

**PROGNOSTIC FACTORS INFLUENCING OUTCOMES OF SPECIALIST  
MULTIDISCIPLINARY TREATMENT OF OESOPHAGOGASTRIC  
CANCER IN A UK CANCER NETWORK**

**Thomas D. Reid MB BCh MRCS (Eng)**

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

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This work has not previously been accepted in substance for any degree and is not concurrently submitted in candidature for any degree.

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For my wife, Sam and my son, Savan

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## SUMMARY

This thesis examines factors influencing the outcomes of patients receiving multidisciplinary stage-directed treatment for oesophagogastric cancer.

The hypotheses tested were: 1.The TNM7 staging system is a more accurate prognostic tool for oesophageal cancer (OC) than TNM6. 2.Use of CT-PET upstages a significant number of patients with occult metastases. 3.OC recurrence patterns differ following definitive chemoradiotherapy (dCRT) and surgery, but overall recurrence rates and survival are comparable for advanced stage disease. 4.An involved circumferential resection margin (CRM+) following oesophagectomy is associated with poorer survival and its incidence can be reduced with neoadjuvant chemoradiotherapy. 5.Early enteral nutrition improves clinical outcomes following upper GI cancer resection. 6.Centralisation of oesophagogastric cancer (OGC) surgery in S.E. Wales is feasible and associated with improved clinical outcomes.

Reclassification with TNM7 resulted in stage re-categorisation of 11.9% of OC patients. Multivariate analysis indicated only TNM7 prognostic group to be independently and significantly associated with survival. CT-PET upstaged OC M stage in 24.0% of patients. Loco-regional OC recurrence was commoner after dCRT ( $p < 0.0001$ ) but distant recurrence commoner after surgery ( $p = 0.001$ ). Disease-free survival was better after surgery for stage I ( $p = 0.069$ ) and II ( $p = 0.011$ ) but comparable with dCRT for stage III

( $p=0.878$ ) and IV ( $p=0.710$ ). CRM+ occurred in 38.0% of all OC patients, and 62.4% of pT3 patients. Multivariate analysis revealed lymphovascular invasion ( $p<0.0001$ ) and CRM+ ( $p=0.002$ ) were independently and significantly associated with disease-free survival. Multivariate analysis revealed EUS T stage ( $p<0.0001$ ) and neoadjuvant chemoradiotherapy ( $p<0.0001$ ) were independently associated with CRM+. Early enteral nutrition (EEN) was associated with reduced hospital stay ( $p=0.023$ ) and less operative morbidity ( $p=0.044$ ) than control management, due to fewer wound infections ( $p=0.017$ ), chest infections ( $p=0.036$ ) and anastomotic leaks ( $p=0.055$ ). Following centralisation, OGC critical care ( $p<0.0001$ ) and total hospital stay ( $p=0.037$ ) were significantly reduced. Serious operative morbidity (Dindo-Clavien grade III+) decreased from 33.3% to 16.7% ( $p=0.066$ ).

## **Chapter 1**

### **Introduction and a review of the literature**



## 1.1 EPIDEMIOLOGY

Oesophageal carcinoma is the eighth commonest cancer worldwide (Parkin 2001), and the ninth commonest cancer in the UK, where it accounted for more than 8000 new diagnoses and more than 7600 deaths in 2008 (Cancer Research UK 2011). The incidence for men and women in the UK is 17.5 and 8.8 per 100,000 respectively (Cancer Research UK 2011). The reported incidence of oesophageal cancer in Wales is higher still at 20.9 and 10.6 per 100,000 respectively (Welsh Cancer Intelligence and Surveillance Unit 2009). Oesophageal cancer has an almost two-fold male predominance overall, however for adenocarcinoma of the oesophagus specifically it is even higher (Cancer Research UK 2011). This male predominance is one of the highest sex differentials of any non-occupational cancer (Cancer Research UK 2011). Oesophageal cancer remains predominantly a disease of old age, with two thirds of cases diagnosed in people over the age of 65 (Cancer Research UK 2011). The last 30 years have seen a marked increase in the UK incidence of oesophageal cancer for both sexes, but particularly males, in whom the incidence has almost doubled between 1975 and 2007.

The epidemiology of oesophageal cancer differs significantly by histological subtype. Squamous cell carcinoma remains the dominant type worldwide, with the highest incidences reported in developing countries, particularly in the so called Asian 'oesophageal cancer belt', extending from Northern Iran through Central Asia to Northern China, where incidence is as high as 200 per 100,000. However, in developed

countries the incidence of squamous cell carcinoma has remained fairly stable or even decreased, while that of adenocarcinoma has increased substantially in recent decades, particularly in men. Adenocarcinoma is now the predominant histological subtype for Caucasian men in the UK. Furthermore, in the UK reported rates of adenocarcinoma are the highest in the world (Bollschweiler et al 2001, Wild et al 2003). The same time period has seen a parallel increase in the incidence of adenocarcinoma of the gastric cardia, which now accounts for more than 50% of gastric cancers, suggesting possible aetiological similarities.

## **1.2 AETIOLOGY**

The aetiology of oesophageal cancer differs for the two predominant histological cell types.

### **1.2.1 Squamous cell carcinoma**

Smoking and alcohol consumption are the predominant risk factors for oesophageal squamous cell carcinoma in Western countries. Smoking and alcohol together have a synergistic effect in promoting the development of oesophageal squamous cell carcinoma, with the risk ranging from 20 to 130-fold higher for various combinations of heavy drinking and smoking (Castellsague et al 1999, Zambon et al 2000, Freedman et al 2007). Alcohol also increases the risk independently of smoking. Estimates of the increase in the risk of oesophageal squamous cell carcinoma associated with alcohol consumption range from 18% for men and 35% for women per 10g/day alcohol consumption, (Weikert et al

2009) to 5-fold for those drinking more than three drinks per day (Freedman et al 2007), up to almost 25-fold higher in men drinking 84 or more drinks per week (Zambon et al 2000). The mechanism of action of alcohol in the development of oesophageal squamous cell carcinoma remains unclear, although possibilities include direct damage to the oesophageal mucosa, an increase in mucosal susceptibility to other carcinogens, or a secondary effect via associated dietary deficiencies. The third main risk factor for squamous cell carcinoma in the developed world is a diet lacking in fruit and vegetables. Risk reductions have been demonstrated for increased consumption of both fruit and vegetables, although in all studies of these effects there exist the confounding effects of smoking and alcohol (Key 2011).

Other dietary and lifestyle factors influencing the risk of squamous cell carcinoma include nutritional deficiencies at a young age, particularly riboflavin, vitamin A and vitamin C, diets rich in nitrosamines, and the consumption of very hot drinks (Iran – IARC Study Group 1979, Pourshams et al 2005, Mosavi-Jarrahi and Mohagheghi 2006). It is postulated that these factors cause an asymptomatic chronic oesophagitis, different from that seen in Western society-related gastro-oesophageal reflux disease, which is thought to be a precursor to squamous cell carcinoma. These aetiological factors are the most important in the high incidence developing countries, where poverty and malnutrition are prevalent.

Oesophageal strictures associated with the ingestion of corrosive agents, particularly in childhood, are associated with a 1000-fold increase in the risk of carcinoma. There is a similarly increased risk in patients with achalasia. The exact size of the increased risk is uncertain but has been estimated as 140-fold with long-standing achalasia, compared with the general population (Brucher et al 2001). The Plummer-Vinson syndrome (dysphagia, iron-deficiency anaemia, koilonychia and oropharyngeal mucosal atrophy) is associated with an increased risk of cervical oesophageal cancer (Ribeiro Jr et al 1996). Finally the rare autosomal dominant condition tylosis palmarum is associated with a very high incidence of squamous cell carcinoma (Varela et al 2011).

