	+
Other bias	+	?	+	?	+	+	+	?
Score /7	**6**	**2**	**3**	**0**	**4**	**3**	**5**	**4**

+, Low risk of bias; -, high risk of bias; ?, unclear risk of bias;

*assessment applies to both datasets from Hu *et al*.

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6.7.4 Table 4. Details of the care pathways for enhanced recovery programmes

[See Supplementary Appendix B for 6.7.4]

6.7.5 Table 5. Summary of effect for secondary outcome measures

Variable	No. of studies	No. of patients ERP (n)	No. of patients Control (n)	SMD (95% C.I.)	p-value	Heterogeneity I^2 (%)	Heterogeneity p-value
CRP	5	140	141	-0.56 (-1.09, -0.03)	0.04	78	0.001
IL-6	2	78	77	-0.62 (-0.94, -0.29)	<0.001	0	0.36
TNFα	2	78	77	-0.19 (-1.35, 0.97)	0.74	92	<0.001
Pain score	2	136	147	-1.78 (-4.07, -0.51)	0.13	98	<0.001
Flatus	4	239	241	-0.95 (-1.42, -0.47)	<0.001	83	<0.001
IV fluids	2	87	78	-2.70 (-5.35, -0.05)	0.05	97	<0.001
Weight loss	2	78	77	-0.79 (-1.11, -0.46)	<0.001	0	0.62
Cost	6	555	723	-1.02 (-1.59, -0.45)	<0.001	94	<0.001

n, number; ERP, enhanced recovery programme group; control, control group; SMD, standardised mean difference; CRP, day one C-reactive protein; IL-6, day one interleukin-6; TNFα, day one tumor necrosis factor alpha; flatus, time to first passage of flatus; IV fluids, duration of intravenous fluid therapy.

6.7.6 Table 6. Review Search Algorithm.

1	exp Stomach Cancer/ or (((gastric or stomach) adj1 cancer$) or ((gastric or stomach) adj1 carcinoma) or ((gastric or stomach) adj1 adenocarcinoma) or ((gastric or stomach) adj1 neoplasm$)).mp.
2	exp surgery
3	gastrectomy.mp
4	2 or 3
5	1 and 4
6	enhanced recovery.mp.
7	ERAS.mp.
8	fast-track.mp.
9	multimodal treatment.mp.
10	perioperative care.mp.
11	early ambulation.mp.
12	6 or 7 or 8 or 9 or 10 or 11
13	length of stay.mp.
14	post-operative morbidity.mp.
15	mortality.mp.
16	hospital readmission.mp.
17	13 or 14 or 15 or 16
18	clinical trial.mp.
19	controlled clinical trial.mp.
20	exp comparative study/
21	meta analysis.mp.
22	multicenter study.mp.
23	multicentre study.mp.
24	randomi?ed controlled trial.mp.
25	18 or 19 or 20 or 21 or 22 or 23 or 24
26	12 or 17
27	5 and 25 and 26

6.7.7 Figure 1. PRISMA Flow Diagram – ERP in Gastric Cancer Surgery

Identification

Records identified through database searching
n = 1566

Records identified through other sources
n = 35

Screening

Records after duplicates removed
n = 1590

Records screened by title/abstract
n = 1590

Records excluded *n* = 1544
- Did not meet inclusion criteria *n* = 1541
- Full text unavailable through British Library, insufficient data in abstract *n* = 1
- Conference abstract with insufficient data *n* = 2

Eligibility

Full text assessed for eligibility
n = 46

Records excluded *n* = 34
- Single element studied *n* = 7
- Distal gastrectomy only *n* = 2
- No control group *n* = 1
- Did not meet inclusion criteria *n* = 24

Included

Studies included in meta-analysis *n* = 12
NB – One study contributed two separate datasets (open and laparoscopic) resulting in 13 datasets

6.7.8 Figure 2. Effect of inclusion in an enhanced recovery programme on length of hospital stay.

Weights are from random-effects analysis. Squares indicate the point estimates of the effect of the intervention (standard mean difference, SMD) and diamonds the summary estimate from the pooled studies; 95 per cent confidence intervals are shown as horizontal bars and in parentheses. SD, standard deviation; CI, confidence intervals; df, degrees of freedom; I^2, I-squared statistic for heterogeneity.

Study or Subgroup	ERP Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 LOHS all studies								
Feng 2013	5.68	1.22	59	7.1	2.13	60	8.8%	−0.81 [−1.19, −0.44]
He 2010	9.4	3.3	41	12.4	3.6	41	8.5%	−0.86 [−1.31, −0.41]
Hu (Lap) 2012	7	1.125	19	7.5	1.25	22	8.0%	−0.41 [−1.03, 0.21]
Hu (Open) 2012	7.5	1.25	21	8.75	1.75	20	7.9%	−0.81 [−1.45, −0.17]
Jeong 2011	11.53	7	228	13.22	8.6	403	9.2%	−0.21 [−0.37, −0.05]
Jiang 2007	5.6	1.3	40	9.4	1.9	40	8.1%	−2.31 [−2.88, −1.74]
Kim 2012	5.36	1.46	22	7.95	1.98	22	7.8%	−1.46 [−2.13, −0.79]
Kiyama 2004	18.1	9.5	47	28.2	22.3	38	8.6%	−0.61 [−1.04, −0.17]
Liu 2010	6.2	1.9	33	9.8	2.8	30	8.2%	−1.50 [−2.06, −0.94]
Tang 2013	11	2.25	19	15	5.1	26	7.9%	−0.95 [−1.57, −0.32]
Wang 2010	6.25	0.54	45	7.75	0.54	47	8.1%	−2.75 [−3.33, −2.18]
Yamada 2010	10.98	5.59	91	9.5	8.61	100	9.0%	0.20 [−0.08, 0.49]
Subtotal (95% CI)			665			849	100.0%	−1.02 [−1.47, −0.56]

Heterogeneity: $Tau^2 = 0.59$; $Chi^2 = 160.23$, df = 11 (P < 0.00001); $I^2 = 93\%$
Test for overall effect: Z = 4.35 (P < 0.0001)

Study or Subgroup	ERP Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.2 LOHS randomized trials								
Feng 2013	5.68	1.22	59	7.1	2.13	60	12.0%	−0.81 [−1.19, −0.44]
He 2010	9.4	3.3	41	12.4	3.6	41	11.6%	−0.86 [−1.31, −0.41]
Hu (Lap) 2012	7	1.125	19	7.5	1.25	22	10.7%	−0.41 [−1.03, 0.21]
Hu (Open) 2012	7.5	1.25	21	8.75	1.75	20	10.6%	−0.81 [−1.45, −0.17]
Jiang 2007	5.6	1.3	40	9.4	1.9	40	11.0%	−2.31 [−2.88, −1.74]
Kim 2012	5.36	1.46	22	7.95	1.98	22	10.4%	−1.46 [−2.13, −0.79]
Kiyama 2004	18.1	9.5	47	28.2	22.3	38	11.7%	−0.61 [−1.04, −0.17]
Liu 2010	6.2	1.9	33	9.8	2.8	30	11.0%	−1.50 [−2.06, −0.94]
Wang 2010	6.25	0.54	45	7.75	0.54	47	11.0%	−2.75 [−3.33, −2.18]
Subtotal (95% CI)			327			320	100.0%	−1.27 [−1.77, −0.77]

Heterogeneity: $Tau^2 = 0.51$; $Chi^2 = 64.99$, df = 8 (P < 0.00001); $I^2 = 88\%$
Test for overall effect: Z = 4.99 (P < 0.00001)

Study or Subgroup	ERP Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.3 LOHS high-quality								
Feng 2013	5.68	1.22	59	7.1	2.13	60	17.2%	−0.81 [−1.19, −0.44]
Kim 2012	5.36	1.46	22	7.95	1.98	22	16.1%	−1.46 [−2.13, −0.79]
Liu 2010	6.2	1.9	33	9.8	2.8	30	16.5%	−1.50 [−2.06, −0.94]
Tang 2013	11	2.25	19	15	5.1	26	16.3%	−0.95 [−1.57, −0.32]
Wang 2010	6.25	0.54	45	7.75	0.54	47	16.5%	−2.75 [−3.33, −2.18]
Yamada 2010	10.98	5.59	91	9.5	8.61	100	17.4%	0.20 [−0.08, 0.49]
Subtotal (95% CI)			269			285	100.0%	−1.20 [−2.06, −0.33]

Heterogeneity: $Tau^2 = 1.10$; $Chi^2 = 100.80$, df = 5 (P < 0.00001); $I^2 = 95\%$
Test for overall effect: Z = 2.71 (P = 0.007)

−2 −1 0 1 2
Favours ERP   Favours control

6.7.9 Figure 3. Effect of inclusion in enhanced recovery programme on the incidence of post-operative complications within 30 days.

Weights are from fixed-effects analysis. Squares indicate the point estimates of the effect of the intervention (odds ratio, OR) and diamonds the summary estimate from the pooled studies; 95 per cent confidence intervals are shown as horizontal bars and in parentheses. Mantel-Haentzel test; CI, confidence intervals; df, degrees of freedom; I^2, I-squared statistic for heterogeneity.

Study or Subgroup	ERP Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
3.1.1 Complications – all studies						
Feng 2013	6	59	17	60	10.9%	0.29 [0.10, 0.79]
He 2010	3	41	7	41	4.7%	0.38 [0.09, 1.60]
Hu (Lap) 2012	12	19	8	22	2.0%	3.00 [0.84, 10.73]
Hu (Open) 2012	14	21	8	20	2.0%	3.00 [0.84, 10.73]
Jeong 2011	42	228	76	403	32.2%	0.97 [0.64, 1.48]
Kim 2012	3	22	4	22	2.5%	0.71 [0.14, 3.63]
Kiyama 2004	3	47	5	38	3.7%	0.45 [0.10, 2.02]
Liu 2010	4	33	6	30	4.0%	0.55 [0.14, 2.18]
So 2008	24	61	21	54	9.7%	1.02 [0.48, 2.16]
Tang 2013	1	19	6	26	3.4%	0.19 [0.02, 1.69]
Wang 2010	7	45	9	47	5.3%	0.78 [0.26, 2.30]
Yamada 2010	34	91	46	100	19.7%	0.70 [0.39, 1.25]
Subtotal (95% CI)		686		863	100.0%	0.82 [0.64, 1.05]
Total events	153		213			

Heterogeneity: Chi^2 = 17.14, df = 11 (P = 0.10); I^2 = 36%
Test for overall effect: Z = 1.57 (P = 0.12)

Study or Subgroup	ERP Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
3.1.2 Complications – randomized trials						
Feng 2013	6	59	17	60	31.1%	0.29 [0.10, 0.79]
He 2010	3	41	7	41	13.3%	0.38 [0.09, 1.60]
Hu (Lap) 2012	12	19	8	22	5.6%	3.00 [0.84, 10.73]
Hu (Open) 2012	14	21	8	20	5.6%	3.00 [0.84, 10.73]
Kim 2012	3	22	4	22	7.1%	0.71 [0.14, 3.63]
Kiyama 2004	3	47	5	38	10.6%	0.45 [0.10, 2.02]
Liu 2010	4	33	6	30	11.3%	0.55 [0.14, 2.18]
Wang 2010	7	45	9	47	15.3%	0.78 [0.26, 2.30]
Subtotal (95% CI)		287		280	100.0%	0.76 [0.49, 1.16]
Total events	52		64			

Heterogeneity: Chi^2 = 14.05, df = 7 (P = 0.05); I^2 = 50%
Test for overall effect: Z = 1.28 (P = 0.20)

Study or Subgroup	ERP Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
3.1.3 Complications – high-quality studies						
Feng 2013	6	59	17	60	23.7%	0.29 [0.10, 0.79]
Kim 2012	3	22	4	22	5.4%	0.71 [0.14, 3.63]
Liu 2010	4	33	6	30	8.7%	0.55 [0.14, 2.18]
Tang 2013	1	19	6	26	7.5%	0.19 [0.02, 1.69]
Wang 2010	7	45	9	47	11.7%	0.78 [0.26, 2.30]
Yamada 2010	34	91	46	100	43.0%	0.70 [0.39, 1.25]
Subtotal (95% CI)		269		285	100.0%	0.56 [0.37, 0.84]
Total events	55		88			

Heterogeneity: Chi^2 = 3.65, df = 5 (P = 0.60); I^2 = 0%
Test for overall effect: Z = 2.81 (P = 0.005)

Odds Ratio M–H, Fixed, 95% CI
0.01   0.1   1   10   100
Favours ERP   Favours control

6.7.10 Figure 4. Effect of inclusion in an enhanced recovery programme on the incidence of readmission within 30 days.

Weights are from fixed-effects analysis. Squares indicate the point estimates of the effect of the intervention (OR) and diamonds the summary estimate from the pooled studies; 95 per cent confidence intervals are shown as horizontal bars and in parentheses. Mantel-Haentzel test; CI, confidence intervals; df, degrees of freedom; I^2, I-squared statistic for heterogeneity.

Study or Subgroup	ERP Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Readmission – all studies							
Feng 2013	0	59	0	60		Not estimable	
Jeong 2011	1	228	4	403	20.6%	0.44 [0.05, 3.96]	
Kim 2012	1	22	0	22	3.3%	3.14 [0.12, 81.35]	
Liu 2010	1	33	0	30	3.6%	2.82 [0.11, 71.78]	
So 2008	11	61	7	54	43.6%	1.48 [0.53, 4.13]	
Tang 2013	5	19	2	26	8.9%	4.29 [0.73, 25.09]	
Wang 2010	1	45	1	47	6.8%	1.05 [0.06, 17.23]	
Yamada 2010	3	91	2	100	13.2%	1.67 [0.27, 10.23]	
Subtotal (95% CI)		558		742	100.0%	1.61 [0.83, 3.12]	
Total events	23		16				
Heterogeneity: Chi² = 2.92, df = 6 (P = 0.82); I² = 0%							
Test for overall effect: Z = 1.42 (P = 0.16)							
1.1.2 Readmission – randomized trials							
Feng 2013	0	59	0	60		Not estimable	
Kim 2012	1	22	0	22	24.3%	3.14 [0.12, 81.35]	
Liu 2010	1	33	0	30	26.0%	2.82 [0.11, 71.78]	
Wang 2010	1	45	1	47	49.7%	1.05 [0.06, 17.23]	
Subtotal (95% CI)		159		159	100.0%	2.01 [0.36, 11.29]	
Total events	3		1				
Heterogeneity: Chi² = 0.32, df = 2 (P = 0.85); I² = 0%							
Test for overall effect: Z = 0.80 (P = 0.43)							
1.1.3 Readmission – high-quality studies							
Feng 2013	0	59	0	60		Not estimable	
Kim 2012	1	22	0	22	9.3%	3.14 [0.12, 81.35]	
Liu 2010	1	33	0	30	10.0%	2.82 [0.11, 71.78]	
Tang 2013	5	19	2	26	24.8%	4.29 [0.73, 25.09]	
Wang 2010	1	45	1	47	19.1%	1.05 [0.06, 17.23]	
Yamada 2010	3	91	2	100	36.8%	1.67 [0.27, 10.23]	
Subtotal (95% CI)		269		285	100.0%	2.45 [0.89, 6.74]	
Total events	11		5				
Heterogeneity: Chi² = 0.94, df = 4 (P = 0.92); I² = 0%							
Test for overall effect: Z = 1.74 (P = 0.08)							

0.01 0.1 1 10 100
Favours ERP   Favours control

CHAPTER 7

Systematic review and meta-analysis of enhanced recovery programmes in oesophageal cancer surgery

7.1 SUMMARY

The aim of this systematic review and meta-analysis was to determine the influence of enhanced recovery programmes (ERPs) on outcomes after oesophageal cancer surgery. PubMed, Embase, the Cochrane library, and ClinicalTrials.gov were searched for all studies on outcomes after oesophagectomy in enhanced recovery or fast-track programmes. The primary outcome measure was post-operative length of hospital stay (LOHS), and secondary outcome measures were selected based on their inclusion in two or more studies. Statistical analysis was performed using standardised mean difference (SMD) and odds ratio (OR) as the summary statistics. Eight studies were included, involving 1091 individuals. Meta-analysis of seven studies reporting LOHS demonstrated a significant reduction after ERP, when compared with control patients [SMD -1.16, (95% confidence interval (CI) -1.86 to -0.46), p=0.001], but with significant heterogeneity between studies [I^2=95%, p<0.00001]. This was associated with decreases in 30-day mortality (p=0.07), post-operative morbidity (p<0.0001) and incidence of anastomotic leak (p=0.03), and no significant difference in the incidence of pulmonary complications (p=0.38) or readmission to hospital (p=0.67).

