Minimally Invasive Gastro-Oesophageal Surgery for Cancer – Current Evidence and Practice

Elizabeth H. Gemmill
B Med Sci BM BS MRCS

Thesis submitted to the University of Nottingham for the degree of Doctor of Medicine (DM)

November 2011

TABLE OF CONTENTS

Abstract

Background

Since its introduction in the early 1990s, minimally invasive gastro-oesophageal surgery for cancer has been growing in popularity. Despite this, published evidence on this type of technique is weak and its role in the management of gastric and oesophageal cancer remains controversial.

Aims

The aim of this thesis was to test the hypothesis that: minimally invasive gastro-oesophageal cancer surgery has superior outcomes compared to control studies of conventional open surgery; but current studies are methodologically inadequate to confirm this.

Methods

The first study (chapter 3) is a systematic review of the literature on minimally invasive gastro-oesophageal cancer surgery, outlining the differences between literature published in Eastern and Western countries

The following 3 chapters outline and use a phase II surgical study to obtain data on minimally invasive gastro-oesophageal cancer (MIGOCS.) The MIGOCS group was set up in 2005 amongst UK surgeons. An online database was developed to enable data collection and comprises 5 sections: demographics; pre-operative staging and assessment; surgical intervention; post-operative course; pathology and clinical outcome. The first study is retrospective collecting data up to December 2006; the second study is prospective with data obtained between December 2006- July 2008 from centres around the UK utilising the MIGOCS database.

Chapter 7 involves analysis of the learning curve in laparoscopic gastro-oesophageal cancer surgery using CUSUM (continuous surveillance monitoring) assessment. By studying operative time at each centre, improvement or deterioration in quality were detected.

Results

The systematic review of minimally invasive gastro-oesophageal surgery consists in the majority of case reports, with no randomised controlled trials of oesophagectomies and 4 (low quality) randomised controlled trials of gastrectomies. It demonstrates a mortality and morbidity of 2.3% and 46.2% respectively for oesophagectomies; 0.1% and 12.7% respectively for gastrectomies. Data from this review suggests that the minimally invasive approach is beneficial compared to open surgery in terms of reduced mortality, respiratory complications, blood loss and quicker return to a good quality of life (but not reduced hospital stay as expected.)

There are currently 60 MIGOCS member consultant surgeons from over 40 UK centres.

The retrospective study obtained data from 7 UK centres with an overall mortality and morbidity of 6.0% and 57% respectively for oesophagectomies and 7.7% and 13% respectively for gastrectomies.

The prospective study collected data from 7 UK centres, comprising a total of 258 minimally invasive oesophagectomies and 33 minimally invasive gastrectomies. Overall mortality and morbidity were 2.5% and 56.6% respectively for oesophagectomies and 10.8% and 27.3% respectively for gastrectomies.

CUSUM analysis varied considerably between centres. The two larger volume centres however demonstrated an improvement in their operative time with experience, with a possible pateau at around 30 procedures.

Conclusions

Published data suggests that the minimally invasive approach to gastro-oesophageal cancer has advantages over conventional open surgery. Data collected in this thesis does not overwhelmingly support published evidence, but does demonstrate that this technique is both safe and feasible even during the early part of a surgeon's learning curve. It is the first study to provide an insight into outcomes of this type of surgery in a multicentre setting in the UK; and has made progress towards a randomised controlled trial.

Weaknesses and Intepretation of Findings

International literature on the subject of minimally invasive gastro-oesophageal surgery is at present limited and subject to both publication and selection bias.

Data presented in this thesis is weakened by the number of operations recorded and centres involved in the studies. This impacts on any interpretation of findings. Further data collection, ideally in the form of a randomised controlled trial is therefore vital.

Declaration

Except where noted in the acknowledgements or text, I declare that this dissertation is my own work, except where acknowledged, and is based on research that was undertaken by me in the Nuffield Department of Surgery, John Radcliffe Hospital, Oxford in conjunction with the University of Nottingham. No material included in this work has been submitted for a previous course, at this or any other academic institution, nor shall I agree to this happening. I am aware of and understand the School policy on plagiarism and the University Policy and Procedure regarding Academic Offences particularly that directed at plagiarism. I acknowledge that my work may be submitted to checks for irregularities e.g. online plagiarism detection software. I am aware that it is my own responsibility to retain a copy of this submitted work and I may be required to submit a second copy if asked by a member of University of Nottingham academic staff. I declare that there are no extenuating circumstances that have not formally been disclosed and which may have affected the standard of my work.

Acknowledgements

The work presented in this thesis could not have been achieved without the help and talents of a great many people. Firstly I am indebted to Mr Peter McCulloch, my supervisor in Oxford who provided me with the opportunity to do this research and whose patient guidance got me started. My thanks also go to my Nottingham supervisor Professor John Scholefield whose words of wisdom helped me finish my research and will always remain with me.

I am also grateful to Dr Gary Collins (Oxford) for his invaluable statistical support and input in evaluating learning curves; to Dr Ken Catchpole (Oxford) for always lending me an ear; to Mr Nick Maynard and Mr Bruno Sgromo (Oxford oesophago-gastric consultants) and to Mr James Catton, Mr Simon Parsons and Mr Neil Welch (Nottingham oesophago-gastric consultants) who inspired and helped keep me sane.

My thanks also go to Dr Peter Walton, Mrs Mary Kennedy and Mr Neal McCann of Dendrite computing systems for their invaluable assistance in setting up the online database and assistance in its ongoing management.

Perhaps one of my greatest thanks though has to go to members of the MIGOCS group, especially Mr Colm O'Boyle, Mr Richard Berrisford, Mr Saj Wajed, Mr Jim Byrne, Mr Don Menzies, Mr Krish Singh, Mr Haythem Ali and Mr Shaun Preston, not just for their donation of data to the register (making my thesis possible); but for their ongoing support and enthusiasm for minimally invasive gastro-oesophageal cancer surgery!

Finally I would like to thank my family and friends for their selfless support and who hopefully know how much I appreciate them. In particular, my thanks go to my father and brother; and to my mother whose courage and determination proved inspirational to the end.

List of Tables

List of Figures

Index of Abbreviations

AJCC	American Joint Committee on Cancer
ALS	Association of Laparoscopic Surgeons of Great Britain and Ireland
ASA	American Association of Anaesthetists
AUGIS	Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
CEBM	Centre of Evidence Based Medicine
CI	Confidence Interval (95% unless otherwise stated)
CLO	Columnar Lined Oesophagus
CONSORT	Consolidated Standards of Reporting Trials
CRAM	Cumulative Risk Adjusted Mortality
CRT	Chemoradiotherapy
CT	Computerised Tomography
CUSUM	Cumulative Sum Control
ECF	Epirubicin, Cisplatin and protracted 5- Fluorouracil
EGC	Early Gastric Cancer
EMR	Endoscopic Mucosal Resection
ESD	Endoscopic Submucosal Dissection
EUS	Endoscopic Ultrasound
GC	Gastric Cancer
HGD	High Grade Dysplasia
HR	Hazard Ratio
HRQL	Health related Quality of Life
IDEAL	Idea, Development, Exploration, Assessment, Long-term study
JJC	Japanese Joint Committee
MIG	Minimally Invasive Gastrectomy
MIGOCS	Minimally Invasive Gastro-Oesophageal Cancer Surgery
MIO	Minimally Invasive Oesophagectomy
MIS	Minimally Invasive Surgery
NICE	National Institute for Clinical Excellence
OC	Oesophageal Cancer
O-POSSUM	Oesophago-Gastric Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity
OR	Odds Ratio

P	Probability value
PDT	Photodynamic Therapy
PET	Positron Emission Tomography
POSSUM	Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity
RCT	Randomised Controlled Trial
RR	Relative Risk
RTI	Respiratory Tract Infection
TNM	Tumour, Node, Metastasis
UICC	International Union Against Cancer
VLAD	Variable Life-Adjusted Display

Chapter 1: Introduction

1.1 Gastric Cancer

1.1.1 Definition and Epidemiology

Gastric cancer (GC) is defined by the World Health Organisation as "a malignant epithelial tumour of the gastric mucosa with glandular differentiation" (Fenogilo-Prieser 2000.) Worldwide, it is the second leading cause of cancer-specific mortality in men and fourth in women (Crew 2006,) representing 3% of all cancers in the UK. GC has an annual incidence of over 8,100 people and mortality of approximately 5,700 people in the UK alone (Cancer Research UK, 2007.) This compares to 192,000 new diagnoses and 158,000 deaths per annum in Europe; with a 5 year survival of around 20% (Allum 2008, Mitry 2008.) Gastric cancer rates are higher in men (17.6 compared with 9.8 females, per 100,000 people newly diagnosed) (Office for Nat Statistics 2003;) and it is essentially a disease of older age, with over 80% cases diagnosed in people over the age of 65 (Cancer Research UK 2003, see figure 1.1.)

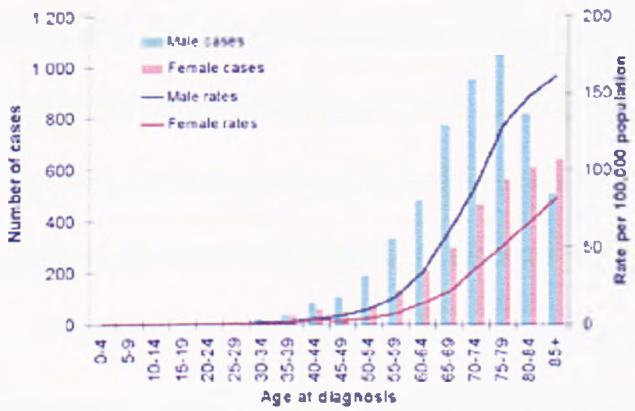


Figure 1.1 New Gastric Cancer cases in the UK 2003 (Source: Cancer Research UK, 2003)

Since 1975, gastric cancer incidence in the UK has been decreasing from an overall rate of 22 to 10 per 100,000 population (Cancer Research UK 2007.)

Worldwide, incidence of gastric cancer is highest in Japan (more than 40 per 100,000 population,) Eastern Asia, Eastern Europe and South America; whereas North America (10 per 100,000 in Canada,) Northern Europe and Africa have amongst the lowest incidences (Fenogilo-Preiser 2000.) Striking differences between gastric cancer rates in East and Western countries are apparent, both in terms of its pathological distribution and survival (Maruyama 1987, Wan 2006.) These differences suggest that ethic origin may play a role in its pathogenesis; however they are not sustained for a prolonged time following a change of environment (Stadtlander 1999, Terry 2002, Kelley 2003.)

Screening is limited to countries with high incidences of GC, such as Japan and China, where it is cost effective and up to 50-80% of cases are detected in the early stages (Fenogilo-Preiser 2000.) In America, where there is no formal screening programme, the American Society for Gastrointestinal Endoscopy recommends endoscopic surveillance of high-risk individuals (with a history of gastric adenoma; familial adenomatous polyposis syndrome; hereditary nonpolyposis colon cancer syndrome; Peutz-Jeghers syndrome and Metenier's disease) every 1 to 2 years (Gore 1997.)

In the absence of formal screening programmes, the majority of cases of GC present late in an advanced pathological state -nearly 65% in the US present with T3/4 tumours and 85% with lymph node metastases (Hundahl 2000.) For those that are suitable for surgery with curative intent, there is a 40-65% risk of relapse and metastasis; and a median survival of 2 years, with a 20-30% 5 year survival rate

(MacDonald 2001.) Following palliative procedures, median survival is 8.1 months and for those having no intervention, median survival is only 5.4 months (Philip 1997, Doglietto 2000, Hartgrink 2002.)

The anatomical subsite distribution of GC has changed over recent years in Europe, with an increase in proximal, particularly cardia tumours and a decrease in distal tumours (Dolan K 1999.) This has lead to the suggestion that the rise in cardia tumours, along with adenocarcinoma of the lower oesophagus may be related to a concurrent rise in gastro-oesophageal reflux disease (Lagergren 1999.)

Cancers of the body and antrum of the stomach have been linked with *Helicobacter pylori* infection (EUROGAST 1993, Eslick 1999, Fenogilo-Preiser 2000.) Whether this is via a process of genetic mutation involving chronic gastritis is unclear; but *H. pylori* is thought to increase the risk of GC by two to threefold and is associated with both diffuse and intestinal types of cancer. Other possible aetiological factors include smoking (Haung 2000, Gonzalez 2003;) dietary fibre intake (Terry 2001;) alcohol (in cardia tumours) (WRCF&AICF 1997;) lower socioeconomic status (CRAG 2002;) and predisposing conditions such as previous gastric surgery (Lundegardh 1994,) peptic ulcer disease (Macintyre 1994) and pernicious anaemia (Ye 2003.) Most gastric cancers are sporadic, but 8-10% have an inherited familial component (Fenogilo-Preisner 2000.)

1.1.2 Diagnosis

Early gastric cancer tends to present with vague symptoms of uncomplicated dyspepsia. Non-specific symptoms (when the cancer is superficial and potentially

curable) are present in up to 50% of cases (Gore 1997.) Awareness of these "at risk" patients is vital for early diagnosis and referral; and table 1.1 highlights recommended referral guidelines for General Practitioners by the Department of Health. These guidelines however were designed to identify symptoms that have a high correlation with gastric cancer i.e. they are almost exclusively symptoms of advanced disease. Therefore since the guidelines are based on health economics, they do in fact contribute little to detecting early disease.

Table 1.1 Guidelines for Referral of Upper Gastrointestinal Cancers (NHS 2000)

- Dysphagia
- Dyspepsia combined with 1 or more of these alarm symptoms:
    - Weight loss
    - Anaemia
    - Anorexia
- Dyspepsia in a patient aged 55 years or more with at least 1 of the following "high risk" features:
    - Onset of dyspepsia less than 1 year
    - Continuous symptoms since onset
- Dyspepsia combined with at least 1 of the following known risk factors:
    - Family history of upper gastrointestinal cancer in more than 1 first degree relative
    - Barrett's oesophagus
    - Pernicious anaemia
    - Peptic ulcer surgery over 20 years ago
    - Known dysplasia

- Atrophic gastritis
- Intestinal metaplasia

- Jaundice
- Upper abdominal mass

Symptoms progress as the disease advances to cause anaemia, dysphagia, early satiety, weight loss, abdominal pain, vomiting and anorexia. Ulcerated tumours may result in bleeding, which can range from occult to massive.

Physical examination of early gastric cancer patients is often unremarkable. More advanced patients may demonstrate cachexia, lower extremity oedema, a palpable tumour mass, hepatomegaly, ascites or bowel obstruction. Lymphadenopathy may be present in the left axilla, left supraclavicular fossa (Virchow's node,) and in advanced (metastatic) cases, a periumbilical (Sister Mary Joseph's) nodule may be detected. Peritoneal seeding may result in ovarian involvement (Krukenberg tumour) or Blumer's rectal shelf (drop metastasis into the peritoneal reflection in the prerectal and post-vesical space.) Advanced cases may rarely present with paraneoplastic syndromes such as cutaneous syndromes (dermatomyositis or acanthosis nigricans,) microangiopathic haemolytic anaemia, and chronic intravascular coagulation leading to venous and arterial thrombi (Trousseau's syndrome.)

The gold standard investigation of GC is flexible endoscopy with biopsy. Clinical diagnosis is very inaccurate in distinguishing with pathological disease and therefore all "at risk" patients with reflux symptoms should be considered for endoscopy, despite an overall detection rate of 1-2% (Allum 2002.) Further information for staging the tumour varies between centres but generally includes endoscopic

ultrasound (EUS,) computed tomography (CT,) staging laparoscopy +/- positron emission tomography (PET) scanning.

Screening for GC is controversial and at present only practised in countries with a high incidence of the disease such as Japan. This can be done by endoscopy, indirect photofluoroscopy or potentially by measuring serum pepsinogen concentration. Pepsinogen is a good marker as its levels are increased by *H. pylori,* which is responsible for gastric inflammation and glandular atrophy. This in turn may develop into GC when severe and extensive (Dinis-Riberio 2004, Yoshihara 2007.) (The pepsinogen I/Pepsinogen II ratio for atrophic gastritis has sensitivity of 96.1% and specificity of 97.7%; separately pepsinogen I has the highest specificity of 90.7% and pepsinogen II has a high sensitivity of 90.7% (Ivani 2010.)

1.1.3 Pathology

Ninety percent of gastric tumours are malignant and of these 95% are gastric adenocarcinomas (Schwartz 1996.) Although the stomach does not normally contain lymphoid tissue, it is the commonest site for gastrointestinal lymphomas. Other malignancies include squamous cell carcinoma, carcinoid tumours, adenoacanthoma and leiomyosarcoma. Gastric tumours can further classified by gross morphological and histopathological features:

i) Macroscopic Classification (Bormann 1926)

- type I polypoid: well circumscribed polypoid tumours
- type II fungating: polypoid tumours with marked centre infiltration
- type III ulcerated: ulcerated tumours with infiltrative margins
- type IV: infiltrating: linitis plastica

ii) *Microscopic Classification*

The Lauren classification is one of the commonest histological grading used, distinguishing gastric adenocarcinomas into two types: intestinal and diffuse (Lauren 1965.)

Intestinal (well-differentiated) tumours consist of big irregular nuclei in large, distinct cells; which form gland-like tubular structures through cell cohesion. Diffuse (undifferentiated) tumours consist of small isolated cells or cell clusters, arranged in a non-polarised fashion; these tend to be associated with early metastasis and a more aggressive clinical course (Lauren 1965, Munoz 1968.)

Further microscopic classification (in addition to the intestinal and diffuse types described above) based on tumour morphology has been proposed by the World Health Organisation:

- papillary adenocarcinoma (exophytic lesions with long, fine or plump finger-like processes containing connective tissue and fibrovascular cores)
- tubular adenocarcinoma (well-defined glandular lumens)
- mucinous/ colloid adenocarcinoma (greater than 50% intra-cellular mucin contain in the lesion.)
- signet-ring cell carcinoma (greater than 50% signet-ring cells, with the cell nucleus compressed to the edge of the cell by cytoplasm unsecreted mucin.) This type of morphology often demonstrates marked desmoplasia and an infiltrative gross appearance. Intramural spread, not involving the mucosa, can appear to form a linitis plastica-type tumour.
- adenosquamous carcinoma
- squamous cell carcinoma

- small cell carcinoma
- undifferentiated carcinoma (containing no glandular or other features such as mucus secretions.)
- other

Pre-Cursor Lesions

Based on studies of chronic *Helicobacter pylori* and its well established association with the development of gastric cancer (Forman 1991, Parsonnet 1991, EUROGAST 1993,) the Correa hypothesis was proposed. This model suggests that there is progression from chronic gastritis to gastric atrophy with intestinal metaplasia to dysplasia prior to malignancy (Correa 1988.) Since gastric mucosa atrophy occurs with age some early phases of the process may be reversible. It is also unclear at present the relationship between intestinal metaplasia and intestinal dysplasia. Dysplasia grading itself is difficult and open to considerable inter-observer variation, with the higher grades being more likely to contain adenocarcinomas cells.

Early Gastric Cancer (EGC)

The term early gastric cancer originated in Japan and refers to adenocarcinomas confined to the mucosa or submucosa regardless of the presence, or absence of lymph node metastasis (Hirota 1993.) EGC is classified according to the Japanese Gastroenterological Endoscopic Society based on the tumour's gross appearance into 3 types (Murakami 1971):

- Type I polypoid: the tumour is greater than 0.5cm above the mucosal surface
- Type II superficial:

    Type IIa elevated: flat elevation, thickening the mucosa less than 0.5cm

Type IIb flat: no or minimal mucosa heightening

Type IIc depressed: superficial, slightly depressed mucosal erosion

- Type III excavated: prominent, ulcer-like excavation/depression of the mucosa

Screening and intensive case finding coupled with heightened population awareness has resulted in a higher percentage of EGC diagnosed in Japan compared with Western countries. This in turn means more patients are suitable for curative surgery and improved surgical outcomes.

Grading

Adenocarcinoma grades are based on the degree of glandular differentiation into well, moderately and poor differentiated subtypes:

- Grade X: cannot be assessed
- Grade 1: well-differentiated (tumour comprises more than 95% of glands)
- Grade 2: moderately differentiated (tumour comprises 50-95% of glands)
- Grade 3: poorly differentiated (tumour comprises less than 49% of glands)

Staging

Treatment decisions are usually formed referring to the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) (Green 2002, UICC 2002.) The Japanese have a separate classification system for gastric cancer patients, formed in association with the Japanese Gastric Cancer Association (JGCA 1998.) The main difference between the two systems is derived from the classification of lymph nodes, the UICC utilises the number of involved lymph nodes, whereas the JGCA system uses the site and distance of metastatic lymph nodes from the primary tumour.

TNM Classification (UICC 2002)

Tumour stage assessed prior to intervention is given the prefix 'c' ('clinical'), postoperatively by a 'p' and during or after neoadjuvant treatment by a 'y'.

- Primary Tumour (T)

  Tx – primary tumour cannot be assessed

  T0 - no evidence of primary tumour

  Tis – carcinoma in situ: intraepithelial tumour without invasion of the lamina propria

  T1 - tumour invades lamina propria or submucosa

  T2 – tumour invades the muscularis propria or submucosa

  T2a – tumour invades muscularis propria

  T2b – tumour invades subserosa

  T3 – tumour penetrates the serosa (visceral peritoneum) without invasion of adjacent structures

  T4 – tumour directly invades adjacent structures

- Regional Lymph Nodes (N)

  A minimum of 15 should be examined. Nodes included are: perigastric nodes along the greater and lesser curvature; and the nodes along the left gastric, common hepatic, splenic and coeliac arteries.)

  Nx – regional lymph node(s) cannot be assessed

  N0 – no regional lymph node metastasis

  N1 – metastasis in 1-6 regional lymph nodes

  N2 – metastasis in 7-15 regional lymph nodes

  N3 – metastasis in more than 15 regional lymph nodes

- Distant Metastasis (M)

  Mx – presence of distant metastasis cannot be assessed

  M0 – no distant metastasis

  M1 – distant metastasis

(n.b. In 2010, subsequent to data collection for this thesis the TNM grading system has undergone further alteration.)

Lymph Node Tiers according to Japanese Rules

Lymph node station

N1:	1. Right cardiac	4. Greater curve
	2. Left cardiac	5. Suprapyloric
	3. Lesser curve	6. Infrapyloric
N2:	7. Left gastric artery	10. Splenic hilum
	8. Common hepatic artery	11. Splenic artery
	9. Coeliac axis	
N3:	12. Hepatoduodenal ligament	15. Middle colic artery
	13. Retropancreatic	16. Para-aortic
	14. Superior mesenteric artery	

Table 1.2: Stage Groupings of Gastric Cancer

Stage	Tumour	Nodes	Metastasis	5 year survival (%) Post surgery
0	Tis	N0	M0	99
Ia	T1	N0	M0	99
Ib	T1	N1	M0	90
	T2a/b	N0	M0	88
II	T1	N2	M0	79
	T2a/b	N1	M0	71
	T3	N0	M0	69
IIIA	T2a/b	N2	M0	52
	T3	N1	M0	46
	T4	N0	M0	52
IIIB	T3	N2	M0	23
	T4	N1	M0	26
	T4	N2	M0	16
IV	Any T	Any N	M1	10

Data for 5 year survival post-surgery from Maruyama *et al* 1986

1.1.4 Treatment

A multidisciplinary approach regarding treatment planning of all patients with gastric cancer is considered mandatory to guarantee optimal quality of care. All management decisions and standards for potentially curative therapy involve members of a specialist team who are involved in policy decisions and adhere to a documented clinical policy agreed throughout each cancer network. All outcomes are audited and participation in National data collection and clinical trials are encouraged. The specialist oesophago-gastric cancer team includes: oesophagogastric surgeons;

medical gastroenterologists; oncologists; radiologists; pathologists; clinical nurse specialists and anaesthetists.

All potential curative therapy options are reviewed in the context of a subjective and objective assessment of patients' physical and mental fitness before reaching a group MDT decision. This allows appropriate treatment and increased continuity of care for the patient. Increased specialisation has improved trial recruitment; training and research opportunities; and provided better perioperative and overall patient outcome.

Surgical resection of the primary tumour and regional lymph nodes remains the treatment of choice for gastric cancer and is recommended for stages Tis-T3 N0-N2 M0 or T4N0M0 (ESMO 2005.) Options of adjuvant or neoadjuvant therapy (in addition to surgery) should also be considered in view of the high frequency of relapses following surgery (Lim 2005.)

Although the treatment determines patient prognosis to a large extent, other factors such as patient co-morbidity (Prytherch 1998) and tumour stage (Siewert 1998, Adachi 2000) at presentation play an important role. Current staging modalities focusing on tumour invasion and lymph node involvement do not take these factors into account. Nomograms, which provide individual prognosis based on prognostic variables, are therefore being developed (Kattan 2003.) The nomograms assist in patient counselling, follow-up scheduling and clinical trial determination. They have been developed for several tumours and have been shown to provide better discriminating predictions, regardless of the extent of lymphadenectomy than the AJCC staging system (Peeters 2005.)

Although surgery remains the mainstay of treatment for gastric cancer, non-surgical options, such as chemoradiotherapy and endoscopic therapy (with curative intent) for HGD and early gastric cancer are available (see under oesophageal cancer treatment for more details of the latter.) However, chemoradiotherapy, chemotherapy or radiotherapy alone, without surgery demonstrate no survival benefit in patients with gastric cancer (SIGN 2002.)

Potentially Curative Treatment

Neo-adjuvant therapy (chemotherapy, chemoradiotherapy, radiation, or immunotherapy, either alone, or in combination) has been used in those with locally advanced tumours or with high risk of recurrence. In this setting, chemotherapy may allow down-staging of an unresectable primary tumour prior to surgery or eradicate occult micrometastatic disease.

Perioperative Adjuvant Chemotherapy

The aim of systemic therapy for gastric cancer is to reduce the chances of recurrence following successful surgical resection. Neo-adjuvant treatment has been shown to increase the survival outcome of selected patients (Sun 2009) and perioperative chemotherapy plus surgery has been adopted as standard practice in the UK (Rao 2008.)

The MRC STO2 (MAGIC) randomised controlled trial compared gastric cancer surgery alone with 3 cycles of pre and post-operative chemotherapy - ECF (epirubicin, cisplatin and protracted 5-FU) - combined with surgery (Cunningham 2003, 2006, Chua 2007.) There were 253 and 250 patients respectively in each arm and the primary trial endpoint was overall survival. The trial demonstrated perioperative

chemotherapy significantly downstaged T and N stage; improved resectability (by 10%;) progression-free (HR 0.66; 95% CI 0.53-0.81; p <0.001) and overall survival (HR for death 0.75; 95% CI 0.60-0.93; p= 0.009;) with an acceptable postoperative mortality rate of 6%. Five year survival increased in the trial from 23% in the control group to 36% in those treated by perioperative chemotherapy. Decreased patient tolerance to chemotherapy was however noted early post-gastrectomy (possibly related to poor food intake capacity) with only 40% patients receiving both cycles of postoperative treatment. The trial recommended considering ECF as standard perioperative chemotherapy treatment for resectable gastric cancer. Further trials such as the MRC ST03 (looking at bevacizumab) are currently evaluating different chemotherapy regimes.

A recent meta-analysis of 17 randomised controlled trials (3838 patients) with a median follow up of 7 years demonstrated that postoperative adjuvant chemotherapy based on a fluorouracil regime was associated with reduced risk of death in patients with gastric cancer compared to surgery alone (GASTRIC Group 2010.) Adjuvant chemotherapy was associated with a statistically significant benefit in terms of overall survival (HR, 0.82; 95% CI 0.76-0.90; P<0.001) and disease-free survival (HR, 0.82; 95% CI 0.75-0.90; P < 0.001;) five year survival increased from 49.6% to 55.3% with chemotherapy.

Intraperitoneal Chemotherapy

Intraperitoneal chemotherapy is attractive in view of the pattern of hepatic and peritoneal recurrence in gastric cancer. The most positive trial comes from Japan and utilises mitomycin C (Hagiwara 1992.) Fifty patients with serosal involvement were

randomised to receive immediate treatment or observation. At 2 years, survival was 68.6% v 26.9%, with the treatment group maintaining an advantage at 3 years. Treatment was reported to be well tolerated. However a subsequent trial aiming to repeat these results was suspended due to serious toxicity (Rosen 1998.)

A recent systematic review of intraperitoneal chemotherapy identified 14 studies, involving 914 patients with gastric cancer, 819 of them receiving intraperitoneal chemotherapy (Matharu 2011.) Twelve studies were rated methodologically poor and there were 2 randomised controlled trials. In the better conducted trials it was concluded that intraperitoneal chemotherapy and surgery prolonged survival more than surgery alone.

Postoperative Chemoradiotherapy

Radiotherapy is not routinely used in gastric cancer treatment. The US GI-Intergroup INT 0116 (SWOG 9008) study compared surgery alone to postoperative chemoradiotherapy (Macdonald 2001.) Following a median follow up of 3.3 years, the trial demonstrated an improved disease-free survival (49% v 32%) and a 9% overall survival benefit (52% v 41%) in the chemoradiotherapy arm. Although treatment related mortality was only 1%, significant gastrointestinal and haematological morbidity occurred (73% having grade 3 or 4 toxicity) and only 64% completed chemoradiotherapy treatment. A criticism of this trial is that 54% of patients receiving surgery alone had a D0 resection, which does not translate into routine practice. (This was verified in a subsequent paper by the group utilising the Maryuama Index, confirming that surgical undertreatment clearly undermines survival – Hundahl 2002.)

A recent study by Dikken *et al* suggested that adjuvant chemoradiotherapy provides survival andnrecurrence benefit over D1 but not D2 resections i.e. limited but not systematic lymphadenectomies (Dikken 2010.) Ninety one patients with gastric adenocarcinomas undergoing surgery with chemoradiotherapy were compared to 694 patients from the Dutch Gastric Cancer group trial (Bonenkamp 1999) with a median follow-up of 19 months. Local recurrence after 2 years was significantly earlier in the surgery alone group (17% v 5%; p= 0.0015.) Separate analysis of patients who underwent D1 resection showed fewer recurrences after chemoradiotherapy (2% v 8%; p= 0.001;) whereas comparison of the D2 groups demonstrated no significant difference. Furthermore, chemoradiotherapy significantly improved survival after a microscopically irradical (R1) resection.

Palliative Chemotherapy

In cases of stage IV (metastatic) gastric cancer, palliative chemotherapy should be considered (Van Cutsem 2008) with ECF regimes being the gold standard in the UK. Early randomised trials of palliative chemotherapy versus best supportive care clearly show improved survival (8-12 months compared with 3-5 months) (Murad 1993, Pyronen 1995, Glimelius 1997.)

A Cochrane review by Wagner *et al* involving 27 studies aimed to assess and compare the efficacy and tolerability of chemotherapy in patients with advanced gastric cancer (Wagner 2006.) Analysis of chemotherapy versus best supportive care (HR= 0.39; 95% CI 0.28-0.52) and combination versus single agent, mainly fluorouracil-based chemotherapy (HR=0.83; 95% CI 0.74-0.93) for advance gastric cancer, demonstrated significant overall survival benefits in favour of chemotherapy and combination chemotherapy respectively.

Surgical Treatment

Surgery is the cornerstone of management in patients with resectable gastric tumours, aiming for tumour free-margins combined with at least D1 resection (1 field lymphadenectomy.) It remains the only potential curative option and is recommended for gastric cancer stages Tis-T3N0-N2M0 or T4N0MO (ESMO 2005) and will be discussed further in chapter 1.4.

1.2 Oesophageal Cancer

1.2.1 Definition and Epidemiology

Oesophageal cancer (OC) is defined as a neoplasm arising from the oesophageal submucosa. It is the ninth commonest cancer diagnosed in the UK and represents 3% of all cancer deaths (Cancer Research UK, 2007.) Worldwide, OC is the fourth most common cancer diagnosed in men, and wide variation occurs between countries and ethnic groups. The highest reported worldwide incidence occurs in the so-called Asian "oesophageal cancer belt," which stretches from eastern Turkey, through north-eastern Iran, northern Afghanistan and southern Russia to northern China.

The incidence of oesophageal cancer per annum in the UK is greater than 7,600 persons and mortality is around 7,400; with the highest rates being recorded in Scotland (Cancer Research UK 2002.) This rate has steadily increased over the last twenty five years, particularly in men, rising from 8.8 to 14.2 per 100,000 population between 1975 and 2004 (European age-standardised,) with a corresponding female rate rising from 4.8 to 5.6. The male to female ratio has increased over recent years with a 5 to 10 fold ratio being reported for adenocarcinomas (Cancer Research UK 2007.) The risk of cancer increases with age, with few people diagnosed before the age of 40 years (see figure below.)

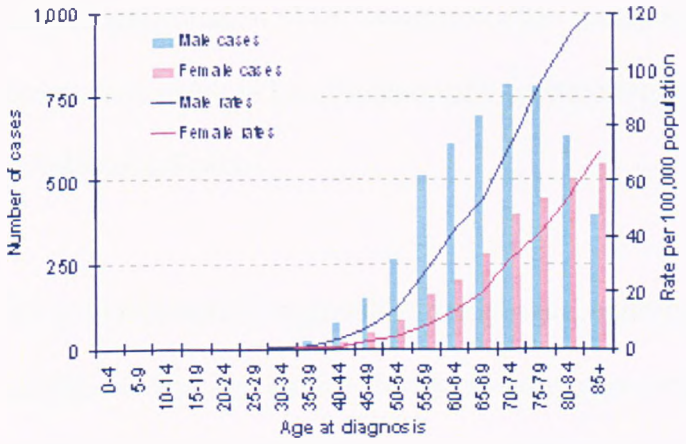


Figure 1.2: New Oesophageal Cancer cases in the UK, 2004 (Source: Cancer Research UK 2007)

Etiological causative factors differ between squamous and adenocarcinomas of the oesophagus. Alcohol, tobacco, social deprivation and male sex have all been demonstrated as risk factors for squamous cell carcinomas (Lagergren 2000, CRAG 2002, Engel 2003;) as well as predisposing conditions such as pernicious anaemia (Ye 2003.) Adenocarcinomas have been linked to obesity, gastro-oesophageal reflux (Chow 1998, Lagergren 1999) and Barrett's oesophagus (Dulai 2002.)

1.2.2 Diagnosis

Most patients with oesophageal cancer present with dysphagia with/without odynophagia. Weight loss is frequently associated and is an independent indicator of poor prognosis- especially if the body mass lost is greater than 10% (Fein 1985.) Other symptoms include those similar to chronic gastro-oesophageal reflux (although cancer is uncommon in this group of patients (Shaheen 2002;) dyspnoea, cough, hoarseness; back, retrosternal or right upper abdominal pain, may also feature and reflect the presence of unresectable disease.

Physical examination of OC patients is often unremarkable, although metastatic disease may result in lymphadenopathy (particularly Virchow's node), hepatomegaly and pleural effusions.

The gold standard of diagnosis is oesophageal endoscopy, which may reveal a friable, ulcerated lesion, and biopsy. Further investigations which assist in staging patients include CT scan, EUS, PET (+/- CT), bone scintography and laparoscopy +/- peritoneal washings. Despite this, shortcomings in clinical staging persist in up to 25-35% of patients (Krasna 1996.) This may result in either unnecessary operations (understaging) or overstaging which denies patients potentially curative surgery (Holsher 1994.)

Population-based screening is untenable except in certain high risk areas such as Anyang County, China (Yang 2002.) This is due to the relatively low incidence of oesophageal carcinoma, minimal early symptoms and rarity of hereditary disease (Jochem 1992, Risk 1999, Lagergren 2000.)

Current chemoprevention trials targeted at oesophageal cancer are mostly aimed at patients with Barrett's oesophagus, where it has been demonstrated that cancer incidence could decrease as much as 45% (Jankowski 2004.) Two large randomised trials at present are looking at this group of patients: the Barrett's Oesophagus Surveillance Study (BOSS) (Bampton 2005) and the Aspirin Esomeprazole Chemoprevention Trial (AspECT) (Jankowski 2006,) their results are eagerly awaited.

1.2.3 Pathology

More than 90% of oesophageal cancers are squamous-cell carcinomas or adenocarcinomas (Daly 2000.) Other rarer types of oesophageal cancer include: melanoma, leiomyosarcoma, carcinoid and lymphomas.

In the West over the last 25 years, the incidence of adenocarcinoma has increased and surpassed that of squamous cell carcinoma (Devesa 1998, Law 2005.)

The cervical oesophagus is an uncommon site of disease; three-quarter of adenocarcinomas are found in the distal oesophagus, whereas squamous-cell carcinomas are found equally in the middle and lower oesophagus (Daly 2000, Siewart 2001.) The incidence of distal adenocarcinomas of the oesophagus, specifically oesophago-gastric junctional tumours has increased; suggesting an association with a concurrent rise in gastro-oesophageal reflux disease (Lagergren 1999.)

Metaplasia-Dysplasia-Carcinoma Sequence

Progression of columnar lined oesophageal epithelium to cancer is thought to occur as a result of locally produced cytokines, oxidative damage and bile acids in the refluxate. These create a microenvironment which stimulates metaplastic stem cells in a stepwise progression via molecular events through metaplasia, dysplasia and eventually adenocarcinoma (Jankowski 1999.)

Dysplasia is defined as "an unequivocal neoplastic alteration of epithelium which has the potential to progress to invasive malignancy but remains confined within the basement membrane within which it arose" (Riddell 1983.) It can further be classified according to nuclear and cytoplasmic architectural dysmaturation into low or high grade (low grade being a more stable phenomenon.)

The natural history of low grade dysplasia is still not fully understood. The majority of patients remain stable or regress to Barrett's metaplasia without dysplasia; however the risk of progression to high grade dysplasia or cancer is between 10-28% (Sharma 2006, Lim 2007.)

High grade dysplasia (HGD) is associated with a focus of invasive adenocarcinoma in 30-40% of patients (Barr 2005.) Therefore if persistent, HGD should be considered for resection or ablation. Once cancer develops it may spread rapidly; 14-21% of T1 (submucosal) lesions and 38-60% of T2 lesions (invading muscle) will spread to lymph nodes (Collard 2001, Siewart 2001.)

Barrett's Oesophagus

Barrett's oesophagus is defined as "a metaplastic condition in which any part of the normal squamous epithelium has been replaced by macroscopically visible columnar epithelium which is histologically confirmed" (Gillies 2010.) In the UK, the diagnosis does not need the histological identification of specialist intestinal metaplasia (Watson 2005,) unlike other parts of the world, such as the USA (Sampliner 1998.)

At endoscopy, Barrett's oesophagus is visualised as an irregular edge of pink mucosa with interspersed tongues of columnar epithelium in otherwise normal pale squamous epithelium. Standard measurement of the extent of Barrett's oesophagus uses the Prague C&M criteria (Sharma 2006.) This measures the circumferential (C value) and maximum extent (M value) of columnar mucosa above the gastro-oesophageal junction.

Barrett's oesophagus is characterised by three histological types:

i) gastric fundal type epithelium with mucus secreting cells

ii) gastric junctional type epithelium with mucus secreting cells

iii) specialised columnar epithelium with mucus secreting goblet cells amounting to intestinal metaplasia.

The mucosal instability of Barrett's oesophagus, especially in longer segments increases the risk of progression to dysplasia and thus carcinoma - the risk of cancer being 30-125 times higher than in the general population, or 0.5% per annum (Theisen 2004.)

The screening of individuals with chronic reflux symptoms to detect Barrett's oesophagus or cancer is not currently recommended in the UK (Loft 2005.) However current UK guidelines recommend individuals with Barrett's oesophagus without dysplasia should undergo surveillance endoscopy every 2 years. This is based on a computerised mathematical model assuming a risk of approximately 1% per annum of developing adenocarcinomas in Barrett's oesophagus (Loft 2005.) Biopsies should be taken from all 4 quadrants of the oesophagus at 2cm intervals, obtaining at least 8 biopsies to confidently diagnose Barrett's oesophagus (Harrison 2007.)

The management of HGD remains controversial (Barr 2006.) Traditionally patients who were fit enough underwent an oesophagectomy. More recently endotherapy techniques, including endoscopic mucosal resection (EMR) have been used as an attractive alternative to radical surgery; however their long-term efficacy remains unclear (Das 2008.)

Staging

Oesophageal cancer is staged according to the UICC guidelines, assisting treatment decisions (and prognosis.)

(Similar to gastric cancer, in 2010, the TNM classification of oesophageal cancer has undergone modification following data collation for this thesis.)

TNM Classification (UICC 2005)

- Primary Tumour (T)

  Tx – primary tumour cannot be assessed

  T0 – no evidence of primary tumour

  T1 - tumour invades lamina propria or submucosa

  T2 – tumour invades the muscularis propria or submucosa

  T3 – tumour penetrates the serosa

  T4 – tumour invades adjacent structures

Regional lymph nodes (N)

  Nx – lymph nodes cannot be assessed

  N0 – no lymph node metastasis

  N1 – distant metastasis

Distant metastasis (M)

  Mx – presence of distant metastasis cannot be assessed

  M0 – no distant metastasis

Tumours of the lower oesophagus: M1a – coeliac node involvement

  M1b – other distant metastasis

Tumours of the thoracic oesophagus: M1b – distant metastasis including non-regional lymph nodes

Tumours of the upper thoracic oesophagus: M1a – cervical node involvement

M1b – other distant metastasis

Table 1.3: Stage Grouping of Oesophageal Cancer

Stage	Tumour	Node	Metastasis	5 Year Survival (%)*
0	Tis	N0	M0	>95
I	T1	N0	M0	50-80
IIA	T2-3	N0	M0	30-40
IIB	T1-2	N1	M0	10-30
III	T3 T4	N1 Any N	M0 M0	10-15
IVA	Any T	Any N	M1a	<5
IVB	Any T	Any N	M2b	<1

* Data from Enzinger P. *et al* (2003)

1.2.5 Treatment

As with gastric cancer, a multidisciplinary approach should be taken to decide the management of oesophageal cancer patients (Adams 2006.) With improved diagnosis, staging and treatment there has been a small but significant improvement in survival from oesophageal malignancy over recent years. At present the treatment of locally advanced oesophageal cancer results in 5 year survival rates of 15-20% (Graham 2007.)

Overall, more than 50% of patients have unresectable or metastatic disease at presentation (Enzinger 2003;) and lymphatic dissemination is an early event, with positive lymph nodes being present in 30-40% of early (submucosal) tumours (Akiyama 1994.)

Although both squamous cell carcinoma and adenocarcinoma of the oesophagus are responsive to chemotherapy, the treatment of choice remains surgical resection with curative intent. (Surgery will be considered later in this chapter.)

Potentially Curative Treatment

Preoperative Radiotherapy

The theoretical advantages of preoperative radiotherapy include: a more easily defined target volume; improved tumour oxygenation at treatment; potential to reduce pre-operative tumour volume and peri-operative tumour cell spillage; reducing the likelihood of microscopic residual disease and local recurrence.

A meta-analysis of 5 randomised trials from 1147 patients in randomised trials compared the outcome of preoperative radiotherapy to immediate surgery (Arnott 2005.) It reported a hazard ratio of 0.89 (95% CI 0.78-1.01) with an absolute survival benefit of 4% at 5 years; which did not meet statistical significance. This would indicate minimal benefit with little evidence of improved respectability.