### **1.2.2 Adenocarcinoma**

Gastro-oesophageal reflux disease (GORD) and obesity are the principal risk factors for oesophageal adenocarcinoma. It has been estimated that 4-9% of the population experience daily heartburn, and up to 20% experience symptoms on a weekly basis (Cameron 1997). Lagargen et al (1999) stratified the risk of developing oesophageal cancer according to the symptoms of GORD. The risk of cancer is estimated to be 7.7 times higher in those with recurrent symptomatic reflux compared to those without symptoms, with even greater risk (44-fold) for those with more frequent, more severe or longer lasting symptoms. However others have found that GORD is not an independent risk factor for oesophageal cancer. (Solaymani-Dodaran et al 2004). The cancer risk associated with reflux is due to the development of Barrett's metaplasia. Barrett's oesophagus was

first described in 1950 and is defined as the replacement of the squamous epithelium by a columnar-lined mucosa in the lower oesophagus (Barrett 1950). The exact prevalence of Barrett's oesophagus is unclear as many patients are asymptomatic. Post-mortem studies estimate it may be as high as 5% (Cameron et al 1990), but endoscopy studies suggest it is found in approximately 1% of unselected patients undergoing endoscopy (Cameron et al 1992), but in 12% of those with symptoms of reflux (Winters Jr et al 1987). The metaplasia arises as a result of chronic reflux, with subsequent changes through increasing grades of epithelial dysplasia to invasive adenocarcinoma (Fitzgerald 2006). The natural history of Barrett's oesophagus remains poorly understood with considerable uncertainty regarding the overall risk of developing cancer within a Barrett's segment, the risk of progression from low grade dysplasia, and the risk of progression to cancer from high grade dysplasia. Numerous studies over the last few decades have estimated the incidence of adenocarcinoma in Barrett's oesophagus, with risk per patient year ranging from 1 in 56 to 1 in 315 (Robertson et al 1988, Miros et al 1991, Katz et al 1998, Oberg et al 2005). Additionally there is geographical variation in incidence between Western countries, with incidence rates in the UK and USA of 1% and 0.5% respectively per year (Jankowski et al 2002). The most notable risk factor for malignant transformation of Barrett's metaplasia is the segment length (Menke-Pluymers et al 1993), but other factors include male sex, age over 45, Caucasian ethnicity, severe reflux symptoms, obesity and heavy smoking (Watson et al 2005).

The obesity epidemic in the Western world, most notably in the USA and UK, has paralleled the rising incidence of oesophageal adenocarcinoma in these countries over the last 30 years. There is a three to six-fold increased risk of oesophageal adenocarcinoma in the overweight (Cheng et al 2000), which is attributed at least in part to the increased reflux and increased incidence of hiatus hernia that is associated with excess intra-abdominal adiposity. However, evidence is also accumulating that the obesity effect is independent of reflux (Lindbald et al 2005). In addition there is a marked sex difference to the obesity effect, with the male (abdominal) fat distribution being particularly associated with cancer risk (Vaughan et al 2002). The role of *Helicobacter pylori* (*H. pylori*) infection in the aetiology of junctional cancer remains unclear but there is evolving evidence of a reduced risk of junctional adenocarcinoma conferred by *H. pylori* infection (Whiteman et al 2010). It is postulated that gastric *H. pylori* infection paradoxically protects the lower oesophagus, by virtue of hypochlorhydria due to gastric atrophy, and ammonia production from the action of bacterial urease, changing the contents of the refluxing gastric juice. The increase in junctional cancer incidence has mirrored a decrease in *H. pylori* incidence in developed countries, and *H. pylori* eradication has become widespread over the last 20 years. Socio-economic deprivation has an adverse effect on adenocarcinoma risk, but this is less strong than for squamous cell carcinoma, and may be confounded by social class related differences in obesity, smoking and

alcohol, the latter two of which both increase reflux by reducing the lower oesophageal sphincter pressure.

It is known that a small proportion of cases of Barrett's oesophagus and oesophageal adenocarcinoma display familial aggregation (Ash et al 2011). However, the exact genetic basis for this remains uncertain, and the vast majority of such cases arise sporadically. Orloff et al (2011) from the Cleveland Clinic, USA, have recently identified three major genes (MSR1, ASCC1 and CTHRC1) that are associated with Barrett's oesophagus related adenocarcinoma. Just over 11% of siblings studied had a germline mutation in one of these three genes, most frequently involving MSR1 (Orloff et al 2011). A further validation series of unrelated patients with Barrett's oesophagus related adenocarcinoma confirmed that two of fifty-eight cases (3.4%) carried a germline mutation in the MSR1 gene (Orloff et al 2011). The genetic basis of Barrett's oesophagus and the risk of malignant transformation into adenocarcinoma is clearly in its infancy at present, and further larger cohort studies are needed to confirm the findings of Orloff et al (2011). However, it is very probable that developments in this area will play a role in risk stratification and premorbid diagnosis in the future.

## **1.3 DIAGNOSIS**

### **1.3.1 Symptoms**

The cardinal symptom of oesophageal cancer is dysphagia, usually progressive, and often accompanied by the vomiting of undigested food.

However, this symptom occurs as a consequence of tumour mass effect in advanced stage disease, and this explains the late presentation of oesophageal cancer.

### **1.3.2 Endoscopy**

Endoscopy and biopsy remains the investigation of choice for diagnosing oesophageal cancer. In addition to providing histological confirmation of the oesophageal malignancy, endoscopy also allows some assessment to be made of the local extent of the tumour. Some of the factors which can be appreciated endoscopically include the proximal and distal extent of the tumour, the length of the tumour, the relationship to the oesophagogastric junction, and whether the lesion can be crossed endoscopically. Barium studies are an alternative diagnostic modality, often reserved for those who cannot tolerate endoscopy, although clearly this technique is disadvantaged by the inability to take biopsies. Arguably the most difficult lesions to diagnose endoscopically are very early cancers arising within a Barrett's segment. Studies have demonstrated failure to diagnose oesophagogastric malignancy at the patient's first endoscopy in as many as 10%, and a further 10-20% require a further endoscopy (Bramble et al 2000, Yalamarathi et al 2004). The principal factors responsible for these deficiencies are failure to suspect malignancy, and consequently the retrieval of inadequate numbers of biopsies. When six or more biopsies are taken from a segment of Barrett's oesophagus, the diagnostic yield to detect high risk premalignant lesions reaches 100% (Fitzgerald RC et al 2001). The current recommendation for Barrett's sampling is four



quadrant biopsies at 2cm intervals along the length of the segment, which has been shown to increase diagnostic accuracy and aid differentiation of high grade dysplasia from adenocarcinoma, particularly when visible mucosal abnormalities are present (Lal et al 1992, Levine et al 1993).

### **1.3.3 Open access endoscopy referral**

Recent UK referral guidelines for suspected cancer from the National Institute for Health and Clinical Excellence (2005) state that patients of any age with alarm symptoms (chronic GI bleeding, dysphagia, progressive unintentional weight loss, persistent vomiting, iron deficiency anaemia, epigastric mass, suspicious barium meal result) or those aged 55 and older with unexplained dyspepsia should be referred urgently for endoscopy or to a specialist. The guidelines also state “In patients aged less than 55 years, endoscopic investigation of dyspepsia is not necessary in the absence of alarm symptoms”. These guidelines have caused concern amongst many upper GI surgeons, as the alarm symptoms prioritising urgent endoscopy are largely markers of advanced, possibly incurable, oesophagogastric cancer (Stephens et al 2005, Bowrey et al 2006). Indeed, the possibility to detect early oesophagogastric cancers in younger patients, the group most likely to benefit from curative treatment, is either delayed or lost altogether if applied rigidly. Furthermore, Sundar et al (2006) reviewed local open access endoscopy results and found that of 228 patients diagnosed with oesophagogastric cancer over a 4 year period, 5 patients who presented with uncomplicated dyspepsia under the age of 55 years had operable cancers.

### 1.3.4 Screening and surveillance

At present there is no role for screening of the general population for oesophageal cancer in the UK. Neither is there any proven benefit in the endoscopic screening of patients with symptomatic reflux, as the absolute risk of cancer in such patients has been shown to be less than 1 in 1000 per annum (Shaheen and Ransohoff 2002), and consequently this is not recommended in the UK (Watson et al 2005). Endoscopic surveillance of patients with known Barrett's metaplasia, with the aim of detecting cancer or high grade dysplasia, is widely practiced in the UK, Europe and the USA. The presumed benefits of surveillance are the earlier detection of oesophageal adenocarcinoma, with an increased opportunity for curative treatment, and consequently better outcomes. However, this practice remains contentious as the benefits have never been proven in a randomised controlled trial, although many non-randomised studies have demonstrated better survival rates with surveillance detected cancers than non surveillance detected cancers (Pera et al 1992, Levine et al 1993, Peters et al 1994, Fountoulakis et al 2004). The current recommendation in the UK guidelines is for surveillance endoscopy to be undertaken every 2 years, for patients with non dysplastic Barrett's (Watson et al 2005). This recommendation has been derived from computer modelling, based on the assumption of a 1% risk of cancer per annum in the UK. In the past, patients were considered eligible for surveillance if their performance status made them potentially suitable for oesophagectomy. However the increasing use of endoscopic treatment modalities for early oesophageal

cancers means that this is no longer necessarily the case. The Barrett's Oesophagus Surveillance Study (BOSS) is a large multicentre UK randomised controlled trial of surveillance vs. questionnaire follow-up for Barrett's. It is envisaged that the results of this study which recruited more than 3400 patients when it closed in 2011 will improve future surveillance practice.