The application of multimodal, standardised approaches to perioperative oesophagectomy care was feasible, safe and associated with a shorter LOHS, reduced post-operative morbidity and mortality, fewer anastomotic

leaks and no increase in pulmonary complications or readmission to hospital.

7.2 INTRODUCTION

Enhanced recovery programmes (ERPs) are well established in colorectal cancer surgical practice and have been shown to be associated with reduced post-operative morbidity and shorter lengths of hospital stay (LOHS) (Varadhan et al., 2010). However, in upper gastrointestinal surgery, and oesophageal cancer resection in particular, the role of ERPs is less certain. No systematic review or meta-analysis of the implementation of a multimodal pathway in oesophagectomy for cancer exists.

Radical oesophageal cancer surgery involves intestinal resection and anastomosis, with periods of starvation implemented to allow for healing of the anastomosis, protected from the stress of oral fluids and diet, while intestinal motility returns (Lewis et al., 2009). Patients are often malnourished at presentation (Nygren et al., 2003) and advanced disease and significant cardiorespiratory morbidity are commonly encountered. In severely malnourished patients, an increased risk of post-operative complications is observed, which can impede recovery (Weimann et al., 2006).

With surgical resection remaining the mainstay of radical curative treatment for esophageal cancer (Allum et al., 2011), patients are faced

with major surgery, which by its very nature carries inherent significant risk, even in well-nourished patients (Allum et al., 2011).

Indeed, UK National Audit figures report an in-hospital mortality of 4.5 per cent (95% CI 3.7-5.5) and complication rate of 29.8 per cent (95% CI 27.9-31.8) in patients undergoing oesophagectomy for cancer (Centre, 2010).

Several controversies exist in esophageal cancer surgery, including the operative approach (minimally invasive vs. open; transhiatal vs. transthoracic vs. tri-incisional), geographical epidemiological variations, and the use of neo-adjuvant and adjuvant treatment.

The aim of this systematic review and meta-analysis was to evaluate existing evidence for the implementation of an ERP in oesophagectomy for cancer.

7.3 METHODS

7.3.1 Data sources, search methods and selection criteria.

A systematic review of published work was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (*Fig. 1)* (Liberati et al., 2009). Sources searched were: MEDLINE via Ovid (from January 1966 to April 2014), Embase (no date restriction), the Cochrane Library database (Cochrane Central

Register of Controlled Trials; no date restriction) and World Health Organization International Clinical Trials Registry Platform (ICTRP; no date restriction). Studies were sought reporting outcomes after oesophagectomy in an ERP.

No limitation was placed on language or publication type, although non-English language studies without extractable data were excluded. Relevant studies were identified using the following MeSH subject headings: esophageal cancer and surgery. These results were combined with MeSH terms: perioperative care, multimodal treatment, early ambulation, length of stay, post-operative morbidity, mortality, hospital readmission and the additional non-MeSH terms enhanced recovery, ERAS and fast-track. Variants, such as oesophagus, oesophageal and oesophagectomy, were also accommodated within the literature search. The ClinicalTrials.gov website was searched for randomised controlled trials (RCTs) involving enhanced recovery in oesophageal cancer surgery. Further articles were identified by hand-searching of references and using the PubMed related articles function. The related articles results were additionally cross-referenced with full results from previous searches. The last search date was 1st April 2014. Outcome events were identified for inclusion if they were reported in an extractable and comparable form in two or more studies. The review search algorithm is shown in Table 4.

7.3.2 Data extraction

Data were extracted independently by two authors (AJB and DSYC) and

any discrepancies resolved to consensus by discussion. The following details were extracted from each study: first author, year of publication, study design (randomised, comparison, case series, prospective or retrospective), number of participants in each group (ERP and Control), inclusion criteria, details of pathways, quality of study and outcome events.

7.3.3 Inclusion and exclusion criteria

All studies reporting outcomes in patients undergoing oesophagectomy for cancer within a multimodal pathway or ERP were included. Studies from which it was not possible to extract data from the published results available from the British Library, and studies reporting outcomes of a single intervention, were excluded.

7.3.4 Outcome measures

The primary outcome was defined as LOHS in days. Secondary outcome measures were incidence of all post-operative morbidity, operative mortality, pulmonary complications, anastomotic leak and readmission to hospital. The construction of the ERP and the evidence underpinning individual elements therein were outside the remit of this study and were not addressed in this review.

7.3.5 Statistical analysis

The meta-analysis was performed in line with the recommendations of the Cochrane Collaboration (Higgins, 2010) and the PRISMA guidelines

(Liberati et al., 2009). Analysis was performed using Review Manager 5.1.7 (The Nordic Cochrane Centre, Copenhagen, Denmark). Statistical analysis was performed using odds ratio (OR) as the summary statistic for dichotomous variables and standardised mean difference (SMD) for continuous variables. The SMD is the number of standard deviations' difference of the intervention as a dimensionless form of the actual findings (Higgins, 2010). A random effects model was used when the I^2 value was greater than 50 per cent and a fixed effects model was used when it was less than 50 per cent. Results were reported with 95 per cent confidence intervals (CI). Where values for mean and standard deviation (SD) were not available, these were imputed from the median and range using methods described by Hozo *et al.* (Hozo et al., 2005), as appropriate to sample size. This involved using the median as a surrogate for mean. Where sample size was greater than 70, SD was imputed as range/6 and where sample size was 15-69, SD was calculated as range/4.

7.3.6 Heterogeneity

The randomised study was examined for quality according to risk-of bias tables from the Cochrane Handbook, (Higgins, 2010) across domains of selection, performance, detection, attrition, reporting, and other bias. Achieving a score of four or more from a maximum of seven was considered to represent high quality. Non-randomised studies were examined for quality using the Newcastle–Ottawa scale (Higgins, 2010) across domains of patient selection methods, comparability of study

groups and assessment of outcome. Non-randomised studies achieving six or more stars from a maximum of nine were considered to be of high quality. Sensitivity analysis was performed for post-operative morbidity, analysing a subgroup comprised of high quality studies alone. The I^2 test was reported for each analysis. Bias was assessed using funnel plots (Egger and Smith, 1998), with asymmetry implying that results were subject to reporting or publication bias between studies and symmetry implying non-bias.

7.4 RESULTS

7.4.1 Included studies

Eight studies, published between 1998 and 2014, fulfilled the criteria for inclusion and were analysed comprising a total of 473 ERP patients and 618 controls (*Table 1*). One report, for which only an abstract was available, was deemed by the authors to contain sufficient data for inclusion, although its quality could not be formally assessed. Where data was unavailable it was sought from corresponding authors by email. No supplementary data was received for analysis.

7.4.2 Characteristics of the included studies

The characteristics of the included studies are shown in *Table 1*, and the details of the main features of the pathways are given in *Table 3*. One

randomised trial was eligible for inclusion. Of the seven included cohort studies, two compared retrospectively collected ERP and control data (Munitiz et al., 2010, Tang, 2013), one compared prospectively collected ERP data with retrospectively collected control data (Brodner et al., 1998), two compared prospectively collected data (Tomaszek et al., 2010, Li et al., 2012) and two did not describe how data were collected (Cao et al., 2012, You et al., 2012).

7.4.3 Primary outcome measure

Seven studies reported LOHS (Brodner et al., 1998, Cao et al., 2012, Munitiz et al., 2010, Tomaszek et al., 2010, Tang, 2013, Li et al., 2012, Zhao et al., 2014). Six of these found a significantly shorter LOHS in the ERP group (Cao et al., 2012, Munitiz et al., 2010, Tomaszek et al., 2010, Tang, 2013, Li et al., 2012, Zhao et al., 2014) and one showed no significant difference (Brodner et al., 1998). A significantly shorter LOHS was demonstrated in the ERP group in the grouped analysis (SMD -1.16, (-1.86. to -0.46), p=0.001) (*Fig. 2*). There was significant heterogeneity between the studies (I^2= 95 per cent, p<0.00001).

7.4.4 Secondary outcome measures:

7.4.4.1 All post-operative morbidity

A significant benefit was demonstrated in ERP groups over control groups across the seven studies (*Fig. 3*) (Brodner et al., 1998, Cao et al., 2012, Munitiz et al., 2010, You et al., 2012, Tang, 2013, Li et al., 2012, Zhao et al., 2014) reporting incidence of post-operative morbidity [OR

0.47 (0.33 to 0.66), p<0.0001] (*Fig. 3, Table 1*). There was no significant heterogeneity between the studies (I^2= 0 per cent, p=0.53). Sensitivity analysis also demonstrated a significant benefit in terms of post-operative morbidity following removal of the low quality study from analysis [OR 0.50 (0.35 to 0.72), p=0.0002]. Heterogeneity between studies remained insignificant (I^2= 0 per cent, p=0.54), (*Fig. 3, Table 2*).

7.4.4.2 Operative mortality

Five studies reported operative mortality (Tang, 2013, Brodner et al., 1998, Cao et al., 2012, Munitiz et al., 2010). A significantly lower mortality was observed in the ERP groups compared with control groups [OR 0.40 (0.15 to 1.07), p=0.07] (*Fig. 4*), with no significant heterogeneity between the studies (I^2= 0 per cent, p=0.51).

7.4.4.3 Specific complications

Six studies reported anastomotic leak rates (Brodner et al., 1998, Cao et al., 2012, Munitiz et al., 2010, Tang, 2013, Li et al., 2012, Zhao et al., 2014), with a significant difference demonstrated between ERP and control groups [OR 0.55 (0.33 to 0.94), p=0.03] in favour of the ERP groups (*Fig. 5*). There was no significant heterogeneity between the studies (I^2= 7 per cent, p=0.37).

No significant difference was demonstrated between ERP and control groups of four studies (Munitiz et al., 2010, Brodner et al., 1998, Cao et al., 2012, Li et al., 2012) specifically reporting the incidence of pulmonary complications [OR 0.78 (0.45 to 1.36) p=0.38], (*Fig. 6*). Again, no

significant heterogeneity was demonstrated between the studies (I^2= 0 per cent, p=0.52).

7.4.4.4 Readmission rate

Readmission rate did not significantly differ between ERP and control groups [OR 1.10 (0.70 to 1.72), p=0.67], (*Fig. 7*). There was no significant heterogeneity between the six studies (Cao et al., 2012, Li et al., 2012, Munitiz et al., 2010, Tang et al., 2010, Tomaszek et al., 2010, Zhao et al., 2014) reporting this outcome (I^2= 0 per cent, p=0.91).

7.4.4.5 Additional outcomes

Other significant benefits that were reported in only one study and were, therefore, not comparable in meta-analysis included reductions in time to passage of flatus and faeces (Zhao et al., 2014); time to return of bowel sounds, time to mobility, discharge from intensive care facilities (Brodner et al., 1998); contrast aspiration (Tang, 2013) and pain scores (two studies but not reported in comparable form) (Brodner et al., 1998, Zhao et al., 2014).

A funnel plot for LOHS lacked symmetry. This reflects the heterogeneity observed for this outcome (*Fig. 2*), potentially representing publication bias. However, when fewer than ten studies are included, the funnel plot is known to be difficult to interpret (Higgins, 2010).

7.4.4.6 Assessment of bias

Using the Newcastle-Ottawa scale (Higgins, 2010), non-randomised studies were assessed for potential bias. From a maximum of nine stars, six studies achieved six or more stars and were deemed high quality (*Table 2a*). The unavailability of a full, English language manuscript precluded full and accurate assessment of bias for the remaining study, reflected by its low score of one, from nine stars. Comparability was the most consistent risk of bias with just one of the papers controlling for factors (Zhao et al., 2014). Using risk-of bias tables from the Cochrane Handbook (Higgins, 2010), the randomised study scored five from a maximum of seven stars and was deemed high quality (*Table 2b*).

7.5 DISCUSSION

This systematic review and meta-analysis is the first to specifically examine the effects of ERPs in patients undergoing surgery for oesophageal cancer. The authors performed an exhaustive search for relevant studies.

The principal findings were that ERPs significantly shortened LOHS and reduced post-operative morbidity, specifically anastomotic leak, without significantly increasing pulmonary complications or rates of readmission to hospital.

The authors acknowledge several potential limitations. Full text was unavailable for one study owing to its foreign-language publication in a Chinese journal (You et al., 2012). While enough data was available for inclusion in the analysis of a single parameter, accurate and full assessment of this study's quality, including assessment of the risk of bias, was not possible. However, this study's inclusion reduced concern regarding bias toward western and mainstream publications, although only one comparable outcome was obtained.

One of the eight studies included was a randomised trial, and five studies included retrospective data or failed to clearly state otherwise. Systematic reviews examining retrospective studies are known to be confounding-sensitive (Higgins, 2010). Assessment of potential bias using funnel plots must be interpreted with caution, owing to the inclusion of fewer than ten studies. In anticipation of similar difficulties, meta-regression analysis was not performed (Higgins, 2010). However, assessment of study quality included a measure of potential for bias. Seven of the eight studies were deemed high quality and included 974 (89 per cent) of 1091 patients. The remaining study (You et al., 2012) provided data for just one outcome measure, post-operative morbidity. Sensitivity analysis with this study removed showed almost identical findings to analysis of the dataset as a whole, suggesting that little or no bias was introduced by this study's inclusion.

Studies included data reaching as far back as 1998 (Brodner et al., 1998) and collected over as many as ten years (Munitiz et al., 2010). This type of sprawled comparison group is likely to have resulted from the limited

number of resections performed at individual centres and the need to recruit sufficient numbers of patients for study. It has the potential to introduce technological bias as technique and technology were likely to have advanced over the study period, potentially improving outcomes in the ERP patients, all of whom were more recently treated than their respective control patients. This factor may have contributed to an improved anastomotic leak rate and post-operative morbidity rate in ERP groups. A major technological factor was the use of an open or minimally invasive surgical approach. In two studies the approach was unclear (You et al., 2012, Zhao et al., 2014), three studies included only open operations (Brodner et al., 1998, Cao et al., 2012, Munitiz et al., 2010) and three included both open and minimally invasive procedures (Tang, 2013, Tomaszek et al., 2010, Li et al., 2012), although the latter approach comprised only 1.5 per cent of patients in one such study (Tomaszek et al., 2010). Inclusion of minimally invasive oesophagectomy (MIO) and laparoscopic-assisted techniques may have introduced bias, trends toward reduced LOHS, post-operative morbidity and mortality in favour of MIO having been demonstrated upon meta-analysis (Biere et al., 2009).

Oesophageal cancer epidemiology shows wide geographical variation, influenced by genetic, behavioural and environmental factors, as yet unquantified. It follows that the use of chemoradiotherapy, and the literature informing it, also varies with by geographical population. In Europe, peri-operative chemotherapy (Cunningham et al., 2006, Ychou et al., 2011), and more recently, preoperative chemoradiotherapy (van Hagen et al., 2012) have been demonstrated to be superior to surgery

alone. In North America, a major trial failed to demonstrate a similar benefit from preoperative chemotherapy (Kelsen et al., 1998), while in Japan, pre-operative chemotherapy represents the standard of care in stage II/III disease (Shitara and Muro, 2009).

The studies included in this review were from geographically diverse populations, across Asia (Cao et al., 2012, You et al., 2012, Zhao et al., 2014, Li et al., 2012), North America (Tomaszek et al., 2010) and Western Europe (Brodner et al., 1998, Munitiz et al., 2010, Tang, 2013), potentially reducing their comparability, but concomitantly permitting a broad perspective on the global use of ERPs in oesophageal cancer. Five included studies did not state whether patients received neoadjuvant chemotherapy (Brodner et al., 1998, Munitiz et al., 2010, You et al., 2012, Tang, 2013, Zhao et al., 2014). In a further two studies, 61 and 67 per cent of patients received neo-adjuvant treatment respectively (Tomaszek et al., 2010, Li et al., 2012), and the remaining study stated the inclusion of such patients but did not quantify the number included (Cao et al., 2012). Patients receiving such therapy have been shown to deteriorate nutritionally (Awad et al., 2012) and some evidence suggests an increased risk of post-operative complications (Voelter et al., 2004) including mortality (Makary et al., 2003). This presented the potential for bias in favour of studies excluding patients receiving neoadjuvant therapy.

The time frame used for readmission rate was not stated in two papers (Munitiz et al., 2010, Tang, 2013), which may have introduced bias. However, data from these studies comprised less than 30 per cent of the

dataset for this outcome and analysis with these studies removed did not alter the findings. A thirty-day readmission rate was analysed from the remaining two studies (Cao et al., 2012, Tomaszek et al., 2010).