Postoperative Radiotherapy

Postoperative radiotherapy has the advantage of targeted use for selected patients at higher risk of recurrence. Most randomised controlled studies include only squamous cell carcinomas. Fok *et al* prospectively looked at adenocarcinomas and squamous cell carcinoma in 130 patients (Fok 1993.) Both curative and palliative resections

were studied (although different radiotherapy doses were administered and groups were analysed separately.) In the study, significant morbidity (37%) and mortality (21%) related to bleeding from the transposed intrathoracic stomach. The median overall survival was shorter in the radiotherapy group (8.7 months v 15.2 months;) however there was a lower intrathoracic recurrence rate (5.1 v 8.5 months in the palliative resection group, although similar - 9.9 v 11.0 months in the curative resection group.) Of note, the radiation dose per fraction (3.5Gy) was high and this may have impacted on results.

A larger Chinese trial (Xiao 2003) included 495 patients randomised to surgery alone or surgery and postoperative radiotherapy. This produced significant results although had questionable ethics (patients were unaware of being in a trial.) Compared to the UK population a higher proportion of stage IIa disease was included, with apparent high quality surgery and wide field radiotherapy. Analysis of results showed 1-, 3- and 5-year survival in stage II disease between the surgery and surgery with postoperative radiotherapy groups (67.5%, 23.3%, 13.1% v 75.5%, 43.2%, 35.1% respectively.) Relapse patterns were different in both arms, with significantly less recurrence in the neck, supraclavicular fossa and mediastinum. Unlike other studies, toxicity to the transposed stomach was minimal.

There is reasonable evidence therefore to suggest postoperative radiotherapy may be of benefit to stage II squamous carcinoma of the oesophagus. In the UK however many patients will have received preoperative chemotherapy and so the addition of postoperative radiotherapy is outside current evidence base. Furthermore the benefit for patients with adenocarcinomas and its justification is less clear outside the context of a clinical trial.

Preoperative Chemotherapy

Preoperative chemotherapy aims to downstage tumours, thereby improving operability and to treat occult disease as early as possible in order to reduce recurrence. In some patients it may improve swallowing and so improve weight and nutritional status preoperatively. However in non-responders are exposed to chemotherapy side-effects as well as delays in surgical intervention. Preoperative chemotherapy appears to achieve consistently good response rates in both adenocarcinomas and squamous cell carcinoma, ranging from 47% (Schlag 1992) to 61% (Bamias 1996.)

The Medical Research Council (MRC) OEO2 study is the largest and probably most influential trial on this topic (forming the basis of recommended treatment in the UK – SIGN 2002.) Eight hundred and two patients were randomised to 2 courses of cisplatin and a 4 day infusion of 5-FU followed 3-5 weeks later by surgery or immediate surgery alone. A 5-year survival benefit was demonstrated to be 23.0% v 17.1% respectively with a HR of 0.84 (95% CI 0.72-0.98.) The treatment effect was found to be consistent for both squamous and adenocarcinomas. The current OEO5 study aims to build on these results comparing OEO2 chemotherapy with 4 cycles of ECX (epirubicin-cisplatin-capecitabine) with a trial target of 1300 randomised patients.

An updated Cochrane review (Malthaner 2006) of 11 randomised trials involving 2019 patients concludes that there is some evidence to suggest that preoperative chemotherapy increases survival but this was inconclusive (HR 0.88; 95% CI 0.75-1.04.) In addition there was no evidence of benefit in terms of tumour recurrence from preoperative chemotherapy (RR 0.81; 95% CI 0.54- 1.22.) Trials reported toxicity risks from chemotherapy that ranged from 11%-90%.

Postoperative Chemotherapy

Few trials address the question of adjuvant postoperative chemotherapy. The American Intergroup Trial (INT0113) had an adjuvant component coupled with preoperative treatment, however only 32% completed the postoperative phase (Kelsen 2007.) This highlights problems with this type of approach, especially in a patient group that often has a prolonged postoperative phase in which performance status often delays chemotherapy. Improved patient selection and postoperative supportive care may make this approach more practical.

Preoperative Chemoradiotherapy (CRT)

The combined effects of chemotherapy and radiotherapy aims to enhance tumour cell death and improve outcome.

The Walsh study has influenced practice especially in America (Walsh 1996.) In the trial, 113 patients with adenocarcinomas received cisplatin and 5-FU with 40 Gy in 3 weeks of radiotherapy. The CRT arm had an overall survival benefit (median 16 v 11 months; 3 year survival 32% v 6%.) Radiotherapy technique and fractionation dose may explain the not inconsiderable morbidity (13%) in this series; and the poor survival in the surgery arm of the trial is also notable compared to other trials.

Consistent pathology reporting is vital and grading of response has been described by Mandard *et al* (Mandard1994.) Five response grades are described from no identifiable tumour (complete response, grade 1) to absence of regression (no response, grade 5.) This paper, looking at clinicopathological correlations following preoperative chemoradiotherapy, demonstrates evidence that pathological complete response confers survival advantage over those with no response; (tumour regression

grade 1-3 versus 4-5 after multivariate analysis was a significant, $p<0.001$, predictor of disease-free survival.)

A systematic overview of preoperative chemoradiotherapy by Geh *et al* analysed 26 trials (1335 patients) for factors influencing pathological complete response (Geh 2006.) It found evidence that increasing radiotherapy dose ($p= 0.006$,) 5-FU doses ($p= 0.003$) and cisplatin ($p= 0.018$) are linked to higher response rates. However increasing radiotherapy treatment time ($p=0.035$) and increasing median age ($p=0.019$) reduced the probability of complete pathological response.

Neoadjuvant Chemotherapy or Chemoradiotherapy?

A review by Courrech Staal *et al* looked at 38 papers, involving 3640 patients receiving neoadjuvant CRT for oesophageal cancer (Courrech Staal 2010.) Toxicity was reported in 10 papers (mostly neutropaenia) and CRT treatment related mortality was 2-3%, (post-operative mortality was not uniformly reported, but in hospital post-oesophagectomy mortality post chemotherapy was 5.2%.) R0 and complete response rates were 88.4% and 25.8% respectively; and 5-year survival was 16-59% in all patients and 34-62% in the complete response group. The authors concluded that chemoradiotherapy has a temporary negative effect on quality of life.

Overall, precise results regarding neo-adjuvant chemoradiotherapy are conflicting and the survival benefits seem to be minimal (Fiorica 2004, Greer 2005, Graham 2007.) Surgery alone for stage III disease is not likely however to be considered acceptable in the UK or America. The good outcomes of surgery alone in stage I and II disease make neoadjuvant therapy more difficult to justify.

Reports of early experiences of CRT in the UK in terms of operative risk and toxicity vary considerably. The results of OEO2 have meant that UK centres have continued with a chemotherapy approach in the current OEO5 study.

Definitive Chemoradiotherapy

With an increasingly elderly population there will be greater numbers of patients "inoperable" on the basis of local disease, co-morbidity and performance status that would benefit from treatment that is not considered palliative. Indeed it is clear that there are long term survivors in series of definitive non-surgical management (Earlam 1980, Al-Sarraf 1997.) In squamous carcinoma (where lymph node spread is unpredictable) there is increasing evidence that primary CRT with surgery as salvage may be beneficial (Wilson 2000, Bedenne 2007.)

A study by Teoh *et al* compared the quality of life in 81 prospectively randomised patients with squamous oesophageal cancer (using EORTC QLQ-C30 and QLQ-OES24 modules) (Teoh 2011.) In patients undergoing either definitive chemoradiotherapy or surgery, the study concluded that at up to 6 months the surgical group had worse physical functioning and fatigue symptoms than the chemoradiotherapy group ($p < 0.001$ and $p + 0.021$ respectively.) At 2 years however these differences became insignificant.

Endoscopic Therapy

Endoscopic interventions have become a viable alternative for some patients with early-stage oesophageal (especially for squamous cell carcinoma) or gastric cancer or HGD, in whom surgical intervention has been deferred. Non-surgical treatments have the advantage of low morbidity and mortality with the preservation of the digestive

tract and better quality of life - compared with surgical alternatives (Ell 2000, NICE 2003.) Techniques can only be considered curative when lymph node metastasis is not present at the time of treatment.

Photodynamic therapy (PDT,) argon beam ablation, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are the best studied non-surgical approaches at present.

PDT has high remission rates for HGD and early-stage oesophageal adenocarcinoma (Tokar 2006,) but it is expensive, not widely available and has treatment related side effects, including photosensitivity reactions, oesophageal strictures, vomiting and chest pain. Histological assessment is the only reliable assessment to accurately measure the depth of HGD, early oesophageal or gastric cancer; the use of ablative therapies that destroy the primary tumour must be considered with caution. They should be considered only in centres where EMR is not accessible and patients are unfit for surgical resection. Ablative techniques are useful to treat residual margins of mucosal lesions that have positive margin involvement post-EMR. Sagawa *et al* reported 27 patients with "intramucosal" EGC with argon beam coagulation (Sagawa 2003.) During a median follow up of 30 months, 96% patients were reported tumour-free, with no complications; however no long-term follow up was stated.

Tumours suitable for EMR or ESD include: elevated or flat lesions less than 2cm in size; depressed lesions less than 1cm without ulceration; mucosal invasion only; well differentiated and no lymphatic infiltration (Clark 2009.) Although Ono *et al* have extended absolute indications to include lesions up to 3cm in size (Ono 2001.)

EMR or ESD, used alone or in combination with ablative techniques can achieve complete remission in more than 90% of patients, although its role in the management of early neoplastic changes is still being defined (Tokar 2006, Pech 2007.) The strip technique of EMR was first described by Tada *et al* (Tada 1993.) Risks include bleeding and perforation, although major complications are less than 1% (Ell 2000.) Benefits including additional staging information can be provided by EMR/ESD since it involves lesion biopsy and may demonstrate pathological evidence of submucosal invasion necessitating an oesophagectomy (Ell 2000, Fujita 2001.) This increase in accuracy compared to PDT means that it is more effective and preferred in the treatment of gastric HGD (SIGN 2002.)

A trial by Ono *et al* demonstrated good treatment results from EMR for EGC (Ono 2001.) Sixty nine percent (278/405) of intramucosal cancers were resected with a clear margin. Of the 127 that did not achieve complete initial resection, 14 were treated operatively and 9 endoscopically; the remainder had intensive follow up. Local recurrence occurred in 17 lesions treated conservatively, 1 lesion treated endoscopically and 5 lesions that had complete resection. There were no gastric cancer –related deaths after a median follow up period of 38 months (range 3-120 months.) Bleeding and perforation (5%) were the 2 reported major complications and there were treatment-related mortality.

Palliative treatment

At diagnosis 50-80% of oesophageal cancers are inoperable -compared with 30-50% of gastric cancers (Bonenkamp 2001, Mitani 2002.) Holistic palliative care is therefore important in the management oesophageal cancer.

Squamous Carcinoma of the Oesophagus

The standard treatment for advanced or recurrent squamous carcinoma is cisplatin-containing chemotherapy. Indications are limited by the age and performance status of patients and the relative infrequency of the disease. The indication to improve symptoms and quality of life are often local and adequately treated by (metal) stenting. However responses around 35% can be achieved with cisplatin and 4-5days 5-FU infusion (Bleiberg 1991.) Response rate is variable and can range from 3-6 months. Radiation however carries a high risk of local complications such as oesophagotracheal fistulae (Enzinger 2003.)

Adenocarcinoma of the Oesophagus

Stage IV (advanced) disease should be considered for palliative chemotherapy, since 15-30% of patients treated with fluorouracil, a taxane (paclitaxel or docetaxel) or irotecan experience tumour shrinkage of at least 50% (Enzinger 2000.) Responses of 35-55% have also been reported using cisplatin in combination with these agents (Ilson 2000, Ross 2002.) However, although symptoms may be palliated by chemotherapy, responses are usually transient, typically lasting no longer than a few months and survival rarely exceeds one year.

Palliative Brachytherapy

Brachytherapy involves placement in the oesophagus (proximal to the tumour) of a high-dose-rate radioactive substance (usually iridium 192.) This is usually done as a daycase procedure and does not require a general anaesthetic. The aim is to get direct tumour cell kill or increase local radiation dose if used in combination with external beam radiation.

A randomised multicentre trial in the Netherlands evaluating 209 patients demonstrated single-dose brachytherapy gave better relief from dysphagia than metal stenting with equivalent cost (Homs 2004.) Stent placement had more complications than brachytherapy (36 of 108 v 21 of 101; p= 0.02,) which were mostly the result of delayed haemorrhage (although dysphagia relief improved more rapidly after stent placement.) Groups did not differ for recurrent or ongoing dysphagia (p=0.81,) or for median survival (p=0.23.) Quality of life scores were in favour of brachytherapy compared with stent placement.

Oesophageal Dilatation

Dilatation alone should be reserved for patients with expected survival less than 4 weeks who are unable to swallow saliva, or for relieving dysphagia whilst more definitive treatment is planned (Allum 2002.)

1.3 Oesophagogastric Junction Tumours

Oesophagogastric junctional adenocarcinomas represent an increasing proportion of oesophageal and gastric malignancies and are predominately a Western phenomenon (Blot 1991, Powell 1992.) This rapid rise is thought to be related to increased adenocarcinoma rates in cases of Barrett's metaplastic epithelium, combined with an increase in proximal gastric tumours (Salvon-Harman 1994;) which in turn may be linked to a rise in gastro-oesophageal reflux disease (Lagergren 1999.)

Adenocarcinomas arising from the oesophagogastric junction pose difficulties in terms of classification and management.

Siewert *et al* (Siewert1996) proposed a classification system based on the three origins of the junctional tumour (see figure 1.3):

- Type I – adenocarcinoma of the distal oesophagus, the tumour centre being 1-5 cm above the anatomical cardia.
- Type II – true tumour of the cardia; the centre is sited less than 1cm above and 2cm below the anatomical cardia.
- Type III – gastric carcinoma with its centre 2-5 cm below the anatomical cardia.

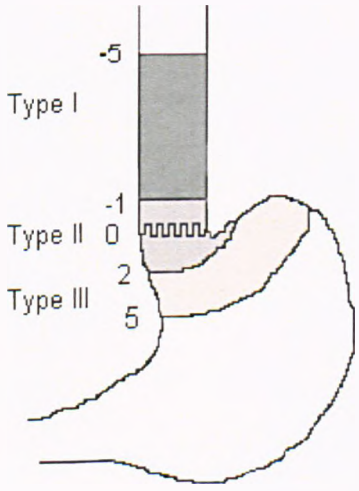


Figure 1.3 Siewert classification

Each type of tumour results in different lymphatic spread: type I spreads in a cephalic direction to mediastinal nodes and caudally to the coeliac axis; whereas type II and III metastasis almost exclusively spread caudally to the coeliac axis, splenic hilum and para-aortic nodes (Stein 2000.) Most surgeons therefore treat type I tumours as oesophageal lesions and type III as gastric carcinomas. Controversy however exists regarding the exact management of type II tumours and whether a total gastrectomy or extended oesophagectomy should be performed, each has its proponents and treatment should be decided on a case by case basis. (Resection for junctional tumours is discussed above in the sections on oesophagectomy and gastrectomy.)

Chapter 1.4 Open Surgery

Surgical resection with curative intent is the treatment of choice for localised oesophageal and gastric cancer, in the absence of medical contraindications. In the Western world (based on studies in the UK and Sweden) resection rates are about 25% (Rouvelas 2005, Al-Sarira 2007.)

The aim of surgery for gastric and oesophageal cancer should be a R0 resection (clearance of proximal, distal and circumferential margins.)

Oesophagectomy remains the highest mortality elective procedure within the sphere of gastro-intestinal surgery, with true in-hospital mortality rates probably remaining around 5-10% globally (Whooley 2001, Jamieson 2004;) with gastrectomy being only slightly less risk (Cummins 2001, SAGOCS 2006.) In the UK recent figures published by the National Oesophago-Gastric Cancer Audit (2010) suggest that in hospital mortality is 4.5% (95% CI 3.7-5.5) for oesophagectomies and 6.0% (95% CI 4.8-7.4) for gastrectomies.

With improved staging, selection and peri-operative care, mortality has fallen and postoperative survival has risen to around 32% at 5 years in contemporary reports (Siewart 2000.)

Evidence suggests that oesophageal and gastric resection should be carried out in high volume specialist units by frequent operators as institutional volume is inversely related to peri-operative mortality and morbidity (Halm 2002, Birkmeyer 2003, Killeen 2005.) This is however subject to ongoing debate (Thompson 2007.) A systematic review and meta-analysis of case volume on cancer mortality by Gruen *et al* compared 101 publications (Gruen 2009.) This demonstrated a significant volume effect; with each doubling of hospital case volume, the odds of perioperative death decreased by 0.1-0.23. The paper did however contain common methodological

limitations such as failure to control for potential confounders, *post hoc* categorisation of provider volume and unit of analysis errors.

1.4.1 Pre-operative Management and Selection of Patients for Oesophageal and Gastric Resection

The aim of pre-operative assessment is to optimise the patient's physiological status and gain an objective evaluation of postoperative outcome. This is especially important given the high mortality and morbidity risks of this type of surgery as outlined above and the high risk of post operative pulmonary complications (Griffin 2002, Bailey 2003.) Despite a number of identified risk factors such as increasing age, impaired functional status, diabetes and impaired pulmonary and cardiac function (Bailey 2003, Steyerberg 2006,) predicting postoperative outcomes remains an inexact science with no consensus on selection criteria; although evidence suggests that poorer outcome correlates with increasing co-morbidity complexity (Golubovic 2002.) Co-morbidity especially cardio-respiratory impairment is common in patients considered for oesophago-gastric surgery (Bailey 2003.) In addition there is a variation in preoperative and socioeconomic risk factors between patients with oesophageal squamous cell carcinoma and adenocarcinomas (Bollschweiler 2000.)

Preoperative clinical Risk Predictors

A common a simple classification of preoperative risk and physical status is that of the American Society of Anaesthesiologists (ASA,) see table below. Although this is a crude scoring system, it does provide a universal global assessment score, with morbidity and mortality increasing as ASA grade increases,

Table 1.4: American Society of Anaesthesiology (ASA) Grading Criteria

Grade	Definition
ASA 1	Normal healthy patient
ASA 2	Patient with mild systemic disease
ASA 3	Patient with a severe systemic disease that limits activity but is not incapacitating
ASA 4	Patient with incapacitating disease that is a constant threat to life
ASA 5	Moribund patient not expected to survive 24 hours with or without surgery

The Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) was proposed in attempt to further evaluate surgical risk. It combines both the patient's physiological score with a score that reflects the magnitude of surgery being undertaken. POSSUM and a later modified system Portmouth-POSSUM (Prytherch 1998) however have been demonstrated to have a poor predictive accuracy for oesophageal surgery (Zafirellis 2002.) Therefore O-POSSUM a risk-adjusted surgically-specific model for predicting outcome after upper gastrointestinal surgery was developed (Tekkis 2004.) O-POSSUM has been demonstrated to accurately predict mortality following gastrectomy but be less so post-oesophagectomy (Largarde 2007,) see table below:

Table 1. 5: O-POSSUM variables

Physiological Score	Operative Severity Score
Age (years)	Operative severity
Cardiac signs/chest radiograph	Presence of malignancy
Respiratory history/chest radiograph	Mode of surgery

the pylorus. Reconstruction commonly involves a Roux-en-Y jejunal loop or Polya reconstruction -although jejunal interposition pouches have been reported (Wan 2006.) The gastroduodenal anastomosis can either be sutured or stapled. A randomised trial by Hori *et al* (Hori 2004) looked at 187 patients receiving a distal gastrectomy and found similar levels of anastomotic complications in both groups (leakage being 1.1% v 2.1% and anastomotic stenosis developing in 4.3% v 1.1% in the mechanical stapling v hand sewn anastomosis respectively; anastomotic bleeding occurred in one patient in both groups.) Other outcome measures such as general complications, length of stay, recovery of gastrointestinal function and radiological diameter of the anastomosis were comparable between groups.

In the case of type III junctional adenocarcinomas, a total gastrectomy is recommended (with a proximal *in situ* 5cm margin.) Controversy exists regarding the management of type II junctional tumours, which some advocate should be treated by extended total gastrectomy rather than subtotal oesophagectomy due to lymph node drainage towards the coeliac axis (von Rahden 2006.)

Reconstruction after gastric resection aims to allow adequate nutritional intake, minimally altering physiology, preventing bile reflux into the oesophagus and not add to the mortality and morbidity of the resection. Duodenal bypass and duodenal continuity comprise the main types of reconstruction. Duodenal bypass involves closure of the duodenal stump and the proximal jejunum, usually using a Roux-en-Y technique, provides continuity. Duodenal continuity techniques involve either joining the gastric remnant to the duodenal stump (Bilroth 1) or interposing a segment of proximal jejunum between the gastric remnant or oesophagus and the duodenal stump. There is no evidence that preservation of duodenal continuity improves quality of life, nutritional parameters or weight (Yu 2002.) Recent Japanese studies suggest a Roux

reconstruction has functional and symptomatic advantages compared to Bilroth 1 reconstruction (Nunobe 2007, Kojima 2008.)

Pouch construction after total gastrectomy should be considered. A study by Lehnert *et al* looked at 19 prospective randomised trials, including 856 patients, comparing reconstructive procedures after total gastrectomy (Lehnert 2004.) Median mortality irrespective of reconstruction was 0% (range 0-22;) and procedure related morbidity was non-significant between groups. Jejunal pouch reconstruction but not restoration of duodenal passage was associated with improved food intake and weight gain in the early post-operative months. Some trials also demonstrated some improvement in long term quality of life.

Lymphadenectomy

The incidence of lymph node metastasis ranges from 3-5% for mucosal tumours, 16-25% for submucosal and 80-90% in patients presenting with stage III or IV disease (Gore 1997, Onate-Ocana 2000.)

Lymphadenectomy, with a minimum of 15 lymph nodes (Van Cutsem 2008) should be performed to increase staging accuracy, reduce locoregional recurrence and thereby improve survival outcome. Controversy exists regarding the exact extent of lymph node dissection and if it should involve a gastrectomy plus nodal sampling (D0); be limited to the perigastric lymph nodes (D1;) or include the regional N1 and N2 lymph nodes beyond the perigastric region (D2) (van de Velde 2005.) The D2 lymphadenectomy definition more recently has been upgraded to the removal of more than 15 nodes irrespective of nodal station, allowing comparison between surgical outcomes in different countries. Extended Lymphadenectomy (D3,) a more radical en bloc resection including third-tier nodes is also occasionally carried out (mostly in

Japan;) and removal of node stations 13-16 (D4) has only been reported to be of benefit in Japan (Maruyama 1987.) An estimation of the likelihood of disease in unresected regional lymph nodes can be calculated by the "Maruyama Index of Unresected Disease" (Kampschoer 1989.)

In the Japanese Rules for Gastric Cancer Surgery the minimum requirement for an effective resection of gastric cancer is a systematic D2 lymphadenectomy.

A Cochrane review by McCulloch *et al* looked at 2 randomised (Bonenkamp 1999, Cuschieri 1999,) and 11 cohort studies of limited (D1) versus extended (D2) lymph node dissection (McCulloch 2004.) Meta-analysis of randomised trials did not derive any survival benefit for D2 resection (risk ratio= 0.95; 95% CI 0.83-1.09,) but demonstrated increased postoperative mortality (RR 2.23; 95% CI 1.45-3.45.) Pre-specified subgroup analysis suggested a possible benefit in stage T3 or greater tumours (RR=0.68; 95% CI 0.42-1.10.) Non-randomised comparison showed no benefit for extended dissection (RR 0.92; 95% CI 0.83-1.02,) but decreased mortality (RR 0.65; 95% CI 0.45-0.93.) Subgroup analysis demonstrated apparent benefit in UICC stage II and IIa. However, a number of confounding variables such as learning curve, lack of blinding, compliance with technique studied and surgical experience (individual and centre) may have affected study outcomes. Treatment decisions regarding the extent of lymphadenectomy tend now to be made on surgical opinion.

Despite the Cochrane review evidence regarding D1 versus D2 remains controversial. The Dutch Gastric Cancer group (Bonenkamp 1999) included in the review (with confounding variables in the study as mentioned above) published an update of results in 2010 (Songun 2010.) The multicentre randomised controlled study involved 711

patients; overall 15 year survival was 21% (82 patients) for the D1 group and 29% (92 patients) for the D2 group (p=0.34.) Gastric cancer-related deaths was significantly higher in the D1 group (48%, 182 patients) compared to the D2 group (37%, 123 patients;) local recurrence between groups was 22% versus 12% respectively; and regional recurrence19% versus 13% respectively. However patients undergoing a D2 procedure had a significantly higher operative mortality compared to D1 resections (10% versus 4%; 95% CI 2-9; p=0.004;) higher complication rate (43% versus 25%; 95% CI 11-25; p<0.0001;) and reoperation rate (18% versus 8%; 95% CI 5-15; p= 0.00016.)

Splenectomy is indicated in addition to gastric resection for cancer when either direct invasion of the spleen or pancreatic tail or removal of the splenic hilum (station 10) lymph nodes -positive nodes being more likely in proximal cancers (Maruyama 1989.) The addition of a splenectomy may increase the risk of thromboembolic and septic complications post surgery (Orsuji 1999.) The evidence of station-10 lymphadenectomy improves survival is conflicting (Schmid 2000, Kikuchi 2002;) in view of these concerns splenectomy is being increasingly avoided unless specifically indicated.

Distal pancreatectomy is indicated in gastric cancer when either direct invasion of the pancreatic tail has occurred, or for removal of the splenic artery (station-11) lymph nodes. There is no place for routine distal pancreatectomy in gastric cancer surgery. En bloc pancreatic resection significantly increases morbidity (including pancreatic leak, fistula, acute pancreatitis and abscess formation) and mortality when compared to gastrectomy with or without splenectomy (in both Western and Japanese studies) (Kitamura 1999.) The survival benefit of station-11 lymphadenectomy in patients with positive nodes is reported to be 15-20% in Japan (Maruyama 1999;) however the

benefit for proximal third cancers were to have a distal pancreatectomy is calculated to be 2% (Raimes 2010) – less than the increased mortality. More recent Japanese studies have now confirmed that there is no survival benefit even for proximal third tumours of the stomach (Kodera 1997.)

Palliation

Tumour size, histological type and differentiation should be considered when selecting patients for palliative surgery. Surgery may be considered in cases of chronic bleeding of gastric body and antral tumours (although laser therapy is often utilised;) and in cases of gastric outlet obstruction. However, in the latter case, the radicality of surgery has to be balanced with the risks of a nutritionally depleted, frail patient who may have a prognosis of less than 6 months and may never sufficiently recover from surgery to derive any benefit. In these cases, a gastrojejunostomy may be performed. In patients with a relatively poor life expectancy placement of a stent may be more beneficial than a gastrojejunostomy (Jernink 2007.)

Post Operative Issues

Nutrition

Nutritional support is important in the post-operative stage, as all patients lose 10% or more of their body weight in the first 3-6 months (Lehnert 2004.) In common with oesophageal cancer resection, nutrition is preferable by the enteral route (Braga 1998, Bozzetti 2001;) and both pre- and post-operative nutritional support has been shown to decrease hospital stay and post-operative complications (Braga 2002, Gianotti 2002.)

Enhanced Recovery

Fast-track or enhanced recovery has successfully been introduced in colorectal surgery (Eskiciogiu 2009) and is increasingly being applied to gastric cancer surgery (Grantcharov 2010, Wang 2010.) This approach aims to reduce post-operative hospital stay, reduce hospital costs and improve patient satisfaction. Wide acceptance of this approach however is limited by concerns regarding patient safety (Kehlet 2005.)

Post-operative Complications

The more common complications post-gastrectomy include:

- cardiopulmonary complications
- duodenal stump leak
- anastomotic leak
- infection (including intra-abdominal sepsis and post-splenectomy infections)
- pancreatic fistula

Late sequelae and complications include: early satiety, early dumping syndrome, reactive hypoglycaemia, diarrhoea, bile reflux and nutritional problems (general malnutrition and weight loss as well as specific deficiencies such as iron and vitamin B12.)

Quality of Life

Potentially curative gastrectomies for cancer have a detrimental effect on patient quality of life. A study by Avery *et al* looked at 58 consecutive patients undergoing curative surgery using a validated questionnaire (EORTC QLQ-C30) and site-specific module (QLQ-STO22) before surgery and for 2 post-operative years (Avery 2010.) Thirty patients (52%) patients were alive after 2 years. In the first 3 post-operative

months HRQL was significantly reduced (mean 10 or more points) in all dimensions except emotional and cognitive function; in this group functional aspects recovered by 6 months.

A study evaluating the benefits of laparoscopic versus open gastrectomy in the first 3 postoperative months found improved global health ($p<0.0001$) in the former group. This prospectively randomised study looked at 164patients and utilised EORTC QLQ-C30 and QLQ-STO22 questionnaires preoperatively and postoperatively on regular follow up visits (Kim 2008.)

1.4.3 Oesophageal Cancer Resection

Patient Selection

Mortality and morbidity post oesophagectomy have been steadily falling over the last 20 years. Reasons for this include: increased specialised units; multidisciplinary approach; better patient selection; earlier diagnosis and improved perioperative management (DoH 2001.) Despite this, oesophagectomy for cancer should only be considered when a potentially curative R0 resection (complete macroscopic and microscopic cancer removal) is planned.

Those with localised tumours (T1, T2) tumours, who are medically fit, should be considered for curative surgery. Neoadjuvant therapy should be considered for T2 tumours. Patients with advanced tumours (T3N1) are recommended for consideration for randomised controlled trials assessing surgery combined with novel multimodal therapies (Allum 2002.)

In addition to meticulous preoperative evaluation to stage the tumour and estimated surgical risk, nutritional support, optimisation of respiratory care and mental preparation of patients should be considered.

Operative Approach

There are various techniques utilised for attempting curative oesophageal cancer resection both in terms of approach and radicality. The method of surgical approach to ensure tumour resection, adequate lymphadenectomy and safe reconstruction depend on tumour location, extent of spread and the fitness, age and morphology of the individual patient. Carcinoma of the hypopharynx and cervical oesophagus tend to undergo pharyngolaryngo-oesophagectomy. Upper middle-third tumours of the oesophagus usually are approached by a three-phase subtotal oesophagectomy such as McKeown's. Middle and lower third tumours can be approached by two-phase subtotal oesophagectomies via right thoracotomy, such as the Ivor-Lewis approach, or by left-sided subtotal oesophagectomy. The transhiatal approach can be considered for upper and lower-third oesophageal tumours.

The transthoracic approach has the benefits of direct visualisation and thorough dissection of the thoracic oesophagus and perioesophageal/perigastric nodal tissue. Therefore it allows complete tumour resection and reduces the risk of residual disease and micrometastatic tumour spillage. The direct transthoracic approach substantially reduces the risk of damage to adjacent structures, particularly the thoracic duct, aorta, bronchus and azygous vein. The commonest open transthoracic procedures are: the Ivor-Lewis oesophagectomy (right thoracotomy and laparotomy) and McKeown 3-stage oesophagectomy (right thoracotomy followed by laparotomy and neck incision

with cervical anastomosis); less common approaches are the left thoracotomy approach and the left thoraco-abdominal oesophagectomy.

The transhiatal oesophagectomy is probably the oncological equivalent of the transthoracic approach, but may have superior outcome in terms of reduced cardiopulmonary complications; no potential anastomotic leakage in the chest (which can result in mediastinitis;) and decreased operative duration -thereby resulting in a lower morbidity and mortality (Wu 2003.) It involves a laparotomy with blunt dissection of the thoracic oesophagus and positions the anastomosis in the neck. Further details of transhiatal oesophagectomy are clearly described elsewhere (Pinotti 1983) as is the Ivor –Lewis oesophagectomy (Crofts 2000.)
At present there are selected indications for a transhiatal oesophagectomy: carcinoma of the hypopharynx and cervical oesophagus; intraepithelial squamous carcinoma of the oesophagus; patients with high grade dysplasia within a Barrett segment (Griffin 2010.)

Four randomised controlled trials comparing transthoracic and transhiatal approaches have failed to demonstrate significant differences between them (Goldminc 1993, Chu 1997, Jacobi 1997, Hulscher 2002.) The strongest evidence comes from the Dutch trial by Hulscher *et al.* This looked at 220 patients with adenocarcinomas of the middle and lower oesophagus. In hospital mortality was not significant between groups (P= 0.45.) Although survival difference was not significant, at five years there was a trend towards survival benefit in the extended approach: disease-free survival was 27% in the transhiatal group compared to 39% in the transthoracic group (95% CI -1 – 24% for the difference;) whereas overall survival was 29% compared with 39% respectively (95% CI -3 – 23%.) Results of this trial remain controversial, since

although no survival benefit was detected between the groups, an ongoing trend towards better 5-year survival for type I tumours was demonstrated. In addition, patients with limited positive nodes (1-8) had significantly better outcome post transthoracic oesophagectomy (where logically extended lymphadenectomy would be most beneficial;) node negative patients did well and higher nodal burden patients did poorly irrespective of surgical radicality.

Whichever approach is utilised, proximal resection is recommended to be 10cm above the macroscopic tumour and 5cm distal to it when the oesophagus is in its natural state -since longitudinal spread is characteristic of all types of oesophageal tumour (Allum 2002.) Adenocarcinoma of the lower oesophagus commonly infiltrates the gastric cardia, fundus and lesser curve. In these cases, the resection, which again should be made 5cm distal to the macroscopic tumour should include some degree of gastric resection and abdominal lymphadenectomy.

Type I oesophagogastric junction tumours are recommended to be treated by a subtotal oesophagectomy with sleeve resection of the gastric cardia and lesser curve in addition to the lymph nodes around the left gastric pedicle (Griffin 2010.) Type II junctional tumours may be treated in a similar fashion dependent on surgical preference.

Lymphadenectomy

Nearly 80% of patients undergoing surgery have positive lymph nodes due to the extensive submucosal lymphatic drainage of the oesophagus. The extent of nodal resection therefore impacts on patient prognosis post complete resection, both in terms of locoregional and systemic recurrence (Wu 2003.) A study by Rizk *et al*

demonstrated the minimal number of nodes required for accurate staging was 18 and involvement of more than 4 lymph nodes had survival similar to M1 disease (Rizk 2006.)

Nodal Dissection Fields

Abdominal single field node dissection involves the right and left cardiac node; lesser curvature, left gastric, splenic artery and hepatic nodes.

Two field lymphadenectomy involves the abdominal dissection described above plus thoracic lymphadenectomy (including para-aortic nodes along the thoracic duct; right and left pulmonary hilar nodes; para-oesophageal nodes; tracheal bifurcation nodes; and in Japan, nodes along the left recurrent laryngeal nerve.)

Three field dissection extends the two field lymphadenectomy to the neck, removing the brachiocephalic, deep lateral and external cervical nodes, and the anterior deep cervical nodes adjacent to the recurrent laryngeal nerve chains in the neck.

In Japan (for squamous cell carcinomas), there is considerable enthusiasm for a 3-field lymphadenectomy (neck, thorax and abdomen); although this has not routinely been adopted in the West (Shimada 2006.) Enthusiasts of this approach argue that up to 30% of patients with mid- or distal oesophageal tumours have concurrent cervical lymph node metastases (Altorki 2002, Lerut 2004.)

Conduit and Anastomosis Placement

The commonest conduit utilised is the stomach (with vagotomy.) When this is not available colonic or jejunal interposition can be used.

Most reconstructions are prevertebral (posterior mediastinal.) This route tends provides the shortest distance between the abdomen and thoracic apex and neck

(Bartels 1993, Gawad 1999.) Alternative less common routes of reconstruction are anterior mediastinal (retrosternal) and rarely presternal. A meta-analysis of 6 randomised controlled trials showed no significant difference in outcome following anterior and posterior mediastinal routes (Urschel 2001.) Relative risk (95% confidence interval; P value) expressed as posterior versus anterior mediastinal route (treatment versus control) was 0.56 (0.17, 1.82; P= 0.34) for mortality; 1.01 (0.35, 2.94; P= 0.98) for leaks; 0.43 (0.17, 1.12, P= 0.08) for cardiac complications; and 0.67 (0.34, 1.33, P=0.26) for pulmonary complications.

Two levels of anastomosis exist: subtotal oesophagectomy with neck anastomosis or oesophagogastrectomy with superior mediastinal anastomosis, each has its proponents. In a randomised trial evaluating 83 patients by Walther *et al*, both procedures were found to be equally safe (with 5 year survival rates of 29% for chest anastomosis and 30% for chest anastomosis (Walther 2003.)) Surgical principle emphasis of anastomotic technique is placed on: adequate blood supply; tension-free anastomosis; accurate epithelial edge approximation; precise layer-to-layer suturing with primary healing.

Studies of sutured versus stapled oesophagogastric anastomosis have demonstrated no difference in leak rates or other complications (Valverde 1995, Law 1997.) The prospective randomized controlled trial by Law *et al* compared patients with squamous cell carcinoma of the thoracic oesophagus undergoing a Lewis-Tanner oesophagectomy; 55 had a hand-sewn anastomosis and 50 a stapled anastomosis. Leakage rates were 1.6% and 4.9% (p= non-significant) for hand-sewn and stapled anatomosis respectively; anastomotic strictures were found in 5 (9.1%) patients in the

hand-sewn group and 20 (40%) in the stapler group (p= 0.0003); anastomotic recurrence occurred in one patient in each group.

The addition of a pyloroplasty (allowing gastric drainage) reduces postoperative gastric outlet obstruction, but has little effect on other early and late complications (Urschel 2002.) This paper was a meta-analysis of 9 RCTs, which included 553 patients (with Jadad scores ranging from 1-4.) Pyloric drainage versus no drainage had a RR 0.92, (95% CI 0.34-2.44, p=0.86) for operative mortality; and RR 0.25 (95% CI 0.04-1.60, p= 0.36) for pyloric drainage complications. For late bilary reflux there was a non-significant trend favouring the non-drainage group; and scintographic gastric emptying time (pyloric drainage/no drainage) was 0.53.

Postoperative Issues

Nutrition

Nutrition is important in the peri-operative period. Some surgeons routinely site feeding jejunostomies either pre- or peri-operatively to help maintain gut integrity and function and provide adequate nutritional support (Sica 2005.) Studies have demonstrated that pre-operative nutritional support (which can be targeted) have improved post-operative outcome and decreased hospital stay (Braga 2002, Gianotti 2002.) In addition to these benefits, post-operative feeding has also been shown to improve wound healing (Braga 1998, 2002.) If possible nutrition should be administered enterally (Braga 1998, Bozzetti 2001.) A recent systematic review comparing 5 RCTs and 1 case-controlled trial (with 344 patients) analysed nutritional access routes following oesophagectomy and failed to find strong evidence supporting single feeding route access (Markides 2011.) However due to the

significant risk of dislodgement of nasojejunal and nasoduodenal tubes, it suggests that feeding jejunostomies may be superior.

Immunonutrition has also been purported to be beneficial in patients undergoing oesophageal resection by reducing inflammatory response and improve post-operative immune response (Sakurai 2007.)

Intensive Care and High Dependency Unit Admission

Historically patients were routinely admitted to intensive care units following oesophagectomy. Increasingly, patients are now being extubated and managed safely in a high dependency environment -with the provision of intensive care for complications (Chandrashekar 2003, Robertson 2006.)

Enhanced recovery

There is increasing interest in the development of standardised care pathways, providing a fast-track or enhanced recovery for patients following oesophagectomy (Cerfolio 2004, Low 2007.) This uses a multi-disciplinary approach; optimising peri-operative parameters affecting patient rehabilitation such as avoiding prolonged mechanical ventilation, early nutritional support, early ambulation and goal-directed management pathways. In addition to reduced length of stay it has been demonstrated to improve patient satisfaction and reduce costs (Zehr 1998, Cerfolio 2004.)

Postoperative Complications

Meticulous attention to the maintenance of fluid balance and respiratory care, including pain control and chest physiotherapy, are essential in the immediate postoperative period. Common complications include:

- respiratory problems (failure, effusions, infection, acute respiratory distress syndrome)
- cardiac problems (arrhythmias, myocardial infarctions, congestive cardiac failure)
- anastomotic leak
- chylothorax
- benign anastomotic strictures
- recurrent laryngeal nerve palsy
- gastric outlet obstruction

Quality of Life

Survivors face a long and difficult path back to a reasonable quality of life, so that oesophagectomy patients appear to derive no benefit unless they survive more than 2 years (Blazeby 2000;) and even after 3 years post-resection may still suffer persistent problems with physical function and specific symptoms (Lagergren 2007, Djarv 2008.) Quality of life is therefore an important outcome measure during surgical treatment making (Parameswaran 2008.)

1.4.4 UK Multicentre Trials of Outcome in Gastric and Oesophageal Cancer Resection

The Assessment of Stomach and Oesophageal Cancer Outcomes from Treatment (ASCOT) multicentre, prospective cohort study commenced in 1999 (Cummins 2001.) It aimed to ascertain the current state of UK practice for treatment of gastro-oesophageal cancer, including stage, co-morbidity and outcomes, at a time of intense public scrutiny. Results were obtained from 24 hospitals between 1st January 1999

and 31st December 2002, comprising of 955 patients undergoing oesophagectomy or gastrectomy (of a total of 2087 cases submitted) (McCulloch 2003.) Of these, 27% were ASA III or IV; 20% had a POSSUM score ≤ 20; operative mortality was 20%. Total morbidity for surgical complications was 108 (18.3%) for gastrectomies (3.2% were anastomotic leaks;) 72 (19.7%) for oesophagectomies (5.5% were anastomotic leaks;) of these cases 10.2% and 10.4% respectively (p=0.905) required a second operation. Medical complication morbidity was 191 (32.4%) for gastrectomies (11.0% cardiovascular related and 20.2% pulmonary;) and 190 (52.1%) for oesophagectomies (15.6% cardiovascular in origin and 40.5% respiratory in causation.)

ASCOT was novel in the ascertaining UK NHS practice. Its participants were self-selected and therefore not necessarily representative of UK practice due to self-selection; and mortality and morbidity results were higher than many contemporary reports; however the Scottish national audit at the time reported similar mortality for gastrectomy (Thompson 2002.) Reported results also compared unfavourably with international results, possibly as a result of differences in patient population and superior treatment effects due to selection and publication biases. ASCOT results were however affected by a number of contributing factors resulting in high mortality rates: low volume centres; liberal selection criteria for operation; high frequency of unrelated systemic disease (occult cardiovascular disease being higher in the UK than many other European countries (British Heart Foundation 2003;) poor quality or inappropriately radical surgery; poor quality post-operative care (McCulloch 2003.) ASCOT managed to collect data from 2/3rds of hospital episode statistics, although individual trust figures varied considerably. Submission was voluntary and unfunded; omitted data varied from 5-10% (Warsi 2002.)

The National Oesophago-Gastric Cancer Audit was set up after MIGOCS and published its findings in 3 reports (2008-2011) collating data from October 2007 to June 2009. Like ASCOT it provides a multicentre report on UK management of gastro-oesophageal cancer, with data on over 17, 000 patients. It encompassed information on patient demographics, diagnosis, staging and treatment planning; curative treatment (including neoadjuvant therapy) and short-term outcomes- such as 30 and 90-day mortality, morbidity, unplanned returns to theatre; palliative oncological, endoscopic and radiological treatment and their short-term outcomes. Unlike the MIGOCS database it more comprehensively covered gastro-oesophageal cancer treatment in the UK and successfully involved many more centres. Although it included minimally invasive resections, data collection was less focussed on technique details than in MIGOCS providing limited feedback to enable procedure development. Below (table 1.6) compares the morbidity, mortality and lymph node retrieval between open and minimally invasive approaches published in the 2010 National Oesophago-Gastric Audit, with the added comparison where information allows from the 2002 ASCOT report.