#### **1.4 STAGE CLASSIFICATIONS**

In 1986, following an agreement between the American Joint Committee on Cancer (AJCC), the Japanese Joint Committee (JJC) and the International Union Against Cancer (IUCC), the TNM staging classification system was introduced. This is the gold standard staging system used globally. Its objectives are to inform the planning of treatment, to help determine prognosis and to allow comparison of outcomes between centres. Periodic updates are published to incorporate the expanding evidence base. The TNM system has recently been revised in a 7<sup>th</sup> edition (Sobin et al 2009), with effect from 2010. This incorporates major modifications for oesophageal cancer, based for the first time on a mathematical data driven approach (Rice et al 2010). Staging can be based on a combination of clinical (radiological) and surgical findings, but ultimately the final stage is set histopathologically by analysis of the resected specimen.

#### **1.4.1 Anatomical site**

The TNM classification of the anatomical site of the primary tumour is derived from the original description by the Japanese Society for Esophageal Diseases (1976), and divides the oesophagus into four parts. The cervical oesophagus from the lower border of the cricoid cartilage to the thoracic inlet at the suprasternal notch. The upper thoracic portion from the thoracic inlet to the level of the tracheal bifurcation. The mid thoracic portion, which is the proximal half of the oesophagus between the tracheal bifurcation and the oesophagogastric junction and the lower thoracic portion which is the distal half. (Sobin et al 2009).

#### **1.4.2 Tumour stage**

The T stage is based on the depth of invasion of the tumour through the different layers of the oesophageal wall. Changes in T stage in TNM7 include the inclusion of high grade dysplasia, along with carcinoma in situ, in the Tis category. In addition T1 has been subdivided into T1a and T1b components to reflect tumour extension confined to the mucosa, or extending into the submucosa respectively. Stage T4 denotes tumour invasion of adjacent structures, and has now been subdivided into T4a and T4b components. The former describes structures that can be resected surgically, in part if necessary, including pleura, pericardium and diaphragm, whereas the latter describes non-resectable structures, such as aorta, trachea and vertebral body. Depth of tumour invasion is established as one of the most consistent negative prognostic indicators

(Ide et al 1994, Lieberman et 1995, Paraf et al 1995, Lozac'h et al 1997, Khan et al 2003).

### **1.4.3 Nodal stage**

The regional lymph nodes are defined according to the anatomical location of the primary tumour. In the cervical oesophagus the regional lymph nodes are the scalene, internal jugular, upper and lower cervical, paraoesophageal and supraclavicular. With regard to the intrathoracic oesophagus the regional lymph nodes are the internal jugular, tracheobronchial, superior mediastinal, paratracheal, perigastric (excluding coeliac), carinal, pulmonary hilar, perioesophageal, left gastric, pericardial, nodes of the lesser curve of the stomach and posterior mediastinal nodes. Lymph node status has long been recognised as one of the most important prognostic markers (Khan et al 2003, Lozac'h et al 1997, Paraf et al 1995). Furthermore, the number of lymph node metastases is also a widely reported prognostic indicator (Ide et al 1994, Lieberman et al 1995, Kawahara et al 1998, Zafirellis et al 2002, Kunisaki et al 2005, Mariette et al 2008). A major update was incorporated into TNM7 (Sobin et al 2009, Rice et al 2012) to take account of the number of lymph node metastases, with N stage sub classifications of N1 (1-2 nodes), N2 (3-6 nodes), or N3 (>6 nodes).

### **1.4.4 Metastasis stage**

The M stage is the assessment of distant metastases. In the previous 6<sup>th</sup> edition of TNM (Sobin and Wittekind 2002) there were M1a and M1b sub

classifications, dependent on the position of the primary tumour and the location of metastases. However in TNM7 this had been simplified to M0 denoting the absence of distant metastases and M1 where there is evidence of metastases.

#### **1.4.5 Stage groupings**

Patients are also allocated a stage group ranging from I to IV. These groups were previously defined on the basis of anatomical T, N and M stages under TNM6. The updated TNM7 contains revised grouping definitions to incorporate the new N stage system, but also contains a new system of prognostic groupings. The latter differ for adenocarcinoma and squamous cell carcinoma, and incorporate additional factors of prognostic relevance for early stage (I and II) tumours. For both histological subtypes these definitions include tumour grade, and for squamous cell carcinoma, site within the oesophagus is also specified. A summary of TNM7 is provided in Appendix 2.

#### **1.4.6 Siewert classification**

In response to the increasing incidence of junctional oesophagogastric tumours, Siewert and Stein (1998) proposed a classification of such tumours into three groups based on endoscopic, radiological and histopathological findings. Type I are adenocarcinomas of the distal oesophagus, with an epicentre 2-5 cm above the cardia which may infiltrate the oesophagogastric junction from above. Type II are true junctional cancers, with an epicentre within 2 cm of the cardia. Type III

are sub-cardial gastric cancers, with an epicentre 2-5 cm below the cardia which may infiltrate the oesophagogastric junction and distal oesophagus from below. These tumours pose a particular difficulty in staging, and there is debate as to which TNM system should be used for each type. In the TNM7 classification, Type I and II are staged with the oesophageal system, and Type III are staged with the gastric system, provided the epicentre is at least 2 cm below the cardia and there is no extension into the oesophagus (Sobin et al 2009).

#### **1.4.7 Histopathological specimen reporting**

High quality histopathological assessment of oesophagectomy specimens facilitates accurate prognostic information for patients and clinicians, provides feedback to surgeons on the quality of resection and the effects of neoadjuvant therapy, and provides feedback for radiologists on the accuracy of staging information (Mapstone 2007). A minimum core data set is defined by the Royal College of Pathologists, and includes TNM stage, along with other pathological markers of prognostic value.

#### **1.4.8 Margin status**

Proximal and distal resection margin status must be assessed as there is good evidence that tumour involvement of either increases the risk of recurrence, although the evidence is stronger for proximal than distal margins (Robey-Cafferty et al 1991, Paraf et al 1995, Mariette et al 2003, Casson et al 2000). Circumferential margin (CRM) status remains an area of contention. Since the seminal study of Sagar et al (1993),

demonstrating the prognostic significance of a positive CRM, a number of other studies of heterogeneous design have sought to clarify the issue (Dexter et al 2001, Khan et al 2003, Griffiths et al 2006, Sujendran et al 2008, Scheepers et al 2009, Saha et al 2009, Mirzenami et al 2010). Many, but not all, (Khan et al 2003) have found some degree of prognostic significance for CRM status. Given this uncertainty, some have suggested CRM status should not be routinely reported following oesophagectomy (Khan et al 2003), but it remains in the core data set until a consensus can be reached, and to provide surgical and radiological feedback (Mapstone 2007).

#### **1.4.9 Tumour differentiation**

Increasing tumour grade has an established negative association with survival in both squamous cell carcinoma and adenocarcinoma of the oesophagus (Robey-Cafferty et al 1991, Paraf et al 1995, Lieberman et al 1995). Where areas of different grades are present, differentiation is taken as that of the highest grade present in a tumour.

#### **1.4.10 Vascular invasion**

Vascular invasion, either venous or lymphatic, has an established prognostic association in oesophageal cancer, using both univariate and multivariate analysis (Robey-Cafferty et al 1991, Ide et al 1994, Paraf et al 1995, Zafirellis et al 2002). Invasion of any venous or lymphatic space should be recorded as vascular invasion (Mapstone 2007).



#### **1.4.11 Response to neoadjuvant treatment**

Oesophageal resection specimens frequently demonstrate histopathological evidence of the effects of chemotherapy or radiotherapy. Several schemes have been suggested for the classification of response to neoadjuvant therapy (Mandard et al 1994, Chirieac et al 2005), but none are universally accepted and their use is largely restricted to the research setting. TNM stage following neoadjuvant therapy is prefixed by 'y', with complete pathological response designated ypT0N0.