The proportions of patients undergoing transhiatal (THO), transthoracic (TTO) and tri-incisional approaches for open oesophagectomy were unclear in two reports (You et al., 2012, Tang, 2013) and varied in the remaining four. Two studies included all three approaches, two favoring THO (Cao et al., 2012, Zhao et al., 2014), and two favoring TTO (Tomaszek et al., 2010, Li et al., 2012). The largest study (Tomaszek et al., 2010) reported a significant difference in surgical approach between treatment groups. The remaining two studies included only TTO (Brodner et al., 1998, Munitiz et al., 2010). THO is known to be associated with shorter LOHS and lower operative mortality (Hulscher et al., 2001), but higher incidence of anastomotic leak (Hulscher et al., 2001, Rindani et al., 1999) when compared with TTO. This disparity between studies, coupled with a variation in the number of patients contributed to this meta-analysis by individual studies, may have introduced bias in these outcomes.

The interventions that comprised individual ERPs were heterogeneous (*Table 4*). While there was overlap between studies' programmes, the variation between them reflects the absence of consensus over which interventions should be included in an ERP for oesophageal cancer surgery. Consistency between programmes may be forthcoming with further experience and published evidence, although this has not been

the observed in colorectal cancer ERPs despite extensive experience and evidence (Wind et al., 2006).

No significant heterogeneity between studies in grouped analysis was demonstrated for post-operative morbidity, anastomotic leak rate, pulmonary complications or readmission to hospital, reflecting the comparability of the studies for these outcomes. However, significant heterogeneity was observed between the four studies reporting LOHS. This was likely a consequence of the heterogeneity between control programmes of individual studies, with wide variation in reported conventional practice and mean LOHS ranging from 7.5 to 15 days. Programmes with a comparatively short LOHS before the introduction of an ERP would find it challenging to reduce LOHS further.

In some instances, data were reported using the median and range or interquartile range. Imputing the mean and SD for these values was not statistically ideal and medians may have been reported in preference to means in order to mask skewed data.

7.6 CONCLUSION

In conclusion, the present meta-analysis of the literature to date supports the development and use of ERPs in oesophageal cancer surgery. The implementation of such multimodal approaches to perioperative management appears feasible and safe, conferring benefits to health care providers and patients alike.

7.7 TABLES AND FIGURES

7.7.1 Table 1. Study characteristics

Authors	Year	Study design	ERP patients	Control patients	Outcomes of interest	Study quality*	NeoAdj Rx	Approach
Brodner *et al.* (13)	1998	RC	42	49	1, 2, 3, 6	6/9	Not stated	Open
Cao *et al.* (15)	2012	UC	55	57	1, 2, 3, 4, 5, 6	7/9	Included (number not stated)	Open
Li et al. (17)	2012	PC	59	47	1, 2, 3, 4, 5, 6		Included (67%)	Open (77.4%) and MIO
Munitiz *et al.* (11)	2010	RC	74	74	1, 2, 3, 4, 5, 6	6/9	Not stated	Open
Tang *et al.* (12)	2013	RC	36	27	1, 2, 3, 4, 5	7/9	Not stated	Open and LAO
Tomaszek *et al.* (14)	2009	RC	110	276	1, 4, 5	7/9	Included, (60.8%)	Open (98.5%) and MIO
You *et al.* (16)	2012	UC	63	54	2	1/9	Not stated	Not stated
Zhao *et al.* (19)	2014	RT	34	34	1, 2, 4, 5	5/9	Not stated	Not stated
TOTAL			**473**	**618**				

ERP, enhanced recovery programme. *According to data available. NeoAdj Rx, neoadjuvant therapy. Outcomes of interest: 1, length of hospital stay; 2, operative morbidity; 3, operative mortality; 4, readmission rate; 5, anastomotic leak; 6, pulmonary complications; RC, retrospective cohort study; UC, Cohort study - unclear data collection; PC, prospective cohort study; RT, randomised trial; MIO, minimally invasive oesophagectomy; LAO, laparoscopic-assisted oesophagectomy.

7.7.2 Assessment of bias

7.7.2.1 Table 2a. Assessment of bias for non-randomised studies

	Brodner et al.	Cao et al.	Li et al.	Munitiz et al.	Tang et al.	Tomaszek et al.	You et al.
Representativeness of the exposed cohort (selection bias)	+	+	+	+	+	+	?
Selection of the non exposed cohort (selection bias)	+	+	+	+	+	+	?
Ascertainment of exposure (selection bias)	+	+	+	+	+	+	?
Demonstration that outcome of interest was not present at start of study (selection bias)	+	+	+	+	+	+	?
Comparability of cohorts on the basis of the design or analysis (performance bias)	- -	- -	- -	- -	- -	- -	? ?
Assessment of outcome (reporting bias)	-	+	-	-	+	+	?
Was follow-up long enough for outcomes to occur (detection bias)	+	+	+	+	+	+	?
Adequacy of follow up of cohorts (detection bias)	+	+	+	+	+	+	+
Score /9 (stars)	**6**	**7**	**6**	**6**	**7**	**7**	**1**

+, Low risk of bias; -, high risk of bias; ?, unclear risk of bias. Two stars available for comparability.

7.7.2.2 Table 2b. Assessment of bias for randomised trial

	Zhao *et al.*
Random sequence generation (selection bias)	+
Allocation concealment (selection bias)	+
Blinding of participants and personnel (performance bias)	-
Blinding of outcome assessment (detection bias)	-
Incomplete outcome data (attrition bias)	+
Selective reporting (reporting bias)	+
Other bias	+
Score /7	**5**

+, Low risk of bias; -, high risk of bias; ?, unclear risk of bias.

7.7.3 Table 3. Details of the care pathways for enhanced recovery programmes

[See Appendix B for 7.7.3]

7.7.4 Table 4. Review search algorithm

1	exp esophageal cancer/ or (((?sophagus) adj1 cancer$) or ((?sophagus) adj1 carcinoma) or ((?sophagus) adj1 adenocarcinoma) or ((?sophagus) adj1 neoplasm$)).mp.
2	exp surgery
3	?sophagectomy.mp
4	2 or 3
5	1 and 4
6	enhanced recovery.mp.
7	ERAS.mp.
8	fast-track.mp.
9	multimodal treatment.mp.
10	perioperative care.mp.
11	early ambulation.mp.
12	6 or 7 or 8 or 9 or 10 or 11
13	length of stay.mp.
14	post-operative morbidity.mp.
15	mortality.mp.
16	hospital readmission.mp.
17	13 or 14 or 15 or 16
18	clinical trial.mp.
19	controlled clinical trial.mp.
20	exp comparative study/
21	meta analysis.mp.
22	multicenter study.mp.
23	multicentre study.mp.
24	randomi?ed controlled trial.mp.
25	18 or 19 or 20 or 21 or 22 or 23 or 24
26	12 or 17
27	5 and 25 and 26

7.7.5 Figure 1. PRISMA Flow Diagram – ERAS in Oesophageal Cancer Surgery

Identification

Records identified through database search
n = 1084

Records identified through other sources
n = 28

Screening

Records after duplicates removed
n = 1106

Records screened by title or abstract
n = 1106

Records excluded *n* = 1075
- Did not meet inclusion criteria *n* = 1073
- Full text unavailable through British Library, insufficient data in abstract *n* = 1
- Conference abstract with insufficient data *n* = 1

Eligibility

Full text assessed for eligibility
n = 31

Records excluded *n* = 23
- Single element studied *n* = 9
- No control group *n* = 4
- Did not meet inclusion criteria *n* = 9
- No comparable extractable outcome measures *n* = 1

Included

Studies included in meta-analysis *n* = 8
LOHS *n* = 7

All complications *n* = 7

Mortality *n* = 5

7.7.6 Fig. 2. Forest plot for length of hospital stay

Study or Subgroup	ERP Mean	ERP SD	ERP Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Brodner 1998	6.29	2.03	42	7.52	4.22	49	14.5%	−0.36 [−0.78, 0.06]
Cao 2012	7.7	1.4	55	14.8	3.7	57	14.2%	−2.50 [−3.00, −2.01]
Li 2012	8	4.5	59	10	4	47	14.6%	−0.46 [−0.85, −0.07]
Munitiz 2010	9	15.5	74	13	16.3	74	14.8%	−0.25 [−0.57, 0.07]
Tang 2013	11	3.75	36	15	6	27	14.1%	−0.82 [−1.34, −0.30]
Tomaszek 2010	10	8	110	13	12	276	15.1%	−0.27 [−0.49, −0.05]
Zhao 2014	7.15	1.23	34	12.52	1.47	34	12.6%	−3.92 [−4.75, −3.09]
Total (95% CI)			**410**			**564**	**100.0%**	**−1.16 [−1.86, −0.46]**

Heterogeneity: Tau^2 = 0.84; Chi^2 = 132.85, df = 6 (P < 0.00001); I^2 = 95%
Test for overall effect: Z = 3.25 (P = 0.001)

Favours ERP   Favours control

Effect of inclusion in an enhanced recovery programme (ERP) on LOHS. SD, standard deviation; CI, confidence intervals; df, degrees of freedom; I^2, I-squared statistic for heterogeneity. Weights are from random-effects analysis. Squares indicate the point estimates of the effect of the intervention (SMD) and diamonds the summary estimate from the pooled studies; 95 per cent confidence intervals are shown as horizontal bars and in parentheses.

7.7.7 Fig. 3. Forest plot for postoperative morbidity

Study or Subgroup	ERP Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
1.2.1 All Patients						
Zhao 2014	2	34	4	34	3.9%	0.47 [0.08, 2.75]
You 2012	5	63	13	54	13.3%	0.27 [0.09, 0.82]
Tang 2013	6	36	7	27	6.9%	0.57 [0.17, 1.95]
Munitiz 2010	23	74	28	74	19.8%	0.74 [0.38, 1.46]
Li 2012	29	59	30	47	17.5%	0.55 [0.25, 1.20]
Cao 2012	16	55	27	57	19.3%	0.46 [0.21, 0.99]
Brodner 1998	20	42	39	49	19.4%	0.23 [0.09, 0.59]
Subtotal (95% CI)		363		342	100.0%	0.47 [0.33, 0.66]
Total events	101		148			

Heterogeneity: Chi^2 = 5.13, df = 6 (P = 0.53); I^2 = 0%
Test for overall effect: Z = 4.35 (P < 0.0001)

Study or Subgroup	ERP Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
1.2.2 High quality studies						
Zhao 2014	2	34	4	34	4.5%	0.47 [0.08, 2.75]
Tang 2013	6	36	7	27	7.9%	0.57 [0.17, 1.95]
Munitiz 2010	23	74	28	74	22.9%	0.74 [0.38, 1.46]
Li 2012	29	59	30	47	20.1%	0.55 [0.25, 1.20]
Cao 2012	16	55	27	57	22.3%	0.46 [0.21, 0.99]
Brodner 1998	20	42	39	49	22.4%	0.23 [0.09, 0.59]
Subtotal (95% CI)		300		288	100.0%	0.50 [0.35, 0.72]
Total events	96		135			

Heterogeneity: Chi^2 = 4.07, df = 5 (P = 0.54); I^2 = 0%
Test for overall effect: Z = 3.78 (P = 0.0002)

Test for subgroup differences: Chi^2 = 0.06, df = 1 (P = 0.81), I^2 = 0%

Odds Ratio M–H, Fixed, 95% CI
0.1 0.2 0.5 1 2 5 10
Favours ERP   Favours control

Effect of inclusion in an enhanced recovery programme (ERP) on the incidence of postoperative morbidity within 30 days. M-H, Mantel-Haentzel test; CI, confidence intervals; df, degrees of freedom; I^2, I-squared statistic for heterogeneity. Weights are from fixed-effects analysis. Squares indicate the point estimates of the effect of the intervention (OR) and diamonds the summary estimate from the pooled studies; 95 per cent confidence intervals are shown as horizontal bars and in parentheses.

7.7.8 Fig. 4. Forest plot for operative mortality

Study or Subgroup	ERP Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
Brodner 1998	0	42	5	49	37.3%	0.10 [0.01, 1.77]
Cao 2012	1	55	3	57	21.4%	0.33 [0.03, 3.31]
Li 2012	1	59	0	47	4.0%	2.44 [0.10, 61.17]
Munitiz 2010	1	74	4	74	29.3%	0.24 [0.03, 2.20]
Tang 2013	2	36	1	27	8.0%	1.53 [0.13, 17.80]
Total (95% CI)		266		254	100.0%	0.40 [0.15, 1.07]
Total events	5		13			

Heterogeneity: Chi^2 = 3.51, df = 4 (P = 0.48); I^2 = 0%
Test for overall effect: Z = 1.83 (P = 0.07)

Effect of inclusion in an enhanced recovery programme (ERP) on the incidence of operative mortality. M-H, Mantel-Haentzel test; CI, confidence intervals; df, degrees of freedom; I^2, I-squared statistic for heterogeneity. Weights are from fixed-effects analysis. Squares indicate the point estimates of the effect of the intervention (OR) and diamonds the summary estimate from the pooled studies; 95 per cent confidence intervals are shown as horizontal bars and in parentheses.

7.7.9 Fig. 5. Forest plot for anastomotic leak

Study or Subgroup	ERP Events	ERP Total	Control Events	Control Total	Weight	Odds Ratio M–H, Fixed, 95% CI	Odds Ratio M–H, Fixed, 95% CI
Cao 2012	5	55	7	57	15.8%	0.71 [0.21, 2.40]	
Li 2012	8	59	5	47	12.2%	1.32 [0.40, 4.33]	
Munitiz 2010	5	74	6	74	14.1%	0.82 [0.24, 2.82]	
Tang 2013	3	36	3	27	7.9%	0.73 [0.13, 3.92]	
Tomaszek 2010	3	110	33	276	46.2%	0.21 [0.06, 0.69]	
Zhao 2014	0	34	1	34	3.7%	0.32 [0.01, 8.23]	
Total (95% CI)		368		515	100.0%	0.55 [0.33, 0.94]	
Total events	24		55				

Heterogeneity: Chi² = 5.39, df = 5 (P = 0.37); I² = 7%
Test for overall effect: Z = 2.20 (P = 0.03)