Both studies demonstrated the difficulties of multicentre data collection. Following initial centre recruitment, regular encouragement of data acquisition is frequently required; with mechanisms for data quality assurance to ensure completed data entries and accurate entries for all eligible patients (the latter also being reliant on the integrity of those entering data.) Support facilities to assist any difficulties encountered in data entry and appropriate database evolution are also beneficial to optimise database success.

	Oesophagectomy (%)			Gastrectomy (%)		
	NA open (n=1541)	**NA minimally invasive (n= 659)**	**ASCOT (n=241)**	**NA open (n=1226)**	**NA minimally invasive (n= 186)**	**ASCOT (n=257)**
30-day mortality	4.1	3.2	3.7	4.7	3.2	4.3
Re-operation	9.9	11.1	10.4	7.3	7.7	10.2
Anastomotic leak	7.4	10.5	5.5	5.7	7.0	3.2
Respiratory complication	13.8	10.8	40.5	6.9	9.7	20.2
Cardiac complication	5.9	3.6	15.6	3.9	3.2	11.0
Wound infection	4.5	2.4	7.9	3.2	3.8	3.9
LN retrieval 1-5	4.5	2.1	11.6	25.5	25.7	39.7
LN retrieval 6-14	26.1	18.8	26.2			
LN retrieval ≥ 15	69.4	79.1	62.2	74.6	74.3	60.3

Table 1.6 Outcomes of Gastro-Oesophageal Cancer Surgery in the UK courtesy of the National Oesophago-Gastric Audits published in 2004 and 2010.
NA= National Oesophago-Gastric Audit (2010 published data)
ASCOT data taken from 2004 AUGIS report
LN= Lymph Node

Chapter 1.5 Laparoscopic Surgery

Advances in surgical technology have made minimally invasive gastric and oesophageal cancer surgery possible and since the early 1990s, it has been gaining popularity (Cushieri 1992, DePaula 1995, Azagra 1999.) Whilst the minimally invasive approach is technically feasible, it is still an investigational technique, with limited evidence regarding its safety and efficacy, and has an as yet undefined role.

Over 5000 cases have been reported in the literature of minimally invasive surgery (MIS) for gastro-oesophageal cancer, with a myriad of techniques used. Most of the published evidence is in the form of case series, with only 3 randomised controlled trials of gastrectomy (Hayashi 2005, Huscher 2005, Lee 2005) and none of oesophagectomy. Case numbers in the reported series tend to be small, with a few exceptions (Kitano 2007;) most are single centre and five year results are limited (Luketich 2003, Cristano 2005.)

A large proportion of the experience reported in the literature regarding laparoscopic oesophago-gastric cancer surgery is anecdotal and mainly comes from South East Asia.

To date, two thirds of the literature published regarding minimally invasive gastrectomies comes from the East where there are high incidences of gastric cancer; whereas laparoscopic oesophageal resection publications mainly are from Western countries (Gemmill 2007.) This difference has resulted in differences in the evolution of the techniques and the data published. Compared to the West, Eastern countries such as Japan and Korea have major differences in their patient population, social influences, surgical philosophy and infrastructure; which impacts on outcomes such

as length of stay and lymph node retrieval, and causes outcomes that may not reflect those found in other settings.

It must be remembered though, that in common with all evidence in surgical literature, information on an evolving technique is subject to considerable imprecision, publication and selection bias (Lilford 2004) and there is continual improvement as the technology advances.

A more detailed analysis of the current evidence and problems in conducting randomised controlled trials will be discussed in later chapters.

1.5.1 Main Approaches in Oesophago-Gastric Cancer

A variety of techniques and practices are described in the literature, each of which has its proponents, with no consensus on which method is optimal.

Gastrectomy

Most minimally invasive approaches are applied to early gastric cancer (confined to the mucosa and submucosa) and encompass a spectrum of techniques, including function preserving surgery and treatment modalities using either laparoscopy or endoscopy. For the purposes of this thesis endoscopic techniques have been excluded. The table below outlines laparoscopic approaches used for gastric cancer:

Table 1.7: Types of Laparoscopic Surgery for Gastric Cancer

- wedge resection

- intragastric mucosal resection
- local resection with adjacent lymphadenectomy
- segmental resection
- pylorus-preserving gastrectomy
- proximal gastrectomy
- laparoscopy-assisted or totally laparoscopic distal subtotal or total gastrectomy (with lymphadenectomy)

Each type of minimally invasive intervention has its prerequisites for clinical application and the extent of lymphadenectomy (like with open surgery) remains controversial. All techniques however tend to be less extensive than conventional distal subtotal or total gastrectomy with D2 lymphadenectomy.

Oesophagectomy

Many different approaches to minimally invasive oesophagectomy are being performed (see table 1.8.) The most common procedure currently being performed is the thoracoscopic oesophagectomy with gastric mobilisation via laparotomy and cervical oesophagogastrostomy (Law 2002.)

Table 1.8: Types of Laparoscopic Surgery for Oesophageal Cancer

- laparoscopic gastric mobilisation, thoracotomy with intrathoracic oesophagogastrostomy
- thoracoscopic oesophagectomy with gastric mobilisation via laparotomy and cervical oesophagogastrostomy

- thoracoscopic oesophagectomy with gastric mobilisation via laparotomy and intrathoracic oesophagogastrostomy
- thoracoscopic oesophagectomy, laparoscopic gastric mobilisation and cervical oesophagogastrostomy
- thoracoscopic oesophagectomy, laparoscopic gastric mobilisation with hand-assisted device
- transmediastinal endodissection
- laparotomy and laparoscopy-assisted transhiatal mobilisation
- total laparoscopic transhiatal oesophagectomy

1.5.2 Potential Benefits and Problems

The potential benefits of a laparoscopic approach to surgery are well known, including better visualisation, reduced post-operative pain, shorter hospital stay (and in some case less high dependency care,) quicker functional recovery and improved quality of life when compared to conventional, open resection (van den Broek 2004, Huscher 2005.) The short term benefits however vary widely in published reports.

Minimally invasive resections have their drawbacks. Procedures tend to take longer (Hyung 2006;) operative costs are higher (Adachi 2001;) learning curves are evident (Kim 2005, Jin 2007) requiring high levels of technical skill and adaptation from other complex gastrointestinal procedures; data on long term follow up is limited and critics question the oncological adequacy of the technique.

The benefits and limitations of a minimally invasive surgical approach to gastric and oesophageal malignancy will be discussed in further detail in subsequent chapters.

Chapter 1.6 Problems in Conducting Randomised Controlled Trails and Possible Solutions

Randomised controlled trials (RCTs) are considered the gold standard approach to compare treatments (NHS HTA 1992.) However RCTs of surgical practice encounter particular methodological issues (Stirrat 1992, McCulloch 2002, Lilford 2003) and frequently result in small, poorly conducted trials; with inadequate, low quality reporting, especially of complications (Martin 2002, Balasubrumanian 2006, Jacquier 2006.) A review of "surgical research" by Horton *et al* demonstrated that nearly half of all novel surgical techniques were reported as case series, with almost 10% reported as RCTs (Horton 1996.)

In order to try and improve the poor quality of RCTs published especially with respect to poor methodology, incomplete and inaccurate reporting, the Consolidated Standards of Reporting Trials (CONSORT) statement was published (Altman 2001.) The statement consists of a flow diagram and checklist to aid RCT reporting, outlining acceptable ways to perform and report clinical trials; thereby facilitating both the critical appraisal and the interpretation of RCTs. Subsequent to the adoption of the CONSORT statement by many leading medical journals, the quality of RCTs has demonstrated an improvement (Moher 2001, Plint 2006.) However, inadequate and low quality reporting standards of surgical interventions are still apparent, making interpretation of their results difficult (Jacquier 2006.)

Medical interventions and trials contrast to surgical ones not just from a quantative but a qualitative perspective. Medical trials are often relatively simple and straightforward involving drug or protocol introductions and are therefore amenable to blinding and standardised protocols. Surgical interventions frequently include

procedures and device development, intrinsically requiring some degree of personalisation. They are influenced by innate preferences' of the surgeon and limited by individual surgical skill; thus inevitably introducing potential confounding factors and contamination. These characteristics, often term "equipoise" are addressed in more detail later. Patient accrual is frequently slow compared to medical drug trials; requiring multicentre involvement in order for trial numbers to obtain statistical significance in a relatively short time period (Dimick 2001.) Recruitment is also difficult if the two treatment arms differ significantly, such as a surgical versus medical trial (Stirrat 1992.)

1.6.1 Development Phases of Surgical Trials

This can be considered in a number of phases, as outlined in the Idea, Development, Exploration, Assessment, Long-term (IDEAL) study recommendations (McCulloch 2009):

(Simulator or animal studies if they exist are considered as stage 0.)

Stage 1. Idea (Proof of Principle.)

Novel techniques describing approach and establishing feasibility are reported as case reports or small case series. At this stage the concept proven, and technical achievements, disasters and notable successes are published. Single case studies can also be used to identify potential adverse side effects, for example reporting to the UK Medical Devices Agency.

Stage 2a. Development

The technique is adopted and disseminated by a cohort of interested surgeons, who develop it by a series of small steps (rarely involving more than 30 patients,)

establishing its effectiveness. Publications are usually uncontrolled, individual, retrospective case series which address safety, technical and procedural success; they tend to constitute poor quality of "evidence."

Stage 2b Exploration

More surgeons learn the procedure, expanding eligible patient selection and refining the technique. This stage is amenable for research databases; explanatory or feasibility randomised clinical trials looking at clinical short-term outcomes; for learning curve evaluation and mentoring issues.

Stage 3 Assessment

The intervention having stabilised can expand, with well-defined indications. Comparative data can be obtained from a controlled trial and for full evaluation the procedure compared with conventional surgery (ECST 1998, Neumayer 2004.) Middle and long-term outcomes, quality of life and cost-effectiveness can be assessed.

Stage 4 Long-term studies (Surveillance and Quality Control)

Continual monitoring of established technique results is required to ensure initial success levels are maintained and identify any adverse effects. This involves audit, registries and rare-case reports. All patients and surgeons qualify to perform the intervention as rare events, long-term outcomes and quality assurance are assessed.

The IDEAL framework of evaluation and stages of surgical innovation by the Balliol collaboration has been utilised to evaluate a number of surgical techniques (McCulloch 2009.) Examples of this include: minimally invasive oesophagectomy (Blazeby 2011) and urology (McCulloch 2011.)

This approach provides a good model for the evolution of novel surgical techniques and offers methods of evaluation at each stage of development. However the order suggested does not always reflect real life situations when technique evolution may result in a systemically different approach or non-operative management. It does not entirely incorporate evaluation by simulation or animal studies prior to human trials such as that by natural orifice transluminal endoscopic surgery (NOTES (Flora 2008;) or address comparison of a non-operative intervention and surgical technique, such proton-pump inhibition versus antireflux surgery for reflux oesophagitis (Lundell 2007.)

The IDEAL framework does not always easily apply to the earliest stages of surgical technique evolution, where there may be no definite divide between the first two stages. A novel approach may be applied out of necessity to solve a problem and repeated on future occasions prior to realisation of the development of an innovative technique. The exact timepoint at which formal scientific and ethical framework needs to be applied is therefore difficult to define and implement.

1.6.2 Potential Problems in Randomised Controlled Trials

1 *Trial Definition*

A clear treatment definition and description are a prerequisite of therapeutic evaluation (Campbell 2000, Altman 2001.) Unlike pharmaceutical interventions, surgical interventions are often complex, multifactorial and difficult to standardise, with healthcare professionals being integral to patient outcome. There is therefore a need to report details of:

- The surgeons' "experience", which may affect morbidity and introduce bias (Bonenkamp 1995, Devereaux 2003, Lilford 2004.)

- The volume of centre activity - since large volume centres tend to have better outcomes (van Lanschot 2001, Halm 2002, Birkmeyer 2003.)
- Explicit reporting of all components of the intervention such as: preoperative care, the principle procedure, peri- and post-operative care (including anaesthetic management and rehabililitation.)
- Outcome measures need clear definition; disease timeline and intervention timing may also impact on outcome.

2. Learning Curve (Practice Effect) and Trial Timing

Ideally innovative techniques should be evaluated by trials performed prior to take up in clinical practice providing a control for intervention comparison (i.e. while there is still equipoise.) However randomisation between familiar and new techniques introduces bias (Bonenkamp 1999, Cook 2009,) a problem that has few parallels in pharmaceutical trials.

Technique development can also be inhibited by too early RCT analysis and reflect the learning curve rather than the therapeutic effect of the procedure (Reeves 1999, Yang 2009.) This learning curve includes the surgeon, procedure, supporting team (surgical, nursing, anaesthetic) and patient. Trial timing is thus complicated by external factors in addition to surgeons learning individually at different rates, usually via an apprenticeship structure (Cook 2004.) This may be improved by collection of comprehensive data including the surgeons personal procedure-based learning (Cook 2007.)

3. Equipoise

Patient preference in entering trials can limit RCT recruitment, especially where there are known disadvantages (Prescott 1999, Harrison 2007.) Many patients do not wish their treatment decision to be made by chance alone (Tournoux 2006.) In type 3 trials (comparing surgical and non-surgical treatments,) 82% of recruitment problems were found to be related to patients' equipoise (Solomon 1995.)

Surgeons are often criticised for their poor understanding of clinical epidemiology (Solomon 1995, Rothenberger 2004.) Their attributes, including surgical knowledge, inherent skills and previous experience will influence any surgical intervention leading to outcome variability (Ergina 2009.) Inherent surgical personalities impact on trials. Surgical affinity for quick decision making with incomplete information (McCulloch 2005,) may result in difficulties in conscious individual certainty despite collective uncertainty, between two treatments required for RCTs. Surgeons also frequently believe catastrophic events will occur without intervention, which may not always be the case, for example delayed surgery in the treatment of necrotising pancreatitis (Buchler 2000.)

4. Sample size

Increasing sample size can improve trial precision; however the rarity of some conditions means that patient recruitment is slow (Solomon 1995) and can be difficult in emergency presentations with consent and randomisation issues (McCulloch 2002.) Long-term studies may help where the learning curve is less integral, but selection criteria and risk-adjustment for patient comorbidity is both complex and important (McCulloch 2009.)

Adequately powered sample sizes can rarely be achieved in single centre studies, where their generalisation is always questionable; multicentre studies however have their own limitations, confounding factors and barriers (McCulloch 2002 and 2005, Mohammed 2009.)

4. Quality Control Monitoring

Surveillance, data quality monitoring, surgeon-specific effects and surgical performance (including identifying surgical outliers) impact on studies and the reliability of any outcomes measured. Quality assurance literature has suggested focussing on structure, process and outcomes to measure the standard of surgical care (Birkmeyer 2004.) However many outcomes assessing short-term clinical measures of technical success and harm are not standardised and thus not reproducible (Ergina 2009.) Additionally they often depend on from whose perspective is being measured e.g. patient versus surgeon. This is especially significant in quality of life studies. The degree of individual surgical vigilance, experience and judgement can also impact on results. This can be significant when an intervention has occurred from the early detection of complications and thus reduced measured outcomes.

5. Masking or Blinding

Blinding the operative surgeon to the actual procedure is difficult, especially where there are visible sequelae and permanent, non-reversible structural changes. It is possible however to blind the surgeon to the allocation group with the outcome being measured by independent third parties or stakeholders with standardised endpoints. The wound itself can even be concealed, though this is seldom done (Poolman 2007.)

Patient blinding by sham or placebo surgery is ethically controversial and tends to be used in cases where a suitable comparison is not available or sham surgery has limited risk (London 2002, Mosely 2002.) This is problematic when assessing subjective outcomes by both clinician/researcher (Moher 1999) and patient (Hrobjartsson 2001.)

The absence of masking can result in bias. This can be of performance (surgical and other care providers or patients choosing concurrent interventions;) attrition (differential follow up withdrawal;) and detection (differential outcome assessment.) (Higgins 2008.)

1.6.2 Proposed Solutions

Despite the quality of RCTs having improved since the publication of the CONSORT statement as outlined earlier, the methodological aspect of many surgical trials still needs addressing. In some cases for ethical or pragmatic reasons RCTs may not feasible, especially in the initial stages of novel surgical technique development. In these situations alternative trial designs and approaches are necessary, often making the technique closer to being amenable to a RCT, such as those described below. These suggestions include those proposed in the IDEAL model (McCulloch 2009.)

Stepped Wedge Trials (Cook and Campbell 1979)

This type of trial design involves the sequential roll-out of an intervention to participants (individuals or clusters) over a number of time periods (Brown 2006.) Although all participants receive the intervention, the order of their involvement is random. This (parallel) trial design is beneficial where the intervention is forecast to be potentially harmful and/or for logistical, financial or practical reasons participation

cannot occur simultaneously. However it introduces complexities to statistical interpretation and increases trial duration. An example of this type of trial is that by Wilmink *et al* which looked at the incidence and mortality of ruptured abdominal aortic aneurysms in a GP setting (Wilmink 1999.)

Tracker Trials (Lilford 2000)

By evaluating, or "tracking" new treatments as they evolve over time, prior to stabilisation (when a RCT can be carried out,) unbiased comparisons can occur at each stage of development, detecting poor performances rapidly and providing an early warning. The protocols and sample size for this type of trial should be flexible in order to maximise data and outcome measurements (which require complex analysis.) Although conceptually attractive, incorporating the difficulties of incremental and stepwise innovation, tracker trials are challenging in practice.

An example of this type of trial is the endovascular aneurysm repair trial (EVAR 2003.)

Expertise-Based Design (Devereaux 2005)

Patients are randomly allocated to surgeons with expertise in different procedures, protecting against bias and allowing surgeons with strong preferences to participate (similar to cluster randomisation.) This type of study requires more surgeons and encounters numerous potential confounding factors.

Databases

Surgical databases are a fundamental part of surgical practice and can allow the retrospective initiated comparative studies of prospectively collected data; evaluation of temporal trends and the identification of late or rare effects of treatment.

The quality of evidence of this type of data, compared to RCTs is a subject of continuing debate (Benson 2000, Raftery 2003.) It requires surgeons to be willing to enter data and be subject to scrutiny of their outcomes. Databases are reliant on the integrity participants in assuring the validity and completeness of data, which often contain inadvertent errors (thus this approach should ideally contain quality control checks.)

Phase II (S) Surgical Studies (McCulloch 2002)

This type of study acts to bridge the gap between case series and randomised controlled trials, similar to oncological phase II studies. It aims to aid development of a satisfactory definition of the procedure; determine adequate measures of surgical quality; evaluate the learning curve of participants; identify suitable sample sizes and end points for a randomised trial, and develop the required consensus and familiarity with working together to allow the trial to develop organically. (This approach has been considered in this thesis regarding the development of minimally invasive gastro-oesophageal cancer surgery, which is currently at stage 2b of the IDEAL guidelines.)

Phase IIS trials aim to indicate suitable timing for a RCT, and using a "tracker" design, enable randomisation to be introduced early (Lilford 2000.)

Quality Control Studies and the Learning Curve

Quality control of evolving techniques can be monitored by studying the learning curve and continuous unit performance surveillance (Beiles 2004, McCulloch 2009.) Several sequential probability ratio tests can be applied to address surgical learning curve such as CUSUM (Cumulative Sum Control) (Novick 2003, Speigelhalter 2004),

VLAD (Variable Life-Adjusted Display) (Lovegrove 1997) or CRAM (Cumulative Risk Adjusted Mortality) plots (Polonieck 1998.)

Charts such as CUSUM, monitor the improvement (or deterioration) of surgical practices and are sensitive to small outcome changes (Steiner 1999,) "triggering" when failure frequency significantly exceeds that which is expected.

Indications of changes in outcome detected by these methods can be utilised to indicated whether a RCT is possible or further prospective data collection (with regular Bayesian analysis) is needed first (Raskob 1985, Felli 1999.)

1.6.4 Conclusions

The IDEAL framework and recommendations provides a description for the development novel surgical techniques and alternative approaches to developing study designs.

Surgical research involves multiple obstacles to performing RCTs. A comprehensive approach should therefore be considered with accurate, standardised clinical and patient-reported outcomes, prospectively design and application of quality control measures. This should occur after initial surgical intervention development, providing evidence-based comparisons between interventions (McCulloch 2009.)

Phase II surgical trials, tracker trials, stepped-wedge and expertise-designed trials are all examples of trials designed to address the need for evidence-based comparisons between established ad novel surgical techniques. In this thesis, a phase II surgical trial design has been utilised as it addresses many of the difficulties encountered in surgical trials, such as trial definition; quality control; learning curves; and aims to encourage a RCT between participants as one of its conclusions. It thus provides the integration of rigorous scientific evaluation and the natural development of minimally

invasive upper gastrointestinal cancer surgery (hopefully overcoming many of the difficulties that have thus far delayed its development.)

Chapter 2 Hypothesis and Aims of this Thesis

The aim of this thesis was to test the hypothesis that: minimally invasive surgery has apparently superior outcomes to conventional, open surgery but current studies are methodologically inadequate to confirm this.

In order to test this hypothesis the following were looked at:

- Problems and possible solutions in conducting a randomized controlled trial of surgical technique.

- The current evidence in the literature regarding minimally invasive gastro-oesophageal cancer surgery.

- The development of a phase II surgical trial (as a means to bridge the gap between case series and randomized controlled trials.) This was aimed to generate data to enable power calculations required to perform a randomised controlled trial.

- Retrospective and prospective results of a study of MIGOCS in a multicentre UK setting. This represented stage 2a and b of the IDEAL guidelines utilising a disease register developed between members of the MIGOCS group.

- Definition of the learning curve associated with new techniques such as MIGOCS utilising CUSUM (cumulative sum control) methodology.

- Development of a randomized controlled trial in minimally invasive surgery comparing it to open techniques. Whilst a RCT was not actually reached in this thesis, it is the ultimate aim and gold standard to be achieved by phase 2 surgical study methodology. It was hoped that this study will aid definition of the techniques used in minimally invasive gastro-oesophageal cancer surgery; help develop consensus; give an idea of required end points and power calculations in order to move towards a RCT.

Chapter 3 – A Systematic Review of Minimally Invasive Resection for Gastro-Oesophageal Cancer

3.1 Introduction

Minimally invasive approaches to gastro-oesophageal cancer surgery have been gaining popularity since the early 1990s. A key question in the evolution this type of approach (like any novel technique) needs to be its safety and efficacy, prior to the widespread dissemination of practice. At present, apart from individual papers (mostly published by single surgeons operating in single centres) the answer to this question remains unknown.

3.2 Methods

3.2.1. Literature Search Strategy

Using PubMed and Embase as primary sources, an electronic literature search of articles published between 1992 and June 2006 (the date of the search) was performed. The main search terms used were: gastric cancer, oesophageal cancer, minimally invasive, laparoscopic and surgery. Logical combinations of these and related terms (stomach, oesophagus, neoplasm, and carcinoma) were used to maximise sensitivity. Articles printed in the English language, or with an English abstract were used and the criteria was further restricted to articles related to humans rather than simulations or animal studies. Articles without an available abstract were not retrieved. Six selected surgical journals (British Journal of Surgery, Surgery, Annals of Surgery, Surgical Endoscopy, Archives of Surgery, European Journal of Surgical Oncology) were hand

searched; apparently relevant articles were identified in the reference list of full text articles and retrieved (as a supplementary strategy.)

3.2.2 Article Selection Process

Full text articles were retrieved from English abstracts that contained pre-selected eligibility criteria. All articles reporting 6 or more minimally invasive resections for gastric or oesophageal carcinomas (including high grade dysplasia but not including benign conditions or Gastro-Intestinal Stromal Tumours- GISTs-) and which provided a minimum set of basic operative technique details and post-operative outcome data were retrieved. Articles using hand assisted and hybrid techniques were included as long as part of the operation was attempted or completed laparoscopically or thoracoscopically. Review articles, case reports, articles containing less than six patients and those that did not specify the surgery performed or the conditions treated were excluded. Robotic, endoscopic studies and those on children were also excluded. Only the most recent article by a set of authors that had published cumulative, sequential or overlapping reports were analysed to avoid inadvertent double analysis of cases. We were interested in evaluating the clinical results of minimally invasive resection, and therefore articles were excluded where the abstract made no mention of any of the following: operative blood loss, operating time, mortality, morbidity, length of hospital stay.

Table 3.1: Inclusion and Exclusion Criteria for Systematic Review

Criteria	Inclusion	Exclusion
Trial Design	Randomised Controlled Trial Case matched series Case series	Review article Case report Duplicate/sequential data
Data	Operative details and post-operative data provided	Minimal outcome data
Number of cases	6 cases	< 6 patients
Pathology	High Grade Dysplasia and Cancer	GISTS, benign conditions
Operative approach	Hand-assisted/hybrid provided approach involved laparoscopic/ thoracoscopic element	Robotic Endoscopic
Age	Adult	Paediatric

3.2.3 Quality Assessment of Retrieved Articles

Each included article was appraised by two reviewers, who independently assessed the methodological quality of the selected articles.

3.2.4 Data Extraction and Recording

A pre-designed proforma (see table 3.2) was utilised for each retrieved full text article to extract relevant operative and outcome information. Articles were classified as case series; case matched studies or randomised trials. Case series were defined as analysis of a series of people undergoing gastrectomy or oesophagectomy (with no comparison group;) case matched studies were analysis of a series of people undergoing oesophagectomy or gastrectomy by a minimally invasive technique with a comparison group (that may be historical) of the same type of surgery but open in

approach. Information on patient numbers, age and sex, tumour site and stage, operations performed and techniques used, operative time, blood loss, conversion rate, complications, morbidity, mortality, adequacy of the cancer resection and indicators of speed and quality of recovery were collected. Results were subdivided into those for gastrectomy and oesophagectomy. Due to very clear differences in the profile of the Western and Eastern literature, separate analyses of the studies from Western and Eastern authors were performed.

(Western included North America, Europe and Australasia; Eastern included the Middle and Far East, in particular Japan, Korea and China.)

Table 3.2: Pre-Determined Criteria for Paper Selection for Further Review

Study Parameters

Study Authors

Journal Citation

Study Design: case series/prospective cohort/non-randomised comparison/RCT/other

Number of patients studied: in minimally invasive group/in other groups

Minimally invasive operations studied: comparator operation

Mortality: number of deaths within 30 days/number of procedures OR Not Recorded

Morbidity: overall complication rate quoted OR Not Recorded

Anastomotic Leak rate: number of reported leaks/number of procedures OR Not Recorded

Respiratory complication rate: total respiratory complications recorded/number of procedures OR Not Recorded

Blood Loss: mean loss in ml, OR Not Recorded

Operating Time: mean time in minutes OR Not Recorded

approach. Information on patient numbers, age and sex, tumour site and stage, operations performed and techniques used, operative time, blood loss, conversion rate, complications, morbidity, mortality, adequacy of the cancer resection and indicators of speed and quality of recovery were collected. Results were subdivided into those for gastrectomy and oesophagectomy. Due to very clear differences in the profile of the Western and Eastern literature, separate analyses of the studies from Western and Eastern authors were performed.

(Western included North America, Europe and Australasia; Eastern included the Middle and Far East, in particular Japan, Korea and China.)

Table 3.2: Pre-Determined Criteria for Paper Selection for Further Review

Study Parameters

Study Authors

Journal Citation

Study Design: case series/prospective cohort/non-randomised comparison/RCT/other

Number of patients studied: in minimally invasive group/in other groups

Minimally invasive operations studied: comparator operation

Mortality: number of deaths within 30 days/number of procedures OR Not Recorded

Morbidity: overall complication rate quoted OR Not Recorded

Anastomotic Leak rate: number of reported leaks/number of procedures OR Not Recorded

Respiratory complication rate: total respiratory complications recorded/number of procedures OR Not Recorded

Blood Loss: mean loss in ml, OR Not Recorded

Operating Time: mean time in minutes OR Not Recorded

Conversion rate: number of conversions to open/number of procedures OR Not Recorded

Length of hospital stay: mean time in days OR Not Recorded

R0 resection rate: number of adequate resections OR Not Recorded

Lymph node retrieval: total number of lymph nodes removed at operation OR Not Recorded

Quality of Life: length of patient follow up and any recorded formal measurement of quality of life post-operatively OR Not Recorded

3.2.5 Statistics

Where data were provided the sum events and denominators of the mean figures were determined. Weighted means were used where the data only gave summary statistics for the study as a whole. Where figures were available for only a subset of the included studies, the number of studies and patients on which the statistic is based is noted. Statistics were limited to simple descriptive calculations with no statistical significance tests for comparison between the various minimally invasive operative techniques. This was felt inappropriate due to reporting bias, considerable variation in the patient selection criteria and different technical approaches to resection performed between articles.

3.3 Results

188 abstracts were analysed for review following the initial search, 132 were rejected and 46 met pre-determined criteria (see figure 2.1.) Of the rejected papers there were 48 case reports; 31 reviews; 18 sequential/ duplicate papers; 14 did not meet minimum outcome criteria; 13 were non-cancer cases; 4 involved robotics; 4 were

endoscopic cases and 2 involved paediatric patients. The 46 selected included 23 oesophagectomy papers and 23 gastrectomy papers; these comprised 3 randomised controlled trials (Lee 2005, Hayashi 2005, Huscher 2005,) 8 case-matched reports (2 and 6 respectively) and 35 (21 and 14 reports respectively) were case series. Most of the papers were from single centre institutions and many recorded retrospectively (16 oesophagectomy and 15 gastrectomy papers.)

Calculation of the Jadad score of the randomised controlled trials is 3 for the papers by Huscher *et al* and Lee *et al*; and 4 for that by Hayashi *et al* (Jadad 1996.) Points were scored for the description of randomisation; withdrawals and dropouts; method of randomisation being appropriate and in the case of the paper by Hayashi *et al*, an appropriate method of blinding was described. Although the Jadad score is quite simplistic, it assists in independently assessing the methodological quality of clinical trials. It demonstrated the quality of evidence of the trials is average and double blinding, difficult to perform in surgical trials was lacking in all 3 papers. Ethical or governance arrangements are mentioned in few papers and unless otherwise stated outcomes were measured by the publishing authors or their clinical teams i.e. results are not blinded and therefore susceptible to bias.

Outcome reporting in other studies was done in nearly all cases by the group responsible both for operating and reporting data i.e. no blinding occurred.

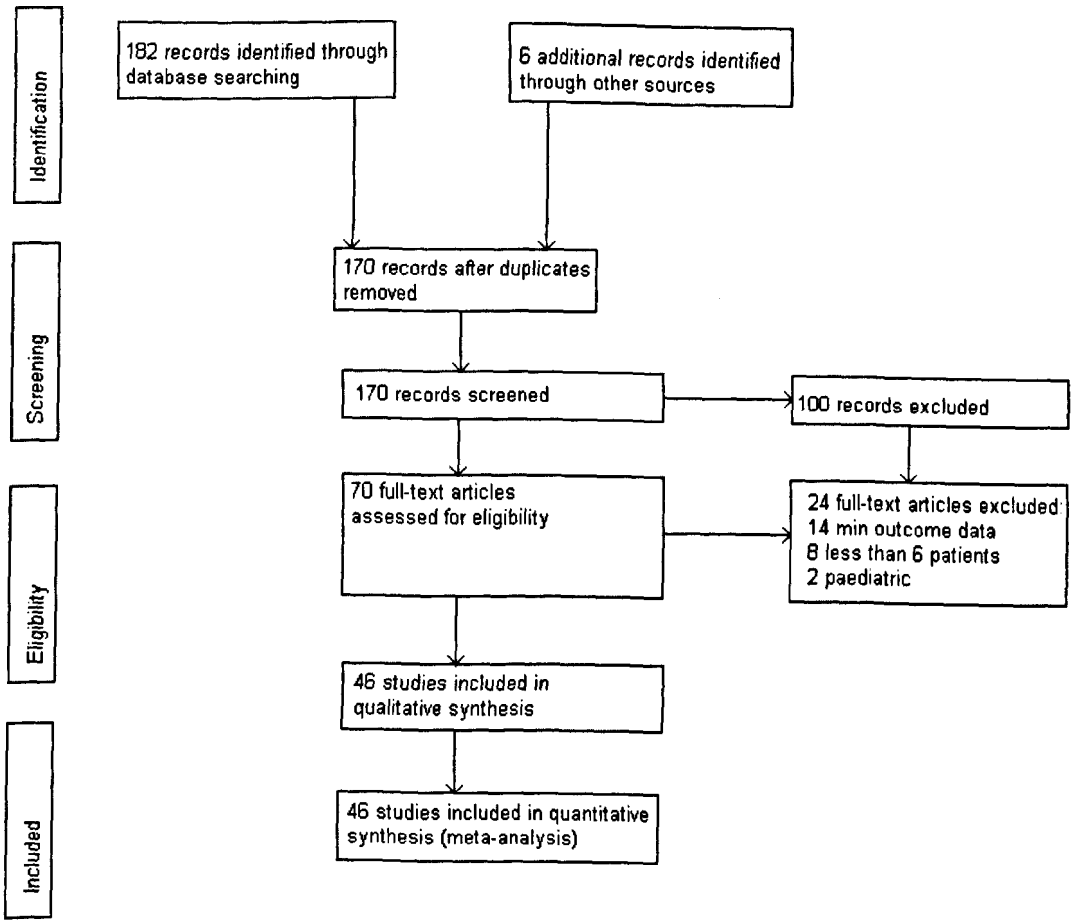


Figure 3.1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) Flow Chart of Study Selection (adapted from Moher 2009)

Case numbers ranged from 11 to 222 patients undergoing oesophagectomy (mean 58 patients) and 7 to 1294 (mean 111 patients) had a gastrectomy.

1398 patients were reported as having undergone some form of minimally invasive oesophagectomy, and 2546 as undergoing laparoscopic or laparoscopy-assisted gastrectomy. 3 patients had oesophago-gastrectomies, 62 underwent wedge resections of stomach or non-classical gastrectomies, 2069 had distal gastrectomies (partial, subtotal or antral), and there were 220 total and 192 proximal gastrectomies. Of the oesophagectomies, 405 patients (7 studies) were performed using a completely minimally invasive technique; 103 (2 studies) used a laparoscopic mobilization and a thoracotomy; 561 patients (8 studies) a thoracoscopic technique with laparotomy for

gastric mobilisation; 82 patients (4 studies) underwent hand-assisted laparoscopic mobilisation and as part of either transhiatal (Van den Broek 2004, Bernabe 2005) or 3-stage procedure (Suzuki 2003, Martin 2005;) and in 41 patients (1 study) another technique was used (a mediastinoscope (Tangoku 2004.) Majority of gastrectomy cases reported were from Eastern authors whilst most of the oesophagectomy studies were from Western countries (see Table 3.2.) (For clarification purposes, 'Eastern countries' refers to the Far East – mainly Japan, Korea and China-, and 'Western countries' refers to Western Europe, North America and Australasia.)

The number of patients who cancer was found to be unresectable following commencement of surgery was not stated in any of the papers.

i) MORTALITY

All reports stated mortality rates. Within 30 days of operation, 32 out of 1398 oesophagectomy patients (2.3%), and 3 out of 2562 (0.1%) of gastrectomy patients died.

ii) MORBIDITY

21 oesophagectomy studies reported morbidity rates. Of a total of 1359 patients 628 had a reported complication (major and minor), (46.2%.) 21 gastrectomy studies reported on morbidity, which affected 323 out of 2534 patients (12.7%.)

iia) RESPIRATORY TRACT INFECTIONS

20 and 18 studies of oesophagectomy and gastrectomy respectively reported on postoperative respiratory tract infections; the cumulative rates being 13.1% (167 out of 1268 patients) and 0.6% (15 out of 2429 patients) respectively.

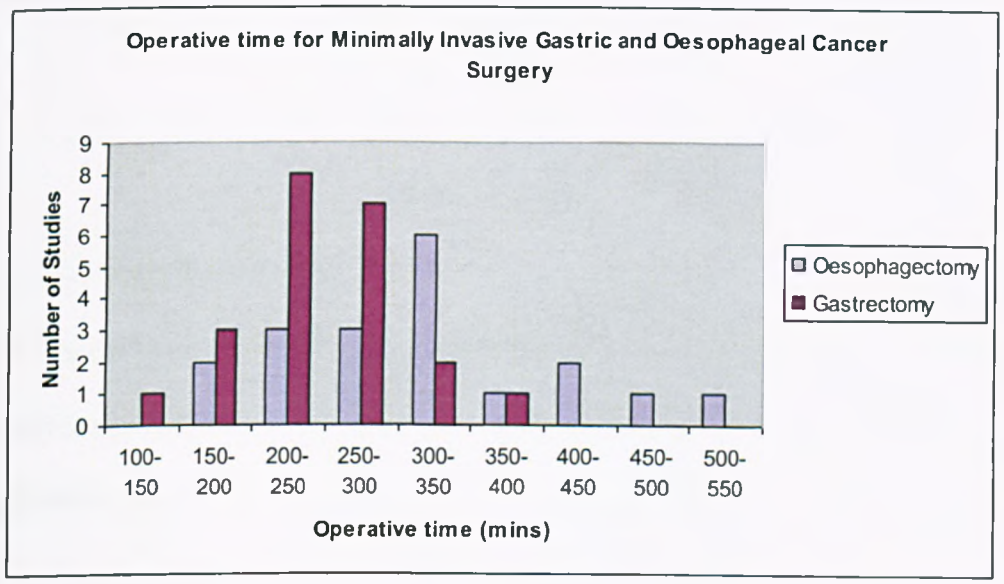
iib) LEAK RATE

22 oesophagectomy studies reported leak rates, affecting 106 out of 1381 patients (7.7%.) 19 gastrectomy studies reported leaks, in 37 out of 2433 patients (1.5%.)

iii) OPERATIVE TIME (see Figure 3.2)

Overall operative time was mentioned in 19 oesophagectomy studies (comprising of a total of 975 patients), with a weighted mean operative time of 281.2 minutes. All gastrectomy studies quoted operative times (total: 2562 patients;) the weighted mean operative time (excluding wedge resections) was 249.9 minutes.

Figure 3.2 Operative Time for Minimally Invasive Gastro-Oesophageal Cancer Surgery

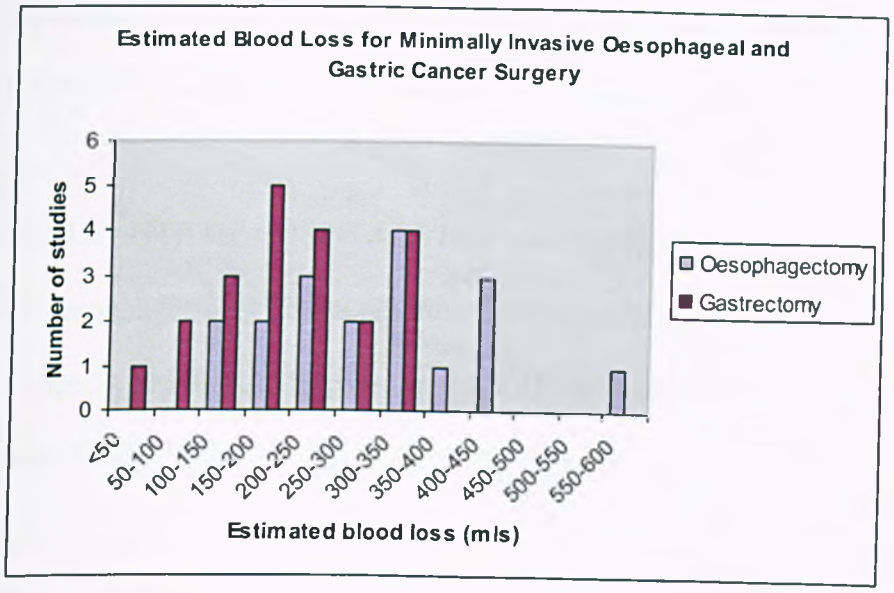


iv) ESTIMATED BLOOD LOSS (see figure 3.3)

19 oesophagectomy studies estimated blood loss (1055 patients,) with a weighted mean loss of 315.7 ml. 21 gastrectomy studies reported estimated blood loss (1171

patients,) the weighted mean loss being 191.6 ml (wedge resections were again excluded from this calculation.)

Figure 3.3 Blood Loss for Minimally Invasive Gastro-Oesophageal Cancer Surgery



v) CONVERSION RATE

19 oesophagectomy and 9 gastrectomy studies reported conversion rates. The mean conversion rate for oesophagectomies was 4.9% (56 of 1138 patients,) and for gastrectomies a mean rate of 1.2 % (21 of 1715 patients.)

vi) LYMPH NODE RETRIEVAL

14 oesophagectomy (607 patients) reported on lymph node retrieval per operation; with a weighted mean number of 17.6 (range of means 2-79.) 18 gastrectomy studies (932 patients) stated lymph node retrieval, with a weighted mean of 28.3 (range 1-78.)

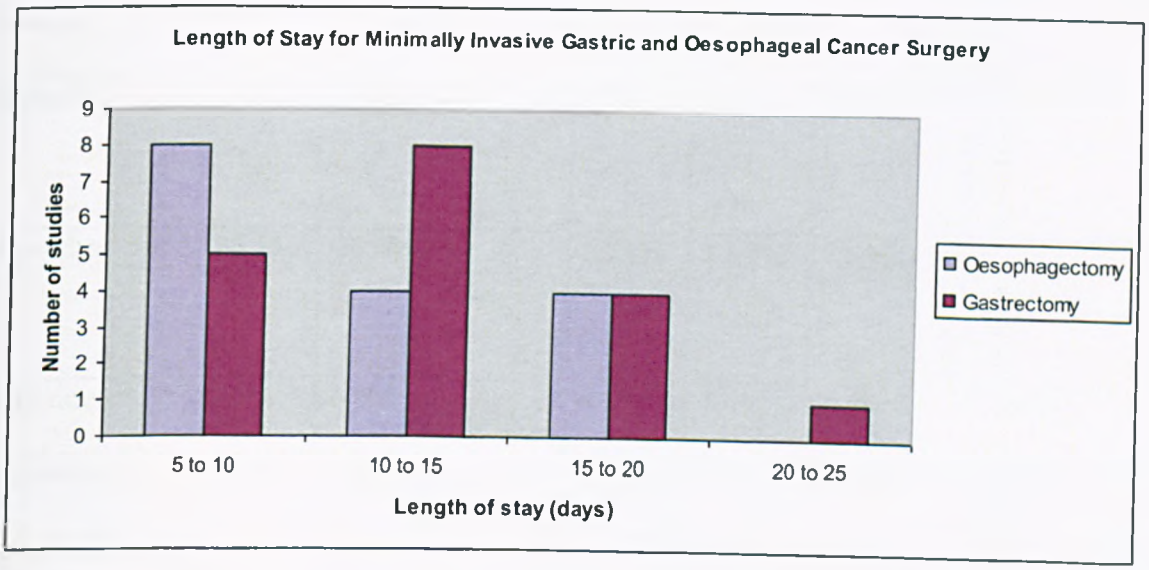
vii) R0 RESECTION RATE

Only 8 oesophagectomy reports (222 patients) and 3 gastrectomy reports (77 patients) stated their R0 rate clearly, with overall (weighted mean) success amongst these being 91.0% for oesophagectomies and 100% for gastrectomies.

viii) LENGTH OF HOSPITAL STAY (see Figure 3.4)

17 oesophagectomy papers reported their length of stay, with a mean of 11.0 days (range 2- 195 days.) This was quoted in 18 gastrectomy papers, with a mean of 13.4 days (range 3-61.)