#### **1.5 PRE-OPERATIVE STAGING**

Accurate radiological staging of patients with oesophageal cancer is crucial, as it allows the most appropriate stage-directed management to be tailored to individual patients, and avoids aggressive surgery with no chance of cure in those with disseminated disease. All staging modalities should define stage in accordance with the TNM classification. The general principles of staging are first to identify those patients who have metastatic disease (M1) at presentation and for whom further staging and curative treatment is inappropriate. Following this, precise locoregional staging is undertaken to establish not only T and N stage, but also the precise margins of the disease and the position of lymph node metastases. The principal modalities used in contemporary staging include computed tomography (CT), endoluminal ultrasonography (EUS), endoscopic mucosal resection (EMR), CT-positron emission tomography (CT-PET) and laparoscopy, all of which have complementary roles.

### 1.5.1 Computed tomography (CT)

Computed tomography is usually the first radiological modality undertaken. The main purpose of CT is to establish the presence or absence of distant metastases, and consequently determine the need to progress to further staging modalities. CT technology has developed considerably over the last decade, with the most recent scanner hardware advances relating mainly to x-ray detectors. Contemporary scanners utilise multiple rows of detectors, arranged along the longitudinal axis of the patient, allowing the acquisition of multiple sets of projection data for each rotation of the gantry assembly (Cody and Mahesh 2007). Such progress has resulted in the findings of many studies of CT accuracy becoming outdated, as many involved older generation scanning technology.

The T stage accuracy of CT compared with histopathology has been variably reported from 43 to 92%, with increased accuracy attributed to new techniques including virtual endoscopy (3D reconstruction from an endoluminal perspective, Kim et al 2006, Panebianco et al 2006, Onbas et al 2006), and hydro-CT (water loading with gas forming granules to enhance oesophageal distension, Ba-Ssalamah et al 2011). One particular area of controversy relating to CT is the loss of the periesophageal fat plane. When present, invasion is unlikely, but when absent it cannot be taken as definite evidence of such, and this may explain CT overestimation of tracheal, bronchial and aortic invasion.

Meta-analysis derived CT N stage sensitivity and specificity are 50% and 83% respectively (van Vliet et al 2008). However, many of the included studies involved CT technology outdated by contemporary standards, and the criteria used to identify malignant lymph nodes are an area of considerable controversy. It is very difficult on CT to differentiate abnormally enlarged lymph nodes that contain tumour, from those enlarged for benign reasons, and size criteria are therefore important. Lymph nodes greater than 1cm in size are likely to be malignant, although size criteria for such involvement have been reported by various authors from 0.5 to 1.5 cm (Fekette et al 1988). Furthermore, mediastinal lymph nodes greater than 1cm diameter can be normal, and conversely normal sized nodes can contain tumour deposits. One study of 23,000 lymph nodes assessed histopathologically following gastric cancer resection, found the mean diameter of a metastatic node was 7.8 mm, and if a cut off of 5 mm was applied, then 38% of metastatic nodes would be missed (Noda et al 1998).

The principal strength of CT is in the assessment of distant metastases, for which meta-analysis derived sensitivity and specificity have been reported as 52% and 91% respectively (van Vliet et al 2008). The main weaknesses of CT with regard to M stage are the assessment of very small lesions and the detection of small volume peritoneal disease. For the latter reason there remains a need for staging laparoscopy for tumours with a component below the diaphragm.

### 1.5.2 Endosonography (EUS)

The principal strength of EUS is in locoregional staging, for which it is the established gold standard, and is recommended for all patients with oesophageal cancer potentially suitable for curative treatment (Allum et al 2011). EUS has been shown to reduce the incidence of open and closed oesophageal surgery (Fockens et al 1998). EUS also allows guided fine needle aspiration (FNA) of suspicious lymph node metastases where indicated. A further benefit of EUS is the accurate determination of the margins and length of disease, which are important from both surgery and radiotherapy perspectives. The main weakness of EUS is that failure to cross stenotic tumours is reported in as many as third of patients (Vrieze et al 2004), which is associated with a poor prognosis (Vickers and Alderson 1998), although valuable staging information can still be obtained using blind endoscopic probes (Twine et al 2009a).

EUS is known to be more accurate at determining T stage than CT (Kienle et al 2002). Reported accuracy ranges from 33 to 90% for T1 tumours, but for T2, T3 and T4 tumours there is less disparity between studies and generally greater accuracy of 75 to 93% (Rosch et al 1992, Grimm et al 1993, Dittler and Siewert 1993, Catalano et al 1995).

For the assessment of lymph nodes EUS provides more information than CT. In addition to size, EUS can determine shape, border demarcation, echo intensity and texture of lymph nodes. The same studies show variation in accuracy for nodal disease, ranging from 42 to 94% for N0

tumours and 74 to 89% for N1 tumours (TNM6 stages) (Rosch et al 1992, Grimm et al 1993, Dittler and Siewert 1993, Catalano et al 1995). Meta-analysis derived EUS N stage sensitivity and specificity are 80% and 70% respectively (van Vliet et al 2008).

Although EUS is not generally suitable for the assessment of distant metastases, it can identify coeliac axis or cervical lymph metastases, and facilitate guided FNA if appropriate.

A further consideration in the utilisation of EUS is the experience of the endosonographer, as results are highly operator dependant. National UK guidelines have recently recommended that centres should perform at least 100 staging examinations annually, and each centre should have at least one fully trained endosonographer (Allum et al 2011). Such guidance strengthens the current argument for centralising specialised staging services in high volume centres.

### **1.5.3 Endoscopic Mucosal Resection (EMR)**

EMR is an emerging modality increasingly used for the staging and treatment of early oesophageal cancer. EMR is indicated for the assessment of areas of Barrett's oesophagus where invasive disease is suspected. One particular advantage of EMR is the opportunity to obtain biopsies that extend deeper into the oesophageal wall than those obtained at standard endoscopy, and this is crucial in the accurate staging of T1 cancers. A recent study has shown submucosa is contained in 88% of EMR biopsies but only 1% of standard biopsies (Wani et al 2010).

Furthermore, there is significantly stronger interobserver agreement on the histopathological interpretation of specimens taken by EMR than standard mucosal biopsies (Mino-Kenudson et al 2007, Wani et al 2010). It is now generally accepted that EMR is more accurate than EUS in staging T1 cancers (Mino-Kenudson et al 2007, Peters FP et al 2008, Curvers WL et al 2008).

#### **1.5.4 CT-positron emission tomography (CT-PET)**

Medical imaging utilising positron emission was first reported at the Massachusetts General Hospital, Boston, USA in 1951. A simple prototype scanner, incorporating two opposed detectors, was built in-house and used for cranial imaging of patients with suspected brain tumours, with encouraging early results (Sweet 1951). Progressive technological development over subsequent decades resulted in the sale by Siemens of the first commercial positron emission tomography (PET) scanner to UCLA, Los Angeles, USA in 1976. As a nuclear medicine technique, PET provides functional rather than anatomical information. The underlying principle is based on positrons (positively charged electron counterparts) emitted by short half-life radionuclides interacting in body tissues with electrons, resulting in the production of gamma rays, which are detectable by conventional means. The most commonly used radionuclide,  $^{18}\text{F}$ , is coupled to the glucose analogue fluorodeoxyglucose (FDG) and injected intravenously. The rate of cellular tracer uptake is proportional to metabolic activity, and once intracellular, FDG cannot be immediately metabolised, unlike glucose, and therefore remains

intracellular until radioactive decay occurs. Malignant tumours usually have higher metabolic rates than normal tissue, enabling their identification with CT-PET (Branstetter et al 2005).

Traditionally PET information was software fused with separate CT data to provide anatomical localisation. More recently integrated CT-PET hardware has been developed (Beyer et al 2000), with the first commercial clinical application in 2001, and since then more than 1000 installations have been established worldwide (Beyer and Townsend 2006). The advantage of integrated scanning is attributable to more accurate co-registration of the CT and PET datasets due to lack of patient movement artefact. The technology is widely used for a raft of different cancers including lung, gastrointestinal, breast and lymphoma (Endo et al 2006).