0.02 0.1 1 10 50
Favours ERP   Favours control

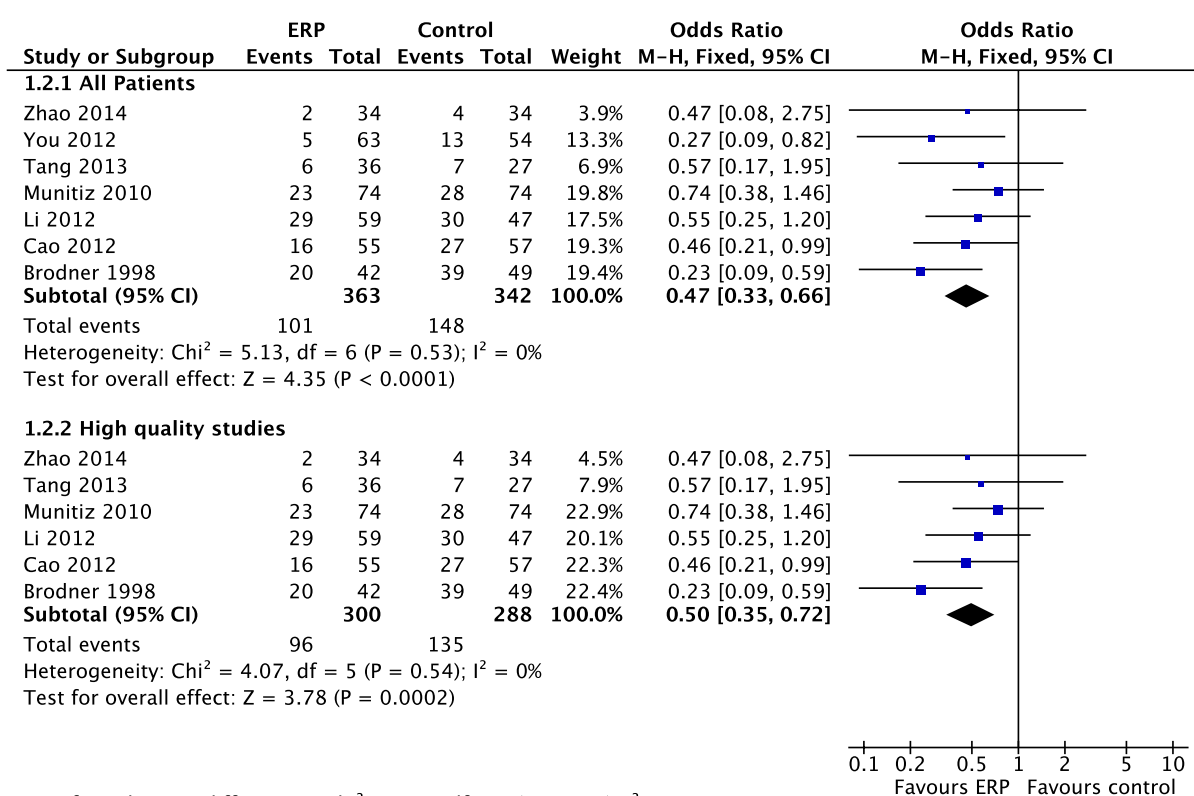Effect of inclusion in an enhanced recovery programme (ERP) on the incidence of anastomotic leak. M-H, Mantel-Haentzel test; CI, confidence intervals; df, degrees of freedom; I^2, I-squared statistic for heterogeneity. Weights are from fixed-effects analysis. Squares indicate the point estimates of the effect of the intervention (OR) and diamonds the summary estimate from the pooled studies; 95 per cent confidence intervals are shown as horizontal bars and in parentheses.
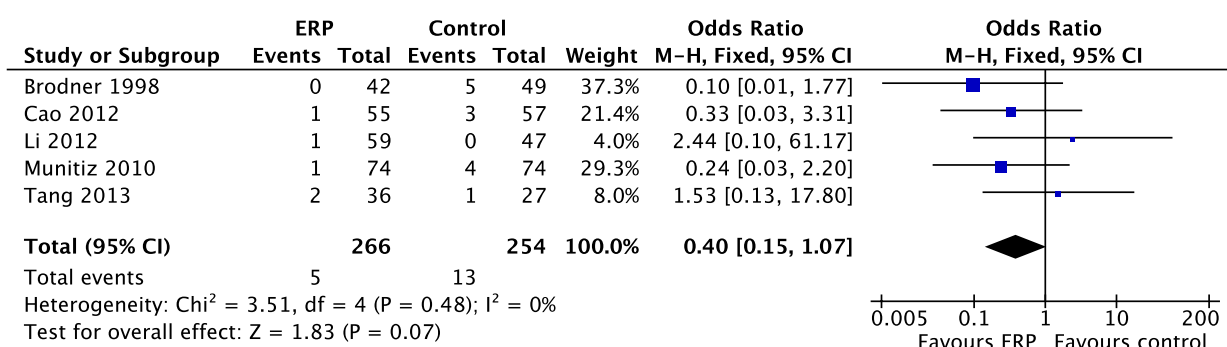
7.7.10 Fig. 6. Forest plot for pulmonary complications

Study or Subgroup	ERP Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
Brodner 1998	4	42	2	49	5.9%	2.47 [0.43, 14.24]
Cao 2012	6	55	11	57	34.2%	0.51 [0.18, 1.50]
Li 2012	13	59	13	47	40.0%	0.74 [0.30, 1.80]
Munitiz 2010	5	74	6	74	19.9%	0.82 [0.24, 2.82]
Total (95% CI)		230		227	100.0%	0.78 [0.45, 1.36]
Total events	28		32			

Heterogeneity: Chi^2 = 2.28, df = 3 (P = 0.52); I^2 = 0%
Test for overall effect: Z = 0.87 (P = 0.38)

Effect of inclusion in an enhanced recovery programme (ERP) on the incidence of pulmonary complications. M-H, Mantel-Haentzel test; CI, confidence intervals; df, degrees of freedom; I^2, I-squared statistic for heterogeneity. Weights are from fixed-effects analysis. Squares indicate the point estimates of the effect of the intervention (OR) and diamonds the summary estimate from the pooled studies; 95 per cent confidence intervals are shown as horizontal bars and in parentheses.
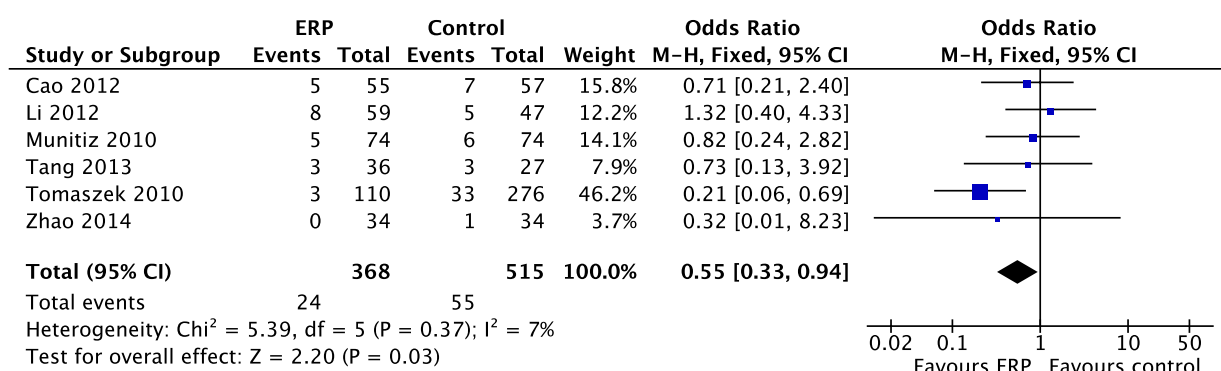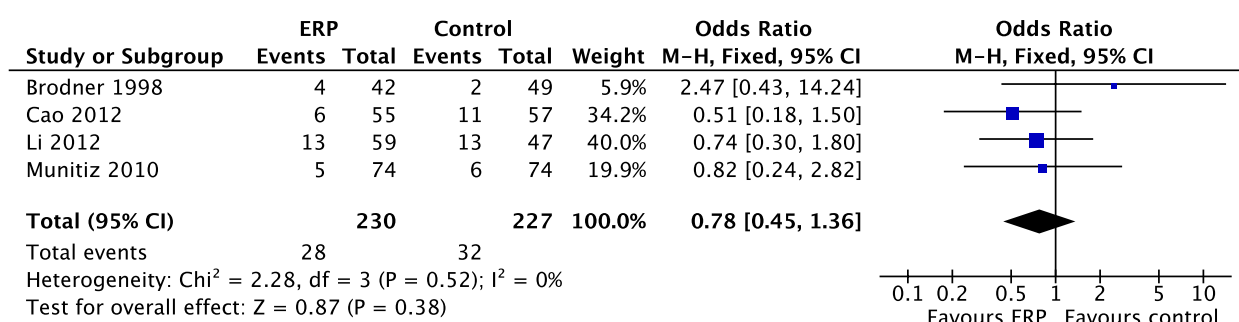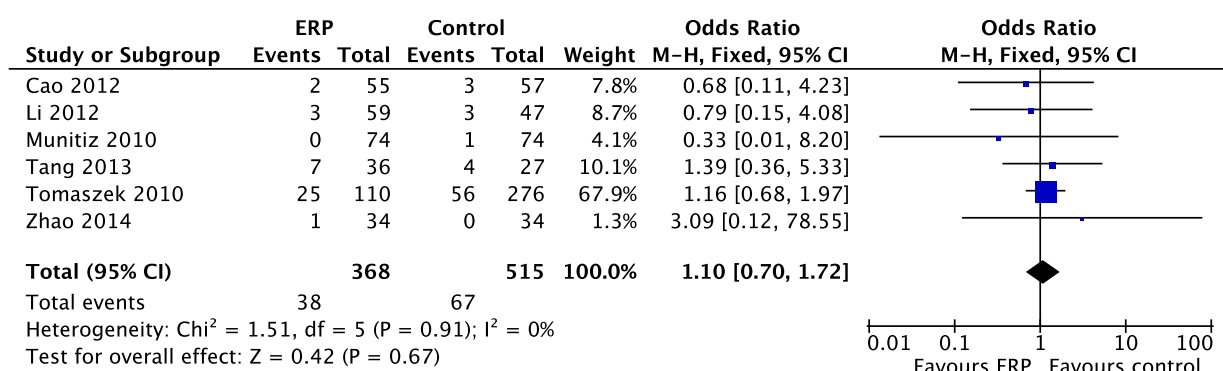
221

7.7.11 Fig. 7. Forest plot for readmission to hospital

Study or Subgroup	ERP Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
Cao 2012	2	55	3	57	7.8%	0.68 [0.11, 4.23]
Li 2012	3	59	3	47	8.7%	0.79 [0.15, 4.08]
Munitiz 2010	0	74	1	74	4.1%	0.33 [0.01, 8.20]
Tang 2013	7	36	4	27	10.1%	1.39 [0.36, 5.33]
Tomaszek 2010	25	110	56	276	67.9%	1.16 [0.68, 1.97]
Zhao 2014	1	34	0	34	1.3%	3.09 [0.12, 78.55]
Total (95% CI)		368		515	100.0%	1.10 [0.70, 1.72]
Total events	38		67			

Heterogeneity: Chi^2 = 1.51, df = 5 (P = 0.91); I^2 = 0%
Test for overall effect: Z = 0.42 (P = 0.67)

Odds Ratio M–H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours ERP   Favours control

Effect of inclusion in an enhanced recovery programme (ERP) on the incidence of readmission to hospital within 30 days. Mantel-Haentzel test; CI, confidence intervals; df, degrees of freedom; I^2, I-squared statistic for heterogeneity. Weights are from fixed-effects analysis. Squares indicate the point estimates of the effect of the intervention (OR) and diamonds the summary estimate from the pooled studies; 95 per cent confidence intervals are shown as horizontal bars and in parentheses.

CHAPTER 8

Outcomes following introduction of an enhanced recovery programme in gastric cancer surgery

8.1 SUMMARY

Enhanced recovery programmes (ERPs) are widely accepted in colorectal surgery, but few studies have investigated their use in gastric cancer surgery.

The aim of this study was to examine the outcomes of gastric cancer surgery in a UK regional cancer centre with specific reference to the introduction of an ERP.

Consecutive 117 patients (median age 71 years, 68 male) undergoing gastrectomy for cancer between May 20th 2008 and August 20th 2013 were studied prospectively before and after the introduction of an ERP (October 2010). The primary outcome measure was Length of hospital stay (LOHS). Secondary outcome measures were critical care burden, 30-day operative morbidity (graded according to Clavien-Dindo) and mortality.

LOHS was significantly shorter in the ERP group (11 vs. 14 days, $p=0.004$), as was the overall duration of critical care admission (0 vs. 1 day, $p<0.0001$). Multivariable analysis revealed inclusion in the ERP to be an independent and significant predictor of LOHS ($p=0.028$). There was no negative effect on morbidity (37.5% vs. 37.8%, $p=0.972$), major morbidity (CD≥3, 8.8% vs. 18.9%, $p=0.115$), mortality (2.5% vs. 8.1%, $p=0.163$) or readmission rate (7.5% vs. 5.4%, $p=0.676$) following introduction of the ERP. A significant cost-saving was observed in the ERP group (median admission cost 1440 vs. 1869 GBP, $p=0.001$).

An ERP in gastrectomy for cancer appeared feasible, safe and cost effective.

8.2 INTRODUCTION

Radical gastrectomy is a potentially curative, but high-risk, invasive procedure for gastric cancer. While remaining the mainstay of radical curative treatment for gastric cancer, (Allum et al., 2011) surgical resection is complex in nature and associated with significant risk of post-operative morbidity and mortality, even in well-nourished patients (Allum et al., 2011). Indeed, UK National Audit figures report an in-hospital mortality of 6.0 per cent (95% CI 4.8-7.4) and complication rate of 19.4 per cent in patients undergoing gastrectomy for cancer (Centre, 2010). Furthermore, 7.4 per cent of patients undergoing gastrectomy for cancer in the UK require further surgery for a complication (Centre, 2010).

Enhanced recovery programmes (ERPs) are well established in colorectal surgery and have demonstrated clear benefits of employing holistic multimodal perioperative strategies in resectional cancer surgery. Such improvements are achieved in the modern ERP through aggregation of the benefits of a number of interventions to optimise physiological, psychological and healthcare system factors surrounding major gastrointestinal surgery. Interventions are combined within a standardised pathway incorporating clear goals for patients and staff

members alike. Benefits include reductions in post-operative morbidity and lengths of hospital stay (Varadhan et al., 2010). However, little attention has been given to the potential role of ERPs in upper gastrointestinal (UGI) cancer surgery. Few studies exist reporting outcomes following implementation of ERPs in gastric cancer surgery, and sample sizes in existing reports are modest (He, 2010, Jeong et al., 2011, Jiang et al., 2007, Kiyama et al., 2003, Liu et al., 2010, So et al., 2008, Tang, 2013, Wang et al., 2010, Yamada et al., 2012). The systematic review and meta-analysis of the implementation of ERPs for gastrectomy for cancer contained within this thesis showed ERPs to be beneficial in reducing length of stay in hospital, post-operative pain scores, duration of intravenous fluid requirement, post-operative weight loss and overall cost. Moreover, no increase in post-operative morbidity or hospital readmission rate was observed.

Nutrition is a central component of gastrointestinal ERPs and radical gastrectomy commonly entails protracted periods of starvation following intestinal resection and anastomosis. Such periods without oral nutrition are employed to allow time for return to normal intestinal motility and to protect anastomoses from the stress of oral fluids and diet (Lewis et al., 2009). Consideration of nutritional requirements is particularly salient in patients requiring upper gastrointestinal cancer surgery, in whom pre-operative malnutrition is frequently present (Nygren et al., 2003). Indeed, severe malnutrition is associated with a higher incidence of post-operative complications and potential prolongation of the recovery period (Weimann et al., 2006).

The aim of this study was, therefore, to analyse the influence of a standardised multimodal peri-gastrectomy pathway for gastric cancer by comparison of intervention and control groups.

8.3 METHODS

8.3.1 Programme

Multimodal programmes for total and sub-total gastrectomy were constructed following an information gathering process inclusive of surgical, oncological, radiological, dietetic, nursing and physiotherapy staff members (Figure 1 – Summary of the ERP). The literature was consulted to inform specific aspects of the pathway. Programme development was led by three consultant surgeons (WL, GC, GB) operating within the regional cancer network. Pathway booklets were created, which served as a unified multidisciplinary patient record, within which all documentation was centralised during the individual patient journey.

8.3.2 Population

Groups were drawn from a consecutive series of patients receiving surgical treatment for gastric cancer within the South East Wales Cancer Network, which serves a population of approximately 1.4 million. The control group comprised patients undergoing open surgery between 20th

May 2008 and 30th September 2010 at two of three NHS Trusts within the network. The network was centralised to a single site on 1st August 2010 and, thereafter, a third NHS Trust also contributed patients to the centralised service. The ERP was implemented for all patients from 1st October 2010 onward, and the ERP group comprised patients undergoing surgery between this date and 20th August 2013.

8.3.3 Surgery

All patients underwent surgery according to decisions of a regional multidisciplinary team (MDT). Surgical procedure included subtotal gastrectomy and total gastrectomy (Table 2), all with D2 lymphadenectomy. Some patients received neoadjuvant therapy (Table 2) and all procedures were performed using an open approach.

8.3.4 Data collection

All data were collected prospectively by named researchers, by attendance at MDT meetings and prospective review of all surgical patients during their hospital admission. Data is, therefore, highly robust. Data collected included age, gender, Welsh Index of Multiple Deprivation overall (WIMD) and health (H-WIMD) deprivation rank (2008), radiological and histopathological stage of disease (TNM7) (Sobin LH, 2009b), surgical procedure performed, operative morbidity related to the Clavien-Dindo grade (CD) (Dindo et al., 2004), 30-day mortality, 30-day readmission, critical care length of stay in days (CC LOS) and total length of hospital stay (LOHS) in days.

8.3.5 Inclusion and exclusion criteria

Patients were included on an intention to treat basis. Patients with benign disease were excluded.

8.3.6 Outcome measures

The primary outcome was defined as length of hospital stay (LOHS) in days. Secondary outcome measures were incidence of post-operative morbidity, according to the Clavien-Dindo classification (Dindo et al., 2004), post-operative mortality and rates of readmission to hospital.