Figure 3.4 Length of Hospital Stay for Minimally Invasive Gastro-Oesophageal Cancer Surgery



ix) QUALITY OF LIFE (POST-OPERATIVE)

Only one paper addressed quality of life (Luketich 2003.) This study included 140 laparoscopic oesophagectomy patients (with cervical anastomosis) and utilised a short-form 36 (SF36) and the Gastro-Oesophageal Reflux disease-Health Related Quality of Life Scale. It found low dysphagia scores and most patients had no reflux. Compared to the US population, physical scores reported were not statistically significant; mental component scores were however slightly but significantly ($p=0.001$) lower than the US mean. Post operative scores indicated preservation of quality of life.

Table 3.3 Differences in Results reported between East and West Centres for Minimally Invasive Gastric and Oesophageal Cancer Surgery

		Oesophagectomy			Gastrectomy	
	Total	East	West	Total	East	West
Number of studies	23	6	17	23	17	6
Number of Patients	1398	293	1105	2546	2427	119
Mortality	2.3%	1.4%	2.5%	0.1%	0.04%	1.7%
Morbidity	46.2%	26.6%	50.4%	12.7%	12.2%	21.5%
Leak rate	7.7%	6.5%	8.1%	1.5%	1.5%	1.1%
Respiratory complications	13.1%	8.1%	14.2%	0.6%	0.6%	0.9%
Blood loss (ml)	315.7	382.4	303.1	191.6	192.2	185.4

Operative time (mins)	281.2	271.3	338.6	249.9	251.8	204.1
Conversion ratio	4.9%	5.1%	4.9%	1.2%	1.0%	6.7%
Hospital stay (days)	11.0	11.3	10.0	13.4	14.1	11.8
R0 rate	91.0%	84.8%	92.6%	100%	100%	100%
Lymph node yield	17.6	22.3	14.9	28.3	10.6	30.0

3.4 Discussion

This review of over 3960 operations reported in 46 papers confirms that minimally invasive gastric and oesophageal cancer surgery is increasingly being reported in the literature from centres worldwide; and that these reports indicate that it is both safe and feasible. However the overall quality of these reports is low and therefore must be treated with great caution. This, combined with the fact that minimally invasive surgery (MIS) remains an investigational technique, not a treatment alternative, adds force to the argument that better evidence on outcomes is urgently needed, so that decisions about adopting it can be made on a more secure basis. Majority of the literature currently consists of case series, one of the weakest study designs recognised by all hierarchies of scientific evidence (CEBM.) Other studies compare historical or select open procedures to laparoscopic procedures, but the validity of such comparisons is extremely doubtful (Kunz 1998, Juni 2002.)

Only 3 randomised trials have been published in the English language, all being small single institution studies of distal gastrectomy; with a low Jadad score of 3 or 4 (Lee

2005, Hayashi 2005, Huscher 2005.) Whilst the results suggest advantages for the minimally invasive approach, it must be considered that these studies by pioneers are likely to favour the minimally invasive approach with which the authors are acknowledged experts. Generalisation of results is therefore likely to be difficult. Larger, multi-institution trials are necessary before any claims can be made for the superiority of the minimally invasive approach in normal surgical practice.

The results also demonstrate differences between East and West. A high proportion of the gastrectomy studies have been carried out in Japan and Korea, where major differences in the patient population, social influences, surgical philosophy and infrastructure affect outcomes such as length of stay and lymph node retrieval, producing results which may not reflect those found in other settings. Restricting the study to the English language literature may have led to the omission of some studies, but is unlikely to have influenced our summary outcome estimates very much (Moher 1996, Egger 1997, Juni 2002.) Among published literature, those with significant results are more likely to be published in English, be cited and published repeatedly; leading to English language bias, citation and multiple publication bias (Egger 1998.) Previous work suggests the omitted studies are likely to be smaller and of lower quality than those included (Colditz 1989.)

The value of less than 6 patients was an arbitrary number used to exclude case reports (which with the exception of one including 5 patients were mostly focussed on 1-3 cases;) but include the maximal number of case series in the study.

Since valid direct comparisons with contemporary open surgery are lacking, it is not possible to make confident statements about the potential benefits of minimally

invasive surgery. Rough comparisons with recent reports on open surgery suggest that reduced mortality, respiratory complications, blood loss and more rapid return of quality of life are areas in which minimally invasive surgery might prove superior. Leak rates were very low for gastrectomy, but were similar to those in reports of open surgery for oesophagectomy. Perhaps surprisingly, length of hospital stay and overall morbidity rates (for oesophagectomy) did not show any evidence of being areas of benefit. Operating times reported appear longer than those that might be expected from open operations, which would mirror the experience of previous laparoscopic procedures. None of these conclusions can be accepted with any certainty because of the large number of clear potential sources of bias in the studies reported. Patients selected for minimally invasive surgery are unlikely to have been representative of the population of cancer patients presenting to the reporting centres. Particularly in the early stages of their experience, prudent surgeons are likely to have selected patients with smaller tumours and to have avoided candidates with obvious serious co-morbidity. Some of the findings reported are unexpected, given the theoretical benefits of minimally invasive surgery. The exceptionally low leak rate amongst laparoscopic gastrectomy patients, for example, could not have been predicted, since there is no reason to expect that laparoscopically formed anatomises will be superior to those performed during open surgery.

Surgeons whose results were unsatisfactory may have been less inclined to publish than those who were happy with their outcomes, and this suspicion of probable publication bias indicate is lent some support by the apparently skewed data on gastrectomy conversion rate. The apparent discrepancies between some of the findings, which suggest excellent outcomes (for example leak rates, mortality, R0 resection rate) and others which suggest no benefit or potential problems (e.g. length

of stay, nodal yield) also suggest a significantly heterogeneous and possibly biased data sample. The reports describe a variety of different techniques, and it is not clear whether any of these carry significant advantages over others. Oesophagectomy in particular has been performed in several ways which differ importantly from each other, and the literature in this area is heavily influenced by one particular unit with a very large series which reports excellent results, but whose technique, perhaps not surprisingly, has gradually evolved through time (Luketich 2002.)

The reporting of outcome data is variable. Whilst all papers stated 30 day mortality rates, 4 papers (2 gastrectomy and 2 oesophagectomy) did not report overall morbidity. Data reporting of all outcomes measured in the review is not universal with all papers, especially gastrectomy conversion rates. Whether this is intentional or an oversight is questionable and may have impacted on results of the review. (Although an attempt to minimise this was made by using weighted means to analyse outcome results.)

Less than half of the papers report seeking and obtaining ethical permission for data collection. This may be as majority of data was collected retrospectively on individual disease-specific registers with anonymous demographics. However the lack of reporting introduces the possibility of hidden bias in patient selection as well as outcome reporting.

Reflecting on these findings with the benefit of experience of previous advances in minimally invasive surgery, it seems clear that there is a danger of repeating scenarios that proved unhelpful to progress in the past. The lack of good quality evidence (with minimal binding,) together with the encouraging results reported from a clearly biased

literature carries the risk of polarising the surgical community into sceptics and enthusiasts without ensuring that the evidence required to reach consensus between the two is obtained. A successful randomised trial requires a group of surgeons with sufficient experience of the procedure to reach agreement on the appropriate question, and to reach consensus on the definition of the procedure to be tested against open surgery. Consensus would be greatly enhanced by previous experience of co-operating and sharing data in a common format and by analysis of individual and unit experience to demonstrate the position on the learning curve of group members. It therefore seems that a prospective non-randomised co-operative study conducted by the surgeons interested in developing these techniques would be a very helpful preliminary step towards a randomised trial. Such a study could allow the evaluation of learning curves, the estimation of treatment effects for the purposed of power calculations, and the development of measures of quality for the procedure. Most importantly, it would promote consensus and co-operation amongst surgeons by requiring them to become familiar with entering their results in standard format. This kind of study would require smaller funds than a RCT, and could be facilitated by nesting it within the activities of relevant specialist organisations, such as AUGIS. We have previously designated this type of study "Phase IIS" by analogy with the Phase II studies regularly performed in oncology (McCulloch 2002.) The problems of the current literature on minimally invasive gastrectomy and oesophagectomy illustrate the need for better evidence with which to make decisions about the future place of this type of surgery. A Phase IIS type study would be very helpful at this stage in the development of these techniques, and could act as a "bridge" between the current case-series based literature and multicentre randomised trials.

Since the publication of the above chapter in the British Journal of Surgery, there have been multiple articles published on the subject of minimally invasive oesophagectomy and gastrectomy. Most papers remain retrospective series of highly selected patients. To date, there have been 2 further reviews on oesophagectomies, although no completed randomised controlled trials (the protocol for the Traditional invasive versus minimally invasive, TIME, trial by Biere *et al* has however been published (Biere 2011).) There has been one further review of gastrectomies (performed in Western centres.)

More recent data from systematic reviews, suggest a mortality rate of 2.9% and morbidity of 46% in minimally invasive oesophagectomies (Decker 2009.) Comparing the totally MIE approach to open surgery, no significant difference was found between groups for major morbidity or pulmonary complications OR 0.88 (95% CI 0.35-2.14) and OR 1.05 (95% CI 0.42-2.66, p=0.91) respectively. It remains acknowledged however that MIE has been reported in case series and case-control studies where bias in study design may have occurred.

Strong *et al* analysed minimally invasive gastrectomies in the West (Strong 2009.) They demonstrated that MIG had similar findings to those published in the East, with decreased length of hospital stay, decreased narcotic use, fewer complications and equivalent short-term oncological outcome (however no overall comparison statistics are quoted.)

Chapter 4 – A Phase II Surgical Trial of Minimally Invasive Gastro-Oesophageal Cancer Surgery

4.1 Introduction

Minimally invasive approaches to gastro-oesophageal cancer surgery are increasingly being reported in the literature, mostly in the form of case series, with few randomised controlled trials of distal gastrectomy (3 to date published in the English language: Lee 2005, Hayashi 2005, Huscher 2005;) and none of minimally invasive oesophagectomy. Further detailed evaluation of minimally invasive surgery in this setting is therefore clearly required as its popularity increases in order to prevent a potential conflict of interest between enthusiasm and safety concerns. This would also aim to satisfy the demands for clinical governance whilst avoiding the stifling of innovation.

The gold standard for the evaluation of interventions is a randomised controlled trial (RCT) (NHS/DoH 1992.) RCTs are notoriously difficult when applied to surgical techniques, especially in terms of defining a learning curve, intervention definition and the need for both quality control and consensus between participating surgeons.

Integration of prospective audit and quality control with modified randomised trials may provide a means of overcoming some of the existing difficulties that need to be recognised in the development of new surgical techniques. In order to do this, we have developed a preliminary phase II surgical trial prior to conducting a RCT, similar to oncological phase II trials (McCulloch 2002.) This would act to bridge the gap between case series and RCTs and aid:

- the development of a satisfactory definition of the procedure , the trial question and quality control measures
- collection of data in order to enable power calculations, identifying suitable sample sizes and end points for a RCT
- allow evaluation of participant learning curves
- enable the evolution of consensus and the required familiarity with trial participants working together to allow organic trial progression.

The aim of this preliminary "phase IIS" study has been to establish and compare the standards of care in minimally invasive gastro-oesophageal cancer surgery, initially by means of a multicentre, retrospective cohort database; followed by a period of co-operative prospective non-randomised data collection. The results of this study would then be analysed and used to design a study involving expanded data collection in a prospective, randomised trial comparing surgical techniques.

4.2 Method

The MIGOCS (Minimally Invasive Gastro- Oesophageal Cancer Surgery) group was established between experienced surgeons in 2005 as independent research collaboration. It has the formal approval of the Association of Upper Gastro-Intestinal Surgeons for Great Britain and Ireland (AUGIS) and the Association of Laparoscopic Surgeons (ALS) and the National Institute for Clinical Evidence (NICE.) More recently, MIGOCS has been adopted by ALS as part of a comprehensive suite of minimal access surgical registers.

The MIGOCS group currently includes over 60 consultant surgeons from centres around the UK and Europe and is concerned with research study. It is not a society, has no supervisory role and does not advise on mentoring, regulation or accreditation issues.

Through expert consensus discussions, utilising an iterative process of development and an initial troubleshooting period, an online registry for recording of results was developed, available at: http://rs1.e-dendrite.com/csp/migocs/frontpages/migocs.

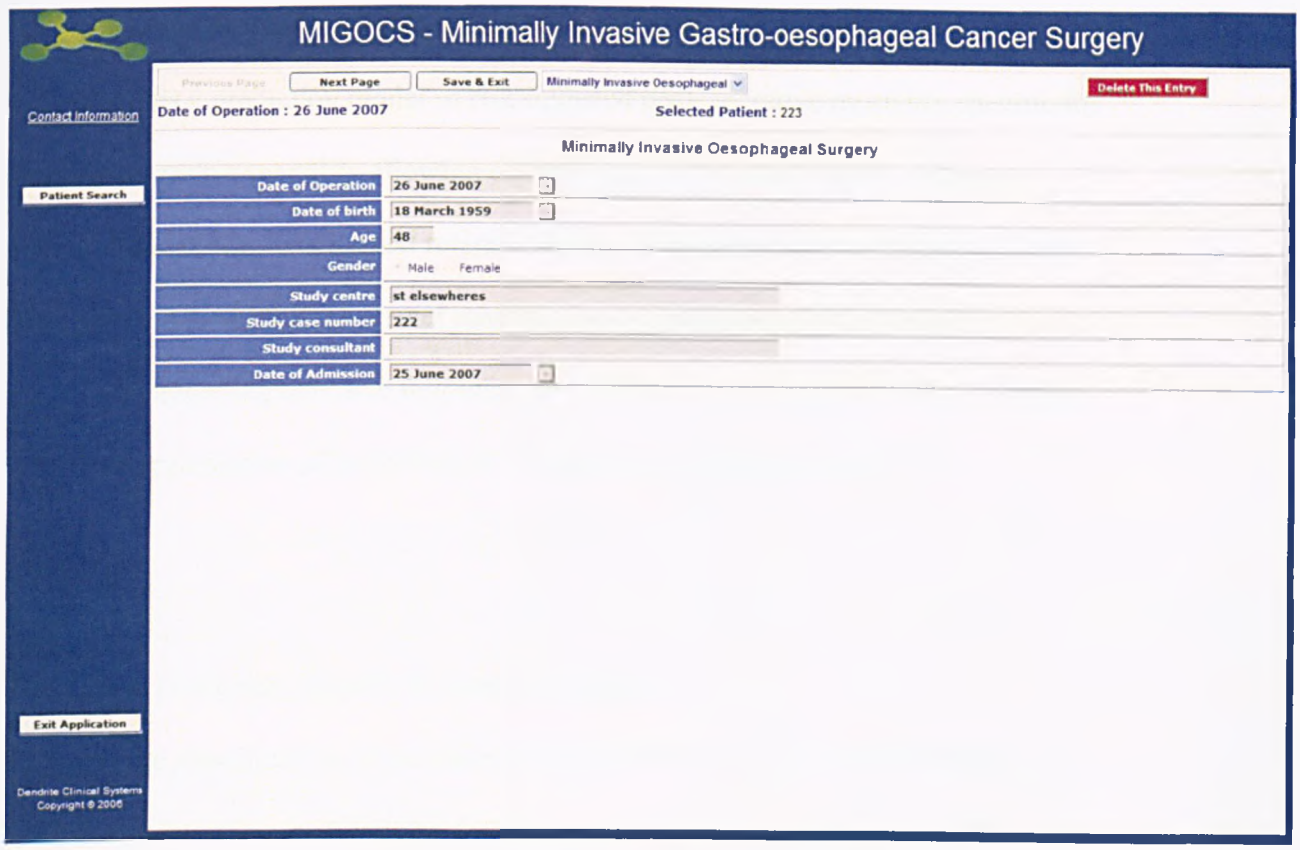
The register consists of 5 sections, comprising: (i) demographic details; (ii) pre-operative assessment and staging; (iii) surgical intervention; (iv) post-operative course; (v) pathology and clinical outcome.

Entry of data on the register was intended to be done by MIGOCS members (or their nominated representatives) in the centre performing the surgery, with technical support as required. Reality however meant that in all but one centre the data was placed on the register by the research fellow with information provided by MIGOCS members.

i) Demographic Details

Only fundamental patient identification is collected on the database (date of birth, gender and date of operation) in order to ensure patient confidentiality and adhere to the Data Protection Act. (Subject to ethical approval this aspect of data collection may be expanded in the future as the trial develops towards randomisation.)

Figure 4.1: Demographic Data Collection as seen on the MIGOCS Register



ii) Pre-Operative Assessment and Staging

Patient selection criteria significantly affect surgical outcomes. The MIGOCS dataset records:

- Initial TNM staging
- Pre-operative chemotherapy
- Staging modalities utilised
- Tumour details - position, dimensions and Siewert type (where relevant.)
- Pre-operative health status - physiological O-POSSUM score (the website is linked to calculation sites) and ASA (American Association of Anaesthetists) grading.

O-POSSUM (Oesophago-Gastric Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity) (Tekkis 2004.)

This provides a prediction model of risk-adjusted post-operative mortality specific for oesophago-gastric mortality allowing comparisons of outcome despite different demographic characteristics and referral patterns. This approach has been demonstrated to accurately predict mortality post-gastrectomy but is poor in accurately predicting outcome following oesophagectomy (Lagarde 2007.) Variables used in the calculation of an O-POSSUM score were stated in chapter 1.

ASA Grade (American Society of Anaesthesiology)

This aids the classification of pre-operative physical status and risk and although it has limitations, it is a useful global tool, is used universally and is familiar. The grades are defined in the table found in chapter 1.

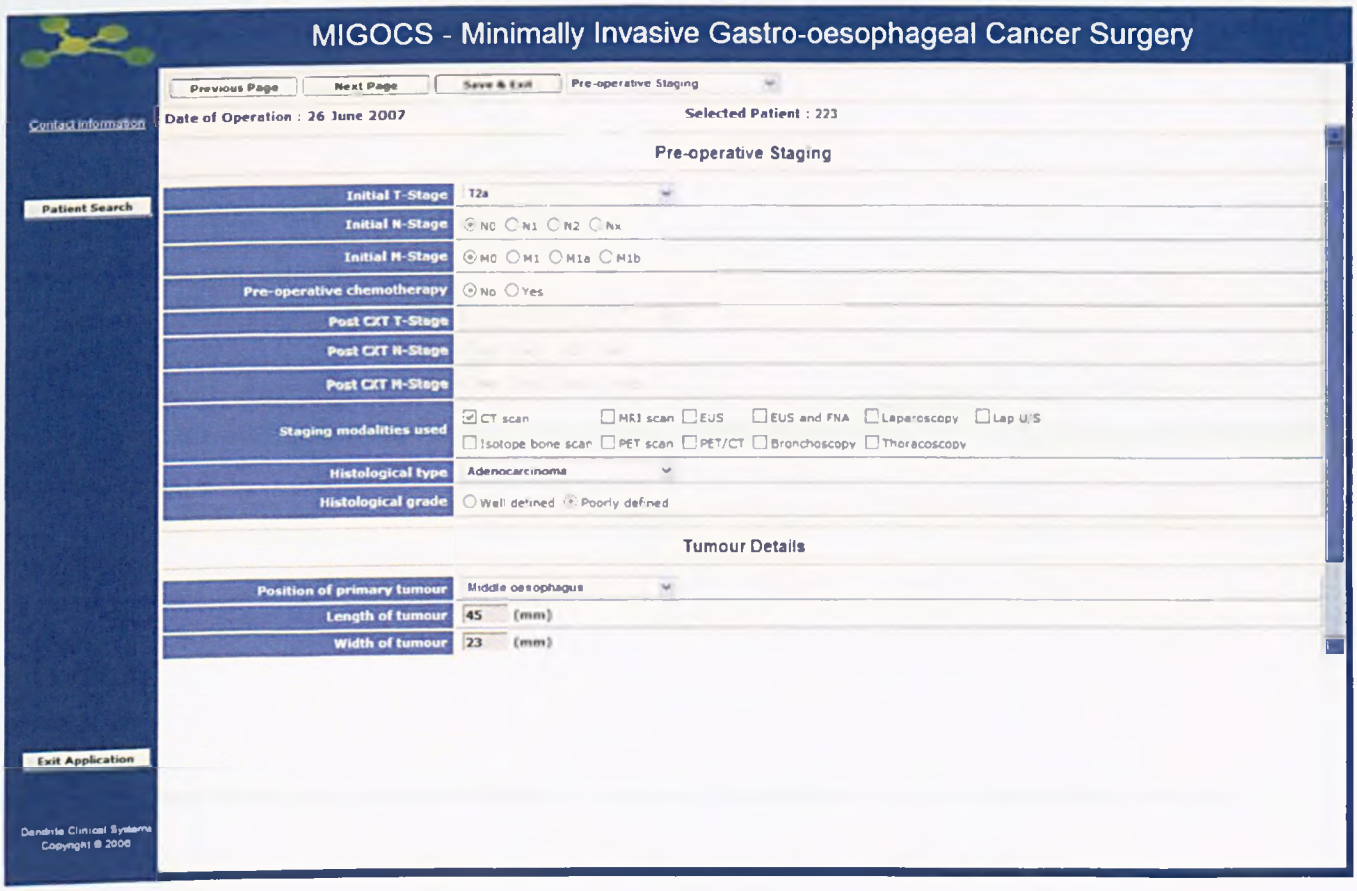
TNM (Tumour Node Metastasis) Stage

This is based on the joint UICC (International Union Against Cancer), AJCC (American Joint Committee on Cancer) and JJC (Japanese Joint Committee) staging classification first developed in 1986 and last updated (prior to work for this thesis) in 2003. The system provides an anatomical classification, where T represents the extent of the primary tumour; N the presence or absence and extent of lymph node involvement; and M the presence or absence of distal metastases. It is outlined further in chapter 1.

Siewert Type

This is explained in further detail in chapter 1. This classifies gastro-oesophageal tumours according to their location (Siewert 1996.) Type I tumours arise 1-5cm above the anatomical cardia and are tumours of the distal oesophagus. Type II tumours are true cardia tumours and arise within 1cm above and 2cm below the anatomical gastric cardia. Type III tumours are gastric in origin and arise 2-5cm below the anatomical cardia.

Figure 4.2: Pre-Operative Data Collected as seen on the MIGOCS Register



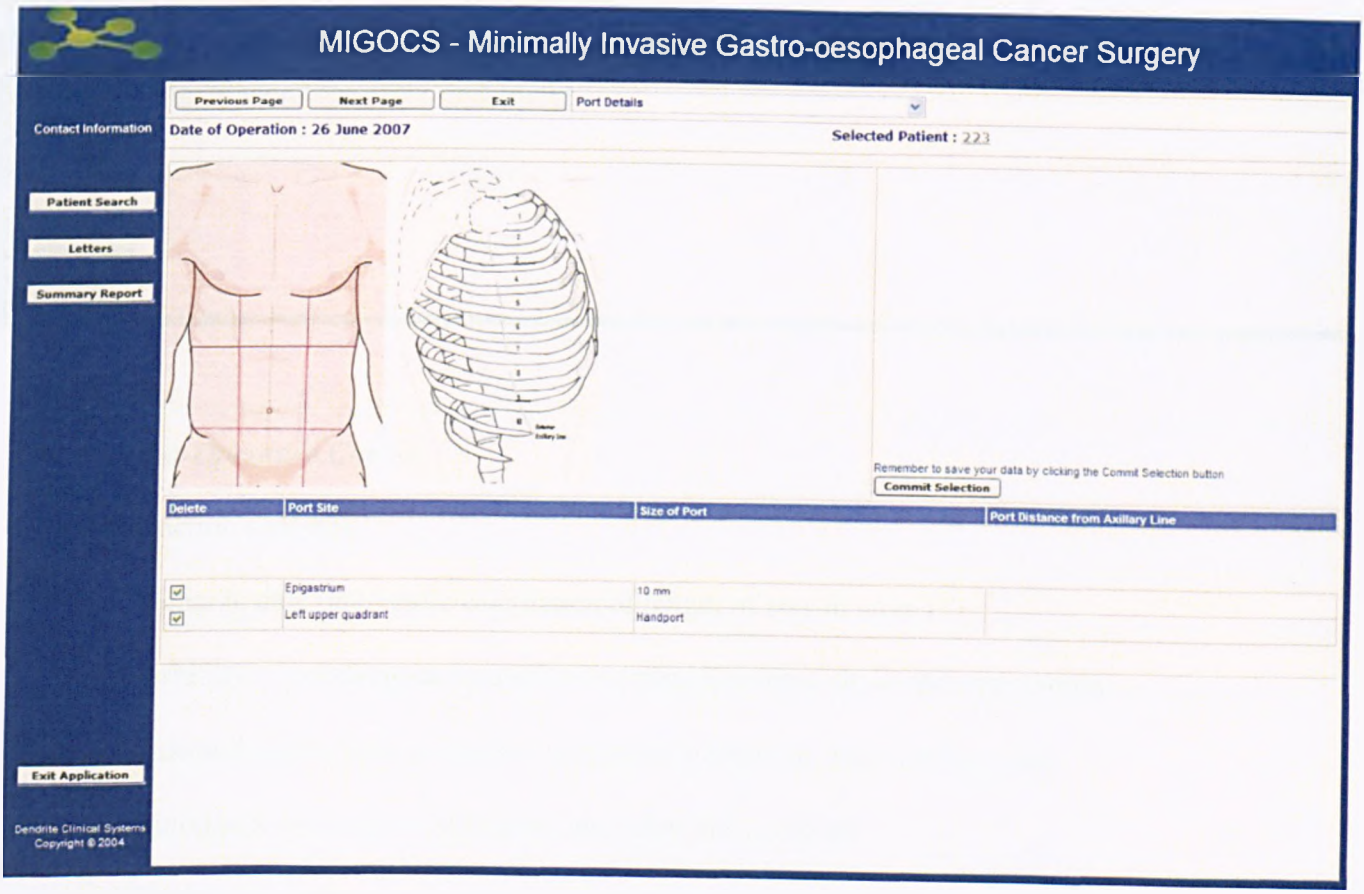
iii) Surgical Intervention

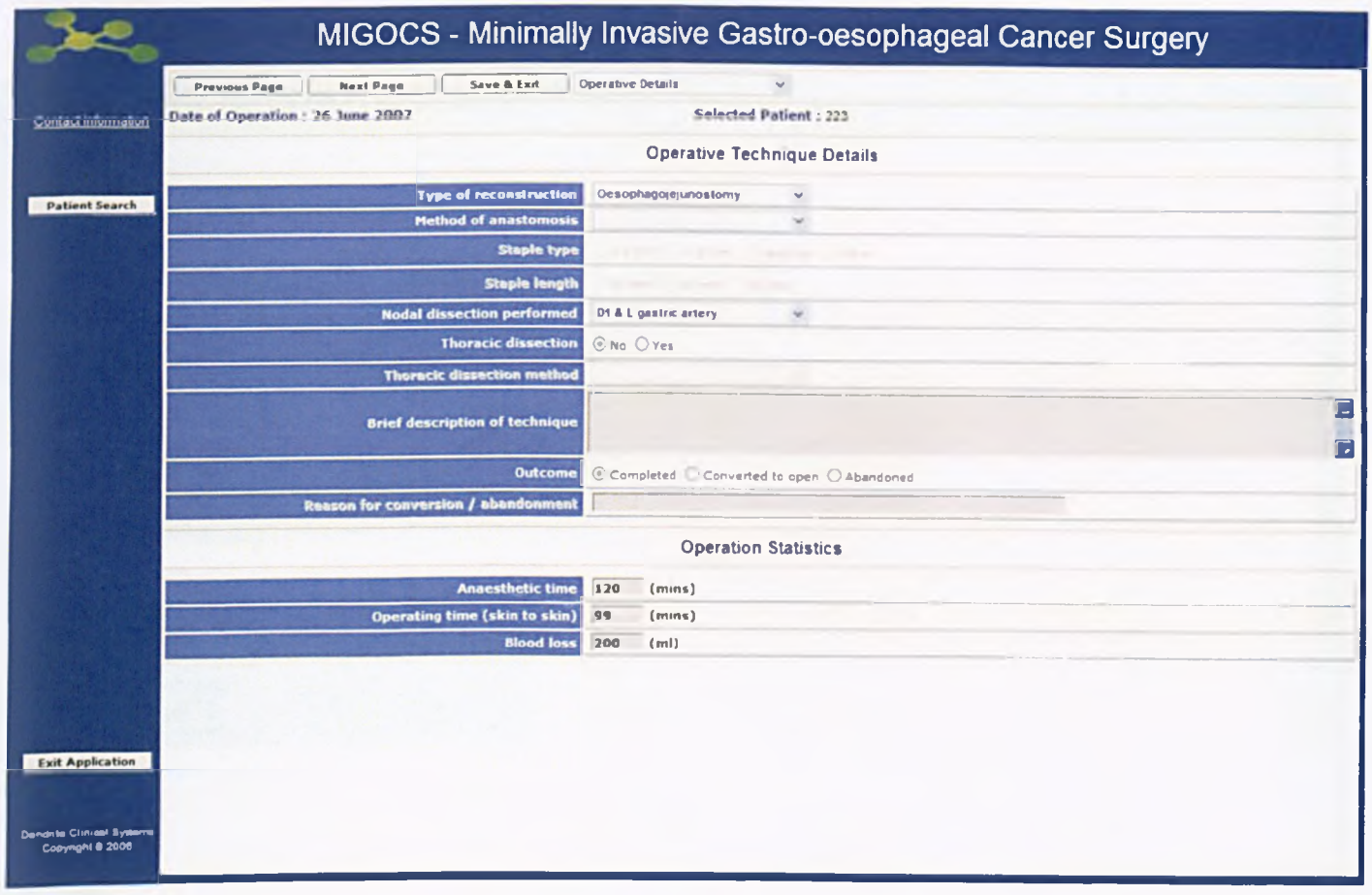
Selected operation details are recorded to enable the evaluation of approaches and techniques. Information requested includes:

- Operating surgeon and assistant(s)

- Port placements and sizes (additionally giving an indication of patient positioning)
- Anastomosis performed (sutured/stapled/both)
- Nodal dissection
- Thoracic dissection details (where applicable)
- Operating statistics - anaesthetic time (mins,) operating duration (mins) and blood loss (mls.)

Figure 4.3: Operative Data Collection on the MIGOCS Register



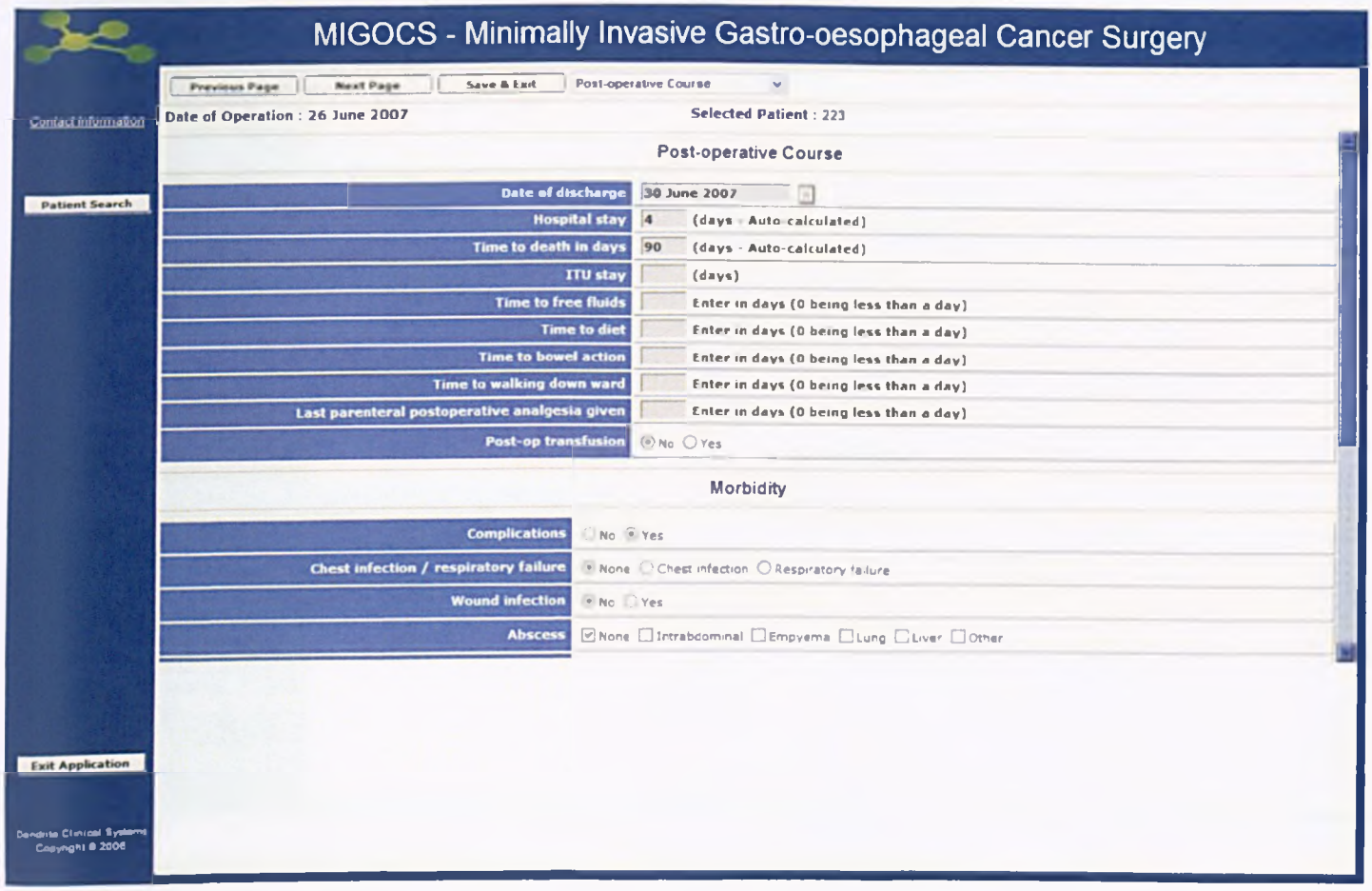


iv) Post-Operative Course

This section analyses:

- Discharge date (automatic calculation of length of stay in days.)
- Morbidity – including cardiorespiratory complications; chyle and anastomotic leaks (and related gastric conduit ischaemia;) infection; haemorrhage; the requirement for a second operation and what this involved.
- Post-operative course - intensive care stay (days;) post-operative transfusion; the number of days to: free fluids, diet, bowel action, walking and cessation of parental analgesia.

Figure 4.4: Post Operative Course Data Collection as seen on the Register



v) Pathology and Clinical Outcome

Recorded data involves:

- Tumour pathology - pTNM staging, the involvement of resection margins, the total lymph node yield and the number that are positive for cancer.
- Clinical outcome - patient health related quality of life at 3, 6 and 9 months post-operatively, date and site of recurrence and date of death (where relevant.)

This final section is currently aimed more at prospective data collection and requires further development – including scoring systems required to evaluate quality of life and 5 year survival data.

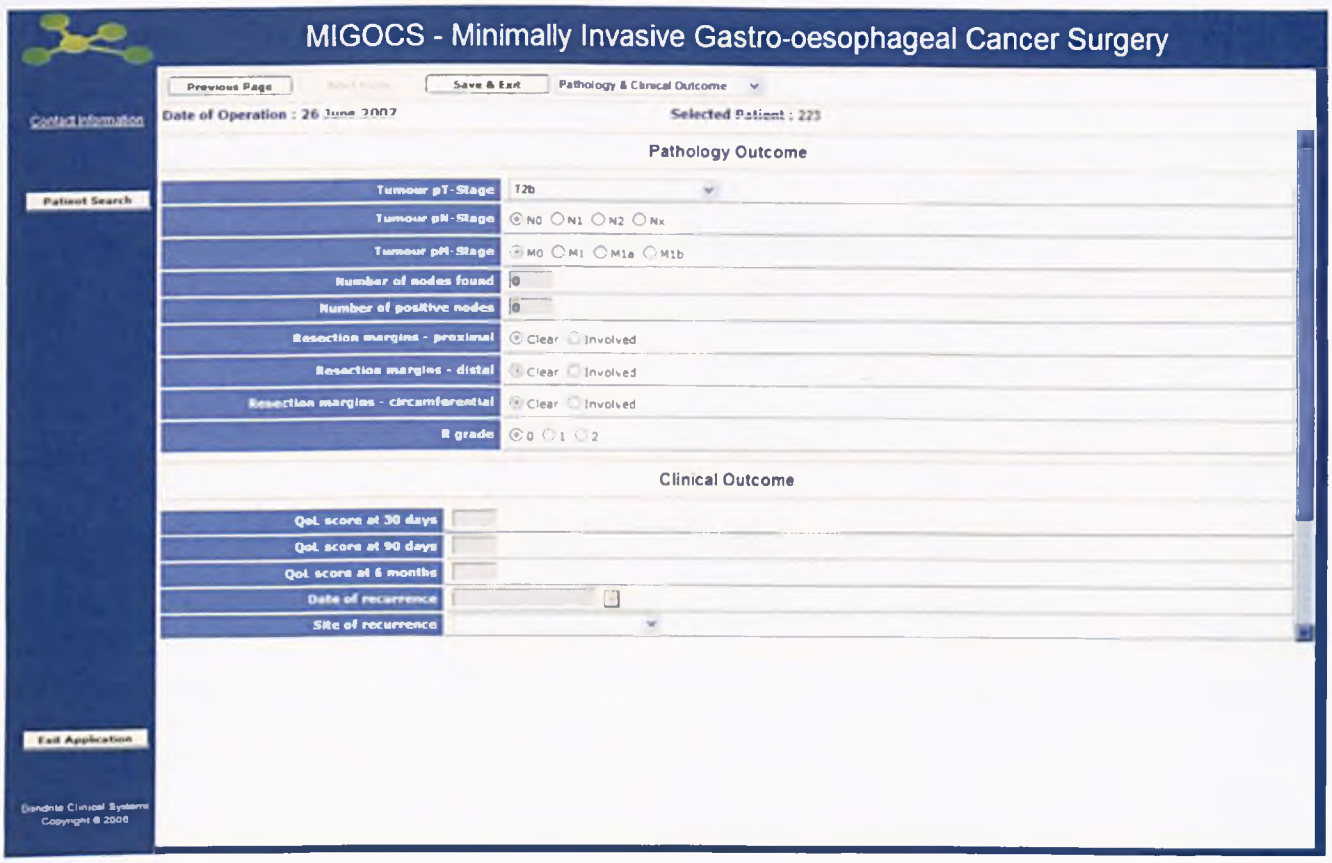


Table 4.5 Pathology Outcome as seen on the MIGOCS Register

To validate complete and accurate data collection, randomised checks of data entry from all units was carried out at regular intervals by a research fellow. This involved email requests of data and/or occasional site visits. Completed data entry was then locked from further alterations. This was done by the register's administrator preventing further retrospective changes to the primary data entry and ensuring no data tampering which may introduce bias or statistical skewing. In the event of missing or incomplete data, units concerned were contacted.

Reports

- Information registered is retrievable by each unit themselves (but not data from of other units.)

- A central office compiled regular anonymised comparative and summary reports, including learning curve analysis.

Consensus Conferences

Regular discussions about technique quality measures and learning curves are mandated, moving towards a randomised controlled trial.

Ethics

The MIGOCS project is based around a disease-specific registry and involves no experimental intervention, which exempts it from Research Ethics oversight, subjecting it instead to the rules of Audit and Governance review, with which it is fully compliant.

4.3 Results

Please see chapters 5 and 6 for a detailed report of results.

4.4 Discussion

The register was initially developed in 2005 following a series of meetings between interested clinicians with experience in upper gastrointestinal cancer surgery, utilising the knowledge gained by one of the group (Mr P McCulloch) from the ASCOT study (Cummins 2001.) Its comprehensive database (aided by its ease of use by online access) means that it helps fulfil the requirements of clinical governance and revalidation of all doctors; thereby providing further incentive for data collection. The database has undergone further modifications since its conception in 2005, following meetings with those using it, using Delphi methodology. The database has retained its

clear layout, with drop-down menus; links have been made to other websites e.g. for the calculation of O-POSSUM scores, and some data fields have been made mandatory. This latter concept has been controversial and prevents users jumping between sections of the register but previous experience from the ASCOT database has shown that making fields mandatory ensures data is complete. A balance was made therefore between the number of mandatory and optional fields, with only certain things such as operation approach and lymph node yield remaining compulsory. In order to encourage complete data entry a downloadable proforma of all data fields was provided on the website (following feedback from participating consultants,) which can be found in appendix 2. Once all data (except follow-up) has been entered data fields can be locked by the system administrator, preventing retrospective data tampering. The follow-up section of the register is still in evolution, especially with respect to quality of life data and the frequency and duration of follow-up required to provide adequate mortality and morbidity information.

The database also collects detailed information on the minimally invasive approach of oesophagectomy or gastrectomy. This is vital as a variety of approaches are used and preferences vary significantly. The detail of data collection on port siting has been criticised and perhaps this could be made more descriptive, including patient positioning for the procedure e.g. prone or left lateral. Diagrams have been developed to make this section more user friendly and obtain more precise recording of port placement during MIOs and MIGs.

Data collection was initially retrospective, to enable clinicians to become familiar with the register and enable its development in the early stages. This enabled feedback to individual units of their performance and a more critical look at the components of

the register from multiple sources. All derivative data from the register was reliant on individual surgeons' honesty in providing accurate information on all cases of their learning curve. With this in mind, data checks by an independent research fellow visiting the units provided quality control.

A number of difficulties were encountered in data collection, some of which were confirmed by the use of a questionnaire to all participants. Time constraints were reported to be the biggest limitation to the placement of data on the register by consultants, especially with the concurrent National Oesophago-Gastric Cancer Audit promoted by AUGIS. (It is hoped that the two sites will be linked in the future to avoid the duplication of data entry and continuing to address the need for clinical governance; although this may give rise to the need for data clerks.) Concerns were voiced regarding publication rights and who gained credit for any publication arising from data entered into the register. Further concerns involved politics between individuals and concerns regarding confidentiality. In order to try and overcome these issues, assistance in data placement on the register was initially provided by the research registrar (although like later data validity checks this was limited by patient case note availability whilst visiting centres.) Publication rights were assured to remain with the centre providing data; however data publication as a group was planned, with individuals remaining anonymous but acknowledged. The register was also supported by the two of the main professional bodies for upper gastrointestinal surgeons in the UK – ALS and AUGIS.

Recruitment was addressed by raising the profile of the group by posters and presentations of data (by the research fellow and Dendrite plc,) as well as stands at major meetings nationally and in Europe.

Funding issues involved an initial grant by Covidien, self funding and application for grants (by private and commercial bodies.)

All surgeons performing minimally invasive upper gastrointestinal cancer surgery are eligible for involvement in this study. Maximising centres and clinicians involved would optimise and increase the detail of evidence regarding this developing technique. The study thus far involves over 60 consultant surgeons in over 40 centres around the United Kingdom and a framework for the involvement of surgeons around the European Union.