In oesophageal cancer the bulk of the published data on staging relates to separate CT and PET scans. The role of CT-PET in assessing T stage is very limited. Identification of a tumour on CT-PET relies upon adequate FDG uptake, and although 95-100% of large tumours demonstrate such uptake, this is less predictable for early stage tumours (T1 and T2) and poorly cellular mucinous tumours. Conversely false positive results may occur due to gastro-oesophageal reflux disease. Studies including adenocarcinoma and squamous cell carcinoma report a failure to detect rate of between 0 to 20% of oesophageal tumours (Rankin et al 1998, Kato et al 2005, Pfau et al 2007), with many of the undetected cancers being early stage lesions. CT-PET has limited value in assessing the perioesophageal fat plane in T3/T4 tumours, although this is due to the CT

component, and the PET data adds nothing in this regard (Choudhary et al 2008).

The accuracy of N stage determination is reported variably. Meta-analysis derived PET N stage sensitivity and specificity are 57% and 85%, representing an improvement over CT for both parameters, and poorer sensitivity yet better specificity compared with EUS (van Vliet et al 2008). Few studies have compared CT-PET compared with separate CT and PET scans, although Yuan et al (2006) have demonstrated 12 and 5% improvements in sensitivity and specificity respectively for the former. N stage accuracy also differs for peritumoural lymph nodes compared with more distant regional nodes, with the former being most difficult to identify due to FDG uptake from the primary tumour (Flamen et al 2000, Yoon et al 2003).

The principal strength of PET is in the detection of distant metastases, where meta-analysis derived sensitivity and specificity have been reported as 71 and 93% respectively (van Vliet et al 2008). These sensitivity and specificity figures represent 19 and 2% improvements over CT in these parameters respectively (van Vliet et al 2008). Recent UK studies of the use of CT-PET in oesophageal cancer, in Leicester and Leeds have reported a change of treatment type as a direct result of this imaging modality in 20 to 40% of patients. This was mainly attributed to upstaging by the detection of occult metastases. However, the caseloads studied were relatively small at 38 and 25 patients (Williams et al 2009, Salahudeen et al 2008).



Additional applications of CT-PET in the treatment of oesophageal cancer include assessment of the response to neoadjuvant therapy, the planning of radiotherapy, and the identification of recurrent disease. However, the role of CT-PET in these areas remains to be defined at present (Bruzzi et al 2007, Choudhary et al 2008, Mujis et al 2010).

### **1.5.5 Staging Laparoscopy**

Current UK guidelines suggest staging laparoscopy for select patients with lower oesophageal or junctional tumours with a gastric component (Allum et al 2011). The principal strengths are the identification of small peritoneal or liver metastases, undetectable by other modalities, and the option to cytologically sample the peritoneal cavity. De Graff et al (2007) recently demonstrated that staging laparoscopy avoids inappropriate laparotomy in 17.1% and 17.2% of patient with lower oesophageal and junction carcinomas respectively. Furthermore, the routine use of peritoneal cytology in patients without overt metastases on laparoscopy, has been found to upstage a further 5% and 9% of patients with oesophageal and junctional tumours respectively (Nath et al 2008).

## **1.6 PRE-OPERATIVE PHYSIOLOGICAL ASSESSMENT**

The aims of physiological assessment are to inform decision making related to treatment type and to allow optimisation of performance status in patients selected for surgery in order to minimise operative risk. Oesophagectomy carries a substantial element of cardiopulmonary stress, and pulmonary complications in particular are a major cause of mortality

(Griffin et al 2002, Bailey et al 2003, NHS Information Centre 2010). Consequently, a raft of clinical risk predictors have emerged that are thought to have an association with surgical outcome, although the reliability of many remain controversial, and there is no consensus on selection criteria for upper GI resectional surgery. Age alone is not an absolute contraindication to surgery, even though comorbidity and organ dysfunction increase with age. It has been reported that in a specialist unit with appropriate case selection, good survival outcomes are achievable for patients over the age of 70 years compared to those under 70 years, although the risk of morbidity is higher (Alexiou et al 1998).

### **1.6.1 Risk assessment**

The American Society of Anaesthesiologists' (ASA) classification of pre-operative physical status is familiar and frequently applied. Although it is used globally the correlation of ASA grade with peri-operative risk has limitations. The Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (POSSUM) was developed by Copeland et al (1991) to better predict surgical risk. The strength of the POSSUM model is that it combines an assessment of physiological status (physiological score) with a measure of the magnitude of an operation (operative severity score). POSSUM and models adapted from it, are widely used and validated in many surgical specialities. Despite this, POSSUM has a poor predictive accuracy related to oesophagectomy (Zafirellis et al 2002). A modified P-POSSUM version was developed in Portsmouth, in recognition of the general overestimation of mortality in low

risk patients, and has been found to have greater accuracy, although it is not specific to oesophagogastric surgery (Prytherch et al 1998). A further O-POSSUM version was therefore derived specifically for oesophagogastric surgery (Tekkis et al 2004). The value of the various POSSUM models in oesophagogastric surgery remains highly controversial, with studies finding both P-POSSUM (Nagabushan et al 2007, Dutta et al 2010) and O-POSSUM (Bosch et al 2011) to be of greater predictive accuracy. Much of the debate relates to the degree of overestimation of mortality associated with each model (Nagabushan et al 2007, Lagarde et al 2007, Dutta et al 2010, Bosch et al 2011).

### **1.6.2 Cardiopulmonary exercise testing**

Cardiopulmonary exercise testing (CPET) is a dynamic and objective test that assesses the ability of a patient to adapt to the increased oxygen demand known to be precipitated during and following thoracic surgery (Saito et al 2007). Increasing exercise results in oxygen consumption exceeding supply, and consequently a switch to anaerobic metabolism to supplement demands. The value for oxygen consumption at this point is the anaerobic threshold, and a value below 11ml/kg/min has been reported to predict greater mortality following major abdominal surgery (Older et al 1999). The other two CPET derived physiological variables of most interest are peak oxygen uptake ( $\dot{V}O_2$  max) and ventilatory equivalent for carbon dioxide ( $\dot{V}_E/\dot{V}CO_2$ ). Few studies have investigated the association between CPET derived variables and outcome in oesophagogastric cancer surgery. The most consistent data exists for

VO<sub>2</sub> max, which has been reported to be significantly lower in those who experience cardiopulmonary morbidity following oesophagectomy (Nagamatsu et al 1994 and 2001, Forshaw et al 2008). Only Nagamatsu et al (1994) found a similar association for anaerobic threshold. A further finding was that the majority of resting lung function variables had no association with subsequent morbidity following oesophagectomy (Nagamatsu et al 1994 and 2001). However, these studies had small sample sizes, and were therefore potentially underpowered to detect small differences, and also lacked clinician blinding to the CPET results. There remains a need for a large-scale study of CPET in oesophagogastric surgery (Hennis et al 2011).

## **1.7 SURGICAL TREATMENT**

The fundamental aim of surgery for oesophageal cancer is to remove all malignant tissue, and provide survival with acceptable quality of life. Many controversies continue to surround the surgical management of oesophageal cancer, including the optimum operative approach, the role of neoadjuvant therapy, the peri-operative care and the configuration of surgical services.

### **1.7.1 Operative approach**

The most appropriate operative approach in oesophageal cancer remains controversial and should preferably be determined by the histological tumour type, tumour location, the extent of the proposed lymphadenectomy, patient factors and the experience of the surgeon

(Allum et al 2011). The main decision for Western patients with distal oesophageal or junction adenocarcinoma is between a transthoracic resection (Lewis 1946, Tanner 1947) with extended en bloc lymphadenectomy, or a transhiatal approach (Orringer 1984). The transthoracic approach risks greater early morbidity in the hope of better long term survival. The transhiatal procedure aims to reduce early pulmonary morbidity, largely by avoiding a thoracotomy, but at the cost of potentially poorer long term survival.

The Lewis Tanner procedure is a two stage approach via an upper midline laparotomy and right posterior lateral thoracotomy. The thoracic stage consists of an en-bloc resection of the oesophagus, thoracic duct peri-oesophageal tissue and mediastinal pleura up to the level of the carina. A complete posterior mediastinal lymphadenectomy is performed to include the subcarinal lymph nodes.