8.3.7 Statistical analysis

Statistical analysis was performed using the Predictive Analytics SoftWare (PASW [SPSS] Statistics v18.0.3, IBM Corporation, Armonk, New York, USA). Grouped data were expressed as median (range) and non-parametric analyses were used throughout. Statistical significance was determined as $p<0.05$. Categorical data were compared using the χ^2 test, except where groups contained counts of fewer than five, when Fisher's exact test (Fisher, 1922) was used. Grouped continuous data were compared using the Mann-Whitney U-test (Mann and Whitney, 1947). Further analysis of LOHS by group was performed using the Mantel-Cox log rank method of Kaplan and Meier (Kaplan and Meier, 1958). This incorporated LOHS into the model in place of survival, using discharge from hospital as the event and resulting in the construction of LOHS plots.

8.4 RESULTS

8.4.1 Details of the patients

A total of 117 consecutive patients undergoing gastrectomy for cancer were included in the study. Patient characteristics and surgical data are shown by group in Table 1.

8.4.2 Primary outcome measure

All measured lengths of stay were significantly shorter in the ERP group than in the Control group (Table 2). This was observed for the total length of stay in hospital (11 vs. 14 days, p=0.004, Figure 1), the overall duration of admission to critical care facilities (0 vs. 1 day, p<0.0001) and length of stay in level 2 (p=0.002) and level 3 environments (p<0.0001).

Multivariable analysis demonstrated inclusion in the ERP to be the sole independent, significant predictor of LOHS (p=0.028, Table 5).

8.4.3 Secondary outcome measures

8.4.3.1 Post-operative morbidity

Rates of overall morbidity were comparable between groups (37.5% vs. 37.8%, p=0.972, Table 5). Major morbidity (Clavien-Dindo Score ≥3) rates were lower in the ERP group, but this did not reach statistical significance (8.8% vs. 18.9%, p=0.115).

Additional specific complications showed similar, but non-significant trends toward lower rates in the ERP group, including respiratory infection

(15.0% vs. 24.3%, p=0.222), respiratory failure (2.5% vs. 10.8%, p=0.058), and anastomotic leak (2.5% vs. 8.1%, p=0.163).

8.4.3.2 Post-operative mortality

A 30-day mortality of 2.5% (n=2) was observed in the ERP group and 8.1% (n=3) in the Control group. This did not, however, reach statistical significance (p=0.163).

8.4.3.3 Readmission rate

The readmission rate was 7.5% (n=6) in the ERP group and 5.4% (n=2) in the Control group. Reasons for readmission are shown in Table 6. No significant difference was demonstrated in readmission rates between ERP and control patients (p=0.676).

8.4.3.4 Cancellation rate

A trend was observed toward a lower rate of cancellation resulting directly from unavailability of critical care facilities, though it did not reach statistical significance (6.1% vs. 16.7%, p=0.073).

8.5 DISCUSSION

This study represents the largest European series of patients undergoing surgery for gastric cancer within an ERP in relation to outcomes.

The principal findings were that ERPs were associated with significantly shorter lengths of stay in hospital and in critical care facilities, as well as reduced cost, without increasing post-operative morbidity or hospital readmission rates. Other significant benefits included a lower critical care related cancellation rate.

This study has several strengths. All data were collected prospectively by an established and experienced MDT whose results are well audited and stand up to international comparisons (Centre, 2010). The study groups were drawn from a large consecutive series, minimising concern over selection bias.

Several potential limitations were identified. This was a retrospective cohort study and, as such, randomisation was not undertaken. This limits the quality of the study when compared with a well-conducted randomised trial. However, a randomised trial is difficult to perform well in this area without access to separate clinical areas and medical and nursing staffs. These were not available in this unit.

The cancer network studied underwent significant change in August 2010, when all oesophagogastric cancer surgery was centralised to the unit studied. This is responsible for the disparity in group size in this cohort study.

A small number of patients within the control group were treated post-centralisation, compared with all patients in the ERAS group. This introduced the potential for confounding variables to influence outcomes

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in the post-centralisation period. It is difficult to be certain how much influence on outcomes was exerted by ERAS and the centralisation of services respectively. Furthermore, two additional surgeons were introduced to the unit when centralisation occurred. This may have influenced outcomes according to recognised learning curve phenomenon (Hopper et al., 2007).

However, the inclusion of centralisation as a variable in multivariable regression analysis alleviated concerns regarding its influence. While ERP emerged as an independent and significant predictor outcome on LOHS, centralisation did not.

In the absence of contemporary consensus regarding which interventions should be included in an ERP encompassing gastric cancer surgery, the ERP was developed based upon principles from related work in other surgical arenas. While it is possible that consistency between programmes may develop with further research, the colorectal experience has been that such variation persists (Wind et al., 2006).

No data were collected on pain or return of gut function. These have been reported in some studies (Feng et al., 2013, He, 2010, Chen Hu et al., 2012, Jiang et al., 2007, Kim et al., 2012, Liu et al., 2010, Wang et al., 2010, Yamada et al., 2012).

There is limited evidence in the literature for ERPs in gastrectomy for cancer, as demonstrated in the meta-analysis performed as chapter six in

this thesis. The majority has emerged from Asia and significant risk of bias exists throughout the literature base. However, the conclusion that ERPs are safe and feasible is supported by the findings in this Western population, with clear agreement between the results of our study and the meta-analysed data.

While the reported mean LOHS following gastrectomy for cancer varied widely, it was uniformly reduced by the introduction of an ERP. The LOHS in control groups ranged from 7.1 to 28.2 days, and in ERP groups was reduced to 5.4 to 18.1 days. LOHS in our unit lay within this range, reducing from 14 to 11 days with the introduction of the ERP.

Our results also agreed with the meta-analytical findings regarding operative morbidity, with no significant decrease in overall morbidity observed. However, a clear trend was seen in the meta-analysis toward a lower rate of operative morbidity in the ERP groups. This was mirrored in terms of major morbidity (Clavien-Dindo Score ≥3) in our study, with a reduction of more than 50%, from 18.9% to 8.8% with the introduction of the ERP. This did not reach statistical significance, perhaps as a result of type II error.

The readmission rate within this study did not increase significantly, in line with the results of the meta-analysis. This is an important finding, demonstrating that patients are not being discharged from hospital prematurely.

8.6 CONCLUSION

In conclusion, this study supports the use of our ERPs in gastric cancer surgery. The implementation of these multimodal approaches to perioperative management appears feasible, safe and cost effective, conferring benefits to health care providers and patients alike.

8.7 TABLES AND FIGURES

8.7.1 Table 1. Details of the patients

Variable		Total	ERP	Control
n		117	80	37
Gender (m:f, %)		68:32	68:32	69:31
Age in years (range)		71 (39-86)	71 (44-83)	71 (39-86)
Histology	HGD	2	1	1
	ACA	115	79	36
	SCC	0	0	0
Rad stage	0	1	0	1
	I	28	22	6
	II	33	22	11
	III	49	32	17
	IV	6	4	2
pTNM	0	5	5	0
	I	24	18	6
	II	22	11	11
	III	32	19	13
	IVa	20	15	5
	No resection	14	12	2
Nodes positive		1 (0-24)	0 (0-24)	1.5 (0-17)

ERP, enhanced recovery programme group; Control, control group; n, number; m, male; f, female; HGD, high grade dysplasia; ACA, adenocarcinoma; SCC, squamous cell carcinoma; Rad stage, radiological TNM7 stage; pTNM, histopathological TNM7stage

8.7.2 Table 2. Lengths of stay according to treatment group.

Variable	Total	ERP	Control	p-value
LOHS	12 (2-60)	11 (3-52)	14 (2-60)	0.006
Ward LOS	11 (0-54)	10.5 (3-48)	13 (0-54)	0.014
CC LOS	1 (0-22)	0 (0-15)	1 (0-22)	<0.0001
ITU LOS	0 (0-11)	0 (0-9)	0 (0-11)	<0.0001
HDU LOS	1 (0-11)	0 (0-6)	1 (0-11)	0.002

LOHS, length of hospital stay; LOS, length of stay in each clinical area (CC, critical care; ITU, intensive therapy unit; CC, critical care; HDU, high dependency unit)

8.7.3 Table 3. Morbidity by Clavien-Dindo (CD) grade according to treatment group (See section 1.9 for details of the CD classification system).

CD Grade	ERP	Control
0	50 (63%)	23 (62%)
I	8 (10%)	0 (0%)
II	15 (19%)	7 (19%)
IIIa	2 (3%)	1 (3%)
IIIb	1 (1%)	0 (0%)
IVa	1 (1%)	1 (3%)
IVb	0 (0%)	2 (5%)
V	3 (4%)	3 (8%)
Any morbidity	30 (37%)	14 (38%)

CD, Clavien-Dindo; ERP, Enhanced recovery programme group; Control, control group;

8.7.4 Table 4. Univariable analysis of factors influencing LOHS.

Variable	X^2	df	p-value
NodesPos	**107.928**	**13**	**<0.0001**
Centralisation	**7.039**	**1**	**0.008**
ERAS	**8.457**	**1**	**0.004**
pTNM7	**14.741**	**5**	**0.012**
pT7	10.025	6	0.124
pN7	4.520	4	0.340
Histology	0.495	1	0.482
pM7	1.646	3	0.649
radTNMstage	1.634	3	0.652
Gender	0.082	1	0.775
Age	0.260	47	0.992

$\underline{X^2}$ Chi square statistic; Df, degrees of freedom, NodesPos, number of positive nodes; Centralisation, operated upon in the centralised unit; ERAS, operated upon within enhanced recover after surgery framework; pTNM7, histopathological TNM7 stage; pT7 / pN7 / pM7; histopathological T / N / M stage; Histology, histopathological cell type; radTNMstage, radiological TNM7 stage.

8.7.5 Table 5. Multivariable analysis of factors influencing LOHS.

Variable	Hazard ratio	95% CI	p-value
ERP	0.579	0.356-0.942	0.028

CI, confidence interval; ERP, operated upon within enhanced recover programme;

8.7.6 Table 6. Reasons for re-admission within 30 days.

Patient number	ERAS n=4 (7.5%)	Control n=2 (5.4%)
1	Abdominal collection	Acute kidney injury
2	Abdominal collection	Constipation
3	Pain	
4	Pancreatic pseudocyst	

8.7.7 Figure 1 – Summary of the ERP

	Total Gastrectomy	Subtotal
Pre-	Patient education; CPX; Post-op level of care requirement predicted (usually HDU); Carbohydrate drinks until 2hr and full diet until 6hr pre-op; No premedication.	
Intra-	Standardised anaesthetic approach	
Post-op Day	Level 1-2 care; H_2O, then feed 10ml/hr via jejunostomy.	Level 1 care; H_2O, then feed 10ml/hr via jejunostomy; Oral fluids.
Day 1	Sit out x2; Walk x2 Achieve 40ml enteral feed (jej)	Sit out x4; Walk x3 Achieve 40ml enteral feed (jej)
Day 2	Sit out x4; Walk x3 Achieve 80ml enteral feed (jej)	
Day 3	Sit out 6hr; Walk x3; Reduce IVI	Sit out 6hr; Walk x3 Reduce IVI; Urinary catheter out
Day 4	Sit out 6hr; Walk x3; Urinary catheter out	Sit out 6hr; Walk x3
Day 5 onward	Sit out 6hr; Walk x3;	
Day X	Discharge	

8.7.8 Figure 2. Kaplan-Meier plot to demonstrate the influence of treatment in ERP (ERAS) on LOHS.

Modified Kaplan–Meier plot for length of stay

Variable	X2	df	p-value
ERAS	8.457	1	0.004

CHAPTER 9

Outcomes following introduction of an enhanced recovery

programme in oesophageal cancer surgery

9.1 SUMMARY

The aim of this study was to examine the outcomes of oesophageal cancer surgery in a UK regional cancer centre with specific reference to the introduction of an ERP.

One hundred and seventeen consecutive patients (median age 63 years, 94 male) diagnosed with oesophageal cancer between May 2008 and August 2013 were studied prospectively before and after the introduction of an ERP (October 2010). The primary outcome measure was total length of hospital stay (LOHS). Secondary outcome measures were critical care length of stay (CCLOS), 30-day operative morbidity (graded according to Clavien-Dindo), 30-day operative mortality, 30-day readmission to hospital.

From 117 studied patients, 81 were treated in the ERP and 36 were controls. Median LOHS was significantly shorter in the ERP group (14 vs. 18.5 days, p=0.032). CCLOS was also significantly lower in the ERP group (CCLOS 1 vs. 3 day, p<0.0001) as well as level two and three LOS analysed separately (p<0.005). The ERP was associated with a significant reduction in major post-operative morbidity (CD ≥3, 18.5% vs. 38.9%, p=0.019). No significant difference was observed in the incidence of specific complications (p>0.05), 30-day readmission to hospital (8.6% vs. 13.9%, p=0.388) or 30-day mortality rate (3.7% vs. 2.8%, p=0.799) between the ERP and CON groups respectively. Cost analysis demonstrated ERP to be associated with a significant cost saving (median 2109 vs. 3498 GBP, p<0.0001).

A non-significant trend toward fewer cancellations related to critical care pressures was observed in the ERP group (7.4% vs. 19.4%, p=0.059).

An ERP in oesophageal cancer surgery was feasible, safe and cost effective.

9.2 INTRODUCTION

Oesophagectomy is a potentially curative, but high-risk, invasive procedure for oesophageal cancer. While remaining the mainstay of radical curative treatment for oesophageal cancer (Allum et al., 2011), surgical resection is complex in nature and associated with significant risk of post-operative morbidity and mortality, even in well-nourished patients (Allum et al., 2011). Indeed, UK National Audit figures report an in-hospital mortality of 6.0 per cent (95% CI 4.8-7.4) and complication rate of 19.4 per cent in patients undergoing oesophagectomy for cancer (Centre, 2010). Furthermore, 7.4 per cent of patients undergoing oesophagectomy for cancer in the UK require further surgery for a complication (Centre, 2010).

Enhanced recovery programmes (ERPs) are well established in colorectal surgery and have demonstrated clear benefits of employing holistic multimodal perioperative strategies in resectional cancer surgery. Such improvements are achieved in the modern ERP through aggregation of the benefits of a number of interventions to optimise

physiological, psychological and healthcare system factors surrounding major gastrointestinal surgery. Interventions are combined within a standardised pathway incorporating clear goals for patients and staff members alike. Benefits include reductions in post-operative morbidity and lengths of hospital stay (Varadhan et al., 2010). However, little attention has been given to the potential role of ERPs in upper gastrointestinal (UGI) cancer surgery. Few studies exist reporting outcomes following implementation of ERPs in oesophageal cancer surgery, and sample sizes in existing reports are modest (He, 2010, Jeong et al., 2011, Jiang et al., 2007, Kiyama et al., 2003, Liu et al., 2010, So et al., 2008, Tang, 2013, Wang et al., 2010, Yamada et al., 2012). The systematic review and meta-analysis of the implementation of ERPs for oesophagectomy for cancer contained within this thesis showed ERPs to be beneficial in reducing length of stay in hospital, post-operative pain scores, duration of intravenous fluid requirement, post-operative weight loss and overall cost. Moreover, no increase in post-operative morbidity or hospital readmission rate was observed.

Nutrition is a central component of gastrointestinal ERPs and radical oesophagectomy commonly entails protracted periods of starvation following intestinal resection and anastomosis. Such periods without oral nutrition are employed to allow time for return to normal intestinal motility and to protect anastomoses from the stress of oral fluids and diet (Lewis et al., 2009). Consideration of nutritional requirements is particularly salient in patients requiring upper gastrointestinal cancer surgery, in whom pre-operative malnutrition is frequently present (Nygren et al.,

2003). Indeed, severe malnutrition is associated with a higher incidence of post-operative complications and potential prolongation of the recovery period (Weimann et al., 2006).

The aim of this study was, therefore, to analyse the influence of a standardised multimodal peri-oesophagectomy pathway for oesophageal cancer by comparison of intervention and control groups.

9.3 METHODS

9.3.1 Programme

A multimodal programme for oesophagectomy was constructed following an information gathering process inclusive of surgical, oncological, radiological, dietetic, nursing and physiotherapy staff members (Figure 1). The literature was consulted to inform specific aspects of the pathway. Programme development was led by three consultant surgeons (WL, GC, GB) operating within the regional cancer network. A pathway booklet was created, which served as a unified multidisciplinary patient record, within which all documentation was centralised during the individual patient journey.

9.3.2 Population

Groups were drawn from a consecutive series of patients receiving surgical treatment for oesophageal cancer within the South East Wales

Cancer Network, which serves a population of approximately 1.4 million. The control group comprised patients undergoing open surgery between 20th May 2008 and 30th September 2010 at two of three NHS Trusts within the network. The network was centralised to a single site on 1st August 2010 and, thereafter, a third NHS Trust also contributed patients to the centralised service. The ERP was implemented for all patients from 1st October 2010 onward, and the ERP group comprised patients undergoing surgery between this date and 20th August 2013.