Chapter 5 – A Retrospective Study of Minimally Invasive Gastro-Oesophageal Cancer Surgery in the UK

5.1 Introduction

In the UK the minimally invasive approach for gastric and oesophageal cancer has been gaining popularity since its introduction in the early 1990s (Cushier 1992, Manama 1994, Dexter 1996, Sutton 2002.) At present, most procedures tend to be carried out by surgeons with a major laparoscopic interest, on carefully selected patients and there is a wide variation in reported techniques and outcomes. Few British centres have published their results of minimally invasive gastric and oesophageal cancer surgery, and those that do tend to be low volume case series and case reports (Singh 2008.) In view of this and the weak evidence regarding the safety and efficacy of laparoscopic surgery for cancer of the oesophagus and stomach (outlined in chapter 3,) a more comprehensive look at procedures currently performed was required.

The MIGOCS group and database was set up in 2005 (as outlined in chapter 4.) Whilst data collection was in principle prospective, there was concern that the results of centres which already had an established programme for minimally invasive surgery before the database was set up should not be overlooked. UK centres already performing this type of surgery prior to the MIGOCS database being fully established therefore invited to contribute to the data collection. (This stage is approximately analogous to IDEAL stage 2a/b.)

5.2 Method

The online database comprises of 24 fields in 5 sections (see chapter 4 for further detail):

- Demographic details (confidential identification.)
- Pre-operative assessment and staging
- Surgical intervention
- Post-operative course
- Pathology outcome

Initial retrospective data collection by participating surgeons was encouraged (aided by visits from an independent research fellow) for a time-limited period. Operation dates from December 1996 to December 2006 (when the data collection ceased) were recorded, provided surgeons could provide all the required fields. All retrospective data was checked and validated against case records by the research fellow to maintain quality control.

For the purposes of this chapter, the following data were extracted: patient selection; mortality; morbidity, specifically leak rate and respiratory tract infection; estimated operative blood loss; operative time; lymph node retrieval; conversion rate; R0 resection success and length of stay. Post-operative complications were further subdivided into major (life-threatening,) and minor (prolonging hospital stay) using definitions proposed by Luketich *et al* (2003) (see table 5.2.)

5.3 Results

26 centres in the UK, comprising 39 consultants with previous experience agreed to take part in the study. Nineteen of these centres had no retrospective data or declined to participate.

Retrospective data was collected from 7 centres, with operations performed between 1996 and 2006. 126 cases were recorded in total, 100 oesophagectomies and 26 gastrectomies. The breakdown of the oesophagectomies by type is shown in the diagram below. Four operations were commenced laparoscopically but 3 of these were abandoned due to unresectable tumours being found intraoperatively (metastatic spread not seen on staging) and 1 was due to the patient having asystole on the table.

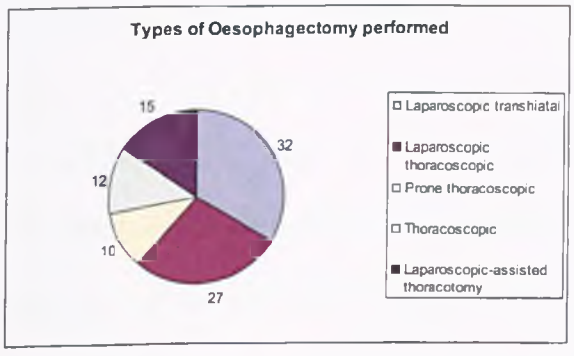


Figure 5.1: Breakdown of Oesophagectomies Performed

All 26 gastrectomies were distal or subtotal, with one being hand-assisted; 4 were local resections.

All lesions were apparently resectable at preoperative staging (CT +/- EUS +/- staging laparoscopy dependent on centre;) 51 of the 126 patients recorded on the database underwent pre-operative chemotherapy.

1. *DEMOGRAPHIC SELECTION*

The mean patient age was 67.1 years; 82 were male and 44 were female. The staging of patients ranged from T1N0 to T3N2. The mean ASA was grade 2 (12 patients were grade 1, 40 were grade 2, 17 were grade 3, and 1 was grade 4; the grade was not recorded in 37 patients.)

2. *MORTALITY*

The overall mortality was 6.0% (6 out of 100) for the oesophagectomy cases and 7.7% for the gastrectomy cases (2 out of 26.) Of the deaths from oesophagectomy, 1 was from a laparoscopic transhiatal procedure (of 32 recorded;) 1 thoracoscopic (of 12;) 1 thoracoscopic/laparoscopic (of 27) and 3 from procedures with laparoscopic mobilisation and right thoracotomy (of 15 recorded.)

3. *MORBIDITY*

57 complications occurred in oesophagectomy patients (30 major and 29 minor, see table 4.1,) giving an overall morbidity of 57%. Complications are also reported by oesophagectomy approach, please see figure 5.2 for further details. There were 4 major (life-threatening) and 9 minor (prolonging hospital stay) complications in the gastrectomy group (please see table 5.2.) Criteria for minor and major complications were based on those of Luketich *et al* (2003.)

Figure 5.2: Oesophagectomy Morbidity Breakdown by Approach

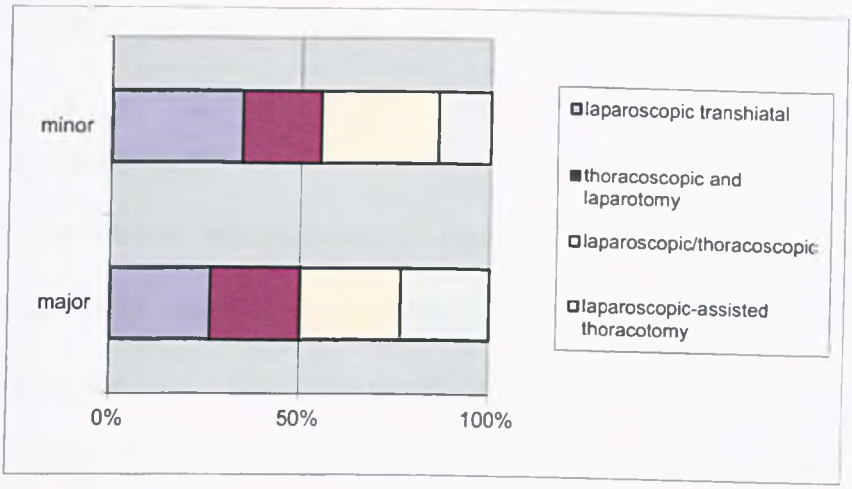


Table 5.1: Hospital Prolonging and Life Threatening Morbidity Related to Minimally Invasive Gastric and Oesophageal Surgery for Cancer

Hospital Prolonging (Minor) Complications	**Oesophagectomy n=100**	**Gastrectomy n=26**
Arrhythmia	12	4
Stricture	7	0
Congestive Cardiac Failure	4	2
Pleural effusion	2	1
Fistula	1	0
Transient Ischaemic Attack	1	0
Port site hernia	1	0
Minor haemorrhage	1	2
Life-threatening (Major) Complications		
Respiratory tract infection	19	3
Anastigmatic leak (confirmed) (including 1 related to conduit ischaemia)	3	0
Myocardial Infarction	3	1
Chylothorax	3	0
Tension pneumothorax	1	0

Multiple Organ Dysfunction Syndrome (MODS)	1	0

i) LEAK RATE

There were no reported leaks from the gastrectomies, and 3 confirmed anastomotic leaks in the oesophagectomy cases (3%.) One leak related to conduit ischaemia; 1 was in a laparoscopic transhiatal operation and 2 were from thoracoscopic procedures. In addition, there were 3 chylothoraces post-oesophagectomy (1 prone thoracoscopic and 2 laparoscopic/thoracoscopic,) all were successfully treated conservatively.

ii) RESPIRATORY TRACT INFECTION

3 gastrectomy cases (11.5%) developed a respiratory tract infection as did 19 oesophagectomy cases (19%) – 7 laparoscopic transhiatal, 1 prone thoracoscopic, 4 thoracoscopic, 2 laparoscopic/thoracoscopic and 5 laparoscopic-assisted thoracotomy (shown in table 5.2.)

4. *BLOOD LOSS*

Blood loss recording was too poor in the gastrectomy cohort to derive an average figure, but no record of blood loss greater than 100ml was received.

The mean estimated blood loss for all oesophagectomies was 694.6 mls (95% CI 503.1 – 886.1.) Looking at each approach individually, the mean blood loss was 627.5 ml for laparoscopic transhiatal, 785.0 ml for prone thoracoscopic, 454.4 ml for thoracoscopic and 883.4 ml for laparoscopic/thoracoscopic and 571.4 for laparoscopic assisted thoracotomy. See figure 5.3:

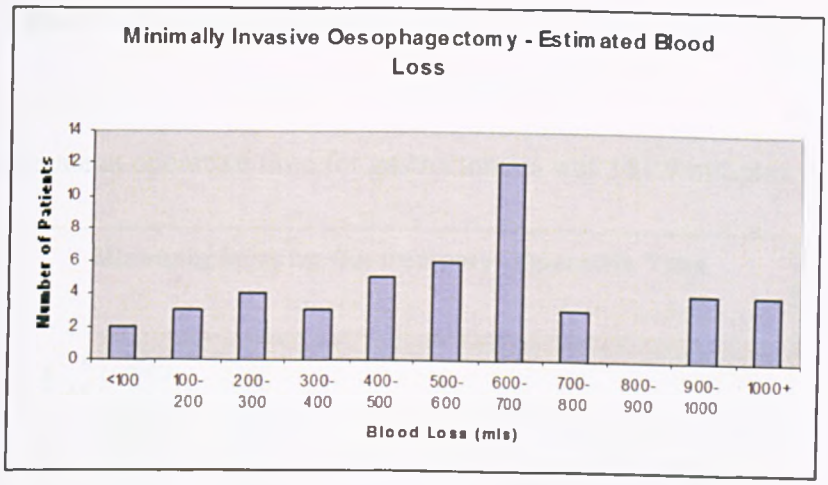


Figure 5.3: Estimated Blood Loss During MIOs

Only 2 gastrectomies recorded intra-operative blood loss, both were estimated at 50 ml.

5. *OPERATIVE TIME*

The mean operative time for oesophagectomies in the study was 287.2 minutes (95% CI 265.4- 309.0.) For each individual approach the average operative time was: 214.3 minutes for laparoscopic transhiatal, 320.9 minutes for prone thoracoscopic, 324.0 minutes for thoracoscopic, 312.5 minutes for laparoscopic/thoracoscopic and 349.0 minutes for laparoscopic-assisted thoracotomy. See figure 5.4:

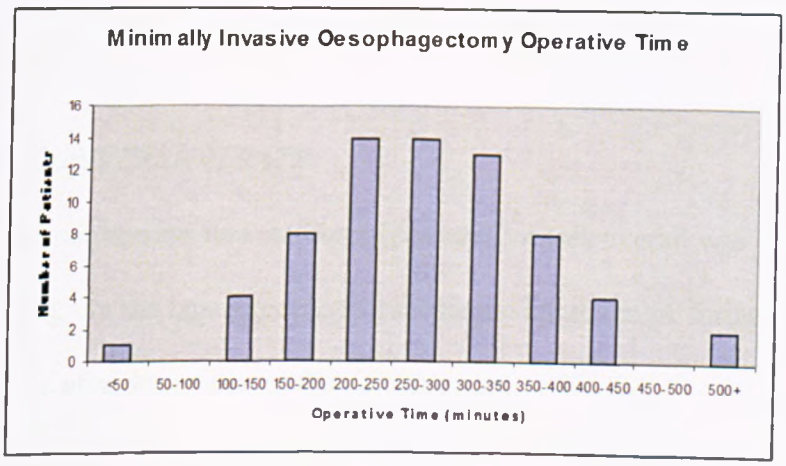


Figure 5.4: Operative Time of MIOs

The mean operative time for gastrectomies was 161.9 minutes. See figure 5.5:

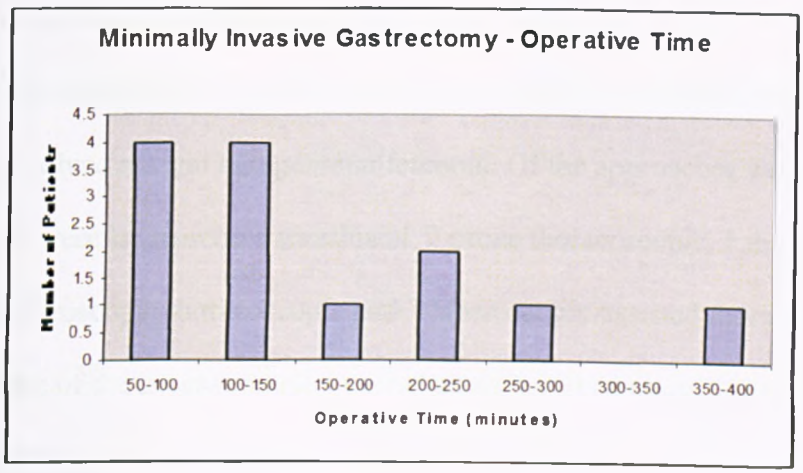


Figure 5.5: Operative Time of MIGs

6. *LYMPH NODE RETRIEVAL*

Mean lymph node retrieval for the oesophagectomy cases was 16.1 (numbers ranged from 0 to 38.) Analysis by approach shows a mean lymph node retrieval of 14.8 by laparoscopic transhiatal approach; 13.0 for prone thoracoscopic; 12.4 for thoracoscopic, 22.1 for laparoscopic/thoracoscopic and 13.6 for laparoscopic-assisted thoracotomy (see table 4.2.)

Lymph node retrieval for gastrectomy cases ranged from 0 to 31 nodes, with a mean of 10.3.

7. *CONVERSION RATE*

The conversion rate for oesophagectomy cases overall was 4 in 100 (4%,) all 4 cases being via the laparoscopic/thoracoscopic approach. A further 7 oesophagectomy cases were abandoned due to the advancement of disease.

No gastrectomy cases (of a total of 26) were converted; 3 however were abandoned due to an inoperable tumour being found.

8. R0 RESECTION SUCCESS

The oesophagectomy R0 resection rate was 82 in 100 (82%,) the most commonly involved margin being circumferential. Of the approaches with incomplete resection, 10 were laparoscopic transhiatal, 2 prone thoracoscopic, 1 thoracoscopic, 2 laparoscopic/thoracoscopic and 3 laparoscopic-assisted thoracotomy.

One of the 26 gastrectomy cases had an involved margin, giving a R0 resection rate of 96%.

9. *LENGTH OF STAY*

The length of hospital stay for gastrectomy cases ranged from 3 to 175 days, with a median of 10 days.

For the oesophagectomies, hospital stay ranged from 7 to 90 days, with a median of 14 days. The median length of hospital stay by approach was 13 days for laparoscopic transhiatal, 10 days for prone thoracoscopic, 14 days for thoracoscopic, 18 days for thoracoscopic/laparoscopic and 13 days for laparoscopic-assisted thoracotomy (see table 5.2.)

Table 5.2: Main Operative Outcomes by Oesophagectomy Technique Utilised

	Respiratory tract Infection (%)	**Estimated Blood Loss (mls)**	**Operating time (mins)**	**Lymph node Yield**	**Length of stay (median days)**
Oesophagectomy Technique Used					
Laparoscopic transhiatal	21.9	627.5	214.3	14.8	13
Prone thoracoscopic	10.0	785.0	320.9	13.0	10

Thoracoscopic	33.3	454.4	324.0	12.4	14
Laparoscopic/thoracoscopic	7.4	883.4	312.5	22.1	18
Laparoscopic assisted thoracotomy	33.3	571.4	349.0	13.6	13

5.4 Discussion

These results show that minimally invasive surgery for both gastric and oesophageal cancer is feasible and safe in a UK setting; although the full benefits, indications and optimal techniques have not yet been determined.

Over 5000 minimally invasive operations for gastric and oesophageal cancer have been reported in the worldwide literature, with wide variation in unit results and techniques.

In comparison to a recent systematic review of this literature (Gemmill 2007,) a relatively high overall morbidity and mortality has been found in this cohort of patients. The existing surgical literature is subject to considerable publication and selection bias, typical of the low methodological quality of case series evidence (Lilford 2004) and in most cases has not been independently verified. Our data may be affected by some early learning curve issues, whilst the setting of previous reports was very different. This is the first multicentre report of minimally invasive surgery (for gastro-oesophageal cancer) in the UK NHS and includes some early experiences. Therefore it is difficult to interpret our morbidity and mortality results in the context of recent world literature.

Estimated blood loss in gastrectomies is apparently very low, consistent with previous reports (Gemmill 2007,) but the mean blood loss for oesophagectomies reported here is moderately high (see figure 5.3,) possibly influenced by a few cases where difficulty was encountered peri-operatively with bleeding vessels. Centres with large experience have suggested that this kind of major intraoperative problem is a feature

of the learning curve and tends not to occur after a certain stage in the experience of a unit (Litle 2002.)

The potential benefits of minimally invasive surgery for length of stay were not verified in this study and were not markedly shorter than for contemporary reports on open surgery. The units supplying data were not involved in fast track policies, such as those by Cerfolio (2004,) Kehlet (2004,) and it is uncertain whether there were delays related to a reluctance to discharge patients early arising from inexperience in some units.

Operative time was comparable to other studies. Operative time for the oesophagectomies demonstrates almost a normal distribution (suggesting a lack of reporting bias,) with most cases taking between 200- 350 minutes. Majority of the gastrectomies cases took 75-150 minutes.

The R0 resection rate and leak rate reported above are acceptable by current standards. The lymph node yield reported is considerably lower than that previously reported in published case series (Gemmill 2007) and that recommended in previous studies of open surgery (SIGN guidelines 2006, Rizk 2006.) It seems likely that this is due to a less than radical approach to nodal dissection. This in turn could be due to an association between enthusiasm for minimally invasive surgery and scepticism about the benefits of radical nodal dissection, or to caution in dissection during the early stages of introducing a procedure. The latter clearly appears plausible. Clearly, the nodal yield for gastrectomy was not adequate for proper UICC staging, but whether the resections were nevertheless oncologically adequate cannot be determined from the data, although calculation of the Maruyama Index (Kampschoer 1989) would give a useful pointer.

All studies of minimally invasive surgery need to be interpreted with care, as selection of patient and tumour characteristics can have considerable affect on outcomes such as operative time (Hyung 2006.) Few papers have published data regarding the learning curve for minimally invasive gastric and oesophageal cancer surgery. One paper, by Jin *et al* recorded 109 operative procedures (gastrectomies) by a single surgeon (Jin 2007.) This paper suggested a multidimensional learning curve, with a slight rising trend involving 3 phases that was achieved after 40 procedures. This curve was broken by unselected operations and the introduction of advanced techniques. This aspect of our results will be discussed in further detail in chapter 6.

This study has a number of limitations: our data was collected retrospectively, over a prolonged time span (although majority of procedures were performed after 2002.) This undoubtedly led to loss of a significant amount of data in some categories, and may have caused inadvertent bias, as there have been advances in inpatient care, pre-operative staging and general laparoscopic operative experiences in the last 5 years. Contributors to the study were also self selected and may be unrepresentative of overall UK practice.

The benefits to patient quality of life that minimally invasive surgery may provide have not been addressed, as no objective data was available. Few studies have looked at this important area, those that do reporting some benefits over open surgery (Luketich 2003, Parameswaran 2007, Yasuda 2007.) Since this outcome measure seems the most likely to yield a significant benefit for minimally invasive surgery, it is clearly important to record reproducible, scientifically valid measures of quality of

life at specific times after surgery to allow a proper evaluation. This point we aim to address in future studies.

Despite these limitations, this study provides data from multiple UK centres with experience in minimally invasive gastric and oesophageal cancer surgery, an area in which there is limited published evidence. It has been demonstrated that the procedure appears safe in terms of R0 resection and leak rate, but is clearly still evolving. Outcomes in terms of lymph node retrieval, morbidity and mortality were inferior to those previously reported, but it is unclear whether the difference is due to more to inexperience or poor selection in this cohort, or the undoubted biases in the published literature.

Chapter 6– A Prospective Phase II Surgical Trial of Minimally Invasive Gastro-Oesophageal Cancer Surgery in the UK

6.1 Introduction

Following on from work reported in chapter 5, further data collection was performed utilising the MIGOCS register. (This is analogous to IDEAL stage 2b.) Data was collated prospectively from centres with an established upper gastrointestinal laparoscopic practice in the UK, many of whom had already provided retrospective data reported in the previous chapter.

Data collection was aimed to not just provide an idea of current practice and outcomes of minimally invasive upper gastrointestinal oncological surgery but to be part of a phase II surgical trial. Therefore it aimed to aid the definition of the procedure; provide information on the learning curve involved; begin to identify suitable sample sizes and timing for a RCT; and develop consensus amongst surgeons to move towards a RCT.

6.2 Method

Data was submitted by MIGOCS members with an active upper gastrointestinal cancer laparoscopic practice prospectively from December 2006. Each centre was subjected to quality control checks by random visits from the research fellow.

The MIGOCS register available online at: http://rs1.e-dendrite.com/csp/migocs/frontpages/migocs.

It consists of 5 sections as previously outlined:

- Demographic details
- Pre-operative assessment and staging

- Surgical intervention
- Post-operative course
- Pathology outcome

For the purposes of this chapter (consistent with chapter 5,) the following data were extracted: patient selection; mortality; morbidity, specifically leak rate and respiratory tract infection; estimated operative blood loss; operative time; lymph node retrieval; conversion rate; R0 resection success and length of stay. Post-operative complications were further subdivided into major (life-threatening,) and minor (prolonging hospital stay) (see table 5.1.)

6.3 Results

Seven centres comprising 14 consultants provided prospective data on their minimally invasive gastro-oesophageal cancer resections, up until August 2008.

278 oesophagectomies were recorded in total and 37 gastrectomies; the breakdown of each is demonstrated in the pie charts below.

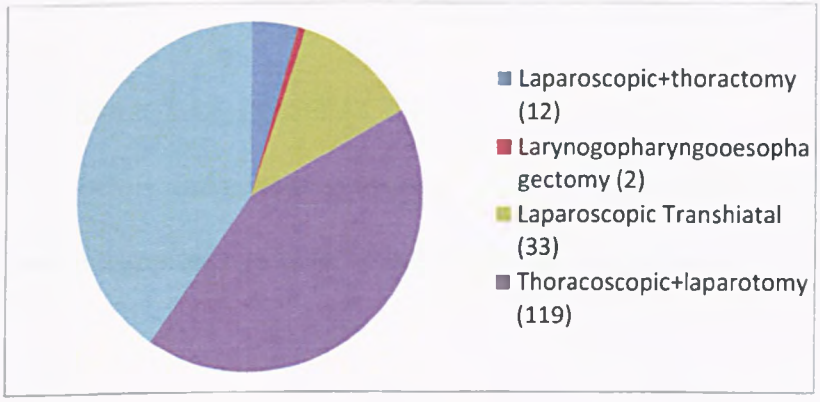


Figure 6.1: Breakdown of Oesophagectomies by Approach

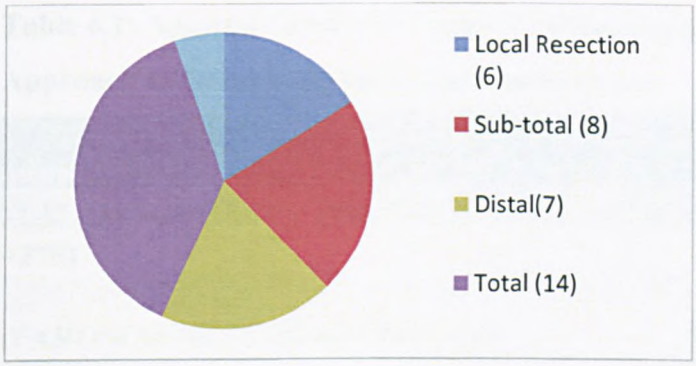


Figure 6.2: Breakdown of Gastrectomies by Approach

For the purpose of this chapter the oesophagectomy data has mostly been analysed by approach (laparoscopic pharyngo-laryngo-oesophagectomies being included in the laparoscopic and thoracotomy group); and due to insufficient numbers, the gastrectomies have been looked as a single group.

258 minimally invasive oesophagectomies were completed (92.8%,) with 13 abandoned procedures (mainly due inoperability of tumour) and 7 procedures were converted to open (mostly due to bleeding or poor views.) Of the gastrectomies, 33 procedures were completed laparoscopically (89.2%,) with no conversions and 4 procedures abandoned due to inoperable tumour.

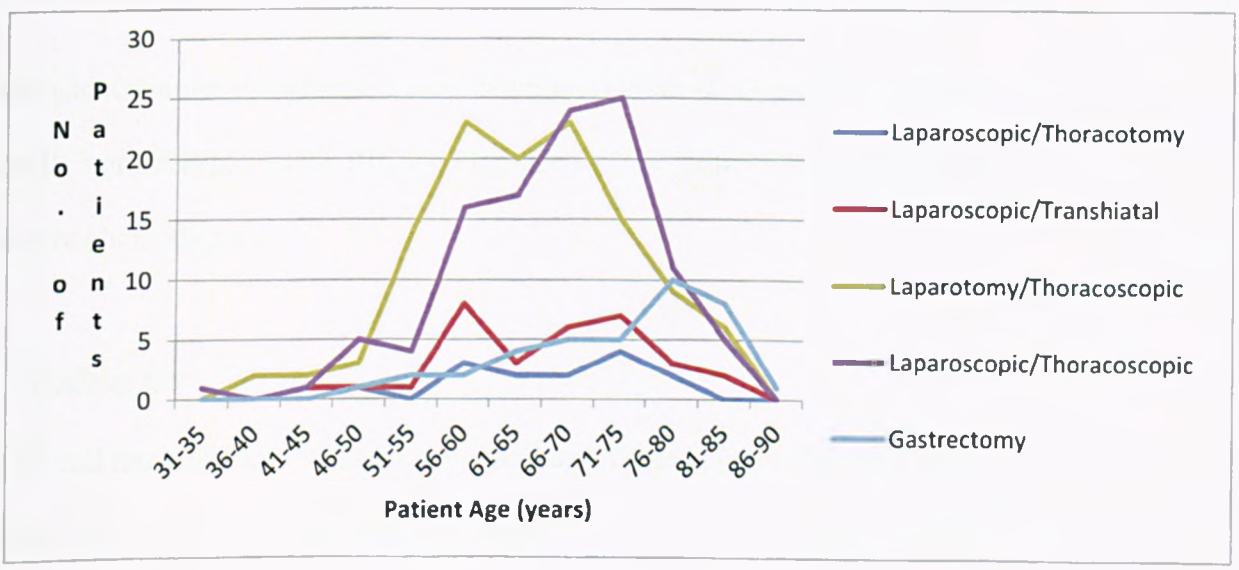
1. DEMOGRAPHIC SELECTION

The table below outlines the average age and gender of people undergoing a laparoscopic approach to both oesophagectomy and gastrectomy:

Table 6.1: Age and Gender of People Undergoing a Minimally Invasive Approach to Oesophagectomy and Gastrectomy

Approach		Age (years)	Gender
TOTAL OESOPHAGECTOMIES	MEAN	65.3	210M, 68F
(N=278)	SD	9.5	
LAPAROSCOPIC+THORACOTOMY			
(n=12+2)	MEAN	66.4	11m, 3f
	SD	9.2	
LAPAROSCOPIC TRANSHIATAL OESOPHAGECTOMY	MEAN	66	20m 13F
(n=33)	SD	9.5	
THORACOSCOPIC+LAPAROTOMY			
(n=119)	MEAN	64	90M, 29F
	SD	9.5	
LAPAROSCOPIC/THORACOSCOPIC OESOPHAGECTOMY	MEAN	66.4	89M, 23F
(n=112)	SD	9.4	
GASTRECTOMIES			
(N=37)	MEAN	72.6	20M, 18F
	SD	10.2	

Figure 6.3: Patient Age Range undergoing Minimally Invasive Oesophagectomy and Gastrectomy



The ASA grade of groups undergoing laparoscopic oesophagectomy and gastrectomy was relatively evenly ranged with a mean of grade 2. (There were: 58 grade 1 patients, 125 grade 2 patients, 27 grade 3 patients, 1 grade 4 patient, the rest were not documented.) O-Possum scores for the oesophagectomies ranged from a mean of 16.8 to 19.1.

The table below demonstrates the grade of oesophageal tumour resected by each minimally invasive approach. 158 oesophagectomies underwent pre-operative chemotherapy (4 laparoscopic plus thoracotomy; 6 laparoscopic transhiatal; 73 thoracoscopic plus laparotomy and 75 laparoscopic/thoracoscopic)

	GRADE	0	I	IIa	IIb	III	Iva	Total
APPROACH								
Laparoscopic+Thoracotomy		0	2	4	1	5	2	14
Laparoscopic Transhiatal		6	7	7	6	6	1	33
Thoracoscopic+Laparotomy		6	15	45	10	42	1	119
Laparoscopic+Thoracoscopic		7	9	60	5	31	0	112
Total		19	33	116	22	84	4	278

Table 6.2: Pre-Operative Histological Grade of Oesophageal Tumour Resected by Approach

Of the gastrectomies performed, 1 was histological grade 0; 19 grade Ia; 9 grade Ib; 5 grade II, 3 grade IIIa; 1 grade IIIb and no grade IV. Six gastrectomies underwent pre-operative chemotherapy.

2. MORTALITY

The overall mortality was 2.5% for the oesophagectomies (7 patients from 278 procedures; 1 out of 33 laparoscopic transhiatal; 5 out of 119 thoracoscopic with

laparotomy and 1 out of 112 laparoscopic/thoracoscopic.) 4 out of 37 patients undergoing gastrectomy died (10.8%.)

3. MORBIDITY

Overall there were a total of 146 (92 major, 54 minor) complications in the oesophagectomy group and 9 in the gastrectomy group (4 major, 5 minor), which is outlined further below. The breakdown of major (life threatening) and minor (hospital prolonging) complications recorded in the figure below is based on criteria used by Luketich *et al* (2003,) as in chapter 5. This is analysed in more detail in table 6.4:

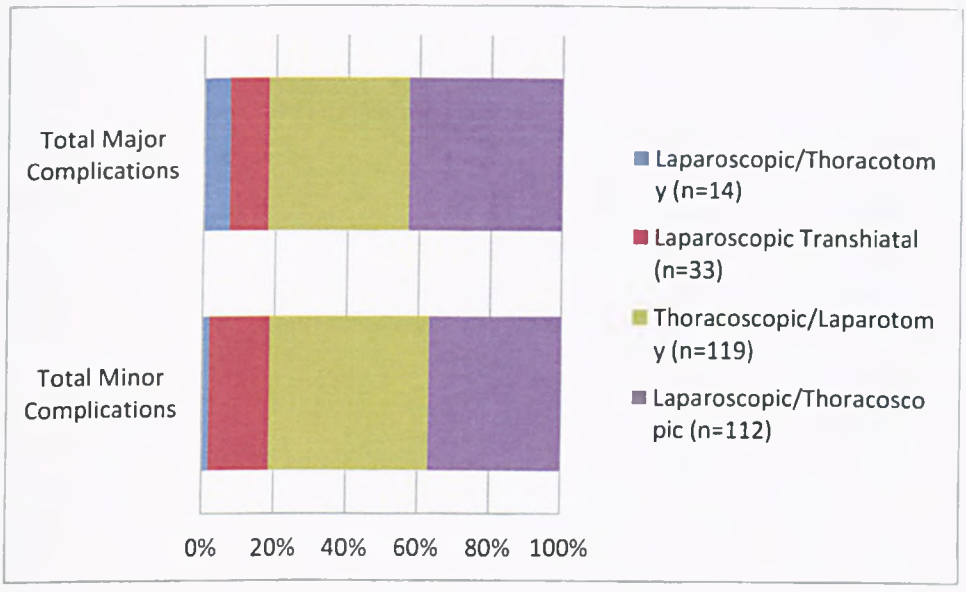


Figure 6.4: Major (Life threatening) and Minor (Hospital prolonging) Morbidity Related to Minimally Invasive Oesophagectomy (by Approach)

Respiratory tract infections (RTIs) and anastomotic leaks are the 2 most commonly reported complications of upper gastrointestinal surgery. In this series, there were 38 RTIs in the oesophagectomy group (13.7%) and 2 (5.4%) in the gastrectomy group; of the anastomotic leaks, there were 22 (7.9%) in the oesophagectomy group and 1

(2.7%) in the gastrectomy group. The next most common major complication occurring was conduit ischaemia (11, 4.0% of oesophagectomies;) in all cases a confirmed leak occurred. This was most common the laparoscopic/thoracoscopic group.

The commonest minor complication in both oesophagectomies and gastrectomies was an arrhythmia (5.8% and10.8% respectively.) The next most frequently occurring minor complications were: strictures, congestive cardiac failure and infection (each affecting 2.5% of oesophagectomy cases.)

Comparing different oesophagectomy approaches, the highest morbidity (both major and minor) was encountered in the laparoscopic transhiatal group.

Table 6.3: Morbidity from Minimally Invasive Gastro-Oesophageal Cancer Surgery

Complication Severity	Complication	Laparoscopic/ thoracotomy (n=14)	Laparoscopic Transhiatal (n=33)	Thoracoscopic/ Laparotomy (n=119)	Laparoscopic/ Thoracoscopic (n=112)	Total Oesophagectomies (n=278)	Gastrectomy (n=37)
Minor	Arrhythmia	0	3	7	6	16	4
	Stricture	0	0	7	0	7	0
	Congestive Cardiac Failure	1	1	3	2	7	0
	Pleural Effusion	0	2	2	0	4	0
	Transient Ischaemic Attack	0	1	0	0	1	0
	Port Site Hernia	0	0	1	1	2	0
	Minor Haemorrhage	0	1	0	0	1	0
	Other infection (Urinary, line sepsis, faecal)	0	1	3	3	7	1
	Recurrent Laryngeal Nerve Injury	0	0	1	8	9	0
Total Minor Complications		1	9	24	20	54	5
Major	Respiratory Tract Infection	3	6	13	16	38	2
	Respiratory Failure	0	0	5	1	6	0
	Leak (confirmed)	2	1	5	14	22	1
	Conduit Ischaemia	1	2	0	8	11	0
	Myocardial Infarction	0	0	3	0	3	1
	Chylothorax	0	0	6	3	9	0
	Tension Pneumothorax	0	0	1	0	1	0
	Major haemorrhage	0	0	0	1	1	0
	Cerebral Vascular Accident	0	0	0	1	1	0
Total Major Complications		6	9	33	36	92	4
Overall Complications		7	18	57	56	146	9

4. BLOOD LOSS

Mean blood loss in the oesophagectomy group was 558mls (95% CI 550- 583) (not all centres recorded this information, so incomplete data entries in this field occurred.) By approach, estimated mean blood loss was: 573ml in the laparoscopic/thoracotomy group; 579ml in the laparoscopic transhiatal group; 546ml in the thoracoscopic/laparotomy group and 563ml in the laparoscopic/thoracoscopic group. A total of 13 patients undergoing oesophagectomy received a transfusion (1 in the laparoscopic/thoracotomy group; 4 in the laparotomy/thoracoscopic group and 8 in the laparoscopic/thoracoscopic group.)

The mean estimated blood loss for minimally invasive gastrectomies was 300ml (95% CI 245-356.) No patients in the gastrectomy group received a post-operative blood transfusion.

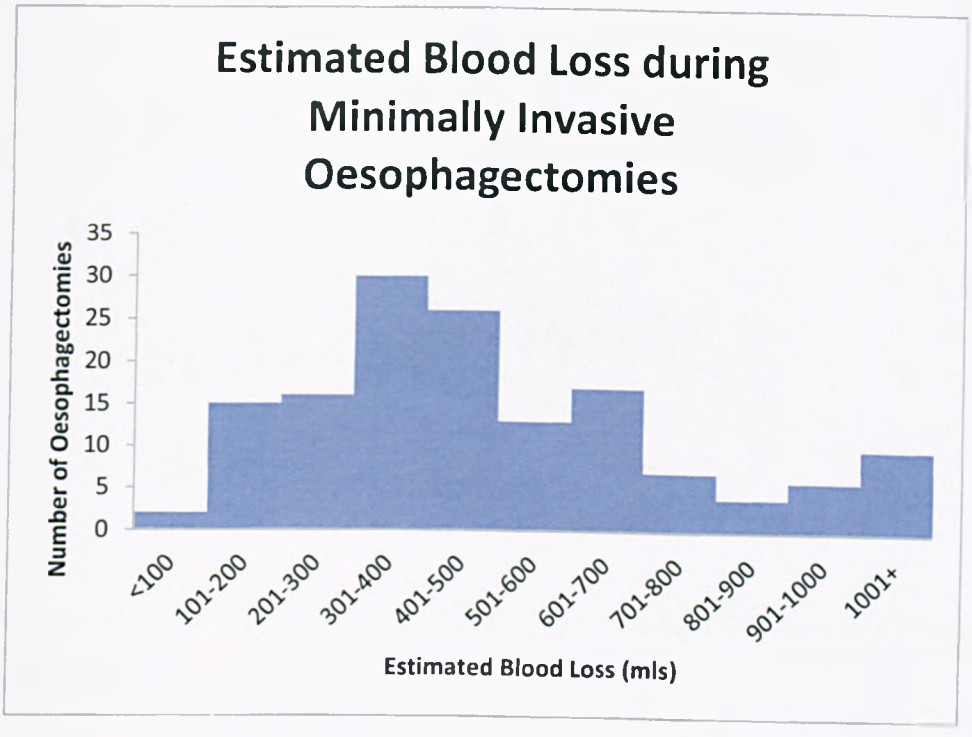


Figure 6.5: Estimated Blood Loss During Minimally Invasive Oesophagectomies

5. OPERATIVE TIME

The mean operating time for laparoscopic oesophagectomies was 281 minutes (95% CI 276-327.) (This breaks down by approach into 207 minutes for laparoscopy/thoracotomy; 193 minutes for laparoscopic transhiatal; 321 minutes for laparotomy/thoracoscopic; and 402 minutes for laparoscopic/thoracoscopic.) The mean operative time for the gastrectomies was 200 minutes (95% CI 106-295.)

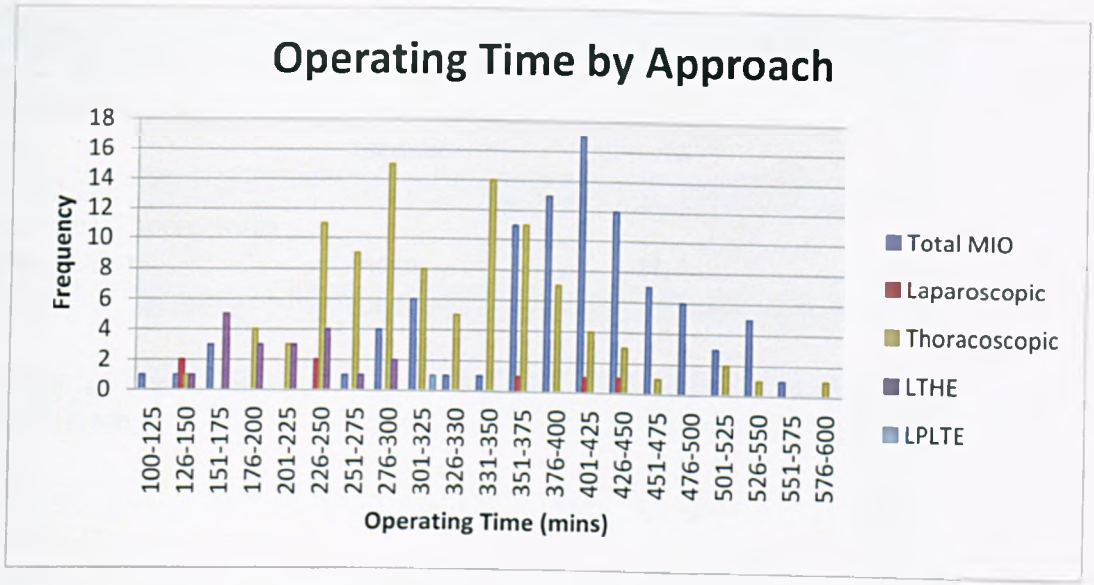


Figure 6.6: Operative Times for Minimally Invasive Oesophageal Cancer Resections

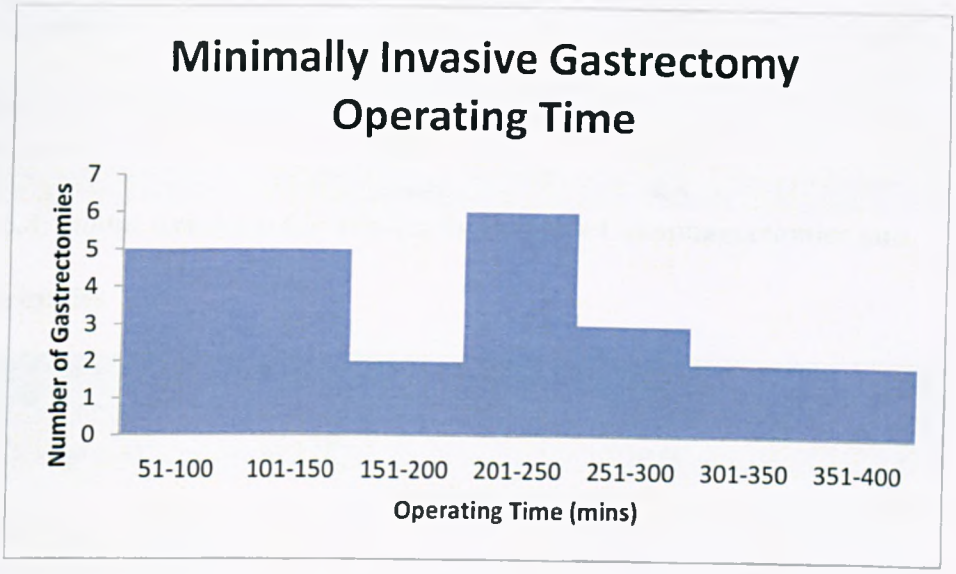


Figure 6.7: Operative Times for Minimally Invasive Gastric Cancer Resections

6. LYMPH NODE RETRIEVAL AND R0 RESECTION RATE

Mean lymph node retrieval for the oesophagectomies was 17.5 (95% CI 13.1-24.1) and for the gastrectomies was 13.2 (95% CI -2.79- 37.9.) This is detailed further in the table below.