A transhiatal resection is performed via the abdomen and neck. Gastric and oesophageal mobilisation is performed under direct vision up to the inferior pulmonary vein. The remainder of the oesophageal dissection is performed using a blunt technique followed by reconstruction using a tubularised gastric conduit with a left cervical anastomosis. Critics of this approach argue that it is an inferior oncological operation, principally due to the lack of a formal mediastinal lymphadenectomy (Hulscher et al 2001). However, proponents argue that long term survival is equivalent to the transthoracic approach (Morgan et al 2007a). Occasionally, a three stage oesophagectomy is employed for middle or upper third tumours (McKeown

1985). This procedure involves abdominal gastric mobilisation, right thoracotomy and cervical anastomosis, and was recommended by McKeown (1985) on the grounds that an anastomotic leak in the neck is less catastrophic than one in the thorax.

In reality, in Western patients there is little evidence of the superiority of one procedure over another in terms of overall survival. The best data was produced by a large Dutch randomised trial which compared transthoracic and transhiatal resection in patients with distal oesophageal and junctional tumours (Hulscher et al 2002, Omloo et al 2007). Operative morbidity rates were significantly lower in the transhiatal group, but in-hospital mortality was similar (Hulscher et al 2002). There was no difference in survival related to operative approach for Siewert type II tumours, but for type I tumours transthoracic resection was associated with a non-significant 14% improvement in 5 year survival in comparison with transhiatal resection (Omloo et al 2007). Transthoracic resection also showed a survival advantage over transhiatal resection for patients with 1 to 8 lymph node metastases, but there was no difference for those who were node negative, or had more than 8 involved lymph nodes (Omloo et al 2007).

### **1.7.2 Minimally invasive oesophagectomy**

A number of minimally invasive oesophageal resection techniques have been described, including thoracoscopic dissection, laparoscopic mobilisation of the stomach in the abdomen for utilisation as a conduit,

and hybrid laparoscopic and thoracoscopic approaches. No randomised trials have yet compared minimally invasive with open techniques. However, several published UK series, from highly regarded units, have raised concerns relating mainly to the high incidence of gastric conduit necrosis following minimally invasive oesophagectomy, for which the reasons are unclear (Safranek et al 2010, Blazeby et al 2011). This presently remains very much an evolving area of practice.

### **1.7.3 Lymphadenectomy**

The aims of lymphadenectomy are to optimise lymph node staging histopathologically, control locoregional disease and improve long term survival. Single-field dissection involves upper abdominal lymphadenectomy only, two-field dissection also includes thoracic lymphadenectomy, and three field dissection includes abdominal, thoracic and cervical lymphadenectomy. The improved accuracy of nodal staging associated with lymphadenectomy is well established (Lerut et al 1992, Dresner and Griffin 2000), but the impact of lymphadenectomy level on locoregional control and long term survival is less certain. There is little justification for oesophagectomy without at least one-field lymphadenectomy. The arguments for routine two-field lymphadenectomy are that more radical surgery increases the chance of R0 resection (microscopically clear margins) and that squamous cell carcinoma and adenocarcinoma of the upper, middle and lower thirds of the oesophagus have mediastinal lymph node metastases in over 70% of cases (Lerut et al 1992, Akiyama et al 1994, Dresner and Griffin 2000). The long term

outcomes of the Dutch trial, demonstrating survival benefit following transthoracic resection for tumours with 1 to 8 lymph node metastases, supports this argument (Omloo et al 2007).

Three-field lymphadenectomy is advocated by the Japanese for squamous cell tumours. Akiyama et al (1994) demonstrated cervical lymph node metastases were present in 25% of squamous cell carcinomas, yet no survival difference was identified for patients who had two or three field lymphadenectomy. Three-field lymphadenectomy is not routine practice in the UK. Indeed squamous cell carcinomas are far less common in the West and such patients are less likely to be surgical candidates owing to a combination of smoking related co-morbidity and high oesophageal tumours.

## **1.8 PERI-OPERATIVE CARE**

### **1.8.1 Enhanced recovery after surgery (ERAS)**

Conventional peri-operative care following gastrointestinal resection and anastomosis was based on prolonged periods of gastrointestinal tract rest until the return of normal gut function, with an acceptance that the stress response was inevitable after major surgery. The last decade has seen radical changes in practice. The now familiar concept of Enhanced Recovery After Surgery (ERAS) was pioneered by Kehlet in Copenhagen, Denmark, following colorectal surgery and challenged many aspects of traditional peri-operative care (Basse et al 2000). The ERAS group was established in 2001 as a European collaboration of university surgical



departments in the UK, Sweden, Denmark, Norway and The Netherlands. ERAS describes an evidence-based multidisciplinary package of measures for patients undergoing colorectal surgery, with the core aim of reducing the stress response to surgery and promoting the return of normal gut and body function (Fearon et al 2005). The components of ERAS include pre-admission information and patient education, the avoidance of pre-operative bowel preparation, reduced pre-operative fasting, carbohydrate loading, anti-thrombotic and antibiotic prophylaxis, goal directed anaesthesia, small surgical incisions or minimal access surgery, avoidance of NG tubes and drains, avoidance of fluid and sodium overload, post-operative nutrition with early oral fluid and dietary intake, early mobilisation and clearly defined discharge criteria. When used in combination, the protocol has been demonstrated in large meta-analyses to significantly reduce morbidity rates and shorten hospital stay following colorectal resection (Gouvas et al 2009, Varadhan et al 2010), and is consequently a mainstay of contemporary colorectal practice. There is also some evidence for the role of ERAS in gynaecological surgery (Sjetne et al 2009) and urological oncology surgery (Arumainayagam et al 2008). In contrast, there is a distinct lack of published data for enhanced recovery in oesophagogastric surgery, with most of the current interest in improving outcomes focussed largely on service reconfiguration and minimally invasive surgery. A single non-randomised Spanish study has recently reported reduced morbidity and mortality, and shortened hospital stay

associated with the use of written enhanced recovery protocols following oesophagectomy (Munitz et al 2010).

### **1.8.2 Post-operative Nutrition**

An appreciation of the impact of nutritional status on surgical outcome dates back to the 1930s, and the work of Studley (1936). It was demonstrated that patients who underwent partial gastrectomy for peptic ulcer disease, who had lost more than 20% of their pre-illness weight had a ten-fold increased operative mortality, compared with those who had lost less than 20% (Studley 1936). Undoubtedly, advances in surgery, anaesthesia, antibiotics and post-operative care have reduced such high rates of complications in malnourished patients, but recent studies confirm significantly increased morbidity and prolonged hospital stay following gastrointestinal surgery in patients with protein depletion (Hill 1994). In the 1980s, there was considerable interest in peri-operative total parenteral nutrition (TPN), with numerous trials in surgical and critically ill patients, many of which were performed in patients not specifically malnourished (Fearon et al 2003). Meta-analysis failed to identify any improvement in operative morbidity or mortality associated with TPN (Heyland et al 1998). There was a shift in emphasis from TPN to enteral nutrition (EN) during the 1990s, due predominantly to EN being more physiological, associated with fewer septic complications related to venous access, and reduced cost. The specific benefits of EN include preservation of gut structure and function (Maxton et al 1989) and the enhancement of gut mediated immunity (Kudsk 2002). The superiority of

EN over TPN in surgical patients has been demonstrated in randomised studies (Bozzetti et al 2001). A recent meta-analysis of EN within 24 hours of gastrointestinal surgery demonstrated significantly reduced mortality, with trends towards reduced operative morbidity and reduced length of hospital stay, but stressed the need for an adequately powered randomised trial to test these findings (Lewis et al 2009). In oesophagogastric surgery, where oral intake is contraindicated, the route of administration of EN is controversial, with nasojejunal tubes being poorly tolerated and the possibility of major complications associated with surgical feeding jejunostomy placement (Hoffmann et al 2001). Consequently, jejunal feeding is not routine in all centres following oesophagogastric surgery in the UK. The latest UK oesophagogastric cancer guidelines recommend nutritional support specifically for “patients who are malnourished or at risk of malnutrition, and have an inadequate oral intake defined as having eaten little or nothing for more than 5 days and/or likely to eat little or nothing for the next 5 days or longer” (Allum et al 2011). This recommendation closely adheres to the 2006 National Institute for Health and Clinical Excellence adult nutrition guidance.