9.3.3 Surgery

All patients underwent surgery according to decisions of a regional multidisciplinary team (MDT). Some patients received neoadjuvant therapy (Table 2) and all procedures were performed using an open approach.

9.3.4 Data collection

All data were collected prospectively by named researchers, by attendance at MDT meetings and prospective review of all surgical patients during their hospital admission. Data is, therefore, highly robust. Data collected included age, gender, Welsh Index of Multiple Deprivation overall (WIMD) and health (H-WIMD) deprivation rank (2008), radiological and histopathological stage of disease (TNM7) (Sobin LH, 2009b), surgical procedure performed, operative morbidity related to the Clavien-Dindo grade (CD, see section 1.9) (Dindo et al., 2004), 30-day mortality, 30-day readmission, critical care length of stay in days (CC LOS) and

total length of hospital stay (LOHS) in days.

9.3.5 Inclusion and exclusion criteria

Patients were included on an intention to treat basis. Patients with benign disease were excluded.

9.3.6 Outcome measures

The primary outcome was defined as length of hospital stay (LOHS) in days. Secondary outcome measures were incidence of post-operative morbidity, according to the Clavien-Dindo classification (Dindo et al., 2004), post-operative mortality and rates of readmission to hospital.

9.3.7 Statistical analysis

Statistical analysis was performed using the Predictive Analytics SoftWare (PASW [SPSS] Statistics v18.0.3, IBM Corporation, Armonk, New York, USA). Grouped data were expressed as median (range) and non-parametric analyses were used throughout. Statistical significance was determined as $p<0.05$. Categorical data were compared using the χ^2 test, except where groups contained counts of fewer than five, when Fisher's exact test (Fisher, 1922) was used. Grouped continuous data were compared using the Mann-Whitney U-test ((Mann and Whitney, 1947). Further analysis of LOHS by group was performed using the Mantel-Cox log rank method of Kaplan and Meier (Kaplan and Meier, 1958). This incorporated LOS into the model in place of survival, using

discharge from hospital as the event and resulting in the construction of LOHS plots.

9.4 RESULTS

9.4.1 Details of the patients

A total of 117 consecutive patients undergoing oesophagectomy for cancer were included in the study. Patient characteristics and surgical data are shown by group in Table 1.

9.4.2 Primary outcome measure

All measured lengths of stay were significantly shorter in the ERP group than in the Control group (Table 2). This was observed for the total length of stay in hospital (14 vs. 18.5 days, p=0.003, Figure 2), the overall duration of admission to critical care facilities (p<0.0001) and independent lengths of stay in level 2 (p=0.038) and level 3 environments (p<0.0001).

Multivariable analysis demonstrated inclusion in the ERP to be the strongest independent, significant predictor of LOHS (p=0.001, Table 4). TNM stage was the only other independent predictor of LOHS (p=0.003).

9.4.3 Secondary outcome measures

9.4.3.1 Post-operative morbidity

Rates of overall morbidity were comparable between groups (56.8% vs. 52.8%, p=0.687, Table 3), but the rate of major morbidity (Clavien-Dindo Score ≥3) was significantly lower in the ERP group than the CON group (18.5% vs. 38.9%, p=0.019, Table 3).

A similar but non-significant trend toward lower incidence of respiratory failure was observed in the ERP group (8.6% vs. 16.7%, p=0.202). No significant difference was observed in the incidence of respiratory infection (24.7% vs. 27.8%, p=0.724) or anastomotic leak (13.6% vs. 13.9%, p=0.964). None was statistically significant.

9.4.3.2 Post-operative mortality

A 30-day mortality of 3.7% (n=3) was observed in the ERP group and 5.6% (n=2) in the Control group. This was not statistically significant (p=0.648).

9.4.3.3 Readmission rate

The readmission rate was 8.6% (n=7) in the ERP group and 13.9% (n=5) in the Control group. Reasons for readmission are shown in Table 6. No significant difference was demonstrated in readmission rates between ERP and control patients (p=0.388).

9.4.3.4 Cancellation rates

A trend was observed toward a lower rate of cancellation resulting directly from unavailability of critical care facilities, though it did not reach statistical significance (6.6% vs 16.7%, p=0.073).

9.5 DISCUSSION

This study represents the largest European series of patients undergoing surgery for oesophageal cancer within an ERP in relation to outcomes.

The principal findings were that ERPs were associated with significantly shorter LOHS, reduced incidence of post-operative morbidity and reduced cost, without an increase in rates of hospital readmission, specific morbidity or mortality. Other significant benefits included a lower critical care related cancellation rate.

This study has several strengths. All data were collected prospectively by an established and experienced MDT whose results are well audited and stand up to international comparisons (Centre, 2010). The study groups were drawn from a large consecutive series, minimising concern over selection bias.

Several potential limitations were identified. This was a retrospective cohort study and, as such, randomisation was not undertaken. This limits

the quality of the study when compared with a well-conducted randomised trial. However, a randomised trial is difficult to perform well in this area without access to separate clinical areas and medical and nursing staffs. These were not available in this unit.

The cancer network studied underwent significant change in August 2010, when all oesophagogastric cancer surgery was centralised to the unit studied. A small number of patients within the control group were treated post-centralisation, compared with all patients in the ERAS group. This introduced the potential for confounding variables to influence outcomes in the post-centralisation period. It is difficult to be certain how much influence on outcomes was exerted by ERAS and the centralisation of services respectively. Furthermore, two additional surgeons were introduced to the unit when centralisation occurred. This may have influenced outcomes according to recognised learning curve phenomenon (Hopper et al., 2007).

However, the inclusion of centralisation as a variable in multivariable regression analysis alleviated concerns regarding its influence. While ERP emerged as an independent and significant predictor of LOHS, centralisation did not.

In the absence of contemporary consensus regarding which interventions should be included in an ERP encompassing gastric cancer surgery, the ERP was developed based upon principles from related work in other surgical arenas. While it is possible that consistency between

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programmes may develop with further research, the colorectal experience has been that such variation persists (Wind et al., 2006). There is very limited evidence in the literature for ERPs in oesophagectomy for cancer, as demonstrated in the meta-analysis performed as chapter seven in this thesis. The majority has emerged from Asia and significant risk of bias exists throughout the literature base. However, the conclusion that ERPs are safe and feasible is supported by the findings in this Western population, with clear agreement between the results of our study and the meta-analysed data.

While the reported mean LOHS following oesophagectomy for cancer varied widely, it was uniformly reduced by the introduction of an ERP. The LOHS in control groups ranged from 7.5 to 15.0 days, and in ERP groups was reduced to 6.3 to 11 days. LOHS in our unit was reduced from 18.5 to 14 days with the introduction of the ERP.

Our results did not demonstrate a significant reduction in overall morbidity, although a trend toward a slightly reduced rate in the ERP was shown (57% vs. 53%). In the meta-analysis, inclusion in an ERP was associated with a significantly lower rate of operative morbidity (OR 0.47 (0.33 to 0.66), p<0.0001). This was mirrored in terms of major morbidity (Clavien-Dindo Score ≥3) in our study, with a reduction of more than 50%, from 38.9% to 18.5% with the introduction of the ERP. This did not reach statistical significance, perhaps as a result of type II error.

The readmission rates within this study were not significantly different, in line with the results of the meta-analysis. In fact the readmission rate in our study showed a trend toward being lower in the ERP group. This is an important finding, demonstrating that patients are not being discharged from hospital prematurely.

9.6 CONCLUSION

In conclusion, this study supports the use of our ERPs in oesophageal cancer surgery. The implementation of these multimodal approaches to perioperative management appears feasible, safe, and cost effective, conferring benefits to health care providers and patients alike.

9.7 TABLES AND FIGURES

9.7.1 Table 1. Details of the patients

Variable		Total	ERP	Control
n		117	81	36
Gender (m:f, %)		80:20	80:20	81:19
Age in years (range)		63 (24-80)	63 (24-76)	64 (37-80)
Histology	**HGD**	1	1	0
	ACA	101	67	34
	SCC	15	13	2
Rad stage	**0 (HGD)**	3	2	1
	I	37	26	11
	II	34	22	12
	III	43	31	12
	IV	0	0	0
pTNM	**0**	2	1	1
	I	32	22	10
	II	26	19	7
	III	31	22	9
	IVa	8	6	2
	No resection	18	11	7
Nodes positive		0 (0-24)	0 (0-24)	1.0 (0-13)

ERP, enhanced recovery programme group; Control, control group; n, number; m, male; f, female; HGD, high grade dysplasia; ACA, adenocarcinoma; SCC, squamous cell carcinoma; Rad stage, radiological TNM7 stage; pTNM, histopathological TNM7stage

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9.7.2 Table 2. Lengths of stay according to treatment group.

Variable	Total	ERP	Control	p-value
LOHS	15 (4-119)	14 (4-47)	18.5 (4-119)	p=0.032
Ward LOS	13 (0-86)	13 (0-41)	14.5 (2-86)	p=0.463
CC LOS	1 (0-70)	1 (0-37)	3 (0-70)	p<0.0001
ITU LOS	0 (0-70)	0 (0-17)	2 (0-70)	p<0.0001
HDU LOS	1 (0-20)	1 (0-20)	2 (0-8)	p=0.038

ERP, Enhanced recovery programme group; Control, control group; LOHS, length of hospital stay; LOS, length of stay in each clinical area (CC, critical care; ITU, intensive therapy unit; HDU, high dependency unit)

9.7.3 Table 3. Morbidity by Clavien-Dindo (CD) grade according to treatment group (See section 1.9 for details of the CD classification system).

CD Grade	ERP	Control
0	35 (43%)	17 (47%)
I	7 (9%)	0 (0%)
II	24 (30%)	5 (14%)
IIIa	3 (4%)	5 (14%)
IIIb	3 (4%)	2 (6%)
IVa	5 (6%)	5 (14%)
IVb	1 (1%)	0 (0%)
V	3 (4%)	2 (6%)
Any morbidity	46 (57%)	19 (53%)

CD, Clavien-Dindo; ERP, Enhanced recovery programme group; Control, control group;

9.7.4 Table 4. Univariable analysis of factors influencing LOHS.

Variable	X2	df	p-value
pT7	67.324	6	<0.0001
pTNM7	47.756	5	<0.0001
pN7	25.549	4	<0.0001
Age	63.760	36	0.003
ERAS	8.964	1	0.003
NodesPos	15.800	9	0.071
Centralisation	3.029	1	0.082
radTNMstage	3.542	3	0.315
Histology	1.890	2	0.389
Gender	0.389	1	0.529
pM7	1.070	3	0.784

$\underline{X}^2$ Chi square statistic; Df, degrees of freedom, pTNM7, histopathological TNM7 stage; pT7 / pN7 / pM7; histopathological T / N / M stage; ERAS, operated upon within enhanced recover after surgery framework; NodesPos, number of positive nodes; Centralisation, operated upon in the centralised unit; radTNMstage, radiological TNM7 stage; Histology, histopathological cell type.

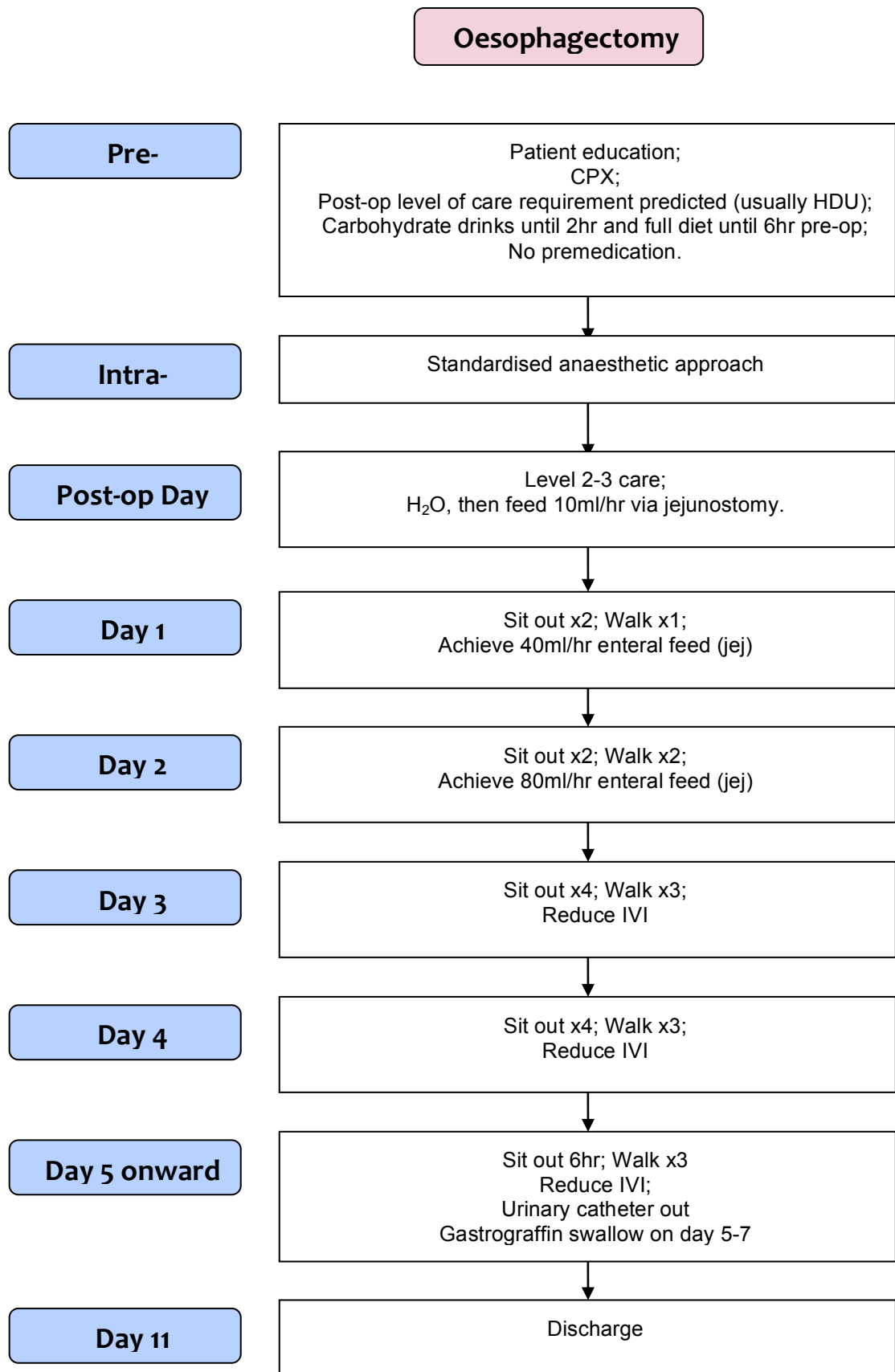### 9.7.5 Table 5. Multivariable analysis of factors influencing LOHS.

Variable	Hazard ratio	95% CI	p-value
ERP	0.380	0.218-0.660	0.001
pTNM stage	0.076	0.013-0.431	0.003

CI, confidence interval; pTNM stage, histopathological TNM7 stage; ERP, operated upon within enhanced recover programme;

9.7.6 Table 6. Reasons for re-admission within 30 days.

Patient number	ERAS n=7 (8.6%)	Control n=5 (13.9%)
1	Pneumonia	Anastomotic leak
2	Pneumonia	Vomiting
3	Pneumonia	Persistent chyle leak
4	Pleural effusion	Hernia
5	Acute urinary retention	Disease progression (symptomatic)
6	Wound infection	
7	Disease progression (spinal metastases)	

9.7.7 Figure 1 – ERAS pathway

Oesophagectomy

Pre-	Patient education; CPX; Post-op level of care requirement predicted (usually HDU); Carbohydrate drinks until 2hr and full diet until 6hr pre-op; No premedication.
Intra-	Standardised anaesthetic approach
Post-op Day	Level 2-3 care; H_2O, then feed 10ml/hr via jejunostomy.
Day 1	Sit out x2; Walk x1; Achieve 40ml/hr enteral feed (jej)
Day 2	Sit out x2; Walk x2; Achieve 80ml/hr enteral feed (jej)
Day 3	Sit out x4; Walk x3; Reduce IVI
Day 4	Sit out x4; Walk x3; Reduce IVI
Day 5 onward	Sit out 6hr; Walk x3 Reduce IVI; Urinary catheter out Gastrograffin swallow on day 5-7
Day 11	Discharge

9.6.8 Figure 2 - Kaplan-Meier plot to demonstrate the influence of treatment in ERP (ERAS) on LOHS.

Modified Kaplan-Meier plot for length of stay

Variable	X2	df	p-value
ERAS	8.964	1	0.003

CHAPTER 10

General discussion and prospect

10.1 General discussion and prospect

Surgery remains the mainstay of curative treatment for gastric and oesophageal cancer. However, oesophagogastric cancer surgery is associated with high risk and outcomes remain poor in comparison to many other malignancies. Centralisation of services and meticulous stage-directed management have permitted improved outcomes (Chan et al., 2013), but better outcome prediction and further improvements to perioperative risk stratification and management are required.