Approach		Node Retrieval	Positive Nodes
Total Oesophagectomies	mean	17.5	2.4
(n=278)	median	16	0
Laparoscopic/Thoracotomy Oesophagectomy	mean	21.4	3.3
(n=14)	median	21	2
Laparoscopic Transhiatal Oesophagectomy	mean	14	4.5
(n=33)	median	12	1
Laparotomy/Thoracoscopic Oesophagectomy	mean	16.5	2.6
(n=119)	median	14	0
Laparoscopic/Thoracoscopic Oesophagectomy	mean	18.7	1.6
(n=112)	median	18	0
Gastrectomy	mean	13.2	3
(n=37)	median	9.5	0

Table 6.4: Nodal Retrieval for Minimally Invasive Oesophagectomies and Gastrectomies

Approach	R0 (%)	R1 (%)	R2 (%)
Total Oesophagectomies (n=278)	70.9	25.5	3.6
Laparoscopic/Thoracotomy Oesophagectomy (n=14)	57.1	42.9	0.0
Laparoscopic Transhiatal Oesophagectomy (n=33)	72.7	24.2	3.0
Laparotomy/Thoracoscopic Oesophagectomy (n=119)	85.7	13.4	0.8
Laparoscopic/Thoracoscopic Oesophagectomy (n=112)	56.3	36.6	7.1
Gastrectomy (n=37)	86.5	8.1	5.4

Table 6.5: Resection Margins for Minimally Invasive Oesophagectomies and Gastrectomies

7. LENGTH OF INTENSIVE CARE AND HOSPITAL STAY

The median length of hospital stay post minimally invasive oesophagectomy was 13.0 days (95% CI 17.4-22.0.) For gastrectomies the median length of stay was 7.0 days (95% CI 13.7-17.9.) The table below outlines length of stay in more detail (n.b. data is skewed):

Approach	Column1	Length of Stay (days)	Intensive Care Stay (days)
Oesophagectomy Approach			
Oesophagectomy overall	MEAN	23	3.9
	MEDIAN	13	0
Laparoscopic/Thoracotomy	MEAN	23.2	4.8
	MEDIAN	14	3.5
Laparoscopic Transhiatal	MEAN	17.4	4.5
	MEDIAN	13.5	2
Laparotomy/Thoracoscopic	MEAN	18.3	7.1
	MEDIAN	13	5
Laparoscopic/Thoracoscopic	MEAN	27.1	1.8
	MEDIAN	13	0
Gastrectomies	MEAN	15.8	1.5
	MEDIAN	7	0

Table 6.6: Length of Hospital and Intensive Care following Minimally Invasive Oesophagectomy and Gastrectomy.

6.4 Discussion

These results, in common with the retrospective data in chapter 5, confirm that minimally invasive gastro-oesophageal cancer surgery is both safe and feasible in a

UK setting. The high mortality rate in the gastrectomy group is however acknowledged and the length of stay in this group is greater than expected. This could be due to a small series (with resultant high percentages on analysis); poor case selection and a reluctance to discharge patients from units inexperienced in MIG (that also do not operate enhanced recovery programmes.) Further data collection is recommended to ascertain the significance of MIG results in this trial.

Patient demographics, including ASA and POSSUM grades are similar to those found in other reports of this type of cancer surgery (ASCOT trial, McCulloch 2003.) The unit policy varied between centres included in the register; some selected patients for this type of surgery however others offered the minimally invasive approach to all comers. The overall demographics in the register demonstrate that the population studied remains approximately representative of those undergoing open as well as laparoscopic upper gastrointestinal resections; (although disease stage tended to be lower in some centres when compared to patients undergoing open surgery.) Prudent surgeons in the early phases of a developing technique such as minimally invasive surgery for gastro-oesophageal cancer frequently however select patients for resection. These include patients with: a good body habitus that are not obese; early stage tumours and patients with low ASA grades/minimal co-morbidity

Mortality rates for MIO (2.5%) are similar to those reported in systematic reviews of this type of surgery (Gemmill 2007, Verhage 2009,) although better than the most recent national data on oesophagectomies, which includes open surgery (Palser 2009.) Morbidity rates for MIO (53%) including rates specific for anastomotic leak and respiratory tract infection are lower than those found on comparable databases

(Wormuth 2006,) although there is wide variation in the classification degree of reported ischaemia. In MIO, intracorporeal gastric conduit formation does not allow flattening and stretching of the stomach in an antero-posterior dimension to the extent utilised in (extracorporeal) open oesophagectomies, resulting in a shorter gastric tube, with a smaller tip prior to anastomosis.

It is difficult to separate whether the gastric tip ischaemia is related to the MIO approach (extra-corporeal gastric conduit formation rates are reported between 2.3% and 9% (Leibman 2006, Palanivelu 2006;) or the width of the gastric tube formation - wider tubes appear to have lower ischemic rates but can result in oncological margin compromise (Berrisford 2008.) It is likely however that gastric tip necrosis is multifactorial, with both of the previously mentioned causative factors, in addition to: failure to mobilise the right crus of the diaphragm sufficiently and a narrow hiatus resulting in constriction of the gastric tube; failure to preserve the gastro-epiploic arcade at the gastric fundus sufficiently; insufficient mobilisation of the pylorus and distal stomach reducing resectable conduit tip; traction forces applied to the conduit during mediatinal mobilisation; and conduit route (Anegg 2008, Berrisford 2009;) all of which are more difficult in a minimally invasive approach compared with an open one.

This centre is currently conducting a randomised controlled trial of ischaemic preconditioning of the gastric conduit 2 weeks prior to resection in the aim of improving perfusion (Berrisford 2009.) This technique in open surgery has been attempted by other centres with potential benefit (Hoelscher 2007, Varela 2008.)

The mortality and morbidity rates for MIG (10.8% and 24% respectively) reported here are greater than that expected when compared to recent national and international

literature (Gemmill 2007, Smith 2007, Yacoub 2008, Palser 2009.) It compares however to that published following the ASCOT trial (McCulloch 2003.) This may be due to the low number of cases resulting in a disproportionally high outcome rate with big percentages; (patient demographics including age and ASA grade for the gastrectomy group were comparable to other series.) Although the high morbidity and mortality could possibly be a reflection of the early stage of the learning curve this trend does not appear to be mimicked in the oesophagectomy group. Again, as with chapter 5, the published literature may be subject to publication bias, unlike the data recorded here which reflects multicentre practice.

Operating time was comparable to the literature, and was shown to decrease with unit experience. This is reflected in CUSUM analysis, which is analysed in further detail in chapter 7.

Estimated blood loss was higher in this data collection than in comparable series. This may be a reflection of the poor recording of this information and statistical outliers increasing the overall mean.

The lymph node yield and ratio are one of the most important factors determining patient postoperative prognosis (Eloubeidi 2002, Lagarde 2006, Yoo 2009.) In this study, the yield for both oesophagectomy (17.5) and gastrectomy (13.4) are less than could be hoped and below that recommended in the literature – 18 and 15 lymph nodes respectively (Risk 2008, Van Cutsem 2008.) It is difficult however to ascertain whether these apparent yields are the result of the radicality of surgery performed or differences in the histological analysis in the laboratory. Indeed more recent studies

have questioned both the methodology (Jamieson 2009) and lymph node yield and ratios (Mariette 2008, Deng 2009) required for accurate staging.

The negative lower confidence interval obtained for gastrectomy lymph node retrieval is also indicative of a low sample size and the broad variation in confidence intervals demonstrates marked difference between units. It is therefore even more difficult to interpret the results obtained in this study with any certainty.

R0 resection rate of the oesophagectomies is also lower than expected, impacting on the oncological quality of surgery. The most commonly involved margin was circumferential, which has the greatest prognostic significance (Griffiths 2006, Sujendran 2008, Wang 2009.) However at least one unit dissected the specimen in the operating theatre in order to optimise the lymph node yield; but in the process, altering the reported from the true circumferential resection margin.

R0 resection rate documented here is lower than that in the world literature of minimally invasive gastrectomies (Gemmill 2007) although it is questionable whether these initial reports were subject to publication bias. Its importance in the resection of gastric cancer is well documented (Wang 2009) and therefore this low rate is of concern. However due to the low numbers of gastrectomies involved in this trial, the overall percentage rate is disproportionately high.

Data on length of hospital stay was again disappointing and did not demonstrate the reduced time compared to open surgery that was predicted and hoped for from the laparoscopic approach. This may be due to overcautious care in centres at the early

stage of their learning curve and a fast-track type policy not being applied like in other units (Kehlet 2006, Low 2007, Gouvas 2009.)

Quality of life analysis has not been addressed in this prospective study, despite it being one of the purported benefits of minimally invasive surgery (Parameswaran 2009;) although it is aimed that this will be a future aspect of study.

Despite the limitations in data collection this prospective study provides further information of minimally invasive gastro-oesophageal oncological surgery in multiple UK centres where there is limited published evidence. Similar to the retrospective study gastrectomy mortality and morbidity are still a concern, however oesophagectomy rates were comparable to national and international published literature. Again, length of stay benefit was not demonstrated and R0 resection rates and lymph node yields were not as good as hoped. It is unclear if these differences when compared to previous publications are a result of technical problems not encountered in open surgery, which will improve with experience or bias in published literature. Further data collection is recommended and comparison to open surgery with specific endpoints such as 5-year survival. (This was not done in the above data collection which was part of a phase II surgical trial.)

CHAPTER 7 – THE LEARNING CURVE ASSOCIATED WITH MINIMALLY INVASIVE SURGERY FOR GASTRO-OESOPHAGEAL CANCER

7.1 Introduction

Acknowledging and identifying the learning curve associated with evolving surgical techniques is important. It was first highlighted and assessed by continuous surveillance of unit performance in the UK following the Bristol Royal Infirmary inquiry (Stark 2000.) Continuous monitoring which acts as a method of quality control can be done by the application of control curves (Mohammed 2001) or instruments that monitor sequential probability ratios such as CUSUM (Cumulative Sum Control) (Novick 2003, Speigelhalter 2004,) VLAD (Variable Life-Adjusted Display) (Lovegrove 1997) or CRAM plots (Cumulative Risk Adjusted Mortality) (Polonieck 1998.) These instruments can be updated after each operation and can be applied to individual surgeons, thereby producing real-time monitoring of performance.

Evaluation of the learning curve has been utilised extensively in the assessment of laparoscopic procedures, such as laparoscopic cholecystectomy (Moore 1995) and laparoscopic urological procedures (See 1993.) A number of publications have utilised CUSUM analysis in the setting of gastro-oesophageal cancer surgery (Kim 2005, Jin 2006, Lee 2006,) although few relate specifically to the minimally invasive approach.

CUSUM charts allow detection of a deterioration (or improvement) in surgical practices and are sensitive to small changes in outcome rates; not overreacting to expected fluctuations due to chance (Steiner 1999.) Limits are set to identify situations where the frequency of failures is significantly greater than expected, causing the system to "trigger." CUSUM can therefore be applied to help determine surgical learning curves and the detection of surgical outliers.

CUSUM methodology has been developed from ammunition production in World War II (Montgomery 1991) evaluating a more homogenous (industrial) dataset than that which is frequently encountered in a surgical environment, with its heterogeneous group of patients both in physiology and clinical presentation. This can result in limitations of traditional CUSUM analysis and a risk-adjusted CUSUM, addressing the level of pre-operative risk has also been proposed (Steiner 2000.)

A CUSUM analysis of the learning curve typically demonstrates a sigmoid curve with a slow beginning, steep acceleration and plateau phase. This represents an initial upward trend where failure exceeds the expected levels; followed by either a plateau phase where the expected and observed failure rate are equal, or a downward slope where the observed outcome is better than the acceptable (expected) one. The point at which the slope either plateaus, or demonstrates a consistent downward trend, demonstrates the number of procedures required to perform the process under study to the required standard.

A number of different variables (both continuous and discrete) can be assessed utilising CUSUM analysis, commonly operation time, conversion rate, major

morbidity and mortality (Novick 1999, Dincler 2003, Grunkemeir 2003;) but other factors such as oncological outcome have also been measured (Jin 2007.) Operative time was used for CUSUM analysis in this study since it allows objective assessment of a surgeons' technical ability; is a commonly reported variable and has been demonstrated to reduce with increasing operative experience (Schlachta 2001, Tekkis 2005.) It is nevertheless a crude measure of outcome and has limitations, especially as speed does not necessarily reflect surgical precision or oncological and post-operative outcome including complications; it also does not take in to account patient or tumour characteristics e.g. obese patients and T3 tumours.

7.2 Methods

Prospective data derived from the MIGOCS register was collated, looking at minimally invasive oesophagectomies from all centres documenting operative time for more than 5 cases. The mean operative time and range of time per centre was initially assessed then more detailed analysis utilising CUSUM methodology was utilised. (Minimally invasive gastrectomies were not looked at, as too few were recorded to allow meaningful analysis to occur.)

CUSUM requires classification of each operation as a success or a failure according to pre-defined criteria. For this purpose, operation time greater than two standard deviations from the overall population mean was defined as a "failure"; similar to that by Novick *et al* (2003.) This allowed an assessment of sequential outcomes and identification of any procedure learning curve. A positive curve indicates that the

acceptable failure rate has been exceeded and conversely a downward, negative slope indicates a failure rate less than the accepted rate.

A zero value (the starting point of the plot) is exactly what is predicted by the risk model. Transitions from overall positive to overall negative values and vice versa can be frequent and reflect normal surgical practice.

The mathematical formula utilised was:

Approach 1 (simple approach): $S_i = \sum (X_j - X_0)$; X_0 is the sample mean

Approach 2:

$S_i = \max(0, S_i - 1 + W_t)$, where $W_t = (X_t - \mu_0) / \sigma_0 - k$; where $k = 0.5g$

and $S_0 = 0$

- g represents the number of standard deviations one wants to detect (2 in this case.)
- μ_0 represents the mean operation time when the process is considered in control.
- σ_0 represents the standard deviation of the series (assumed to exhibit no serial correlation.)

Initial data analysis involved that obtained from all centres providing greater than 5 cases, except Exeter. Data from Exeter was analysed separately as operative times were provided combined with anaesthetic time and therefore adjustments had to made accordingly. (Future data from this site has been requested to record separate

anaesthetic and operative times in order for more accurate comparisons between centres to be made.)

7.3 Results

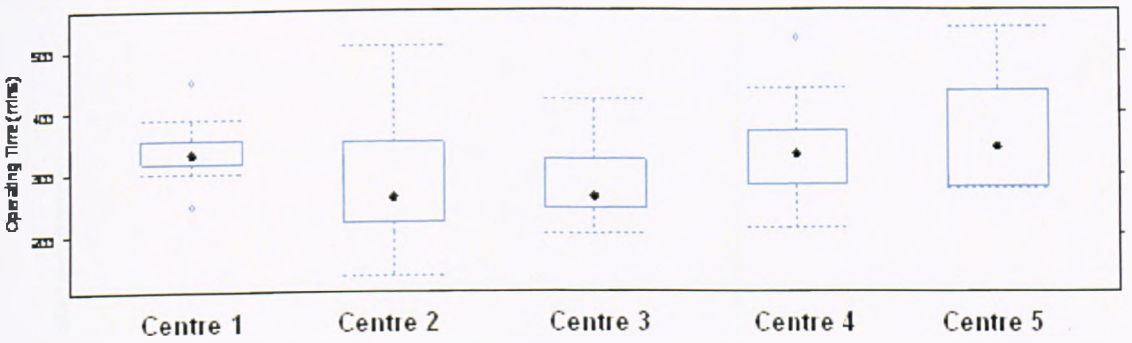
Operative time was initially assessed by mean operative time and range by centre (including all those recording over 5 minimally invasive oesophagectomies on the MIGOCS register.)

An overall mean was then calculated from which 2 standard deviations could be calculated in order to identify a "trigger" value for CUSUM analysis. A box plot (figure 7.1) and index plot (figures 7.2 and 7.3) were also created to further appreciate the variation of operating time between centres.

Table 7.1 Minimally Invasive Oesophagectomies, Mean and Range of Operative Times by Centre

CENTRE (number)	NUMBER OF OPERATIONS	MEAN OPERATING TIME (mins)	RANGE (mins)
Colchester General Hospital (1)	15	338	(245, 450)
Hull Royal Infirmary (2)	45	283	(135, 510)
Imperial (3)	15	287	(200, 420)
Maidstone & Tunbridge Wells (4)	25	335	(210, 520)
Worthing & Southland Hospital (5)	5	375	(273, 540)
Royal Devon & Exeter (includes anaesthetic time)	96	402	(104,745)
OVERALL OPERATIVE TIME (Exeter excluded)	105	308	(135, 540)

Figure 7.1: Box Plot of MIO Operating Times by Centre



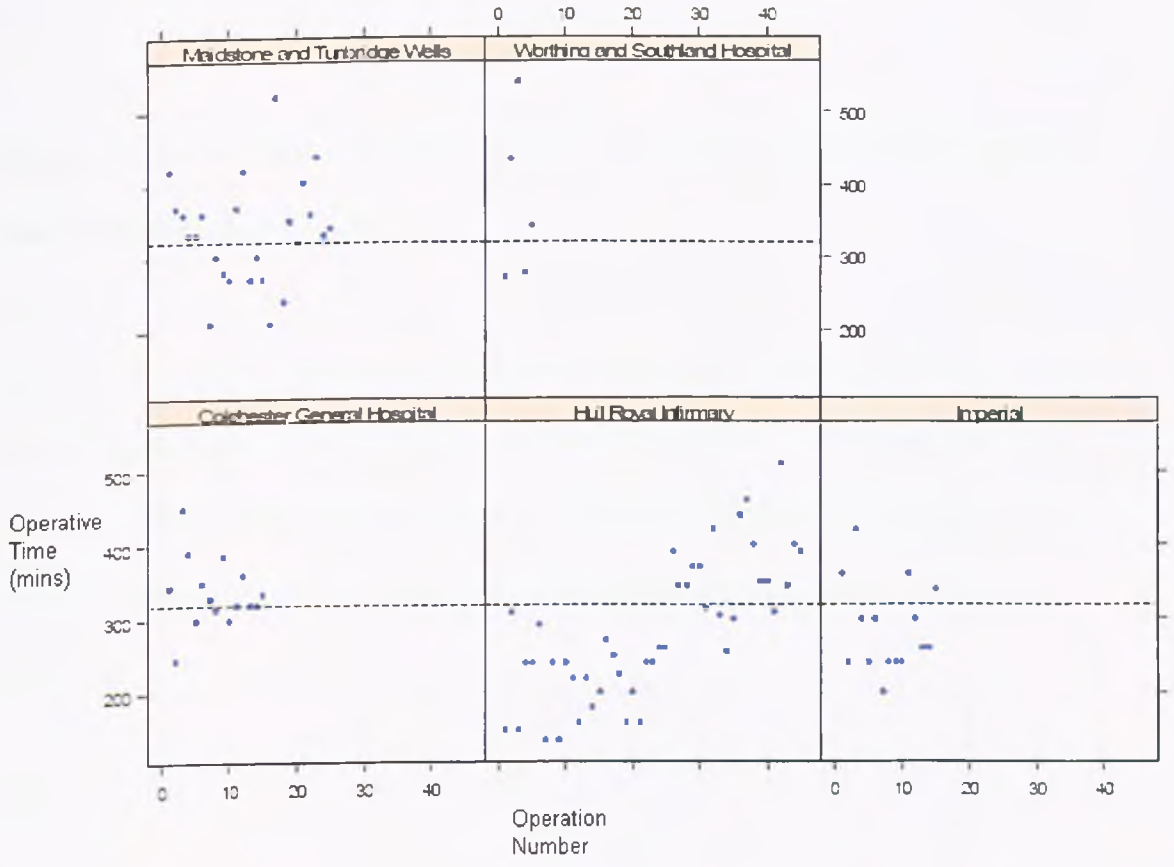


Figure 7.2: Index Plot of Operating Times by Centre (dotted line represents mean operative time of the entire series)

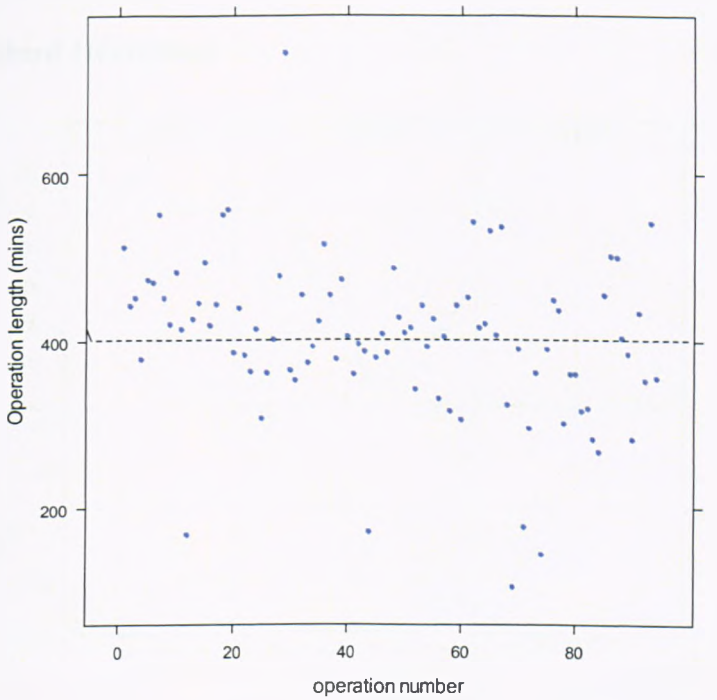
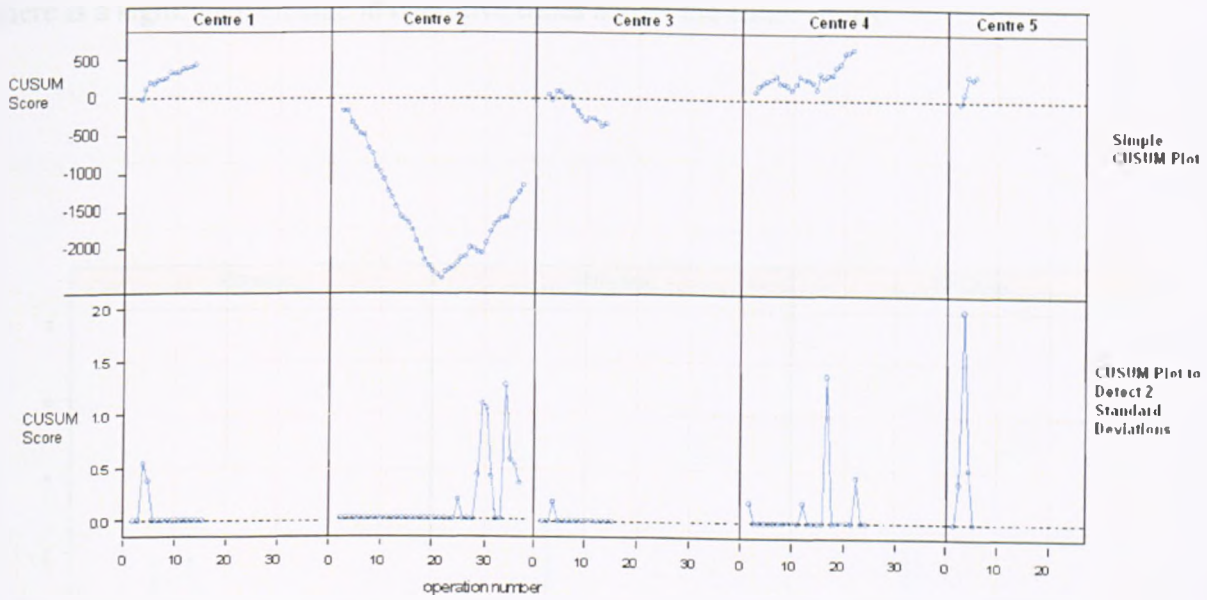


Figure 7.3: Index Operating (and included Anaesthetic) Time at Exeter (dotted line represents Mean Time)

The operative times at all the centres studied demonstrates a range of values. In the case of Exeter many of these are clustered around the mean, with outliers; however this is not obviously the case in all centres. Therefore CUSUM analysis is of benefit to look at operative time in more detail and to give more informative results.

Figure 7.4: Simple CUSUM Plot and CUSUM Analysis to detect a change of 2 Standard Deviations



Only 6 centres provided enough data for CUSUM analysis in the prospective series. (Data from Exeter as mentioned above has been analysed separately as data provided combined operative and anaesthetic time.)

In the graph, a downward trend represents an improvement in performance by the centre (i.e. operating time is less than the average operating time of the entire series.) It can thus be observed from the initial simple CUSUM analysis that the first 25 operations at Hull Royal Infirmary (centre 2,) resulted in a better than expected performance, followed by 20 operations that took longer than expected, but the CUSUM remained below the horizontal line (in control.) Centres 1 (Colchester) and 3 (Imperial) demonstrated a relatively stable performance remaining close to the horizontal line. Centre 4 and 5 (Maidstone and Worthing) took longer than expected in there operative time, although operative numbers are low.

Approach 2, is designed to detect a change in 2 standard deviations is demonstrated in the lower half of the above graph. For all 5 centres there is no evidence to suggest that there is a significant change in operative times across the entire series.

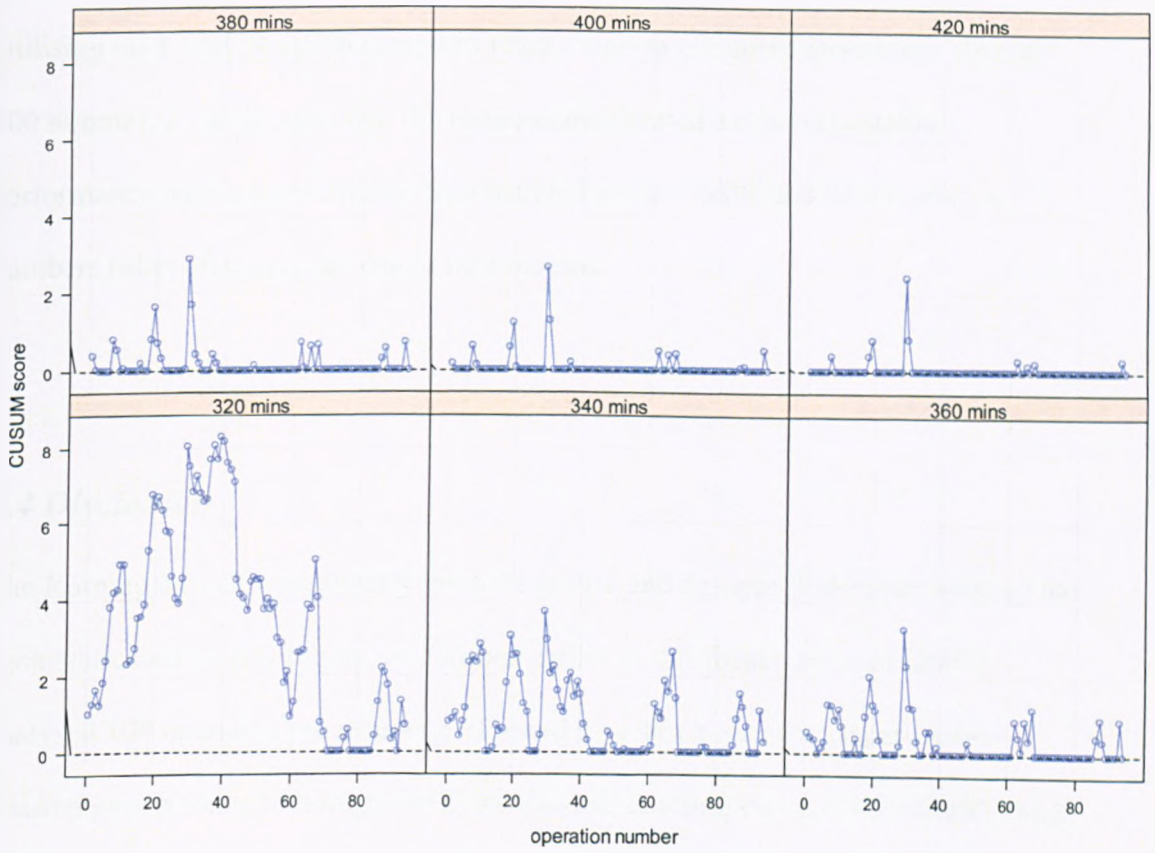


Figure 7.5: Exeter CUSUM Plot- Effect of changing the mean operative time (to detect a change of 2 standard deviations)

The mean operative time for the Exeter series in 402 mins (standard deviation of 95 minutes); higher for that of other series, but it does include anaesthetic time. This is difficult to separate into separate components using data provided by the centre. By

assuming a lower mean operating time say 320mins, then the CUSUM will produce lots of false alarms as seen in the lower left figure. Alternatively, imposing an acceptable mean operating time which is much higher, say 420mins, then the CUSUM will rarely alert. From looking at this data, it can be seen that the acceptable mean operating time should be something which is pre-specified.

Utilising the CUSUM graph closest to Exeter's mean operative/anaesthetic time at 400 minutes, it can be seen that the centre demonstrated a relatively stable performance with improvements demonstrated in the middle and later operative numbers (after 30 cases,) as should be expected.

7.4 Discussion

The learning curve for minimally invasive gastric and oesophageal cancer surgery has been addressed by few papers, as outlined earlier in this thesis. Jin *et al* (2007) analysed 109 operative procedures performed by a single surgeon (laparoscopy-assisted gastrectomy;) finding a multidimensional learning curve, with a slight rising trend involving 3 phases that was achieved after 40 procedures. This curve was broken by unselected operations and the introduction of advanced techniques.
An initial slow rising trend is commonly seen in the analysis of minimally invasive oesophagectomies, possibly resulting from operating in pairs, mentorship, carefully selected patients, hybrid techniques and the realisation of "zones of discomfort."

Using our data, CUSUM analysis of oesophagectomies is limited by the relatively small number of procedures undertaken to date by the centres providing data, but

illustrates how CUSUM is beneficial in the development of a novel technique. Looking at the initial data, variation is demonstrated between the 4 centres with experience of over ten procedures (see figures 6.1 and 6.4.) One centre consistently over performed (i.e. the surgeons were significantly faster than average) until the final few procedures, when their performance suddenly deteriorated. This is probably explained by a change in approach from thoracoscopic with laparotomy to a more demanding thoracoscopic/laparoscopic technique, which coincided with this. The first and third centres demonstrate a relatively stable surgical outcome, suggesting that they have almost reached a plateau in their learning curve. The use of the derivative graphs where only deviation greater than 2 SD was represented on the graph seemed very helpful in detecting trends and changes. It is believed that the complete experience has been recorded from these centres from the first case, which suggests that prior experience with other complex laparoscopic surgery, together with a measured approach, can eliminate the learning curve for this procedure, at least for operative time. It is impossible with the information obtained from the centres providing data (on operative time alone) to determine the exact number of procedures that need to be performed in order to demonstrate an improvement in surgical outcome. In particular, the absence of precise information on prior surgical experience – with this procedure or other complex laparoscopic surgery- and patient selection, hampers practice effect (learning curve) analysis and data interpretation.

Analysis of the Exeter data has demonstrated the importance of uniformity of data, which although is specified in the register, was not provided by the centre (all operative time included anaesthetic time.) This made it difficult to compare the centre to others in the register. It did however outline the benefit of a pre-specified acceptable mean operative time, as this will affect the "trigger" value at which

CUSUM will alert a problem. Data from Exeter has provided information on the largest number of operations performed by any one centre included in the register. In conjunction with the data from Hull (the second largest contributor to the dataset,) CUSUM analysis appears to suggest that a learning curve appears to plateau at after at least 30 cases. (This contrasts to the 50 cases recommended in the literature for MIG – Fujiwara 2005, Kim 2005- and 40 cases by Jin- 2007.) To date of writing this thesis a value at which the learning curve appears to have been overcome has not previously been mentioned in the published literature. (This value may have important implications in proctorship and introduction of minimally invasive oesophagectomy programmes.)

Another limitation of the CUSUM in this chapter is that it was applied to each centre rather than to individual surgeons (2 surgeons were involved in operations at Maidstone and Exeter in roughly equal numbers of operations and a second surgeon responsible for small numbers of cases in Hull and Southampton.) Whilst this affects the outcome of learning curves and introduces a confounding factor it was felt that for published outcomes to the MIGOCS group, data feedback by centre provided greater anonymity. In addition many centres perform minimally invasive resections with 2 consultants present, as recommended by the consensus statement on MIO by AUGIS in 2008 during the operative learning curve. It is therefore difficult to determine the exact learning curve of individuals independently.

Operative learning curve is only one of five encountered in minimally invasive operations; there is also the anaesthetic assessment, patient selection, team formation, post operative care and management of postoperative complications.

Despite all its limitations, CUSUM is a good tool for providing continuous surveillance and is clearly useful in detecting improvement (or deterioration) in performance. Thus it helps maintain quality control, demonstrating objective and quantified recording of results that allows early detection of problems, leading to potential review and remedial action that would prevent future failures.

CHAPTER 8: THESIS CONCLUSIONS, CRITIQUE AND FUTURE PROSPECTS

This thesis presents a phase II surgical study of minimally invasive gastro-oesophageal cancer surgery from multiple centres in the United Kingdom. This approach has been used as other methodologies such as case series provide weak quality of evidence (CEBM) in evaluating this type of surgery.

8.1 Thesis Summary

Surgery remains the treatment of choice for patients with gastro-oesophageal cancer beyond its earliest stages. This type of surgery however carries high morbidity and mortality rates, with studies demonstrating that patients can take 2 years before returning to a reasonable quality of life post-operatively. Therefore options such as minimally invasive surgery which have the potential to provide shorter post-operative stay; quicker return to function and improved quality of life have been gaining in popularity since their introduction in the early 1990s.

RCTs are problematic to perform in surgery due to a number of factors such as learning curves, definition of the trial and blinding. The development of novel surgical techniques also makes trial timing difficult. The optimal trial design should incorporate a comprehensive approach after the initial surgical intervention development. An example of this is a phase II surgical trial utilised in this thesis. This addresses trial definition, quality control, the learning curve and aims to encourage the development of a RCT between participants (thereby integrating natural technique development with rigorous scientific evaluation.)

Following a systematic review of the literature, we know that the majority of the published literature on laparoscopic gastro-oesophageal surgery for cancer is in the form of case series. Up to the date of writing this thesis, there were no randomised controlled trials (RCTs) of minimally invasive oesophagectomies (MIOs) and 4 small, single centre RCTs of minimally invasive gastrectomies (MIGs.) Most of the evidence on MIOs comes from Western centres (America, Australia and Europe) and most of that on MIGs comes from Eastern centres (Japan and Korea.)

The MIGOCS (Minimally Invasive Gastro-Oesophageal Cancer Surgery) group was established in 2005 and now has over 60 consultant members from around the UK and Europe. It is a research collaboration which through consensus discussions and iterative development has established a registry for this type of surgery (available at: http://rs1.e-dendrite.com/csp/migocs/frontpages/migocs.) The registry comprises of five sections: demographic details; pre-operative assessment and staging; operative intervention; post-operative course; pathology and clinical outcome.

8.2 Findings from this Thesis

Retrospective data was initially collated from 7 UK centres and recorded 100 oesophagectomies and 26 gastrectomies (approximately analogous to IDEAL stage 2a/b.) From the oesophagectomy group there were 57 complications (30 major, 27 minor, which included 3 anastomotic leaks and 19 respiratory tract infections) and 6 deaths; in the gastrectomy group there were 13 morbidities(4 major, 9 minor) and 2 deaths. These morbidity and mortality results were higher than expected. Length of

stay results (14 and 10 days respectively for MIO and MIG) and estimated blood loss for the oesophagectomies were also greater than predicted and lymph node yield was lower than hoped. Operative time, R0 resection and leak rate were however acceptable and established MIO and MIG in a multicentre setting in the UK as safe but clearly evolving with the need for more studies to evaluate it further.

Prospective data collection collected between December 2006 and August 2008 involved 278 oesophagectomies and 37 gastrectomies (IDEAL stage 2b.) Most oesophagectomies were laparoscopic/thoracoscopic or laparoscopic/thoracotomy. In the oesophagectomy group there were 146 complications (92 major and 54 minor, including 22 anastomotic leaks and 38 respiratory tract infections); there were 7 deaths. This was comparable to nationally published data. In the gastrectomy group, there were 9 complications (4 major and 5 minor) and 4 deaths. Again gastrectomy morbidity and mortality were higher than expected (although this could be a reflection of the low number of cases recorded.) Estimated blood loss and length of stay were higher than expected; R0 and lymph node yield were lower than predicted. Other variables were acceptable.

CUSUM allows continuous surveillance of performance of individual surgeons or units with early warning of quality or outcome deterioration. It is especially important in the early phases of a novel technique in monitoring the learning curve of the procedure, such as demonstrated in this thesis with minimally invasive gastro-oesophageal cancer surgery. Majority of the units evaluated in this thesis demonstrated improvements in their learning curves, however data sample sizes were small resulting in limitation of result interpretation. The two larger centres (Hull and

Exeter) did however demonstrate the beginnings of an apparent plateau in their learning curves at around 30 procedures.

With reference to the aims of a phase II surgical study:

- The procedure has been defined; although which approaches should be evaluated in a RCT needs further clarification (see chapters 1 and 8.)
- A trial question has been evaluated.
- Effective quality control measures have been undertaken
- Data has been collected, however more data is required (especially of gastrectomies) in order to accurately calculate end points and power calculations. (Although data thus far has enabled some basic analysis.)
- Participant learning curve has been evaluated, by means of CUSUM analysis
- Although no definite date for a RCT into minimally invasive gastro-oesophageal cancer surgery in the UK has been set, opinion regarding potential participation has been improving. However whether it will be the future gold standard has yet to be determined.

This approach, including quality control measures and addressing the trial question demonstrates improved evidence compared with case series, the most commonly published evidence of minimally invasive gastro-oesophageal cancer surgery present in the literature. In addition, utilizing the IDEAL recommendations, the approach described in this thesis (a phase 2 surgical study) represents stage 2a/b of surgical innovation stages, with the need for randomized controlled trials and long-term

studies still required. The initial hypothesis of this thesis that current methodology of this type of surgery is inadequate to enable comparison to conventional, open surgery is thus confirmed.

Subsequent to the establishment of the MIGOCS group and database, NICE (the National Institute of Clinical Excellence) has published overview statements on thoracoscopically assisted oesophagectomies and laparoscopic gastrectomies as part of its interventional procedures guidance (NICE 2006, 2008.) These both recommend submission of data to the MIGOCS registry. In addition AUGIS and ALS have sponsored meetings between interested surgeons on the topic of minimally invasive gastro-oesophageal cancer resections.

A consensus meeting sponsored by AUGIS was held in the Pelican Centre at Basingstoke in March 2008 proposing a classification system of minimally invasive oesophagectomies:

- Minimally Invasive Oesophagectomy (MIO) with cervical anastomosis
- MIO with intra-thoracic anastomosis
- Laparoscopically Assisted Oesophagectomy (LAO) with standard thoracotomy and intra-thoracic anastomosis
- LAO with mini-thoracotomy and intra-thoracic anastomosis
- LAO with thoracotomy and cervical anastomosis
- Thoracoscopically Assisted Oesophagectomy (TAO) with laparotomy and cervical anastomosis.

The meeting further suggested that the minimally invasive approach was an additional technique for oesophageal resection, which should only be offered to those fit enough for open surgery. It offered advice regarding patient selection, introducing MIO into clinical practice and recommended data entry for audit and learning curve analysis.

8.2.1 Thesis Strengths

This thesis reports the first multicentre report of minimally invasive gastro-oesophageal cancer resections in the UK (data collection being supported by AUGIS, ALS and NICE.) It includes detailed data collection on aspects of minimally invasive surgery: patient demographics; tumour staging and characteristics; intra-operative details; post-operative and oncological outcomes. During the latter stages of data collection, information was concurrently collated by the National Oesophago-Gastric Audit, which has since published its findings, but contains less detailed information specific to the minimally invasive approach.

The study reported in this thesis contained integral quality control measures, such as mandatory fields on the database and utilisation of a research fellow to visit centres involved and validate data entry.

The methodology utilised in this thesis involved analysis of learning curves and helping to establish consensus between participants. This helped provide feedback to clinicians on their own performance and anonymous comparison to other centres. This information has additionally been helped give an indication towards the number of procedures required for proctorship and to reach a plateau. (Data was presented at the consensus meeting for MIO, hosted by AUGIS in Basingstoke in 2008.)

8.2.2 Thesis Weaknesses

One of the biggest flaws to this thesis and study is the limited data collection and involvement of centres. This was a result of a number of difficulties, many of which have previously been mentioned, such as: politics between individuals and units; concerns regarding publication rights and utilisation of data collected; time limitations and the optimal time for data collation.

Selection bias has undoubtedly occurred during data collection. Patients undergoing this relatively new and still investigational technique are likely to have less co-morbidity; have smaller tumours and morphologically be better for this approach. In addition not all centres offered this approach to all comers, increasing the likelihood of bias.

The thesis and study has not concentrated on quality of life and long term follow up data collection which are important outcome measures in minimally invasive surgery (especially when comparing it to conventional open surgery.)

8.3 Improvements and Areas for Future Study

Further data collection, initially as a prospective case series as part of a phase II surgical trial, especially of gastrectomies needs to occur. MIG numbers were too low in this study to provide an accurate reflection of its current status and outcome within the UK in a multicentre setting (and which to date has not been published by any other group.) This data would then enable power calculations and end points to be made. In addition further evaluation of learning curves could be made (for gastrectomies as well as oesophagectomies.) A specific primary outcome that requires

measuring is 5-year survival. Other secondary endpoints would include morbidity, especially respiratory tract infection and anastomotic leak and oncological outcome, with particular reference to lymph node yield (and positivity,) circumferential margin involvement and tumour recurrence. These measures would thus allow comparison to open surgery.

Improvements

Evaluation of patient subgroups, for example by ASA grading or HGD versus T4 tumours would provide information on who might benefit most from minimally invasive approaches. It would require oncological evaluation of this type of surgery (especially if it were to be offered in preference to open surgery to those with potentially the best prognosis); conversely to offer it to those with a poor prognosis oncological adequacy is less of an issue than quality of life and return to normal function post surgery. Subgroup evaluation would also help determine which patients should be selected in the early stages of the learning curve, potentially reducing its steepness.

Further thesis and trial improvement could be made by extending data collection. Initially by linking up with the National Audit data collection to prevent duplication of data entry (this was considered but unfortunately not taken further;) and international data collection. Around thirty consultant surgeons involved in this type of surgery were contacted, some as part of the European Union Network of Excellence on gastric cancer, and approximately a half expressed an interest in taking part in an international multicentre randomised controlled trial. (Unfortunately this was not taken further by the student's supervisor.)

Establishing Consensus

The trial reported in this thesis aimed to help establish consensus between participants to help move towards a randomised controlled trial.

Regular group meetings, providing feedback on factors such as learning curve and data reports and to aid technique discussion were held. This included a meeting at Trinity College, Oxford where Delphi methodology was used to aid feedback on the problems associated with establishing a minimally invasive oesophagectomy service.

Centres involved in the trial were visited by the student to aid data entry and to encourage it (further entry and registration for the database was encouraged by presentations and attendance of meetings nationally and internationally.)

It was also intended for group publication of data after the first 100 cases, to help reassure publication concerns and provide some incentive for data collection to participants. Unfortunately despite multiple drafts, including trial participants, the final draft did not progress far beyond the supervisor's desk.

More active involvement with AUGIS and ALS would also have helped establish national consensus (beyond an initial meeting) as well as assist in proctorship issues (which in turn would have aided relationships between centres.)

Conclusion

Using the IDEAL framework, minimally invasive gastrectomy and oesophagectomy utilising a phase 2 surgical trial approach has been studied at stage 2a and 2b. A randomised controlled trial is now needed initially in a UK setting of both MIO and

MIG (IDEAL stage 3.) This would need to compare conventional practice i.e. open surgery with minimally invasive surgery (utilising at least one approach in the case of oesophagectomies); thereby providing sufficient evidence levels for optimal practice.

REFERENCES

Adachi Y, Shiraishi N., Suematsu T. *et al.* Most important lymph node information in gastric cancer: multivariate prognostic study. *Ann Surg Oncol.* 2000; **7**: 503-507

Adachi Y, Shiraishi N., Shiromizu A. *et al.* Laparoscopy-Assisted Billroth I Gastrectomy Compared with Conventional Open Gastrectomy. *Arch Surg.* 2000; **135**: 806-810.