### **1.8.3 Fluid management**

The dangers of excessive saline administration have been recognised for the last century (Evans 1911). Although physiology has evolved highly efficient homeostatic mechanisms for maintaining fluid and electrolyte balance in situations of water deficit or excess, or sodium deficit, it is far less effective in dealing with sodium excess (Macafee et al 2005). The

reasons for this may relate to the relatively recent occurrence of sodium excess, in evolutionary terms, due to dietary changes and medical therapy (Lobo 2004). This situation is compounded by the stress response to surgery or critical illness, such that post-operative patients are even more vulnerable to fluid or sodium excesses than healthy individuals (Lobo 2004, Allison 2004). The stress response causes anti-diuresis and oliguria, mediated by vasopressin, catecholamines and the renin-angiotensin-aldosterone system. Water and sodium are thus retained, even in situations of overload. Moreover, the use of saline can result in hyperchloraemia, further compromising the ability to excrete sodium and water (Wilcox 1983).

Fluid overload due to excess administration is recognised as a cause of delayed return to normal gut function (Lobo et al 2002), impaired wound or anastomotic healing and can potentially lead to prolonged hospitalisation and even increase mortality (Brandstrup et al 2003, Tambyraja et al 2004, Lobo 2006). Despite these dangers, knowledge of recommended fluid and electrolyte requirements amongst UK surgeons of varying levels of seniority is poor, (Lobo et al 2001 and 2002), and intravenous fluid prescription is at best idiosyncratic (Stoneham et al 1997). Indeed, the recent British guidelines on intravenous fluid therapy (GIFTASUP) highlighted the dangers of sodium and fluid excess, and in particular the overuse of normal saline (Powell-Tuck et al 2009). Moreover, the establishment of ERAS programmes has subjected post-operative fluid management to even closer scrutiny. Early post-operative resumption of

oral hydration, with a consequent reduced need for intravenous fluid therapy, is a simple but effective way of limiting fluid excess, and a core component of ERAS protocols in colorectal surgery (Basse et al 2000, Fearon et al 2005). The situation in upper gastrointestinal surgery is more complex, with the oral route frequently unavailable in the immediate post-operative period. It has been postulated that the use of early jejunal nutrition after upper GI resection reduces the need for supplementary intravenous fluid and therefore limits the dangers of fluid and sodium excess, but this issue has not been studied to date.

## **1.9 NEOADJUVANT AND ADJUVANT THERAPY**

### **1.9.1 Neoadjuvant therapy**

The majority of patients with oesophageal cancer present with advanced disease (stages III and IV). Of the minority suitable for potentially curative surgery, most will eventually develop recurrence, supporting the theory that systemic micro metastases are present at diagnosis, but are not detectable by contemporary staging modalities. Systemic disease requiring systemic treatment forms the basis of the argument in favour of neoadjuvant therapy, although the optimal regimen remains uncertain. The two largest randomised studies of neoadjuvant chemotherapy vs. surgery alone reported conflicting results. The UK based OEO2 trial demonstrated a 9% improvement in 2-year survival with chemotherapy (Medical Research Council Oesophageal Cancer Working Group 2002), and this subsequently became the standard of care in the UK over the last

decade. However, the corresponding US Intergroup trial failed to identify any survival difference (Kelson et al 1998). The most comprehensive meta-analysis to date demonstrates significant survival benefits for both chemotherapy (HR 0.87, 95% CI 0.79-0.96,  $p=0.005$ ) and chemoradiotherapy (HR 0.78, 95% CI 0.70-0.88,  $p<0.0001$ ) when compared with surgery alone (Sjoquist et al 2011). The largest randomised trial of neoadjuvant chemoradiotherapy vs. surgery alone, in 363 patients with oesophageal cancer from the Netherlands, has recently reported substantially improved overall survival (median 49 vs. 26 months, 2-year 67 vs 52%) and increased R0 resection rates (92.3 vs. 64.9%) for neoadjuvant chemoradiotherapy (Gaast et al 2010). The benefits were applicable to both squamous cell carcinoma and adenocarcinoma, although were greater for the former. The evidence comparing neoadjuvant chemotherapy with chemoradiotherapy is weaker, with only two comparatively underpowered randomised trials reported, meta-analysis of which showed a non-significant trend towards improved survival after chemoradiotherapy (HR 0.88, 95% CI 0.76-10.01,  $p=0.07$ ). An adequately powered trial of these two differing neoadjuvant regimens is urgently needed (Hingorani et al 2011).

### **1.9.2 Adjuvant therapy**

The recovery after oesophagectomy precludes the majority of patients with oesophageal cancer from receiving adjuvant therapy within an appropriate time frame. Furthermore, the data are not supportive of this approach to treatment. A recent meta-analysis of 1001 patients treated with adjuvant

chemotherapy for oesophageal squamous cell carcinoma in China failed to demonstrate any significant difference in outcome (Zhang et al 2008). Consequently adjuvant therapy is not currently recommended routinely in the UK (Allum et al 2011).

## **1.10 NON SURGICAL TREATMENT OPTIONS**

### **1.10.1 Endoscopic techniques**

Endoscopic techniques play an integral role in the multidisciplinary staging and treatment of oesophageal cancer. Current recommendations are that such procedures should only be considered when recommended by a specialist MDT, should be performed in high volume tertiary referral centres by trained clinicians, and the results carefully audited (Allum et al 2011). A number of techniques are used including endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), photodynamic therapy (PDT), and ablation using laser, argon plasma coagulation (APC), electrocoagulation, cryotherapy and radio frequency ablation (RFA). These techniques are used to remove dysplasia and early cancer, and also to address field change abnormalities such as Barrett's metaplasia. However, it is also important that patients have adequate control of reflux and helicobacter pylori eradication. The major limitation of all these modalities is the failure to treat regional lymph nodes. The risk of lymph node metastases relates to the depth of tumour invasion and the histological cell type, being more likely in squamous cell carcinoma than adenocarcinoma (Kodama et al 1998, Curvers et al 2008, Griffin et al

2011). The differentiation of mucosal (T1a) from submucosal (T1b) tumours is crucial, as Griffin et al (2011) have recently demonstrated that the risk of lymph node metastases in oesophageal adenocarcinoma is 0% of the former but 12% of the latter. On this basis therapeutic endoscopy is unsafe for submucosal (T1b) tumours (Griffin et al 2011). Endoscopic resection is appropriate for mucosal node negative (T1a N0) cancers and mucosal dysplasia (Allum et al 2011), where consistent 5-year disease-free survival of 95% with low treatment-related morbidity has been reported (Takeshita et al 1997, Inoue et al 2002, Ciocirlan et al 2007). There is a lack of randomised controlled trial data comparing endoscopic therapy with surgical resection, with much of the evidence base derived from retrospective studies subject to treatment selection bias. Nevertheless, endoscopic therapy is associated with a similar overall survival to surgery, but significantly reduced treatment-associated morbidity when compared with surgery (Das et al 2008).

### **1.10.2 Definitive chemoradiotherapy (dCRT)**

The optimum treatment for locally advanced oesophageal cancer in the UK is considered to be neoadjuvant chemotherapy followed by surgery. However, fewer than 30% of patients currently undergo surgery (NHS Information Centre 2010). Long term survival following definitive chemoradiotherapy (dCRT) for squamous cell carcinoma and adenocarcinoma has been reported in a number of studies (Cooper et al 1999, Gwynne et al 2011, Bedenne et al 2007, Stahl et al 2005, Chan et al 1999, Coia et al 2000, Kaneko et al, 2003, Geh 2001, Chiu et al 2005).



Three randomised studies have found similar overall survival rates for squamous cell carcinoma treated with dCRT and surgery (Chiu et al 2005, Stahl et al 2006, Bedenne et al 2007), although they were underpowered to detect the equivalence of dCRT. No randomised trials have yet compared dCRT to surgical based treatment for adenocarcinoma, although a recent stage-for-stage comparison for oesophageal cancer of all cell types from the S.E. Wales cancer network reported similar overall 2 year survival following dCRT and surgery with or without neoadjuvant therapy (Morgan et al 2009). Definitive chemoradiotherapy is a recommended treatment for localised squamous cell carcinoma, and is also considered a valid therapeutic option for patients with adenocarcinoma deemed unsuitable for surgery (Allum et al 2011). Treatment with dCRT is currently used in the UK in both of these scenarios (NHS Information Centre 2010). An additional consideration when determining oesophageal cancer treatment is health related quality of life (HRQL). Both treatment types have been reported to compromise HRQL in the first few months, but the effect is far greater for surgically based approaches than for dCRT. However, by one year HRQL scores are similar for both treatment types (Avery et al 2007). The role of dCRT in treating fit patients with potentially operable adenocarcinoma remains uncertain, and is clearly an area for further investigation.