This thesis examines existing and novel physiological and body composition risk assessment modalities and perioperative management programmes in oesophagogastric cancer surgery. It examines the utility of CT and BIA body composition measures, as well as CPX testing, in predicting outcomes following major oesophagogastric surgery. It goes on to explore the impact of the introduction of enhanced recovery programmes in this arena.

10.1.1 Bioelectrical impedance analysis

Despite documented surface electrode measurement of bioelectrical tissue properties reaching back over 40 years, little use has been made of BIA technology in the surgical arena. The findings reported in this thesis demonstrated that BIA-measures of fat-free mass (FFM) and muscle mass (MM) provided useful predictive information regarding length of hospital stay (LOHS) and survival after oesophagogastric

cancer surgery. Both FFM and MM were shown to be independent and significant predictors of LOHS.

Methods of minimising muscle wasting and promoting weight maintenance or even weight gain pre-operatively should be sought, with assessment of the impact of such methods on outcomes.

Modern BIA analysers permit the performance of a simple and quick reading, yielding a wide range of variables spanning direct physical conduction measures, such as resistance and reactance, through to complex derived measures of fluid volumes, mineral stores, ion levels and body composition, such as those studied in this thesis. Each of these variables may have significant utility in the arena of surgery, oesophagogastric and beyond. In particular, future work should investigate the impact of fluid volumes, such as extracellular and intracellular volumes, on outcomes in the perioperative period. These measures are to some degree accessible to the clinical team during the patient journey and targeted fluid management, with individual BIA-directed goals may be the next area for marginal gain in the perioperative care of these patients.

10.1.2 CT-measured psoas muscle density

In addition to derived measures of body composition, such as those in BIA that employ complex calculations based on published algorithms, radiological imaging modalities can offer further insight into a patient's body composition.

Oesophagogastric cancer staging requires an extensive set of radiological investigations, which represents a valuable resource for the multidisciplinary team in the preoperative assessment of patients for surgery. The findings in this thesis suggest that CT-measured psoas muscle density (PMD) holds significant and independent predictive value in relation to survival, a greater density predicting longer survival. PMD did not appear to offer useful predictions of perioperative outcomes of morbidity, mortality and LOHS. As the use of this type of measurement to profile patients' body composition grows in popularity, emerging technology and methods should be further explored as potential areas for improved risk and outcome prediction. The most extensive work in this area has come from Englesbe and colleagues, who have led on the concept of morphometric analysis, or analytic morphomics, in the assessment of the surgical patient (Englesbe et al., 2012, Englesbe et al., 2010, Englesbe et al., 2013, Harbaugh et al., 2013, Lee et al., 2011a, Lee et al., 2011b, Sabel et al., 2011). The application of this type of detailed analysis of existing available radiology should be encouraged in oesophagogastric cancer, with full exploration of their value in outcome prediction.

10.1.3 Cardiopulmonary exercise testing

CPX is increasingly being used in pre-operative assessment as a demonstration of the capacity of a patient to cope with the physiological stresses of surgical intervention.

Chapters four and five within this thesis represent the largest series to date of patients with gastric and oesophageal cancer respectively, undergoing CPX testing as a pre-operative assessment for surgery.

In gastric cancer, VE/VCO_2 was found to be of greater predictive value than other CPX variables for operative morbidity and survival. Indeed, a VE/VCO_2 cut-off of 34 emerged as a significant predictor of survival.

Conversely, in patients with oesophageal cancer, VO_2 peak was found to be of greater predictive value than other CPX variables for operative morbidity, LOHS and survival. Multivariable analysis demonstrated VO_2 peak to be an independent, significant predictor of LOHS, and a cut-off of 22 ml/kg/min emerged as a significant predictor of survival. A high VE/VCO_2 was also associated with operative morbidity in this cohort.

A clear point to emerge from this thesis regarding CPX is the importance of interpreting results from CPX testing, and indeed additional assessment modalities, in combination rather than in isolation. Convincing evidence of suitably reliable individual cutoffs to determine the appropriate treatment modality in isolation have not been identified and the holistic interpretation of available data by an experienced MDT continues to provide the most appropriate assessment of the contemporary oesophagogastric cancer patient as an individual.

Future work should further explore the variables examined herein, performing CPX with blinding of anaesthetist and surgeon responsible for surgery. This may remove the confounding effect of non-blinding by reducing the differences in consequent perioperative management employed to accommodate and minimise the risks identified by CPX.

However, logistical factors would present significant challenges to performing this type of study within our centre and ethical implications may well be unsurpassable.

A specific group of interest would be those patients whose CPX results suggested that they were borderline physiologically fit to undergo surgery. Randomising patients within this sub-group to either surgery or definitive chemoradiotherapy could provide meaningful evidence on patient selection for surgery in this challenging group of patients.

A number of patients studied within our unit experienced difficulty with the performance of the CPX test. It is a recognised limitation of CPX testing that in some cases, the patient may be either unable or unwilling to achieve maximal cardiovascular effort, often for physical reasons including joint disease, poor coordination and inflexibility. A less studied CPX variable exists that may offer a way to overcome this difficulty. The oxygen uptake efficiency slope (OUES) has been demonstrated as an objective, effort-independent estimation of cardiorespiratory functional reserve in cardiac patients and normal subjects (Baba et al., 1996, Baba et al., 1999b, Baba et al., 1999a). No study exists in the literature exploring the prognostic value of OUES in oesophagogastric surgical patients, and only a single, passing reference to OUES in surgical patients was identified outside of cardiothoracic surgery (Colson et al., 2012).

10.1.4 Systematic review and meta-analysis of ERPs

This thesis contains the most comprehensive systematic review and meta-analysis to date to examine the effects of ERPs in patients undergoing surgery for gastric cancer and oesophageal cancer respectively.

Following the success of ERPs in colorectal surgery, it is perhaps surprising that similar approaches to formally structure the peri-operative management of oesophagogastric cancer patients have been slow to emerge.

In both the gastric and oesophageal meta-analyses, significant reductions in length of hospital stay (LOHS, $p=0.001$, $p<0.001$) were observed within ERPs. These were not associated with any increase in morbidity, mortality or readmission and, in fact, a reduction in morbidity was observed in oesophageal ERPs ($p<0.0001$). Clear cost benefits were also shown in gastric cancer ERPs ($p<0.001$). It was concluded that ERPs in oesophagogastric cancer surgery appear feasible and safe.

Further high-quality randomised trials of ERPs in this arena are needed, particularly from the Western World, to address the paucity of studies from Europe and North America in comparison to Asia. Future meta-analysis of the literature would then be more reliably applicable to the Western developed world, as well as the East.

10.1.5 Oesophagogastric ERP outcomes

As discussed directly above, it is surprising that few studies have reported the impact of multimodal peri-operative care programmes in

oesophagogastric cancer. This thesis examines outcomes in the largest European series of gastric and oesophageal cancer operated within an ERP or fast-track surgery programme.

The findings mirror those from the wider literature, as demonstrated in the meta-analyses herein. LOHS following gastrectomy and oesophagectomy was three and four and a half days shorter respectively within ERPs compared with control patients (p=0.004, p=0.032), without negative effects on morbidity, mortality or readmission rate. Additional cost benefits, averaging a saving of over 400 GBP per gastrectomy and almost 1400 GBP per oesophagectomy, were observed in the ERP group (p=0.001, p<0.0001). These results led to the conclusion that ERPs for oesophagogastric cancer in this unit, similarly to the wider literature, appear feasible, safe and cost effective.

Comparing the relative value of the ERPs for gastric and oesophageal cancer surgery in our unit, both appear to be similarly valuable. With regard to the above-mentioned significant reductions in LOHS, ERP inclusion was the strongest factor influencing LOHS within multivariable analysis. The effect on the incidence of major morbidity was greater within the oesophageal ERP than the gastric ERP, with a statistically significant reduction seen within the oesophageal ERP. The effect on specific complications, mortality and readmission was very similar between ERPs. The influence on cost was also more profound in the oesophageal ERP, predominantly as a result of the greater reliance upon critical care for oeosophagectomy prior to the introduction of the ERP and

also the greater reduction in length of stay achieved within the oesophageal ERP, as compared with the gastric ERP (4.5 vs. 3 days).

While ERPs for gastric and oesophageal cancer were both particularly beneficial, the oesophageal ERP was, therefore, shown to offer slightly greater benefits to patients, in terms of morbidity and LOHS, and also to healthcare provider, in terms of morbidity, LOHS and cost, than the gastric ERPs.

Future work should seek to disseminate the practice described within these programmes and further refine the detail within them, actively incorporating evidence-based advances in the peri-operative management of these high-risk and complex surgical patients.

10.2 CONCLUSION

In conclusion, the findings in this thesis have offered new and deepened insights into areas of pre-operative risk assessment and outcome prediction. Future work should seek to build on the utility identified using these predictive approaches, harnessing available technology to develop multimodal, reproducible, evidence-based tools for risk and outcome prediction. This could offer clinicians and patients a more accurate assessment of the possible outcomes and help to accurately identify those patients most likely to benefit from surgical intervention.

Additional work on the perioperative management of patients in ERPs should seek to aggregate the marginal gains, which continue to emerge

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within the literature, into programmes that offer a structured and coordinated approach to the management of these complex patients, whose post-operative journey is made difficult by nutritional factors, analgesic challenges and often operative morbidity.

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APPENDIX A

Publications and communications derived from work in this thesis

Published abstracts

Beamish AJ, Davies LI, Karran A, Thomas C, Witherspoon J, Blake P, Barlow R, Foley K, Howells G, Roberts SA, Lewis WG.
Prognostic significance of CT muscle density in upper gastrointestinal cancer.
In press: *Gastroenterology.*

Beamish AJ, Blake P, Chan DSY, Karran A, Lewis WG.
Systematic review and meta-analysis of enhanced recovery programmes in gastric cancer surgery.
Gastroenterology 2013; 144(5) (Suppl 1):S-220 (IF: 12.032)

Beamish AJ, Chan DSY, Karran A, Blake PA, Lewis WG.
Systematic review and meta-analysis of enhanced recovery programmes in esophageal cancer surgery.
Gastroenterology 2013; 144(5) (Suppl 1):S-219 (IF: 12.032)

Beamish AJ, Karran A, Blake PA, Chan DSY, Lewis WG.
Prognostic value of cardiopulmonary exercise testing (CPX) variables in upper gastrointestinal (UGI) cancer surgery.
British Journal of Surgery 2013; **100** *(Suppl 7)*: 85 (IF: 4.839)

Beamish AJ, Chan DSY, Reid TD, Barlow R, Howell I, Blackshaw G, Clark G, Lewis WG.
Enhanced recovery after upper gastrointestinal surgery (ERAUGIS) improves outcomes in upper gastrointestinal (UGI) cancer.
Proceedings of the ALSGBI Conference 2012.

Oral presentations to learned societies

Beamish AJ, Davies LI, Karran A, Thomas C, Witherspoon J, Blake P, Barlow R, Foley K, Howells G, Roberts SA, Lewis WG.

Prognostic significance of CT muscle density in upper gastrointestinal cancer.

- Association of Surgeons of Great Britain and Ireland, Harrogate (May 2014).

Blake P, Davies LI, **Beamish AJ**, Karran A, 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).

Beamish AJ, Karran A, Blake P, Reid TD, Chan DSY, Appadurai I, Bahlmann UB, Davies R, Lewis WG.

Prognostic value of cardiopulmonary exercise testing (CPX) in gastric cancer (GCa) surgery.

- International Gastric Cancer Congress, Verona (June 2013). ***Awarded Best Oral Presentation Prize.***

Beamish AJ, Chan DSY, Blake P, Karran A, Lewis WG.

Systematic review and meta-analysis of enhanced recovery programmes in gastric cancer surgery.

- International Gastric Cancer Congress, Verona (June 2013).

Beamish AJ, Chan DSY, Reid TD, Barlow R, Howell I, Blackshaw G, Clark G, Lewis WG.

Enhanced recovery after upper gastrointestinal surgery (ERAUGIS) improves outcomes in upper gastrointestinal (UGI) cancer.

- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (at the Digestive Diseases Federation Congress), Liverpool. (June 2012).

- RCSEng ERAS symposium, Cardiff. (June 2012).

Poster presentations to learned societies

Beamish AJ, Davies LI, Karran A, Blake P, Lewis WG.
Prognostic significance of CT muscle density in Upper GI cancer.
Digestive Diseases Week, Chicago, (May 2014).

Beamish AJ, Chan DSY, Blake P, Karran A, Lewis WG.
Systematic review and meta-analysis of enhanced recovery programmes in gastric cancer surgery.
Digestive Diseases Week, Orlando, USA. (May 2013).
Association of Surgeons of Great Britain and Ireland, Glasgow (May 2013).

Beamish AJ, Chan DSY, Karran A, Blake PA, Lewis WG.
Systematic review and meta-analysis of enhanced recovery programmes in esophageal cancer surgery.
Digestive Diseases Week, Orlando, USA. (May 2013).

Beamish AJ, Karran A, Blake P, Reid TD, Chan DSY, Appadurai I, Bahlmann UB, Davies R, Lewis WG.
Prognostic value of cardiopulmonary exercise testing (CPX) in gastric cancer (GCa) surgery.
- Association of Surgeons of Great Britain and Ireland, Glasgow (May 2013).
- Digestive Diseases Week, San Diego, USA. (May 2012).
- European Society of Esophagology, Newcastle. (Nov 2011).