Adachi Y, Shiraishi N, Ikebe K. *et al.* Evaluation of the cost for laparoscopic-assisted Billroth I gastrectomy. *Surg Endosc.* 2001; **15**(9): 932-936

Adams R, Morgan M, Mukherjee S. *et al.* A prospective comparison of multidisciplinary treatment of oesophageal cancer with curative intent in a UK cancer network. *EJSO.* 2007; **33**(3): 307-313

Akiyama H., Tsurumaru M., Udagawa H. *et al.* Radical lymphnode dissection for cancer of the thoracic esophagus. *Ann Surg.* 1994; **220**: 364-373

Al-Sarira A.A, David G, Willmott S. *et al.* Oesophagectomy practice and outcomes in England. *BJS.* 2007; **94**: 585-591

Al-Sarraf M, Martz K, Herskovic A. *et al.* Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with oesophageal cancer: an Intergroup study. *J Clin Oncol.* 1997; **15**: 277-284

Allum W.H, Griffin S.M, Watson A. *et al.* on behalf of AUGIS, BSG and BASO. Guidelines for the management of oesophageal and gastric cancer. *Gut.* 2002; **50**(v): 1-23

Allum W.H. for the European Union Network of Excellence (EUNE) for Gastric Cancer Steering Group. Gastric Cancer in Europe. *BJS.* 2008; **95**: 406-408

Altorki N, Kent M, Ferrara C. *et al.* Three field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. *Ann Surg.* 2002; **236**: 177-183

Anegg U., Lindenmann J., Maier A. *et al.* Influence of route of gastric transposition on oxygen supply at cervical oesophagogastric anastamosis. *BJS.* 2008; **95**: 344-349

Arnott S.J, Duncan W, Gignoux M. *et al.* Preoperative treatment for esophageal carcinoma. *Cochrane Database Syst Rev.* 2005; **19**(4): CD001799

Asao T, Hosouchi Y., Nakabayashi T. *et al.* Laparoscopically assisted total or distal gastrectomy with lymph node dissection for early gastric cancer. *BJS.* 2001; **88**: 128-132.

The Association of Upper Gastrointestinal Surgeons (AUGIS) and the Association of Laparoscopic Surgeons of Great Britain and Ireland ALS.) A Consensus View and Recommendations on the Development and Practice of Minimally Invasive Oesophagectomy. Hardwick R. 2008. http://www.augis.org

Avery K, Hughes R, McNair A. *et al.* Health-related quality of life and survival in the 2 years after surgery for gastric cancer. *EJSO.* 2010; **36**(2): 148-154

Avital S, Zundal N., Szomstein S. *et al.* Laparoscopic transhiatal esophagectomy for esophageal cancer. *Am J Surg.* 2005; **190**: 69-74.

Azagra J.S, Goergen M, De Simone P. *et al.* Minimally invasive surgery for gastric cancer. *Surg Endosc.* 1999; **13**:351-357

Bailey S.H, Bull D.A, Harpole D.H. *et al.* Outcomes after esophagectomy: a ten year prospective cohort. *Ann Thorac Surg.* 2003; **75**: 210-216

Bamias A, Hill M.E, Cunningham D. *et al.* Epirubicin, cisplatin and protracted venous infusion of 5-flurouracil for esophagogastric adenocarcinoma. *Cancer.* 1996; **77**: 1978-1985

Bampton P.A, Schloithe A, Bull J. *et al.* Improving surveillance for Barrett's oesophagus. *BMJ.* 2005; **332**: 1390-1393

Bann S, Moorthy K., Shaul T. *et al.* Laparoscopic Transhiatal Surgery of the Esophagus. *J Soc Laparoendosc Surg.* 2005; **9**: 376-381.

Barr H, Maynard N.D. Controversial topics in surgery: high-grade dysplasia in Barrett's oesophagus. *Ann R Coll Surg Eng.* 2006; **89**: 586-590

Barr H, Shepherd N.A. The management of dysplasia. In: *BSG Guidelines in Gastroenterology.* 2005: 32-36

Bartels H, Thorban S, Siewert J.R. Anterior versus posterior reconstruction after transhiatal oesophagectomy: a randomized controlled trial. *BJS.* 1993; **80**(9): 1141-1144

Bedenne L, Michel P, Bouche O. *et al.* Chemoradiation Followed by Surgery Compared with Chemoradation Alone in Squamous Cancer of the esophagus. FFCD 9102. *J Clin Oncol.* 2007; **25**: 1160-1168

Beiles C.B., Morton A.P. Cumulative sum control charts for assessing performance in arterial surgery. *ANZ J Surg.* 2004; **74**: 146-151

Bernabe K.Q, Bolton J. S., Richardson W.S. Laparoscopic hand-assisted vs open transhiatal esophagectomy - a case control study. *Surgical Endoscopy.* 2005; **19**: 334-337.

Berrisford R.G., Wajed S.A., Sanders D. *et al.* Short-term outcomes following totally Invasive oesophagectomy. *BJS.* 2008; **95**: 602-610

Berrisford R.S., Veeramootoo D., Parameswaran R. *et al.* Laparoscopic ischaemic conditioning of the stomach may reduce gastric-conduit morbidity following minimally invasive oesophagectomy. *Eur J Cardiothorac Surg.* 2009; **36**:888-893

Biere S.S.A.Y.E, Maas K.W, Bonavina L. *et al.* Traditional invasive vs minimally invasive esophagectomy: a multi-center, randomized trial (TIME-trial.) *BMC Surgery.* 2011; **11**:2

Birkmeyer J.D., Dimick J.B., Birkmeyer N.J. Measuring the quality of surgical care: structure, process, or outcomes?n *J Am Coll Surg.* 2004; **198**: 626-632

Birkmeyer J.D., Stukel T.P., Siewers A.E. *et al.* Surgeon volume and operative mortality in the United States. *NEJM.* 2003; **349**(22): 2117-2127

Blazeby J.M, Blencowe N.S, Titcomb D.R. *et al.* Demonstration of the IDEAL recommendation for evaluating and reporting surgical innovation in minimally invasive oesophagectomy. *BJS.* 2011; **98** (4): 544-551

Blazeby J.M, Farndon J.R, Donovan J. *et al.* A prospective longitudinal study examining the quality of life of patients with esophageal carcinoma. *Cancer.* 2000; **88**(8): 1781-1787

Bleiberg H, Jacob J.H, Bedenne L. *et al.* A randomized phase II trial of 5-flurouracil and cisplatin (DDP) versus DDP alone in advanced esophageal cancer. *Proc Soc Clin Oncol.* 1991; m**10**: A447

Blot W.J., Devesa S.S., Kneller R.W. *et al.* Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA.* 1991; **265**: 1287-1289

Bollschweiler E, Schroder W, Holscher A.H. *et al.* Preoperative risk analysis in patients with adenocarcinomas or squamous cell carcinoma of the oesophagus. *BJS.* 2000; **87**: 1106-1110

Bonavina L, Bona D., Binyom P.R. *et al.* A Laparoscopy-Assisted Surgical Approach to Esophageal Carcinoma. *Journal of Surgical Research.* 2004; **117**: 52-57.

Bonenkamp JJ, Hermans J, Sasako M, Van de Velde CJH. Extended lymph-node dissection for gastric cancer. *NEJM.* 1999.**340**:908-914

Bonenkamp JJ, Hermans J, Sasako M, Van de Velde CJH. Tumour load and surgical palliation in gastric cancer. *Hepatogastroenterology.* 2001; **48**(41): 1219-1221

Bonenkamp J.J., Songun I., Hermans J. *et al.* Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet.* 1995; **345**: 745-748

Bormann R. Gaschwulste. Des Magens and Duodenums. In: Henke F, Lubarsch O, eds. *Handbuche der Speziellen Pathologischen Anatomie and Histologie.* Berlin: Springer-Verlag. 1926: 865

Boutron I., Estellat C., Ravaud P. A review of blinding in randomized controlled trials found inconsistent and questionable. *J Clin Epidemiol.* 2005; **58**: 1220-1226

Bozzetti F., Braga M., Gianotti L. *et al.* Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomised multicentre trial. *Lancet.* 2001; **358**(9292): 1487-1492

Braga M., Gianotti L., Nespoli *et al.* Nutritional approach in malnourished surgical patients: a prospective randomized study. *Arch Surg.* 2002; **137**(2): 1740-1780

Braga M., Gianotti L, Vignali A. *et al.* Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet. *Crit Care Med.* 1998; **26**(1): 24-30

Braghetto I, Csendes. A., Cardemil G. *et al.* Open transthoracic or transhiatal esophagetomy versus minimally invasive esophagectomy in terms of morbidity, mortality and survival. *Surg Endosc.* 2006 **20**: 1681-1686.

British Heart Foundation.International statistics. www.heartstats.org

Cancer Research UK: http:info.cancerresearchuk.org/cancerstats

Carboni F, Lepiane. P, Santoro R. *et al.* Laparoscopic surgery for gastric cancer: preliminary experience. *Gastric Cancer.* 2005; **8**: 75-77.

Centre for Evidenced-based Medicine (Oxford) http:www.cebm.net

Cerfolio R.J, Bryant A.S, Bass C.S *et al.* Fast tracking after Ivor Lewis esophagogastrectomy. *Chest.* 2004.; **126** (4): 1187-1194

Chandrashekar M.V, Irving M, Wayman J. *et al.* Immediate extubation and epidural analgesia allow safe management in a high-dependency unit after two-stage oesophagectomy. Results of eight years of experience in a specialized upper gastrointestinal unit in a district general hospital. *Br J Anaesth.* 2003; **90**(4): 474-479

Chow W.H., Blot W.J., Vaughan T.L. *et al.* Body mass index and risk of adenocarcinoma of the esophagus and gastric cardia. *J Natl Cancer Inst.* 1998; **90**(2): 150-155

Chu K.M, Law S.Y, Fok M. *et al.* A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma. *Am J Surg.* 1997; **174**(3): 229-235

ChuaY.J. and Cunningham D. The UK NRCI MAGIC Trial of Perioperative Chemotherapy in Resectable Gastric Cancer: Implications for Clinical Practice. *Ann Surg Oncol.* 2007; **14**(10): 2687-2690

Clarke G.W.B. Endoscopic and surgical treatment of early gastric cancer. In: Griffin S.M, Raimes S.A, editors. *Upper gastrointestinal surgery: a companion to specialist surgical practice.* 4th edition. London: W.B. Saunders. 2010: p157-170

Clinical Resource and Audit Group (CRAG). Scottish Audit of Gastric and Oesophageal Cancer: Report 1997-2000. Edinburgh: CRAG; 2002. [Cited 6 August 2009]. Available from url: http://www.show.scot.nhs.uk/org

Colditz G.A, Miller J.N, Mosteller F. How study design affects outcome in comparisons of therapy. I: Medical. II: Surgical. *Statistics in Medicine.* 1989; **8**: 441-466

Collard J-M, Otte J-B, Fiasse R *et al.* Skeletonizing en bloc esophagectomy for cancer. *Ann Surg.* 2001; **234**: 25-32

Collins G, Johnson E., Kroshus T. *et al.* Experience with minimally invasive esophagectomy. *Surgical Endoscopy.* 2006; **20**: 298-301.

Cook J.A., Ramsay C.R., Fayers P. Statistical evaluation of learning curve effects in surgical trials. *Clin Trials.* 2004; **1**: 427-427

Cook J.A., Ramsay C.R., Fayers P. Using the literature to qualitify the learning curve. *Int J Technol Assess Health Care.* 2007; **23**: 255-260

Cook J.A. The challenges faced in the design, conduct and analysis of surgical randomised controlled trials. *Trials.* 2009; **10**: 9

Correa P. A human model of gastric carcinogenesis. *Cancer Res.* 1988; **80**: 3554-3560

Correa P. Human gastric carcinogenesis: a multistep and multifactorial process- 1st American society award lecture on cancer epidemiology and prevention. *Cancer Res.* 1992; **52**: 6735-6740

Courrech Staal E.F, Aleman B.F, Boot H. *et al.* Systematic review of the benefits and risks of neoadjuvant chemoradiation for oesophageal cancer. *BJS.* 2010; **97**(10): 1482-1496

Crew K.D., Neugut A.I. Epidemiology of gastric cancer. *World J Gastroenterol.* 2006; **12**:354-362

Crofts T.J. Ivor-Lewis oesophagectomy for middle and lower third oesophageal lesions- how we do it. *J R Coll Surg Edinb.* 2000; **45**: 296-303

Cummins J, McCulloch P. ASCOT: a comprehensive clinical database for gastro-oesophageal cancer surgery. *ESJO.* 2001; **27**: 709-713

Cunningham D, Allum W.H, Stenning S.P. *et al.* Outcome of perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *NEJM;* 2006:**355**: 11-20

Cunningham D, Allum W, Weeden S. Perioperative chemotherapy in operable gastric and lower oesophageal cancer: a randomised, controlled trial of the UK NCRI Upper

GI Clinical Studies Group (the MAGIC trial, ISRCTN 93793971). *Eur J Ca Suppl* 2003: **1**: S18

Cuschieri A, Shimi S, Banting S. Endoscopic esophagectomy through a right thoracoscopic approach. *J R Coll Surg Edinb.* 1992;**37**:7-11

Cuschieri A., Weeden S., Fielding J. *et al.* Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer.* 1999; **79**: 1522-1530

Daly J.M, Fry W.A, Little A.G. *et al.* Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. *J Am Coll Surg.* 2000; **190**: 562-572

Das D, Ishaq S, Harrison R. *et al.* Management of Barrett's oesophagus in the UK: overtreated, and underbiopsied but improved by the introduction of a national randomised trial. *Am J Gastroenterol.* 2008; **103**(5): 1079-1089

Decker G, Coosemans W, de Leyn P. *et al.* Minimally invasive esophagectomy for cancer. *Eur J Cardio-thoracic Surgery.* 2009; **35**: 13-21

Del Genio A, Rossitti. G, Napolitano V. *et al* Laparoscopic esophagectomy in the palliative treatment of advanced esophageal cancer after radiochemotherapy. *Surgical Endoscopy.* 2004; **18**: 1789-1794.

Deng J., Liang H., Sun D. *et al.* The Prognostic Analysis of Lymph Node Positive Gastric Cancer Patients following Curative Resection. *J Surg Res.* 2010, **161** (1): 47-53

DePaula A.L, Hashiba K, Ferreira E.A. *et al.* Laparoscopic transhiatal esophagectomy with esophagogastroplasty. *Surg Laparosc Endosc.* 1995; **5** :1-5

Department of Health. Guidance on commissioning cancer services. Improving outcomes in upper gastrointestinal cancers. The annual. London: NHS Executive. 2001.

Devereaux P.J., Bhandari M., Clarke M. *et al.* Need for expertise based randomised controlled trials. *BMJ.* 2005; **330**: 88

Devesa S.S, Blot W.J, Fraumeni J.F Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer.* 1998; **83**: 2049-2053

Dexter S.P.L, Martin. I. G., McMahon M.J. Radical thoracoscopic esophagectomy for cancer. *Surg Endosc.* 1996; **10**: 147-151.

Dikken J.L, Jansen E.P.M, Cats A. *et al.* Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. *J Clin Oncol.* 2010; **28**(14): 2430-2436

Dimick J.B, Diener-West M, Lipsett P.A. Negative results of randomized clinical trials published in the surgical literature: equivalency or error? *Arch Surg.* 2001; **136**: 796-800

Dinis Riberio M,Yamaki G,Miki K *et al.* Meta-analysis on the validity of pepsinogen test for gastric carcinoma, dysplasia or chronic atrophic gastritis screening. *J Med Screen.* 2004; **11**:141-147

Djarv T., Lagergren J., Blazeby J.M. *et al.* Long term health-related quality of life following survival for oesophageal cancer. *BJS.* 2008; **95**: 1121-1126

Doglietto G, Pacelli F, Caprino P *et al.* Surgery: independent prognostic factor in curable and far advanced gastric cancer. *World J Surg.* 2000; **24**: 459-464

Dolan K, Sutton R, Walker S.J, *et al.* New classification of oesophageal and gastric tumours derived from changing patterns in epidemiology. *Br J Cancer.* 1999; **80**: 834-42

Dulai G.S., Guha S., Kahn K.L. *et al.* Preoperative prevalence of Barrett's oesophagus and esophageal adenocarcinoma: A systematic review. *Gastroenterology.* 2002; **122**(1): 26-33

Dulucq J.-L, Wintniger. P., Stabilini C. *et al.* Laparoscopic and open gastric resections for malignant lesions. A prospective, comparative study. *Surg Endosc.* 2005; **19**: 933-938.

Dresner S.M, Griffin S.M. Pattern of recurrence following radical oesophagectomy with two-field lymphadenectomy. *BJS.* 2000; **87**(10): 1426-1433

Earlam R, Cunha-Melo J.R. Oesophageal Squamous cell carcinoma. II. A critical review of radiotherapy. *BJS* 1980; **67**: 457-461

Egger M, Zellweger-Zahner T, Schneider M. *et al.* Language bias in randomised controlled trials published in English and German. *The Lancet.* 1997: **350**: 326-329

Egger M, Davey Smith G. Meta-analysis bias in location and selection of studies. BMJ. 1998; 316(7124): 61-66

Ell C., May A., Gossner L. *et al.* Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. *Gastroenterol.* 2000; **118**(4): 670-677

Eloubeidi M.A., Desmond R., Argoedas M.R. *et al.* Prognositic Factors for the Survival of patients with esophageal carcinoma in the U.S.: the importance of tumour length and lymph node status. *Cancer.* 2002; **51**: 1434-1443

Engel L.S., Chow W.H., Vaughan T.L. *et al.* Population attributable risks of esophageal and gastric cancers. *J Natl Cancer Inst.* 2003; **95**(18); 1404-1413

Enzinger P.C, Kulke M.H, Clarke J.W. *et al.* Phase II trial of CPT-11 in previously untreated patients with advanced adenocarcinoma of the esophagus and stomach. *Prog Proc Am Soc Oncol.* 2000; 19: 315a, abstract.

Enzinger P.C, Mayer R.J. Medical Progress: Esophageal Cancer. *EJM.* 2003; **349**: 2241-2252

Ergina P.L., Cook J.A., Blazeby J.M. *et al.* for the Balliol Collaboration. Surgical Innovation and Evaluation 2 – Challenges in evaluating surgical innovation. *Lancet.* 2009; **374**: 1097-1104

Eskiciogiu C, Forbes S.S, Aarts M-A. et al. Enhanced Recovery after Surgery (ERAS) Programs for Patients Having Colorectal Surgery: A Meta-Analysis of Randomized Trials. J Gastrointest Surg. 2009; 13: 2321-2329

Eslick G., Lim L., Byles J. *et al.* Association of *Helicobacter Pylori* infection with gastric carcinoma: a meta-analysis. *Am J Gastroenterol.* 1999: **94**: 2573-2579

ESMO (European Society for Medical Oncology) Minimum Clinical Recommendations for diagnosis, treatment and follow-up of gastric cancer. *Ann Oncol.* 2005: **16**(1): i22-i23

Esteban Varela J, Hiyashi. M., Nguyen T. *et al.* Comparison of laparoscopic and open gastrectomy for gastric cancer. *Am J Surg.* 2006; **192**: 837-842.

The EUROGAST Study Group. An international association between *Helicobacter pylori* infection and gastric cancer. *Lancet.* 1993; **341**: 1359-1362

Fein R, Kelsen D.P, Geller N. *et al.* Adenocarcinoma of the esophagus and gastroesophageal junction: prognostic factors and results of therapy. *Cancer.* 1985; **56**: 2512-2518

Fenogilo-Prieser C, Cameiro F, Correa P *et al.* Gastric carcinoma. In: Hamilton S, Aaltonin L, eds. *Pathology and Genetics. Tumours of the Digestive System*, vol 1. Lyon, France: Lyon Press; 2000: 37- 52

Fiorica F, Di Bona D, Schepis F. *et al.* Preoprative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. *Gut.* 2004; **53**:925-930

Flora E.D, Wilson T.G, Martin I.J. *et al.* A review of natural orifice transluminal endoscopic surgery (NOTES) for intra-abdominal surgery: experimental models, techniques, and applicability to the clinical setting. *Ann Surg.* 2008; **247**: 583-602

Fok M, Sham J.S, Choy D. *et al.* Postoperative radiotherapy for carcinoma of the esophagus: a prospective randomized controlled study. *Surgery.* 1993; **113**: 138-147

Forman D., Newell D.G., Fullerton F. *et al.* Association between infection and *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. *BMJ.* 1991; **302**: 1302-1305

Fujita H., Sueyoshi S., Yamana H. *et al.* Optimum treatment strategy for superficial esophageal cancer: endoscopic mucosal resection versus radical esophagectomy. *World J Surg.* 2001; **32**(10): 424-431

Fujiwara M., Kodera Y., Miura S. *et al.* Laparoscopy-assisted distal gastrectomy with systemic lymph node dissection: a phase II study following the learning curve. *J Surg Oncol.* 2005; **91**: 26-32

GASTRIC (Global Advanced/Adjuvant Stomach Tumour Research Internal Collaboration) Group. Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer. *JAMA.* 2010; **303** (17): 1729-1237

Gawad K.A, Hosch S.B, Bumann D. *et al.* How important is the route of reconstruction after esophagectomy: a prospective randomized study. *Am J Gastroenterol.* 1999; **94**(6): 1490-1496

Geh J.L, Bond S.J, Bentzen S.M. *et al.* Systematic overview of preoperative (neoadjuvant) chemoradiotherapy trials in oesophageal cancer: evidence of a radiation and chemotherapy dose response. *Radiother Oncol.* 2006; **78**: 236-244

Gemmill E.H, McCulloch P. Minimally Invasive Resection for Gastro-oesophageal Cancer: A Systematic Review. *BJS.* 2007. **94**:1461-1467

Gianotti L., Braga M., Nespoli L. *et al.* A randomised controlled trial of preoperative oral supplementation with a specialised diet in patients with gastrointestinal cancer. *Gastroenterol.* 2002; **122**(7): 1763-1770

Gillies R, Tawil A, Barr H. *et al.* Barrett's Oesophagus. In: Griffin S.M, Raimes S.A, editors. *Upper gastrointestinal surgery: a companion to specialist surgical practice.* 4th edition. London: W.B. Saunders. 2010: p 293-306

Glimelius B, Ekstrom K, Hoffman K. *et al.* Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol.* 1997; **8**: 163-168

Godris-Petit G, Munoz-Bongrand. N., Honigman I. *et al.* Minimally Invasive Esophagectomy for Cancer: Prospective Evaluation of Laparoscopic Gastric Mobilization. *World Journal of Surgery.* 2006; **30**: 1434-1440.

Goldminc M, Maddern G, Le Prise E. *et al.* Oesophagectomy by a transhiatal approach or thoracotomy: a prospective randomized trial. *BJS.* 1993; **80**(3): 367-370

Gonzalez C.A., Pera G., Agudo A. *et al.* Smoking and the risk of gastric cancer in the European prospective investigation into cancer and nutrition (EPIC.) *Int J Cancer.* 2003; **107**: 625-634

Gore R. Gastrointestinal cancer. *Radiol Clin North Am.* 1997; **35**:295-310

Gouvas N., Tan E., Windsor A. *et al.* Fast-track vs standard care in colorectal surgery: a meta-analysis update. *Int J Colorectal Dis.* 2009; **24**(10): 1119-1131

Graham A.J, Shrive F.M, Ghali W.A. *et al.* Defining the Optimal Treatment of Locally Advanced Esophageal Cancer: A Systematic Review and Decision Analysis. *Ann Thorac Surg.* 2007; **83**: 1257-1264

Grancharov T.P, Kehlet H. Laparoscopic gastric surgery in an enhanced recovery programme. *BJS.* 2010; **97**: 1547-1551

Green F.L, Page D.L, Fleming I.D. *et al.* AJCC Cancer Staging Manual. 6th edition. New York: Springer. 2002.

Greer S.E, Crellin A.M, Glynne-Jones R. Preoperative (neoadjuvant) chemoradiotherapy in oesophageal cancer. *BJS.* 2001; **88**(3): 338- 356

Greer S.E, Goodney P.P, Sutton J.E. *et al.* Neoadjuvant chemoradiotherapy for esophageal carcinoma: a meta-analysis. *Surgery.* 2005; **137**(2): 172-177

Griffin S.M. Surgery for cancer of the oesophagus. In: Griffin S.M, Raimes S.A, editors. *Upper gastrointestinal surgery: a companion to specialist surgical practice.* 2nd edition. London: W.B. Saunders. 2001: p121-153

Griffin S.M. Surgery for cancer of the oesophagus. In: Griffin S.M, Raimes S.A, editors. *Upper gastrointestinal surgery: a companion to specialist surgical practice.* 4th edition. London: W.B. Saunders. 2010: p 91-113

Griffin S.M, Shaw I.H, Dresner S.M. Early complications after Ivor-Lewis subtotal esophagectomy with two-field Lymphadenectomy. Risk factors and management. *J Am Coll Surg.* 2002; **194**: 287-197

Griffiths E.A., Pritchard S.A., Mapstone W.P. *et al.* Emerging aspects of oesophageal and gastro-oesophageal junction cancer histopathology- an update for the surgical oncologist. *World J Surg Oncol.* 2006; **4**: 82

Gruen R.L, Pitt V, Green S. *et al.* The effect of provider case volume on cancer mortality: systematic review and meta-analysis. *CA Cancer J Clin.* 2009; **59**(3): 192-211

Hagiwara A, Takahashi T, Kojima O. *et al.* Prophylaxis with carbon-adsorbed mitomycin against peritoneal recurrence of gastric cancer. *Lancet.* 1992; **339**(8794): 629-631

Halm E.A, Lee C, Chassin M.R. Is volume related to outcome in health care? A systematic review and methodological critique of the literature. *Ann Intern Med.* 2002; **137** (6): 511-520

Harrison R, Perry I, Haddadin W. *et al.* Detection of intestinal metaplasia in Barrett's esophagus: an observational comparator study suggests the need for minimum of eight biopsies. *Am J Gastroenterol.* 2007; **102**: 1-8

Hartgrink H, Putter H, Kranenbarg E *et al.* Value of palliative resection in gastric cancer. *BJS.* 2002; **89**: 1438-1443

Haung X.-E., Tajima K., Hamajima N. *et al.* Effects of dietary, drinking and smoking habits on the prognosis of gastric cancer. *Nutr Cancer.* 2000; **38**: 37-52

Hayashi H, Ochiai T, Shimada H. *et al.* Prospective randomized study of open vs laparoscopy-assisted distal gastrectomy with extraperigastric lymph node dissection for early gastric cancer. *Surg Endosc.* 2005; **19**: 1172-1176

Higgins J.P.T., Altman D.G. Asssessing the risk of bias in included studies. In: Higgins J.P.T., Green S., eds. Cochrane handbook for systemic reviews of interventions version 5.0.1 (updated September 2008). Chichester: John Wiley & Sons, 2008.

Hiki N, Shimoyama. S, Yamaguchi H. *et al.* Laparoscopy-Assisted Pylorus-Preserving Gastrectomy with Quality Controlled Lymph Node Dissection in Gastric Cancer Operation. *J Am Coll Surg.*2006; **203**(2): 162-169.

Hirota T, Ming S.C, Itabashi M. Pathology of early gastric cancer. In Nishi M, Ichikarwa H, Nakajima T. *et al.* eds. *Gastric Cancer.* Tokyo: Springer-Verlag. 1993: 66-86

Hoelscher A., Schneider P.M., Gutschow C. *et al.* Laparoscopic Ischemic Conditioning of the Stomach for Esophageal Replacement. *Ann Surg.* 2007; **245**: 241-246

Holsher A.H, Dittler H.J, Siewert J.R. Staging of squamous oesophageal cancer: accuracy and value. *World J Surg.* 1994: **18**; 312-320

Homs M.Y, Steyerberg E.W, Eijkenboom W.M. *et al.* Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomized trial. *Lancet.* 2004: **364**: 1487-1504

Hori S, Ochiai T, Gunji Y. *et al.* A prospective randomized trial of hand-sutured versus mechanically stapled anastamosis for gastroduodenostomy after distal gastrectomy. *Gastric Cancer.* 2004; **7**(1): 24-30

Horiuchi T, Shimamatsuya. T., Chiba Y. Laparoscopically Assisted pylorus-preserving gastrectomy. *Surg Endosc.* 2001; **15**: 325-328.

Horton R. Surgical research or comic opera: questions, but few answers. *Lancet.* 1996; **347**: 984-985

Huang J.Q., Sridhar S., Chen Y. *et al.* Meta-analysis of the relationship between Helicobacter pylori seropositivity and gastric cancer. *Gastroenterolgy.* 1998; **114**(6): 1169-1179

Huang X-E, Tajima K, Hamajima N *et al.* Effects of dietary, drinking and smoking habits on the progress of gastric cancer. *Nutr Cancer.* 2000; **38**: 30-36

Hulscher J.B, van Sandick J.W, de Boer A.C. *et al.* Extended transthoracic resection compared with limited transhiatal resection for adenocarcinomas of the oesophagus. *NEJM.* 2002; **347**(21): 1662-1669

Hulscher J.B, Tijssen J.G, Obertop H. *et al.* Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. *Ann Thorac Surg.* 2001; **72**(1): 306-313

Hundahl S.A., Phillips J.L., Menck H.R. The National Cancer Data Base report on poor survival of US gastric carcinoma patients treated with gastrectomy. *Cancer.* 2000; **88**: 921-932

Hundahl S.A, Macdonald J.S, Beneditti J. *et al.* for the Southwest Oncology Group and the Gastric Intergroup. Surgical treatment variation in a prospective randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. *Ann Surg Oncol.* 2002; **9**(3): 278-286

Huscher C.G, Mingoli A, Sgarzini G. *et al.* Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomised prospective trial. *Ann Surg.* 2005; **241**(2): 232-237

Hyung W.J, Song C, Cheong J.H. *et al.* Factors influencing operation time of laparoscopy- assisted subtotal gastrectomy: Analysis of consecutive 100 initial cases *ESJO.* 2007; **33**: 314-319

Ilson D.H, Forastiere A, Arquette M. *et al.* A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. *Cancer J.* 2000; **6**: 316-323

International Agency on Research on Cancer. Schistosomes, Liver Flukes and *Helicobacter pylori.* IARC monographs on the evaluation of carcinogenic risks to humans, vol 61. 1994. Lyon: *Internal Agency for Research on Cancer.*

Irvani S, Hashemi M.R, Moghadam K.G. et al. Accuracy of serum pepsinogens I and II, gastric-17 and anti-helicobacter pylori antibodies in histological diagnosis of atrophic gastritis. Minerva Gastroenterologica e Dietologica. 2010; 56(1): 13-17

Jacobi C.A, Zieren H.U, Muller J.M. *et al.* Surgical therapy of esophageal carcinoma: the influence of surgical approach and esophageal resection on cardiopulmonary function. *Eur J Cardiothorac Surg.* 1997; **11**(1): 32-37

Jadad A.R, Moore R.A, Carroll D. *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clin Trials.* 1996; **17**: 1-12

Jamieson G.G, Mathew G, Ludemann R. *et al.* Postoperative mortality following oesophagectomy and problems in reporting its rate. *BJS.* 2004; **91** (8): 943-947

Jamieson G.G., Thompson S.K. Detection of lymph node metastases in oesophageal cancer. *BJS.* 2009; **96**: 21-25

Jankowski J, Hawk E. A methodological analysis of chemoprevention in the Gastrointestinal tract. *Nature Clin Pract Gastro.* 2006; **3**: 101-111

Jankowski J, Moayyedi P. Aspirin as chemoprevention for Barrett's esophagus: a large RCT underway in the UK. *J Natl Cancer Inst.* 2004; **96**: 885-887

Jankowski J.A, Wright N.A, Meltzer S.J. *et al.* Molecular Evolution of the Metaplasia-Dysplasia-Adenocarcinoma Sequence in the esophagus. *Am J Pathol.* 1999; **154**: 965-973

Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma. 2nd English edition.*Gastric Cancer.* 1998; **1**: 10-24

Jeurnink S.M, van Eijck C.H, Steyerberg E.W. *et al.* Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. *BMC Gastroenterol.* 2007; **7**: 18

Jin S-H, Kim D-Y, Kim H *et al.* Multidimensional learning curve in laparoscopy-assisted gastrectomy for early gastric cancer. *Surg Endosc.* 2007; **21**: 28-33

Jobe B.A, Kim. C. Y., Minjarez R.C. *et al.* Simplifying Minimally Invasive Transhiatal Esophagectomy With the Inversion Approach. Lessons Learnt From the First 20 Cases. *Arch Surg.* 2006; **141**: 857-866.

Jochem V.J., Fuerst P.A., Fromkes J.J. Familial Barrett's oesophagus associated with adenocarcinoma. *Gastroenterology.* 1992; **102**: 1400-1402

Juni P, Holenstein F, Sterne J, *et al.* Direction and impact of language bias in meta-analyses of controlled trials: empirical study. *International Journal of Epidemiology.* 2002; **31**: 115- 123

Kattan M.W, Karpeh M.S, Mazumdar M. *et al.* Postoperative nomogram for disease-specific survival after R0 resection for gastric carcinoma. *J Clin Oncol.* 2003; **21**(10): 3647-3650

Kehlet H. Future perspectives and research initiatives in fast-track surgery. *Langenbecks Arch Surg.* 2006; **391**: 495-498

Kehlet H, Williamson R, Buchler M.W. *et al.* A survey of perceptions and attitudes among European surgeons towards the clinical impact and management of postoperative ileus. *Colorectal Dis.* 2005; **7**(3): 245-250

Kelley J.R, Duggan J.M. Gastric cancer epidemiology and risk factors. *J Clin Epidem.* 2003; **56**: 1-9

Kelsen D.P, Ginsberg R, Pajak T.F. *et al.* Chemotherapy followed by surgery compared with surgery alone for esophageal cancer. *NEJM.* 1998; **339**: 1979-1984

Kelsen D.P, Winter K.A, Gunderson L. *et al.* Long-Term Results of RTOG Trial 8911 (USA Intergroup 113): A Random Assignment trial Comparison of Chemotherapy Followed by Surgery Compared With Surgery Alone for Esophageal cancer. *J. Clin. Oncol.* 2007; **24**:3719-3725

Kikuchi S, Nemoto Y, Natsuya K. *et al.* Which patients with advanced, proximal gastric cancer benefit from complete clearance of spleno-pancreatic lymph nodes. *Anticancer Res.* 2002; **22**: 3513-3517

Kileen S.D, O'Sullivan M.J, Coffey J.C. *et al.* Provider volume and outcomes for oncological procedures. *B.J.S.* 2005; **92**: 389-92

Kim M-C, Choi. H.-J., Jung G-J. *et al.* Techniques and complications of laparoscopy-assisted distal gastrectomy (LADG) for gastric cancer. *European Journal of Surgical Oncology.*2007; **33(6)**:700-705.

Kim M-C, Jung G-J, Kim H-H. Learning curve of laparoscopic-assisted distal gastrectomy with systematic lymphadenectomy for early gastric cancer. *World J Gastroenterol.* 2005; **11**(47): 7508-7511

Kim Y.W, Bae. J. M., Lee J.H. *et al* .The role of hand-assisted laparoscopic distal gastrectomy for distal gastric cancer. *Surg Endosc.* 2005; **19**(11): 29-33.

Kim Y.W, Baik Y.H, Yun Y.H. *et al.* Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial. *Ann Surg.* 2008; **248**(5): 721-727

Kitamura K, Nishida S, Ichikawa D. *et al.* No survival benefit from combined pancreaticosplenectomy and total gastrectomy for gastric cancer. *BJS.* 1999; **86**: 119-122

Kitano S, Shiraishi. N, Uyama I. *et al* and the Japanese Laparoscopic Surgery Study group. A Multicentre Study on Oncologic Outcome of Laparoscopic Gastrectomy for Early Cancer in Japan. *Ann Surg.* 2007; **245**(1): 68-72.

Kodera Y, Yamamura Y, Sasako M. *et al.* Lack of benefit from compbined pancreaticosplenectomy in D2 resection for proximal-third gastric carcinoma. *World J Surg.* 1997; **21**: 622-627

Kojima K, Yamada H, Inokuchi M. *et al.* A comparison of Roux-en-Y and Bilroth-1 reconstruction after laparoscopic-assistedd distal gastrectomy. *Ann Surg.* 2008; **247**: 962-967

Krasna M.J, Flowe J.L, Atta S. *et al.* Combined thoracoscopic/laparoscopic staging of esophageal cancer. *J Thorac Cardiovasc Surg.* 1996; **111**: 800-806

Lagarde S.M., Ten Kate F.J.W., Reitsma J.B. *et al.* Prognostic factors in adenocarcinoma of the esophagus and gastroesophageal junction. *J Clin Oncol.* 2006; **26**: 4347-4353

Largarde S.M, Maris A.K, de Castro S.M. *et al.* Evalluation of O-POSUM in predicting in-hospital mortlity after resection for oesophageal cancer. *BJS.* 2007; **94**: 1521-1526

Lagergren J., Bergstrom R., Nyren O. Association between body mass and risk of adenocarcinoma of the esophagus and gastric cardia. *Ann Intern Med.* 1999; **130**(11): 883-890

Lagergren J., Bergstrom R., Lindergren A. *et al.* The role of tobacco, snuff and alcohol use in the aetiology of cancers of the oesophagus and gastric cardia. *Int J Cancer.* 2000; **85**(3): 340-346

Lagergren J., Ye W., Lindgren A. *et al.* Hereditary risk of cancer of the esophagus and gastric cardia. *Cancer Epidemiol Biomarkers Prev.* 2000: **9**; 757-760

Lagergren P, Avery K.N, Hughes R. *et al.* Health related quality of life among patients cured by surgery for esophageal cancer. *Cancer.* 2007; **110**(3): 686-693

Lauren R. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma: an attempt at a histo-clinical classification. *Acta Pathol. Microbiol. Scand.* 1965; **64**: 31-49

Law S, Fok. M., Chu K.M *et al.* Thoracoscopic esophagectomy for esophageal cancer. *Surgery.* 1997; **122**: 8-14.

Law S, Fok. M., Chu K.M *et al.* Comparison of handsewn and stapled esophagogastric anastamosis after esophageal resection for cancer: a prospective randomized controlled trial. *Ann Surg.* 1997; **226**(2): 169-173

Law S, Wong J. Use of minimally invasive oesophagectomy for cancer of the oesophagus. *Lancet Oncol.*2002; **3**: 215-222

Law S, Wong J. Current management of esophageal cancer. *J Gastrointest Surg.* 2005; **9**: 291-310

Lee J.H., Ryu K.W., Lee J.H. *et al.* Learning Curve for Total Gastrectomy with D2 Lymph Node Dissection: Cumulative Sum Analysis for Qualified Surgery. *Ann Surg Oncol.* 2006; **13**(9): 1175-1181

Lee J.H., San H.S., Lee J.H. A prospective randomized study comparing open vs laparoscopy-assisted distal gastrectomy in early gastric cancer *Surg Endosc.* 2005; **19**: 168-173.
1176

Lee S-I, Choi. Y.-S., Joong Park D. *et al.* Comparative Study of Laparoscopy-Assisted Distal Gastrectomy and Open Distal Gastrectomy. *J Am Coll Surg.* 2006; **202**: 874-880.

Lehnert T, Buhl K. Techniques of reconstruction after total gastrectomy for cancer. *BJS.* 2004; **91**(5): 528-539

Leibman S, Smithers. B. M., Gotley D.C *et al.* Minimally invasive esophagectomy-short- and long-term outcomes. *Surg Endosc.* 2006; **20**: 428-433.

Lerut T, Nafteux P, Moons J. *et al.* Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. *Ann Surg.* 2004; **240**: 962-972

Lilford R, Braunholtz D, Harris J *et al.* Trials in surgery. *BJS.* 2004; **91**: 6-16

Lim C.H, Treanor D, Dixon M.F. *et al.* Low-grade dysplasia in Barrett's esophagus has a high risk of progression. *Endoscopy.* 2007; **39**: 581-587

Lim L, Michael M, Mann G.B. *et al.* Adjuvant therapy in gastric cancer. *J Clin Oncol.* 2005; **23**(25): 6220-6232

Loft D.E, Alderson D, Reading R.C. Screening and surveillance in columnar-lined oesophagus. In: Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus. A report of the British Society of Gastroenterology. 2005; p 28-31. http://www.bsg.org.uk

London A.J., Kadane J.B. Palcebos that harm: sham surgery controls in clinical trials. *Stat Methods Meth Res.* 2002; **11**: 413-427

Low D.E. Evolution in perioperative management of patients undergoing oesophagectomy. *BJS.* 2007; **94**: 655-656

Low D.E., Kunz S., Schembre D. *et al.*Esophagectomy- It's Not Just About Mortality Anymore- Standardized Periopertive Clinical Pathways Improve Outcome in Patients with Esophageal Cancer. *Gastrointest Surg.*2007; **11**: 1395-1402

Luketich J.D, Alvelo-Rivera M., Buenaventura P.O, *et al.* Minimally Invasive Esophagectomy - outcomes in 222 patients. *Ann Surg.* 2003; **238**(4): 486-495.

Lundegardh G., Adami H.O.,Helmick C. *et al.* Risk of cancer following partial gastrectomy for benign ulcer disease. *BJS.* 1994; **81**(8): 1164-1167

Lundell L, Miettinen P, Myrvold H.E. *et al.* Nordic GORD Study Group. Seven-year follow-up of a randomized clinical trial comparing proton-pump inhibition with surgical therapy for reflux oesophagitis. *BJS.* 2007; **94**(2): 198-203

Macdonald J.S, Smalley S.R, Beneditti J. *et al.* Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastro-oesophageal junction. *NEJM.* 2001; **345** (10): 725-730

Macintyre I.M., O'Brien F. Death from malignant disease after surgery for duodenal ulcer. *Gut.* 1994; **35**(4): 451-454

Malthaner R.A, Collin S, Fenlon D. Preoperative chemotherapy for resectable thoracic esophageal cancer. *Cochrane Syst Rev.* 2006; **3**: CD001556

Mandard A.M, Dalibard F, Mandard J.C. *et al.* Pathological assessment of tumour regression after preoperative chemoradiotherapy of esophageal carcinoma. *Cancer.* 1994; **73**: 2680-2686

Mariette C., Piessani G., Briez N. *et al.* The Number of Metastatic and Examined Lymph Nodes Are Indepent Prognostic Factors in Esophageal Cancer Regardless of Neoadjuvant Chemoradiation or Lymphadenectomy Extent. *Ann Surg.* 2008; **247**: 365-371

Markides G.A, Al-Khaffraf B, Vickers J. Nutritional access routes following oesophagectomy- a systematic review. Eur J Clin Nutrition. 2011 (16th March online.)

Maruyama K. Results of surgery correlated with staging. In: Preece P.E., Cuschieri A., Wellwood J.M. (eds) Cancer of the Stomach. London: Grune & Stratton, 1986: 145-163

Maruyama K, Gunven P, Okabayashi K. *et al.* Lymph node metastases of gastric cancer. General pattern in 1931 patients. *Ann Surg.* 1989; **210**: 596-602

Maruyama K., Okabayashi K., Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World J Surg.* 1987; **11**(4): 418-425

Martin D.J, Bessell. J. R., Chew A. *et al.* Thoracoscopic and laparoscopic esophagectomy. *Surg Endosc.* 2005; **19**: 1597-1601.

Matharu G, Tucker O, Alderson D. Systematic review of intraperitoneal chemotherapy for gastric cancer. *BJS.* 2011; DOI: 10.1002/bjs.7586 (epub ahead of print)

Mcanama O.J, Rogers J, Williams N.S. Right thoracoscopically assisted oesophagectomy for cancer. *BJS.* 1994; **81**: 231-234

McCulloch P. from http:www.nds.ox.ac.uk.[Cited June 2008]

McCulloch P. Developing appropriate methodology for the study of surgical techniques. *J R Soc Med.* 2009; **102**: 51-55

McCulloch P. The IDEAL recommendations and urological innovation. *World J Urol.* 2011; **29** (3): 331-336

McCulloch P., Altman D.G., Campbell W.B. *et al.* for the Balliol Collaboration. Surgical innovation and Evaluation 3 – no surgical innovation without evaluation: the IDEAL recommendations. *Lancet.* 2009; **374**: 1105-1112

McCulloch P, Nita M.E, Kazi H. *et al.* Extended versus limited lymph nodes dissection technique for adenocarcinomas of the stomach. *Cochrane Database Syst Rev.* 2004

McCulloch P, Taylor I, Sasako M *et al.* Randomised trials in surgery: problems and possible solutions. *BMJ.* 2002: **324**: 1448-51

McCulloch P, Ward J, Tekkis P.P. Mortality and morbidity in gastro-oesophageal cancer surgery: initial results of ASCOT multicentre prospective cohort study. *BMJ.* 2003; **327**: 1192-1197

Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without postoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet.* 2002; **359**: 1727-1733

Mitani M., Kuwabara Y., Shinoda N. *et al.* The effectiveness of palliative resection for advanced esophageal carcinoma: Analysis of 24 consecutive cases. *Surg Today.* 2002; **32**(9): 784-788

Mitry E., Rachet B., Quinn M.J. *et al.* Survival Analysis: Survival from cancer of the stomach in england and Wales up to 2001. *Br J Cancer.* 2008; **99**: s16-s18

Mochiki E, Kamiyama. Y., Aihara R. *et al.* Laparoscopic assisted distal gastrectomy for early gastric cancer: Five years' experience. *Surgery.* 2005; **137**: 317-22.

Mohammed M.A., Cheng K.K., Rouse A. *et al.* Bristol, Shipman, and clinical governance: Shewhart's forgotten lessons. *Lancet.* 2001; **357**: 463- 467

Mohammed M.A., Deeks J.J., Girling A. *et al.* Evidence of methodological bias in hospital standardized mortality ratios: retrospective database study of English hospitals. *BMJ.* 2009; **338**: 817-820

Moher D, Fortin P, Jadad A.R. *et al.* Completeness of reporting trials published in languages other than English: implications for conduct and reporting of systematic reviews. *Lancet.* 1996; **347**(8998): 363-366

Moher D., Jones A., Lepage L. Use of the CONSORT statement and quality of reports of randomized trials: a comparative before- and- after evaluation. *JAMA.* 2001: **285**: 1992-1995

Moher D, Liberati A, Tetzlaff J. *et al.* The PRISMA Group. Preferred Reporting Items for Systematic reviews and Meta-Analyses. The PRISMA Statement. 2009. PLoS Med 6(6). Doi: 10.1371/journal.pmed1000097

Montgomery DC *Introduction to Statistical Quality Control*, Second Edition. New York: John Wiley and Sons; 1991.

Mosely J.B., O'Malley K., Petersen N.J. *et al.* A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *NEJM.* 2002; **347**: 81-88

Munoz M, Corea P, Cuello C. *et al.* Histological types of gastric carcinoma in high and low risk areas. *Int J Cancer.* 1968; **3**: 809-818

Murad A, Santiago F, Petroianu A. *et al.* Modified therapy with 5-flurouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer.* 1993; **72**: 37-41

Murakami T. Pathomorphological diagnosis. Definition and gross classification of early gastric cancer. *Gann Monogr.* 1971; **11**: 53-55

Office for National Statistics:http:www.statistics.gov.uk

Onate-Ocana L.F., Aiello-Crocifoglio V., Mondragon-Sanchez R. *et al.* Survival benefit of D2 lymphadenectomy in patients with gastric adenocarcinoma. *Ann Surg Oncol.* 2000; **7**: 210-217

National Institute for Clinical Excellence (NICE). Interventional overview of photodynamic therapy for high-grade dysplasia for Barrett's oesophagus. London: National Institute for Clinical Excellence (NICE); 2003 {cited 6 August 2009}. Available from url: http://www.nice.org.uk/pdf/ip/232overview.pdf

National Institute for Clinical Evidence (NICE). Thoracoscopic Assisted Oesophagectomy. http://www.nice.org.uk IPG189 August 2006

National Institute for Clinical Evidence (NICE). Laparoscopic gastrectomy. http://www.nice.org.uk IPG269 July 2008

National Oesophago-Gastric Cancer Audit 2010. 3rd Annual Report. The NHS Information Centre.

Nguyen N.T, Roberts P., Follett D. *et al.* Thoracoscopic and Laparoscopic Esophagectomy for Benign and Malignant Disease: Lessons learned from 46 consecutive procedures. *Journal of the American College of Surgeons.* 2003; **197**: 902-913.

NHS Executive Referral Guidelines for Suspected Cancer. London: HMSO; 2000

Nunobe S, Okaro A, Sasako M. *et al.* Bilroth 1 versus Roux-en-Y reconstruction: a quality of life survery at 5 years. *Int J Clin Oncol.* 2007; **12**: 433-439

Ohgami M, Otani. Y., Kumai K. et al .Curative Laparoscopic Surgery for Early Gastric Cancer: Five Years Experience. *World J Surg.* 1999; **23**: 187-193.

Ono H, Gotoda T, Shirao K. *et al.* Endoscopic mucosal resection for treatment of early gastric cancer. *Gut.* 2001; **48**: 225-229

Orsuji E, Yamaguci T, Sawai K. *et al.* Total gastrectomy with simultaneous pancreaticosplenectomy or splenectomy in patients with advanced gastric carcinoma. *B J Cancer.* 1999; **79**: 1789-1793

Palanivelu C, Prakash. A., Senthilkumar R. *et al* . Minimally Invasive Esophagectomy: Thoracoscopic Mobilisation of the Esophagus and Mediastinal Lymphadenectomy in Prone Position- Experience of 130 Patients. *J Am Coll Surg.* 2006; **203**: 7-16.

Parameswaran R., McNair A., Avery K.N.L. *et al.* The Role of Health-Related Quality of Life Outcomes in Clinical Decision Making in Surgery for esophageal Cancer: a Systematic Review. *Ann Surg Oncol.* 2008; **15**: 2372-2379

Parameswaran R., Blazeby J.M., Hughes R. *et al.* Health-related quality of life following minimally invasive oesophagectomy. *BJS.* 2009; **97**: 525-531

Parameswaran R., Veeramootoo D., Krishnadas R. *et al.* Comparative Expereince of Open and Minimally Invasive Esophagogastric Resection. *World J Surg* 2009; **33**:1869-1875

Parsonnet J., Friedman G.D., Vandersteen D.P. *et al. Helicobacter pylori* infectionand the risk of gastric carcinoma. *NEJM.* 1991; **325**: 1127-1131

Peeters K.C, Kattan M.W, Hartgrink H.H. *et al.* Validation of a nomogram for predicting disease-specific survival after an R0 resection for gastric carcinoma. *Cancer.* 2005; **103**(4): 703-707

Peracchia A, Rosati. RFumagalli U. *et al.* Thoracoscopic Esophagectomy: Are There Benefits? *Sem Surg Oncol.* 1997; **13**: 259-262.

Philip P, Ajani J. Gastric carcinoma. In: Pazdur R, ed. *Medical Oncology: a Comprehensive Review.* 2nd ed. Houston TX; 1997

Pinotti H.W. A new approach to the thoracic esophagus by the abdominal transdiaphragmatic route. *Langenbecks Arch Chir.* 1983; **359** (4): 229-235

Poolman R.W., Struijis P.A., Krips R. *et al.* Reporting of outcomes in orthopaedic randomized trials: does blinding of outcome assessors matter? *J Bone Joint Surg.* 2007; **89**: 550-558

Powell J., McConkey C.C. The rising trend in adenocarcinoma of the oesophagus and gastric cardia. *Eur J Cancer Prevent.* 1992; **1**: 265-269

Prytherch D.R., Whitley B., Higgins B. *et al.* POSSUM and Portsmouth POSSUM for predicting mortality. *BJS.* 1998; **85**: 1217-1220

Pyrhonen S, Kuitunen T, Nvandoto P. *et al.* Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer.* 1995; **71**: 587-591

Raimes S. Surgery for cancer of the stomach. In: Griffin S.M, Raimes S.A, editors. *Upper gastrointestinal surgery: a companion to specialist surgical practice.* 4th edition. London: W.B. Saunders. 2010: p 123-156

Rao S., Cunningham D. Clinical commentary: Survival of cancer of the stomach in England and Wales up to 2001. *Br J Cancer.* 2008; **99**: S19-20

Reeves B. Health-technology assessment in surgery. *Lancet.* 1999; **353** s1: S13-S15

Riddell R.H, Goldman H, Ransohoff D. *et al.* Dysplasia in inflammatory bowel disease. Standardised classification with provisional clinical application. Hum Pathol. 1983; **14**: 931-966

Risk J.M., Mills H.S., Garde J. *et al.* The tylosis esophageal cancer (TOC) locus: more than just a familial cancer gene. *Dis Esophagus.* 1999: **12**: 173-176

Rizk N, Venkatraman E, Park B. *et al.* The prognostic importance of the number of involved lymph nodes in esophageal cancer: implications for revisions of the American Joint committee on Cancer staging system. *J Thorac Cardiovasc Surg.* 2006; **132**: 1374-1381

Robertson S.A, Skipworth R.J, Clarke D.L. *et al.* Ventilatory and intensive care requirements following oesophageal resection. *Ann R Coll Surg Eng.* 2006; **88**(4): 354-357

Rosen H.R, Jatzko G, Repse S. *et al.* Adjuvant intraperitoneal chemotherapy with carbon-adsorbed mitomycin in patients with gastric cancer: results of a randomized multicenter trial of the Austrian Working group for Surgical Oncology. *J Clin Oncol.* 1998; **16**(8): 2733-2738

Ross P, Nicholson D, Cunningham D. *et al.* Prospective randomised trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubin, cisplatin, and PVI 5-FU in advanced esophago-gastric cancer. *J Clin Oncol.* 2002; **20**: 1996-2004

Rotheberger D.A. Evidence-based practice requires evidence. *BJS.* 2004; **91**: 1387-1388

Rouvelas I., Zeng W., Lindblad M. *et al.* Survival after surgery for oesophageal cancer: a population-based study. *Lancet Oncol.* 2005; **6**: 864-870

Sagawa T, Takayama T, Oku T. *et al.* Argon plasma coagulation for successful treatment of early gastric cancer with intremucosal invasion. *Gut.* 2003; **52**: 334-339

SAGOCS. Scottish Audit of Gastric and Oesophageal Cancer. Report 1997-2000. A prospective audit. http://www.crag.scot.nhs.uk/commitees/CEPS/reports.[Cited January 2006]

Sakurai Y, Matsui T, Yoshida I. *et al.* Randomized clinical trial of the effects of perioperative use of immune-enhancing enteral formula on metabolic immunological status in patients undergoing esophagectomy. *World J Surg.* 2007.Aug 7. In press.

Sakuramoto S, Kikuchi. S., Kuroyama S. *et al* . Laparoscopy-assisted distal gastrectomy for early gastric cancer. *Surg Endosc.* 2006; **20**: 55-60.

Salvon-Harman J.C., Cady B., Nikulasson S. *et al.* Shifting proportions of gastric adenocarcinomas. *Arch Surg.* 1994; **129**: 381-388

Sampliner R.E. The Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's oesophagus. *Am J Gastroenterol.* 1998; **93**: 1028-1032

Schlag P.M. randomised trial of preoperative chemotherapy of squamous cell cancer of the esophagus. *Arch Surg.* 1992; **127**: 1446-1450

Schmid A, Thybusch A, Kremer B. *et al.* Differential effects of radical D2-lymphadenectomy and splenectomy in surgically treated gastric cancer patients. *Hepatogastroenterology.* 2000; **47**: 579-585

Schwartz G. Invasion and metastasis in gastric cancer: in vitro and in vivo models with clinical considerations. *Semin Oncol.* 1996; **23**: 316-324

Shaheen N, Ranschoff D.F. Gastroesophageal Reflux, Barretts Esophagus and esophageal Cancer. *JAMA.* 2002; **287**: 1972-1981

Sharma P, Dent J, Armstrong D. *et al.* The development and validation of endoscopic grading system for Barrett's esophagus: the Prague C&M criteria. *Gastroenterology.* 2006; **131**: 1392-1399

Sharma P, Falk G.W, Weston A.P. *et al.* Dysplasia and cancer in a large multicenter cohort of patients with Barrett's oesophagus. *Clin Gastroenterol Hepatol.* 2006; **4**:566-572

Shimada H, Okazumi S, Maysubara H. *et al.* Impact of the number and extent of positive lymph nodes in 200 patients with thoracic esophageal squamous cell carcinoma after three-field lymph node dissection. *World J Surg.* 2006; **30**: 1441-1449

Sica G.S, Sujendran V, Wheeler J. *et al.* Needle catheter jejunostomy at esophagectomy. *J Surg Oncol.* 2005; **9**: 35-41

Siewert J.R., Bottcher K., Stein H.J. *et al.* Relevant prognostic factors in gastric cancer: ten-year results of the german Gastric Cancer Study. *Ann Surg.* 1998; **228**: 449-461

Siewert J.R., Feith M, Werner M. *et al.* Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/ topographic classification in 1002 consecutive patients. *Ann Surg.* 2000: **232**(3): 353-361

Siewert J.R, Stein H.J. Adenocarcinoma of the gastroesophageal junction: classification, pathology and extent of resection. *Dis Esophagus.* 1996; **9**: 173-182

Siewart J.R, Stein H.J, Feith M. *et al.* Histologic tumour type is an independent prognostic parameter in esophageal cancer: lessons learnt from more than 1,000 consecutive resections at a single centre in the Western world. *Ann Surg.* 2001; **234**: 360-367

SIGN (Scottish Intercollegiate Guidelines Network.) Management of oesophageal and gastric cancer- a national clinical guideline. 2nd edition. Edinburgh: NHS Scotland; 2006. www.sign.ac.uk

Singh K.K, Rohatgi A, Rybinkina I. *et al.* Laparoscopic gastrectomy for gastric cancer: early experience among the elderly. *Surg Endosc.* 2008; 22(4): 1002-1007

Sipponen P., Riihela M., Hyvaranin H. *et al.* Chronic nonatrophic ("superficial") gastritis increase the risk of gastric carcinoma. A case-control study. *Scad J Gasteroenterol.* 1994; **29**: 336-340

Songun I, Putter H, Meershoek-Klein E. *et al.* Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol.* 2010; **11**(5): 439-449

Smith J.K., McPhee J.T., Hill J.S. *et al.* National Outcomes after Gastric Resection for Neoplasm. *Arch Surg.* 2007; **142**:387-393

Smithers B.M, Gotley. D. C., Martin I. *et al.* Comparison of the Outcomes Between Open and Minimally Invasive Esophagectomy. *Ann Surg.* 2007; **245**(2): 232-240.

Stadtlander C.T.K-H, Waterbor T. Molecular epidemiology, pathogenesis and prevention of gastric cancer. *Carcinogenesis.* 1999; **20**(12): 2195-2207

Stark J., Gallivan S., Lovegrave J. Mortality rates after surgery for congenital heart defects in children and surgeons' performance. *Lancet.* 2003; **355**(9208): 1004-1007

Stein H.J, Feith M, Siewert J.R. Cancer of the esophagogastric junction. *Surg Oncol.* 2000; **9**: 35-41

Steiner S.H., Cook R.J. Monitoring surgical performance using risk-adjusted cumulative sum charts. *Biostatistics.*2000; **1**(4): 441-452

Steyerberg E.W, Neville B.A, Koppert L.B *et al.* Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. *J Clin Oncol.* 2006; **24**: 4277- 4284

Stirrat G.M, Farrow S.C, Farndon J. *et al.* The challenge of evaluating surgical procedures. *Ann R Coll Surg Eng.* 1992; **74**: 80-84

Strong V.E, Devaud N, Karpeh M. The role of laparoscopy for gastric surgery in the West. *Gastric Cancer.* 2009; **12**: 127-131

Sujendran V., Wheeler J., Baron R. *et al.* Effect of Neoadjuvant chemotherapy on circumferential margin positivity and its impact on prognosis in patients with resectable oesophageal cancer. *BJS.* 2008; **95**(2): 191-194

Sutton C.D, White S.A, Marshall L.J. *et al.* Endoscopic-assisted transthoracic oesophagogastrostomy without thoracotomy for tumours of the lower oesophagus and cardia. *EJSO.* 2002; **28**: 46-48

Suzuki Y, Urashima M., Ishibashi Y. *et al.* Hand-assisted laparoscopic and thoracoscopic surgery (HALTS) in radical esophagectomy with three-field lymphadenectomy for thoracic esophageal cancer. *EJSO.* 2003; **31**: 1166-1174.

Tada M, Murakami A, Yania H. *et al.* Endoscopic resection of early gastric cancer. *Endoscopy.* 1993; **25**: 445-450

Tangoku A, Yoshino S., Abe T. *et al.* Mediastinoscope-assisted transhiatal esophagectmy for esophageal cancer. *Surg Endosc.* 2004;**18**:383-389.

Tanimura S, Higashino. M., Fukunaga Y *et al.* Laparoscopic gastrectomy with regional lymph node dissection for upper gastric cancer. *BJS.* 2006; **94**: 204-207.

Tekkis P.P, McCulloch P, Polonieki J.D. *et al.* Risk adjusted prediction of operative mortality in oesophagogastric surgery with O-POSSUM. *BJS.* 2004; **91**: 288-295

Tekkis P.P, Senagore A.J, Delaney C.P *et al.* Evaluation of the learning curve in laparoscopic colorectal surgery: comparison on right-sided and left-sided resections. *Ann Surg.* 2005; 242(1): 83-91

Teoh A.Y, Yan Chiu P.W, Wong T.C. *et al.* Functional performance and quality of life in patients with squamous esophageal carcinoma receiving surgery or chemoradiation: results from a randomized trial. *Ann Surg.* 20011; **253**(1): 1-5

Terry MB, Gaudet MM, Gammon MD. The Epidemiology of Gastric Cancer. *Sem Rad Onc.* 2002;**12** (2):111-127

Terry P., Lagergren J., Ye W. *et al.* Antioxidants and cancers of the oesophagus and gastric cardia. *Int J Cancer.* 2000;**87**: 750-754

Terry P., Lagergren J., Ye W. *et al.* Inverse association between intake of cereal fibre and rate of gastric cardia cancer. *Gastroenterology.* 2001; **120**: 387-391

Theisen J, Nigro J.J, DeMeester T.R. *et al.* Chronology of the Barrett's metaplasia-dysplasia-carcinoma sequence. *Dis Esophagus.* 2004; **17**: 67-70

Thompson A.M, Park K.G.M. for the Scottish Audit of Gastric and Oesophageal Cancer. Does hospital size influence the outcome of patients with gastric cancer undergoing surgery. *BJS.* 2002; **89** (S): 89

Thompson A.M, Rapson T, Gilbert F.J. *et al.* Hospital volume does not influence long-term survival of patients undergoing surgery for oesophageal or gastric cancer. *BJS* 2007; **94**: 578-584

Tinoco R, El-Kadre L., Tinoco A *et al.* Laparoscopic transhiatal esophagectomy: outcomes. *Surgical Endoscopy.* 2007; **21**(8): 1284-1287

Tokar J.L, Haluszka O, Weinberg D.S. Endoscopic Therapy of Dysplasia and Early-Stage Cancers of the Esophagus. *Sem Rad Oncol.* 2006; **17**: 10-21

Tsugane S, Sasazuki S, Kobayashi M *et al.* Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. *Br J Cancer.* 2004; **90**(1): 128-134

UICC (International Union Against Cancer.) in: Sobin L.H, Wittekind Ch, eds. TNM classification of malignant tumours. 6th edition. New York, Chichester, Weinheim, Brisbane, Singapore, Toronto: Wiley-Liss.2002.

Urschel J.D, Blewett C.J, Young J.E.M. *et al.* Pyloric drainage (pyloroplasty) or no drainage in gastric reconstruction after esophagectomy. A meta-analysis of randomised controlled trials. *Dig Surg.* 2002; **19**(3): 160-164

Urschel J.D, Urschel D.M, Miller J.D. *et al.* A meta-analysis of randomized controlled trials of route of reconstruction after esophagectomy for cancer. *Am J Surg.* 2001; **182**(5): 470-475

Valverde A, Hay J.M, Fingerhut A. *et al.* Manual versus mechanical esophagogastric anastamosis after resection for carcinoma: a controlled trial. French Association for Surgical research. *Surgery.* 1995; **120**(3): 476-483

Van Cutsem E, Dicato M, Arber N. *et al.* The neo-adjuvant, surgical and adjuvant treatment of gastric adenocarcinoma. Current expert opinion derived from the Seventh World Congress on Gastrointestinal Cancer, Barcelona, 2005. *Ann Oncol.* 2006; **17**(6): v13-v18

Van de Velde C.J. Resection for gastric cancer in the community. *Semin Oncol.* 2005; 32(**6** s9): s90-s93

Van den Broek W.T, Makay O, Berends F.J *et al.* Laparoscopically assisted transhiatal resection for malignancies of the distal oesophagus. *Surgical Endoscopy.* 2004; **18**: 812-817.

Van Lanschot J.J., Hulscher J.B., Buskens C.J. *et al.* Hospital volume and hospital mortality for esophagectomy. *Cancer.* 2001; **91**:1574-1578

Varela E., Beavis K.M., Hinojosa M.W. *et al.* Laparoscopic Gastric Ischaemic Preconditioning Prior to Esophagogastrectomy: Technique and Review. *Surg Innovation.* 2008; **15**(2): 132-135

Verhage R.J.J.,Hazebroek E.J., Boone J. *et al.* Minimally Invasive Surgery compared to Open Procedures in Esophagectomy for Cancer: a Systematic Review. *Minerva Chir.* 2009; **64**: 135-146

Von Rahden B.H, Stein H.J, Siewert J.R. Surgical management of esophagogastric tumours. *World J Gastroenterol.* 2006; **12**(41): 6608-6613

Wagner A.D, Grothe W, Behl S. *et al.* Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev.* 2005; (**2**): CD004064

Walsh T.N, Noonan N, Hollywood D. *et al.* A comparison of multimodal therapy and surgery for esophageal adenocarcinomas. *NEJM.* 1996; **335**: 462-467

Walther B, Johansson J, Johnsson F. *et al.* Cervical or thoracic anastamosis after esophageal resection and gastric tube reconstruction: a prospective randomized trial comparing sutured neck anastamosis with stapled intrathoracic anastamosis. *Ann Surg.* 2003; **238**(6): 803-812

Wan A, Allum W.H. Gastric Cancer. Oesophagus and Stomach p105-109. In: Surgery 24:3. Elsevier: Oxford, London 2006.

Wang D, Kong Y, Zhong B. *et al.* Fast-track surgery improves postoperative recovery in patients with gastric cancer: a randomized comparison with conventional postoperative care. *J Gastrointest Surg.* 2010; **14**: 620-627

Wang S-Y, Yeh C-N, Lee Y-L *et al.* Clinical Impact of Positive Surgical Margin Status on Gastric Cancer Patients Undergoing Gastrectomy. *Ann Surg Oncol.* 2009; **16**: 2738-2743

WarsiA, White S, McCulloch P. Completeness of data entry in three cancer surgery databases. *EJSO.* 2002; **28**: 850-856

Watson A, Shepard N.A. British Society of Gastroenterology guidelines for the diagnosis and management of Barrett's columnar-lines oesophagus: the definition of "Barrett's" columnar-lines oesophagus. http://www.bsg.org.uk/clinical-guidelines/oesophageal/index.html; 2005; 4-6 ; accessed April 2011

Webb P.M, Crabtree J.E, Forman D. Gastric cancer, cytotoxin-associated gene A positive, Helicobacter pylori and serum pepsinogens: an international study. The Eurogast Study Group. *Gastroenterology.* 1999; **116**(2): 269-272

Weber K.J, Reyes. C. D., Gagner M *et al.* Comparison of laparoscopic and open gastrectomy for malignant disease. *Surgical Endoscopy.* 2003; **17**: 968-971.

Whooley B.P, Law S, Murthy S.C. *et al.* Analysis of reduced death and complication rates after esophageal resection. *Ann Surg.* 2001; **233**: 338-344

Wilson K.S, Lim J.T. Primary chemotherapy-radiotherapy and selective oesophagectomy for oesophageal cancer: goal of cure with organ preservation. *Radiother Oncol.*2000; **54**: 129-134

World Health Organisation (WHO) Tomours of the stomach. In Hamilton S.R, Aaltonin L.A. eds. World Health Organisation classification of tumours. Tumours of the digestive tract. Lyon. IARC Press. 2000: 37-68

Wormuth J.K., Heitmiller R.F. Esophageal conduit necrosis. *Thorac Surg Clin.* 2006; **16**: 11-22

Wong S.K.H, Chan. A., Lee D.W.H *et al* Minimal invasive approach of gastric and esophageal mobilization in total pharygolaryngoesophagectomy. Total laparoscopic and hand-assisted laparoscopic technique. *Surgical Endoscopy.* 2003; **17**: 798-802.

(WRCF and AICR)World Cancer Research Fund and American Institute for Cancer Research: food, nutrition and prevention of cancer: a global perspective. Washington: American Institute of Cancer Research; 1997.

Wu A.W, Xu G.W, Wang H.Y. *et al.* Neoadjuvamt chemotherapy versus none for resectable gastric cancer. *Cochrane Database Syst Rev.* 2007; (**2**): CS005047

Wu P.C, Posner M.C. The role of surgery in the management of oesophageal cancer. *Lancet Oncol.* 2003; **4**: 481-488

Xiao Z.F, Yang Z.Y, Liang J. *et al.* Value of radiotherapy after radical surgery for esophageal carcinoma: a report of 495 patients. *Ann Thorac Surg.* 2003; **75**: 331-336

Yacoub D., Athanasiou T., Tekkis P. *et al.* Laparoscopic assisted distal gastrectomy for early gastric cancer: is it an alternative to the open approach? *Surg Oncol.* 2008; XX: 1-12

Yamamoto S, Kawahara. K., Maekawa T. *et al.* Minimally Invasive Esophagectomy for Stage I and II Esophageal Cancer. *Annals of Thoracic Surgery.* 2005; **80**: 2070-5.

Yang H., Berner A., Mei Q. *et al.* Cytologic screening for esophageal cancer in high-risk population in Anyang County, China. *Acta Cytol.* 2002; **46**: 445-452

Yang S.H., Zhang Y.C., Yang K.H. *et al.* An evidence-based medicine review of lymphadenectomy extent for gastric cancer. *Am J Surg.* 2009; **320**: 43-46

Yano H, Monden. T., Kinuta M. *et al.* The usefulness of laparoscopy-assisted distal gastrectomy in comparison with that of open distal gastrectomy for early gastric cancer. *Gastric Cancer.* 2001; **4**: 93-97.

Yasuda K, Inomata. M., Shiraishi N. *et al* Laparoscopy-assisted distal gastrectomy for early gastric cancer in obese and non-obese patients.. *Surgical Endoscopy.* 2004; **18**: 1253-1256.

Ye W., Nyren O. Risk of cancers of the oesophagus and stomach for histology or subsite in patients hospitalised for pernicious anaemia. *Gut.* 2003; **52**(7): 938-941

Yoo M.W., Park D.J., Ahn H.S. *et al.* Evaluation of the Adequacy of Lymph Node Dissection in Pylorus-Preserving Gastrectomy for Early Gastric Cancer Using the Maruyama Index. *World J Surg.* 2010; **34**(2): 291-295

Yoshihara M, Hiyama T,Yoshida S. *et al.* Reduction in gastric cancer mortalityby screening based on serum pepsinogen concentration: A case-control study. *Scan J Gastroenterol.* 2007;m**42**: 760-764

Yu W, Seo B.Y, Chung H.Y. Postoperative body-weight loss and survival after curative resection for gastric cancer. *BJS.* 2002; **89**: 467-470

Yumiba T, Yamasaki Y, Momiyama T. *et al.* Quality of life after laparoscopic assisted distal gastrectomy for early gastric cancer: compared with conventional distal gastrectomy. 2006. Abstract. European Association of Endoscopic Surgeons, 10th Congress, Berlin

Zafirellis K.D, Fountoulakis K, Dolan S.P. *et al.* Evaluation of POSSUM in patients with oesophageal cancer undergoing resection. *BJS.* 2002; **89**: 1150-1155

Zehr K.J, Dawson P.B, Yang S.C. *et al.* Standardized clinical care pathways for major thoracic cases reduce hospital costs. *Ann Thorac Surg.* 1998; **66**: 914-919

APPENDIX 1

Presentations and Publications Arising from this Thesis

Presentations

Minimally Invasive Gastro-Oesophageal Cancer Surgery (MIGOCS): Early Results of a UK Multicentre Phase IIS Study.
Gemmill E.H., McCulloch P. on behalf of MIGOCS (for AUGIS and ALS)
Oral presentation at EAES, Stockholm, June 2008

Minimally Invasive Oesophageal and Gastric Oncological Surgery: A Phase IIS Study of UK-wide Experience.
Gemmill E.H., McCulloch P. on behalf of MIGOCS (for AUGIS and ALS)
Oral presentation at ASGBI Bournemouth, May 2008.

Minimally Invasive Gastro-Oesophageal Cancer Surgery (MIGOCS) Group Results 2008. Presentation to the Association of Upper Gastro-Intestinal Surgeons of Great Britain and Ireland, Consensus Conference on Minimally Invasive Oesophagectomies, Basingstoke. March 2008.

Minimally Invasive Surgery for Gastro-Oesophageal Cancer- Current UK Practice
Gemmill E.H, McCulloch P. on behalf of MIGOCS (for AUGIS and ALS)
Poster presentation at SARS – Birmingham, January 2008

What's the Evidence that Gastro-Oesophageal Cancer Surgery is Better? DM 1st year report to the Nuffield Department of Surgery, University of Oxford.
Oral presentation, December 2007.

Minimally Invasive Surgery for Gastric and Oesophageal Cancer: the Current Evidence.
Gemmill E.H, McCulloch P. on behalf of MIGOCS for AUGIS and ALS
Poster presentation at BASO – ACS, London, November 2007.

Publications

Minimally Invasive Resection for Gastro-Oesophageal Cancer- a Systematic Review. Gemmill E.H, McCulloch P. *BJS.* 2007; **94** (12): 1461-1467

Minimally Invasive Surgery for Gastric and Oesophageal Cancer: the Current Evidence. Gemmill E.H, McCulloch P. on behalf of MIGOCS for AUGIS and ALS. *ESJO.* 2007; **33**(9): 1107 (abstract)

Current practice and results from minimally invasive gastro-oesophageal cancer surgery in the UK. Gemmill E.H, McCulloch P. *BJS*; 2007; **94**(S2): 47 (abstract)

Minimally invasive oesophageal and gastric oncological surgery: a phase IIS study of UK-wide experience. Gemmill E.H, McCulloch P. *BJS.* 2008; **95**(S3): 12 (abstract)

Study of Minimally Invasive Resection for Gastro-Oesophageal Cancer Surgery in the UK 1996-2006. Gemmill E.H., McCulloch P., O'Boyle C., Menzies D., Ali H., Byrne J. and Singh K. for the MIGOCS group. (Currently submitted)

Lessons from the Experience of Teams Developing Minimally Invasive Oesophagectomy in the UK: a Delphi Consensus Study. McCulloch P., Gemmill E.H., Sheena Y., Ali H., Berrisford R.G., Byrne J., Nisar A., O'Boyle C., Menzies D., Wajed S. (Currently submitted.)

Appendix 2

MIGOCS Register Proforma

AUGIS

The Association of Upper Gastrointestinal Surgeons
Minimally Invasive Gastro-oesophageal Cancer Surgery
Page 1; Version 1.0

Demographics and other identifiers

Unique patient-identifier

Date of birth dd / mm / yyyy

Gender ○ Male ○ Female ○ Unknown

Study centre

Study case number

Study case consultant

Date of admission dd / mm / yyyy

Pre-operative staging

Initial T-stage

○ None (high grade dysplasia)
○ T1
○ T1a
○ T1b
○ T2
○ T2a
○ T2b
○ T3
○ T3a
○ T3b
○ T4
○ T4a
○ T4b
○ TX (unknown)

Initial N-stage

○ N0
○ N1
○ N2
○ NX

Initial M-stage

○ M0
○ M1
○ M1a
○ M1b

Pre-operative chemotherapy

○ No
○ Yes

Post-CXT T-stage

○ None (high grade dysplasia)
○ T1
○ T1a
○ T1b
○ T2
○ T2a
○ T2b
○ T3
○ T3a
○ T3b
○ T4
○ T4a
○ T4b
○ TX (unknown)

Post-CXT T-stage

○ N0
○ N1
○ N2
○ NX

Post-CXT T-stage

○ M0
○ M1
○ M1a
○ M1b

Staging modalities used

☐ CT scan
☐ MRI scan
☐ EUS
☐ EUS and FNA
☐ Laparoscopy
☐ Lap U/S
☐ Isotope bone scan
☐ PET scan
☐ PET scan / CT scan
☐ Bronchoscopy
☐ Thoroscopy

The Association of Upper Gastrointestinal Surgeons
Minimally Invasive Gastro-oesophageal Cancer Surgery

Unique patient identifier

Date of procedure dd / mm / yyyy

Pre-operative staging continued ...

Histological type

- ○ Adenocarcinoma
- ○ Squamous
- ○ Small cell
- ○ Undifferentiated
- ○ GIST
- ○ Lymphoma
- ○ Others

Histological grade

- ○ Well defined
- ○ Poorly differentiated

Tumour details

Position of primary tumour

- ○ Upper oesophagus
- ○ Middle oesophagus
- ○ Lower oesophagus
- ○ Gastro-oesophageal junction
- ○ Barrat's oesophagus
- ○ Hiatus hernia
- ○ Fundus of stomach
- ○ Body of stomach
- ○ Antrum
- ○ Pylorus

Length of tumour mm

Width of tumour mm

Pre-operative health status

Physiological O-POSSUM score use www.riskprediction.org.uk

ASA grade

- ○ Grade 1
- ○ Grade 2
- ○ Grade 3
- ○ Grade 4
- ○ Grade 5
- ○ Unknown

Operating surgeon 1

Operating surgeon 2

Mentor

Position of primary tumour

- ○ Total oesophagectmy (G01.1)
- ○ Sub-total-oesophagectomy (G01.1)
- ○ Partial oesophagectomy (G01.1)
- ○ Oesopho-gastrectomy (G01.1)
- ○ Extended total gastrectomy with D2 node dissection (G27.1)
- ○ Total gastrectomy with other node dissection (G27.5)
- ○ Sub-total gastrectomy (G28.3)
- ○ Distal gastrectomy (G28.3)
- ○ Segmental gastrectomy (G28.8)
- ○ Local resection of part of stomach (G29.2)

Hand assisted

- ○ Well defined
- ○ Poorly differentiated

The Association of Upper Gastrointestinal Surgeons
Minimally Invasive Gastro-oesophageal Cancer Surgery

Unique patient identifier

Date of procedure dd / mm / yyyy

Port details

	Port 1	Port 2	Port 3
Port site	○ Left upper quadrant	○ Left upper quadrant	○ Left upper quadrant
	○ Right upper quadrant	○ Right upper quadrant	○ Right upper quadrant
	○ Epigastrium	○ Epigastrium	○ Epigastrium
	○ Left flank	○ Left flank	○ Left flank
	○ Umbilical area	○ Umbilical area	○ Umbilical area
	○ Right flank	○ Right flank	○ Right flank
	○ Hypogastrium	○ Hypogastrium	○ Hypogastrium
	○ Left iliac fossa	○ Left iliac fossa	○ Left iliac fossa
	○ Right iliac fossa	○ Right iliac fossa	○ Right iliac fossa
	○ Ribspace 1	○ Ribspace 1	○ Ribspace 1
	○ Ribspace 2	○ Ribspace 2	○ Ribspace 2
	○ Ribspace 3	○ Ribspace 3	○ Ribspace 3
	○ Ribspace 4	○ Ribspace 4	○ Ribspace 4
	○ Ribspace 5	○ Ribspace 5	○ Ribspace 5
	○ Ribspace 6	○ Ribspace 6	○ Ribspace 6
	○ Ribspace 7	○ Ribspace 7	○ Ribspace 7
	○ Ribspace 8	○ Ribspace 8	○ Ribspace 8
	○ Ribspace 9	○ Ribspace 9	○ Ribspace 9
	○ Ribspace 10	○ Ribspace 10	○ Ribspace 10
Port site	○ 5 mm	○ 5 mm	○ 5 mm
	○ 10 mm	○ 10 mm	○ 10 mm
	○ 12 mm	○ 12 mm	○ 12 mm
	○ 15 mm	○ 15 mm	○ 15 mm
	○ 30 mm	○ 30 mm	○ 30 mm
	○ Handport	○ Handport	○ Handport
	○ Endostitch	○ Endostitch	○ Endostitch
	○ Nathanson retractor	○ Nathanson retractor	○ Nathanson retractor
Port distance from axillary line	○ mid-axilla -14	○ mid-axilla -14	○ mid-axilla -14
	○ mid-axilla -12	○ mid-axilla -12	○ mid-axilla -12
	○ mid-axilla -10	○ mid-axilla -10	○ mid-axilla -10
	○ mid-axilla -8	○ mid-axilla -8	○ mid-axilla -8
	○ mid-axilla -6	○ mid-axilla -6	○ mid-axilla -6
	○ mid-axilla -4	○ mid-axilla -4	○ mid-axilla -4
	○ mid-axilla -2	○ mid-axilla -2	○ mid-axilla -2
	○ On mid axillary line	○ On mid axillary line	○ On mid axillary line
	○ mid-axilla +2	○ mid-axilla +2	○ mid-axilla +2
	○ mid-axilla +4	○ mid-axilla +4	○ mid-axilla +4
	○ mid-axilla +6	○ mid-axilla +6	○ mid-axilla +6
	○ mid-axilla +8	○ mid-axilla +8	○ mid-axilla +8
	○ mid-axilla +10	○ mid-axilla +10	○ mid-axilla +10
	○ mid-axilla +12	○ mid-axilla +12	○ mid-axilla +12
	○ mid-axilla +14	○ mid-axilla +14	○ mid-axilla +14
	○ mid-axilla +16	○ mid-axilla +16	○ mid-axilla +16
	○ mid-axilla +18	○ mid-axilla +18	○ mid-axilla +18
	○ mid-axilla +20	○ mid-axilla +20	○ mid-axilla +20

Unique patient identifier

Date of procedure dd / mm / yyyy

Operative technique details

Type of reconstruction
- ○ No anastomosis
- ○ Gastrojejunostomy
- ○ Oesophagojejunostomy
- ○ Jejunal loop interposition
- ○ Colon interposition
- ○ Oesophagogastrostomy (neck)
- ○ Oesophagogastrostomy (chest)
- ○ Gastrojejunostomy Roux-en-Y
- ○ Billroth II

Method of anastomosis
- ○ Sutured
- ○ Stapled
- ○ Both

Staple type
- ○ 3.5 mm
- ○ 4.8 mm
- ○ Vascular
- ○ Other

Staple length
- ○ 30 mm
- ○ 40 mm
- ○ 60 mm

Nodal dissection performed
- ○ D0
- ○ D1
- ○ D2
- ○ D1 & L gastric artery
- ○ 2-field
- ○ Other

Thoracic dissection
- ○ No
- ○ Yes

Thoracic dissection method
- ○ Laparoscopic through hiatus
- ○ Thorascopic
- ○ Blind transhiatal
- ○ Prone thorascopic
- ○ Combined laparoscopic & blind
- ○ Combined thorascopic & laparoscopic
- ○ Combined thorascopic & blind

Brief description of technique

Outcome
- ○ Completed
- ○ Converted to open
- ○ Abandoned

Reason for abandonment / conversion

Operation statistics

Anaesthetic time min

Operating time (skin to skin) min

Blood loss ml

Unique patient identifier

Date of procedure dd / mm / yyyy

Post-operative course

ITU stay	days	
Time to free fluids	days	
Time to diet	days	
Anaesthetic time	days	
Time to bowel action	days	
Time to walking down ward	days	
Last parenteral post-op analgesia given	days	
Post-operative transfusion	○ No	○ Yes

Morbidity

Complications	○ No	○ Yes
Chest infection / respiratory infection	○ None ○ Chest infection	○ Respiratory infection
Wound infection	○ No	○ Yes
Abscess	○ None ☐ Intra-abdominal ☐ Empyema	☐ Lung ☐ Liver ☐ Other
Haemorrhage	○ No	○ Yes
Haematoma	○ No	○ Yes
DVT / PE	○ None ○ Confirmed DVT	○ Suspected DVT ○ Confirmed PE
MI / CCF / arrhythmia	○ None ☐ MI ☐ CCF	☐ Arrhythmia ☐ Cardiac arrest ☐ Unstable angina
Anastomotic / staple line leak	○ None ○ Confirmed leak	○ Suspected leak
Conduit ischaemia	○ No	○ Yes
Chylothorax	○ No	○ Yes

Unique patient identifier

Date of procedure dd / mm / yyyy

Morbidity continued ...

Other complication	○ No	○ Yes
Nature of other complication		
Was a secondary operation performed	○ No	○ Yes
Reason for secondary operation		

Pathology outcome

Tumour pT-stage	○ Tis ○ T1 ○ T2 ○ T2a ○ T2b	○ T3 ○ T3a ○ T3b ○ T4 ○ TX (unknown)
Tumour pN-stage	○ N0 ○ N1	○ N2 ○ NX
Tumour pM-stage	○ M0 ○ M1	○ M1a ○ M1b
Nodes found		
Nodes positive		
Resection margins - proximal	○ Clear	○ Involved
Resection margins - distal	○ Clear	○ Involved
Resection margins - circumferential	○ Clear	○ Involved
R grade	○ 0 ○ 1	○ 2

Unique patient identifier

Date of procedure dd / mm / yyyy

Clinical outcome

Quality of life score at 30 days

Quality of life score at 90 days

Quality of life score at 6 months

Date of recurrence dd / mm / yyyy

Site of recurrence

- ○ Anastomosis
- ○ Other local recurrence
- ○ Regional lymph nodes - chest
- ○ Regional lymph nodes - abdomen
- ○ Liver
- ○ Lung / pleura
- ○ Peritoneal cavity / ascites
- ○ Bone
- ○ Brain
- ○ Other

Death in hospital ○ No ○ Yes

Date of death dd / mm / yyyy

Cause of death

- ☐ Primary cancer
- ☐ Recurrent or secondary upper GI cancer
- ☐ Treatment-related complications
- ☐ Other illness
- ☐ Trauma
- ☐ Other
- ☐ Unknown