Appendix B - 6.7.4 Table 4. Details of the care pathways for enhanced recovery programmes

Details of Pathway	Pre-operative	Peri-operative	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Discharge	Other elements	Analgesia
Feng et al.	Carbohydrate drink pre-op;	Temperature regulation 36°C; avoid drains	LA wound intitration; 1000Kcal orally; NGT and UC out;	1000 – 1200Kcal orally;	1000 – 1200Kcal orally;	1000 – 1200Kcal orally;	1000 – 1200Kcal orally;	1000 – 1200Kcal orally;	When criteria met (mean 5.68 days)	Parenteral nutrition if oral intake insufficient.	NSAID, LA infiltration intra-op and at 24hr
He et al.	Unclear – foreign language paper								Not stated (mean day 9)		Not stated
Hu et al. (Lap)	Oral nutritional supplements for 5-7 days pre-op	Restrict IV fluids;	500ml oral liquid + IV supplement	1000ml oral fluid + IV supplement	Full oral diet				When achieve: full diet; flatus; no nausea/ vomiting	Avoid bowel cleansing; NGT out when flatus passed; no tubes/pain; able to perform ADLs; willing	
Hu et al. (Open)											
Jeong et al.	Admitted 2 days pre-op;		NGT removed;		Sips of water;	Semi-fluid diet if water tolerated; Closed suction drain removed		Discharge if uncomplicated	Day 7		PCA d1-3
Jiang et al.	Shortened pre-op fasting	No NGT; no abdominal drain;	Unclear – foreign language paper						Not stated (mean 6 days)	Early post-op oral feeding; early mobilisation;	Not stated
Kim et al.	Education; carbohydrate IV & drink 22:00	Ambulation day 0; LAPD;	Nil orally; continue ambulation	Sips of water then clear liquid	Full liquid diet	Soft diet			Day 4 if achieve: soft diet without nausea, vomiting or other complication		LAPD; NSAID; Paracetamol
Kiyama et al.	Printed information to patients		Walked by auxiliary nurse			Unclear – foreign language paper		Unclear – foreign language paper	Day 14		Not stated

Details of Pathway	Pre-operative	Peri-operative	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Discharge	Other elements	Analgesia
Liu et al.	Carbohydrate loading;	Carbohydrate loading; Clear fluids until 2h pre-op, solids until 6h; Minimal incisions; Avoid drains; Free fluids d0; Intraoperative antiemetic; Sit out for 20mins;	UC removed; Semiliquid diet; Stand out for 20mins	Semiliquid diet; Walk length of ward for 1h	IV fluids stopped; Semiliquid diet; Walk length of ward for 2h	Semiliquid diet; Further mobilisation as tolerated	Solid diet		When oral intake 70% pre-op level, IVI stopped and mobilising safely (Mean day 6)	Oral diet as soon as tolerated; Hospital contact numbers given	PCA for 48h; Regular paracetamol and NSAID
So et al.	Written information; Counselling and education from upper GI nurse, pain nurse, dietitian and physiotherapist; Referral to social worker if anticipated discharge difficulties		NGT removed (TG); Start structured mobilisation programme		NGT removed (STG); Liquid and solid diet; Protein supplementation (STG)		Liquid and solid diet; Protein supplementation (TG)		Not stated (median day 8)	Drains removed "once output clear"; LMWH and pressure stockings; Printed pathway as a checklist	PCA
Tang et al.	Multi-professional team ERP education; Pre-op education with consultant and specialist nurse; written information on milestones	Limit opiates; epidural / paravertebral block; extubated in theatre;	Seen by specialist nurse; chest physio.; sit out of bed	Seen by specialist nurse; chest physio; sit out of bed; walk >10m	Seen by specialist nurse; chest physio; sit out of bed; walk length of ward x2	Seen by specialist nurse; chest physio; sit out of bed; walk length of ward x3	Seen by specialist nurse; chest physio; remove NGT; walk freely; oral shower; oral fluids; epidural down, oral analgesia; reduce jejunostomy feed	Seen by specialist nurse; Full mobilisation and daily activities; info leaflet; ensure patient jejunostomy self-care safe; discharge	When milestones met; day 7		Epidural anaesthesia / paravertebral block

6.7.4 - Table 4. [Continued]

Details of Pathway	Pre-operative	Peri-operative	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Discharge	Other elements	Analgesia
Wang et al.	Preoperative information	Carbohydrate drink until 2h pre-op, solids until 6h; No pre-anaesthetic medication; No NGT or remove immediately post-op; Restricted fluid regime; Minimally invasive incision; No abdominal drain; Clear water orally	At least 500ml oral fluids; UC out; Mobilise out of bed ≥four times	At least 1L oral intake; Continue to mobilise	Stop epidural analgesia; Oral intake as tolerated; Continue to mobilise;	Continue as per day 3; Check discharge criteria			When discharge criteria met (median day 6)	Stepwise plan for oral intake: water, semifluids, then solids	Mid-thoracic epidural; Local anaesthetic to wound
Yamada et al.	Full diet until midnight pre-op; Rehydration solution up to 3h pre-op 1000ml; Mild bowel prep	Remove NGT immediately post-op; No drain in STG;		Water and oral nutrition supplement; Walk length of ward	Soft food; Epidural analgesia stopped; LMWH twice daily when epidural catheter out;			Regular diet of solid food; Discharge if meets criteria	Day 7 if criteria met		Mid-thoracic epidural; IV NSAID twice daily (d1-2), then 100mg paracetamol thrice daily

NGT, nasogastric tube; PCA, patient-controlled analgesia; UC, urinary catheter; IVI, intravenous infusion; TG, total gastrectomy; STG, sub-total gastrectomy; LMWH, low molecular weight heparin; IV, intravenous; NSAID, non-steroidal anti-inflammatory drug; ADL, activities of daily living; LAPD, local anaesthetic pump device - pre-peritoneal infusion.

Details of Pathway	Pre-operative	Perioperative	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Discharge	Other elements	Analgesia
Brodner et al.	-	Intraoperative TEA	BD pain team review	BD pain team review	BD pain team review	BD pain team review	BD pain team review	BD pain team review	-	Early extubation; forced mobilisation; early sedative withdrawal	Epidural (T6-9); PCA; pain team
Cao et al.	Education – nurse educator; Drink 2h pre-op, eat 6h pre-op; Fructose and protein loading	No pre-med; Maintain normothermia; Autologous blood transfusion; No routine drains; No routine ITU;	Epidural PCA	-	-	-	-	-	7.7 days (median)	No routine NGT; Early extubation; Jej feeding	Epidural PCA
Li et al.	Education – clinical nurse consultant; illustrated booklet; breathing training;	Avoid feeding jej; extubation in theatre; 6 hour observation then level 1 care.	Chair ≥3 times daily; walk with physio	Chair ≥3 times daily; walk with physio ; UC out	Chair ≥3 times daily; walk with physio; sips of water	Chair ≥3 times daily; walk with physio	Epidural removed; barium esophagram, then feed; Chest tube and drain out	Discharge	Day 7		Epidural,
Munitiz et al.	-	Extubation in theatre; Judicious IVI	Physio TPN; Judicious IVI	Physio TPN; Judicious IVI	Physio TPN; Judicious IVI	Physio; TPN; Discharge from ITU Drains and UC out	Physio Oral liquids; Stop TPN; Contrast study	Physio	Day 7-9	Daily VTE prophylaxis; Daily PPI; Attention for 'alarm signals';	Epidural (T6-9), infusion rate managed by anaesthetist

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Details of Pathway	Pre-operative	Perioperative	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Discharge	Other elements	Analgesia
Tang et al.	Multi-professional team ERP education; Pre-op education with consultant and specialist nurse; written information on milestones	Limit opiates; epidural / paravertebral block; extubated in theatre;	Seen by specialist nurse; chest physio; sit out of bed	Seen by specialist nurse; chest physio; sit out of bed; walk >10m	Seen by specialist nurse; chest physio; sit out of bed; walk length of ward x2	Seen by specialist nurse; chest physio; sit out of bed; walk length of ward x3	Seen by specialist nurse; chest physio; remove NGT; walk freely; shower; oral fluids; epidural down, oral analgesia; reduce jejunostomy feed	Seen by specialist nurse; Full mobilisation and daily activities; info leaflet; ensure patient jejunostomy self-care safe; discharge	When milestones met; day 7		Epidural anaesthesia / paravertebral block
Tomaszek et al.	Nutritional counseling from nutritionist	-	-	-	-	-	-	-	Day 7	Jej feeding for 4 weeks; Routine contrast swallow	
You et al. *(full text unavailable)*	-	-	-	-	-	-	-	-	-	-	-
Zhao et al.	Nurse Consultant education;	Avoid NGT, drains; early extubation; level 1 care	Jej feed (20ml/hr); >2hr out of bed; physio; UC out; bed at 30°, chest tube suction; give albumin	Jej feed (40ml/hr); >4hr out of bed; physio; give albumin	Jej feed (60-80 ml/hr); >6hr out of bed; physio; give albumin	Contrast swallow, oral fluids; Jej feed (60-80 ml/hr); >6hr out of bed; physio	Full liquid diet; Jej feed (60-80 ml/hr); >6hr out of bed; physio	Jej tube out; discharge on soft diet	Day 7	No presanaesthetic medication; autologous transfusion (limit allogeneic) where required	Epidural PCA

TEA, thoracic epidural analgesia; BD, twice daily; PCA, patient-controlled analgesia; ITU, intensive therapy unit; -, not specified; NGT, nasogastric tube; Jej, jejunostomy tube; IV, intravenous infusion; Physio, physiotherapy; TPN, total parenteral nutrition; UC, urinary catheter; IVI, intravenous infusion; VTE, venous thromboembolism; PPI, proton pump inhibitor; Jej, jejunostomy.

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Appendix C:

Bwrdd Iechyd Prifysgol
Caerdydd a'r Fro

**Cardiff and Vale
University Health Board**

**Ysbyty Athrofaol Cymru
University Hospital of Wales**

Heath Park,
Cardiff, CF14 4XW
Phone 029 2074 7747
Fax 029 2074 3838
Minicom 029 2074 3632

Parc Y Mynydd Bychan,
Caerdydd, CF14 4XW
Ffôn 029 2074 7747
Ffacs 029 2074 3838
Minicom 029 2074 3632

Eich cyf/Your ref
Ein cyf/Our ref
Welsh Health Telephone Network 1872
Direct line/Llinell uniongyrchol

Tel: 029 20746986
Fax: 029 20745311
CAV_Research.Development@wales.nhs.uk

From: Professor JI Bisson
R&D Director
R&D Office, 2nd floor TB2
University Hospital of Wales
Cardiff
CF14 4XW

11 February 2013

Mr Wyn G Lewis
Consultant Upper GI Surgeon
UHW
Heath Park
Cardiff

Dear Mr Lewis

**Cardiff and Vale UHB Ref: 11/SUR/5311 : Bioelectrical Impedance Analysis in
Surgical Patients**

Thank you for your recent correspondence addressing the reviewers' comments on
the above project. Your response and revised documents were reviewed by the
Chair of the Cardiff and Vale Research Review Service (CaRRS).

The Panel is now satisfied with the scientific quality of your proposal, and I can
confirm that the following documents have received favourable scientific review:

Document	Version	Date
Protocol	5	03/01/13

As this is an unfunded study, please ensure that you have the support of your
Directorate RD Lead confirming that the Directorate is able to support your study
financially before proceeding to apply for ethics and governance review. Once you
have obtained this confirmation, please follow the application instructions below to
apply for review by a NHS Research Ethics Committee and NHS R&D governance
review:

For NHS REC review:
• Contact the Cardiff & Vale UHB R&D Office to obtain the sponsor's
representative signatures needed prior to your submission to the NHS
Research Ethics Committee (on your NHS REC form).

Version 1.0. 09.06.10

Bwrdd Iechyd Prifysgol Caerdydd a'r Fro yw enw gweithredol Bwrdd Iechyd Lleol Prifysgol Caerdydd a'r Fro
Cardiff and Vale University Health Board is the operational name of Cardiff and Vale University Local Health Board

UHW129X

For NHS R&D governance review:

- Contact the Cardiff & Vale UHB R&D office to obtain the sponsor's representative signature needed on the IRAS NHS R&D form prior to your submission to the National Institute for Social Care and Health Research – Permissions Coordinating Unit (NISCHR PCU).
- The following signatures/authorisations must be obtained in Q23 the SSI form prior to submission to NISCHR PCU: Prof Keith Harding, Directorate RD Lead for General Surgery
- Once the above signatures/authorisations are in place you should submit the IRAS NHS R&D form and Site Specific Information (SSI) form and all supporting study documentation to NISCHR PCU who will coordinate completion of governance checks prior to R&D permission being granted.

The Panel noted the following points which you should address in order to facilitate completion of the governance review:

- Appropriate Good Clinical Practice (GCP) training must be completed by the CI / PI / delegated researchers.

Final R&D permission to begin your study in Cardiff & Vale UHB will be issued following completion of the governance review by Cardiff and Vale UHB and NISCHR PCU.

YOU SHOULD NOT BEGIN YOUR PROJECT BEFORE RECEIVING WRITTEN CONFIRMATION OF NHS R&D PERMISSION TO BEGIN.

Please ensure that you notify NISCHR PCU if any changes to your protocol or study documents are required by the Research Ethics Committee in order to obtain a favourable ethical opinion.

If you require any further information or assistance, please do not hesitate to contact the staff in the R&D Office.

Yours sincerely,

Professor Jonathan I Bisson
Chair of the Cardiff and Vale Research Review Service (CaRRS)

CC   Prof Keith Harding, R&D Lead
Andrew Beamish, Clinical Research Fellow

Enc. IS-RP-007 'Obtaining a Sponsor Signature – Information Sheet'

Link: 'Gaining NHS research permission from Cardiff and Vale UHB – Guidance for researchers' http://www.cardiffandvaleuhb.wales.nhs.uk/opendoc/180875

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

CONSENT FORM

Bioelectrical Impedence Analysis (BIA) in Surgical Patients

Name of Researcher: Mr W G Lewis

Px ID:

Please initial each box

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___   _____
Name of patient   Date   Signature

_____   ___/___/20___   _____
Name of person   Date   Signature
taking consent

Copies: 1 - participant; 1 - researcher file; 1 - medical notes.

April 2014, v.2

Bioelectrical Impedence Analysis (BIA)

What is BIA?

Bioelectrical impedence analysis (BIA) is a quick, simple to perform and safe technique for estimating body composition or make up. BIA measures key nutritional parameters, including body fat, total body water, and lean muscle mass. Previous studies have demonstrated a link between these BIA parameters and outcomes after surgery.

Aims

The aims of our study are to:

1. Assess if BIA can predict how you will recover after surgery.

2. Assess if closely monitoring body composition can help us improve patient safety and management after surgery.

What will it mean for me?

Between one and ten BIA measurements will be taken around the time of your operation to assess your nutritional status and any change over the course of your treatment. The first will be during an outpatient appointment before your surgery and will be repeated on the morning of your surgery (day 0), and on post-operative days 1, 2, 3, 5 and 7. Each test take less than 10 minutes to perform.

Technique

- We will measure your height and weight during your first assessment.

- **We ask that you do not eat for 2 hours prior to assessment.**

- Your bladder should be empty.

- We will ask you to lie on the examination bed for the assessment and the back of your right hand and right foot will be cleaned with an alcohol wipe.

- Two 'sticky' electrodes will be placed on the back of your hand and back of your foot.

- The analysis will take approximately 5-10 seconds and you will not feel anything during the test.

- Your data will then be stored anonymously for analysis at a later date.

Information for Patients: Bioelectrical Impedance Analysis (BIA):

April 2014, v.3

We thank you for taking the time to read this information leaflet, and we hope that you will be able to help with our study. Please be assured that if you decide not to take part in the study, it will not affect your subsequent treatment at the University Hospital of Wales.

If you have any questions or would like further information then please ask your doctor, or contact Specialist Nurse Anita Willicombe or Tracy Parsons, Ward C2, UHW.

Bioelectrical Impedence Analysis (BIA)

Beth yw BIA?

Techneg syml, cyflym a saff yw BIA sy'n galluogi amcangyfrif cyfansoddiad y corff. Mae BIA yn mesur paramedrau maethol allweddol, gan gynnwys, braster corff, cyfanswm dŵr y corff, a màs cyhyr heb lawer o fraster. Dangoswyd gan astudiaethau gorffennol fod cyswllt rhwng paramedrau BIA â chanlyniadau ar ôl llawdriniaeth.

Nodau.

Ein amcanion ôr astudiaeth hon yw:

1. Asesu os yw BIA yn gallu rhagweld sut rydych yn gwella ar o^l llawdriniaeth.

2. Asesu os yw arolygu cyfansoddiad y corff yn gallu helpu ni wella diogelwch a rheolaeth cleifion ar ôl eu llawdriniaeth.

Beth bydd hyn yn ei olygu i fi?

Bydd rhwng un a deg mesuriad BIA yn cael ei gymryd o gwmpas adeg eich llawdriniaeth i asesu eich statws maethiannol, ac unrhyw newid yn hwn yn ystod cwrs eich triniaeh. Bydd yr mesuriad cyntaf fel claf allanol cyn eich llawdriniaeth a bydd yn cael ei ailadrodd ar bore eich llawdriniaeth (diwrnod 0), ac a diwrnodau 1, 2, 3, 5 a 7 ar ôl eich triniaeth. Bydd pob prawg yn cymryd llai na deg munud i'w berfformio.

Techneg.

- Byddwn yn mesur eich taldra a pwysau yn eich asesiad cyntaf
- Byddwn yn gofyn i chi beidio bwyta am ddau awr cyn eith asesiad
- Dylech eich bledren fod yn wag
- Byddwn yn gofyn i chi orwedd ar y gwley arholi ar gyfer asesu a bydd tu nol eich llaw dde a troed chwith yn cael ei olchi gyda 'alcohol wipe'
- Ryw 5-10 eiliad bydd yr asesiad yn ei gymryd a byddech ddim yn teimlo unrhywbeth yn ystod yr adeg hwn.
- Bydd eich data yn cael ei storio yn ddienw ar gyfer ar gyfer dadansoddiad ar adeg hwyrach

Gwybodaeth I Gleifion: Bioelectrical Impedance Analysis (BIA):

April 2014, v.3

Rydym yn diolch i chi am cymryd amser i ddarllen yr daflen wybodaeth hwn, a rydym yn gobeithio byddech yn gallu help hefo ein astudiaeth. Ni fydd eich triniaeth yn Ysbyty Athrofaol Cymru yn cael ei effeithio os nad ydych yn penderfynu cymryd rhad yn yr astudiaeth.

Os oes gennych unrhyw cwestiynnau neu os faswch yn hoffi mwy o wybodaeth, gofynwch eich doctor, neu cyswlltwch gyda Nyrs Arbenigol, Anita Willicombe neu Tracy Parsons, Ward C2, UHW.