### **1.11 SERVICE CONFIGURATION**

The organisation of oesophagogastric cancer surgery services in the UK remains a subject of considerable controversy and contentious conflict.

The Calman-Hine report (The Expert Advisory Group on Cancer to the Chief Medical Officers of England and Wales 1995) was the first comprehensive cancer report to be produced in the UK, and set out principles for the organisation and delivery of cancer care. It promoted a paradigm shift from a model of generalist delivered cancer surgery to a fully specialised service, and introduced the concepts of cancer centres and cancer units. However, whilst the report provided a vision for cancer services it failed to establish any central plan for implementation. Subsequent NHS organisational change and the devolution of government within the UK in the late 1990s resulted in prolonged and patchy uptake of these recommendations. Nevertheless, central support from the Department of Health in England continued for the development of national clinical standards in cancer care. Specific NHS Executive (2001) guidance for upper GI cancer was published in 2001. It recommended that surgical treatment of oesophagogastric cancer be centralised in units serving populations of at least one million. Compliance with this guidance has been strongly supported and largely achieved in England but received lesser resource and support in Wales. Indeed the most recent audit of oesophagogastric cancer surgery in Wales found that many surgeons' case loads were small, staging strategies were idiosyncratic, open and close operations were common, operative mortality high and long term survival poor (Pye et al 2001).

A wealth of evidence supports the relationship between surgeon or unit case volumes and short term outcomes in oesophagogastric resectional

surgery, particularly operative mortality (Matthews et al 1986, Birkmeyer et al 2003, Swisher et al 2000, Van Lanshot et al 2001, Bachmann et al 2002, Skipworth et al 2010, Anderson et al 2011). There is also emerging evidence of an association between surgical volume and long term survival (Birkmeyer et al 2007, Van de Poll-Franse et al 2011). However, most published reports are based on population studies, with little data on actual improvements following service reconfiguration. Following almost a decade of negotiation between politicians, management from multiple health boards, and clinicians, an agreement was reached to centralise oesophagogastric cancer surgery for the S.E. Wales region on a single site in Cardiff. The centralised service serves a population of 1.4 million and commenced in August 2010.

## 1.12 AIMS AND HYPOTHESES

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

1. To compare oesophageal cancer stage categorisation and survival using TNM6 and TNM7.
2. To determine the influence of CT-PET in the staging algorithm of patients with potentially operable oesophageal cancer.
3. To determine the relative incidence and pattern of oesophageal cancer recurrence following definitive chemoradiotherapy and surgery.
4. To determine the prognostic significance of an involved circumferential resection margin (CRM+) after potentially curative oesophagectomy, to identify factors predictive of CRM+, and to assess the influence of differing neoadjuvant therapy regimes on CRM+ rates.
5. To determine if early enteral nutrition following upper GI cancer resection improves clinical outcomes.
6. To assess the outcomes of the first year of centralised oesophagogastric cancer surgery performed on a single site in S.E. Wales, compared with control data from the previous year.

The hypotheses tested are:

1. The TNM7 staging system is a more accurate prognostic tool for oesophageal cancer than TNM6.
2. The use of CT-PET upstages a significant number of patients with occult oesophageal cancer metastases, and avoids inappropriate radical treatment.
3. Oesophageal cancer recurrence patterns differ following dCRT and surgery, but overall recurrence rates and survival are comparable for advanced stage disease.
4. An involved CRM following oesophagectomy is associated with poorer survival and its incidence can be reduced with neoadjuvant chemoradiotherapy.
5. Early enteral nutrition improves clinical outcomes following upper GI cancer resection.
6. Centralisation of oesophagogastric cancer surgery in S.E. Wales is feasible and associated with improved clinical outcomes.

## **Chapter 2**

### **Relative prognostic value of TNM7 vs. TNM6 in staging oesophageal cancer**

## 2.1 SUMMARY

The aim of this study was to determine the influence of the new TNM7 oesophageal cancer system on stage categorisation and survival when compared with historical controls.

Two hundred and two patients with oesophageal cancer who underwent oesophagectomy (118 neoadjuvant chemotherapy) were studied. Patients originally classified and staged using TNM6 were retrospectively re-staged using TNM7.

TNM7 re-classification resulted in stage re-categorisation in 11.9% of patients (9.9% down staged, 2.0% up staged) when compared with TNM6. Five year survival for stages I, II, and III was 78, 46 and 18% using TNM6, compared with 62, 51 and 18% respectively using TNM7. Univariate analysis revealed that histological grade ( $p=0.006$ ), pT ( $p<0.0001$ ), TNM6 pN ( $p<0.0001$ ), TNM7 pN ( $p<0.0001$ ), number of lymph node metastases ( $p<0.0001$ ), TNM6 stage group ( $p<0.0001$ ), TNM7 stage group ( $p<0.0001$ ) and TNM7 prognostic group ( $p<0.0001$ ) were all associated with survival. Multivariate analysis revealed that only the TNM7 prognostic group was independently and significantly associated with survival.

TNM7 is a better prognostic tool than TNM6 and represents an important advance in staging oesophageal cancer.

## 2.2 INTRODUCTION

The Tumour, Nodes, Metastases (TNM) Classification system, published by the International Union Against Cancer (UICC) is the gold standard cancer staging system used worldwide (Sobin et al 2009). Its objectives include assisting in the planning of therapy, informing prognosis, allowing evaluation of results and facilitating information exchange between treatment centres, and is updated periodically to incorporate evidence base evolution (Sobin et al 2009). However, the 2002 TNM 6<sup>th</sup> Edition (TNM6) (Sobin and Wittekind 2002) has been considered to be a tool of limited prognostic value in oesophageal cancer, mainly because lymph node (N) stage was limited by definition as a binary variable (N0 or N1), regardless of the actual lymph node metastasis count.

The recently published TNM 7<sup>th</sup> edition (TNM7) replaced TNM6 with effect from 2010, and incorporated major modifications with regard to oesophageal cancer in particular related to the individual T, N and M stage criteria, and stage groups (Sobin et al 2009). Moreover, TNM7 introduced a new system of prognostic groups in which other prognostic variables are combined with T, N and M categories, for stage I and II tumours, which also differs for adenocarcinoma (ACA) and squamous cell carcinoma (SCC). Prognostic grouping for both cell types takes account of tumour grade, but for SCC, the anatomical site within the thoracic oesophagus is now also incorporated (Sobin et al 2009). However, the principal TNM7 upgrade relates to the classification of lymph node stage, which has a major influence on defining specific stage groups. The number of lymph



node metastases has long been considered to be the key and defining prognostic factor for patients diagnosed with oesophageal cancer (Kawahara et al 1998), and in addressing this issue TNM7 reclassifies lymph node positive tumours into 3 groups (N1-3) based on the relative burden of nodal metastases. Anatomical stage groups have also been revised and expanded to account for this modified N stage. A summary of TNM7 and the stage groupings is shown in Appendix 2.

The aims of this study were to determine the influence of the new TNM7 staging system on oesophageal cancer histopathological stage categorisation and related survival, when compared with historical control data derived with TNM6, and to determine the relative accuracy of TNM6 and TNM7 in predicting prognosis. The setting was a regional upper gastrointestinal cancer network in S.E. Wales serving a population of 1.4 million.

## **2.3 METHODS**

### **2.3.1 Details of the patients**

Consecutive patients who underwent potentially curative surgery for oesophageal cancer were identified from a prospectively maintained database. Patients were excluded if there had been a complete pathological response to neoadjuvant treatment, involved longitudinal resection margins, high grade dysplasia in the absence of invasive malignancy, or if complete histological information on the numbers of involved lymph nodes was missing. Complete pathological data were

available on 202 patients, all of whom underwent oesophagectomy between 1998 and 2010. The median age of the patients was 61 years (range 35 to 79). There were 161 (79.7%) males and 41 (20.3%) females. One hundred and sixty-nine patients had adenocarcinomas (83.7%), and 33 patients had squamous cell carcinomas (16.3%).

### **2.3.2 Staging and surgery +/- neoadjuvant therapy**

Pre-operative staging involved computed tomography (CT) and endoluminal ultrasonography (EUS) and was in accordance with TNM6 definitions. All patients were discussed at a regional specialist multi-disciplinary team meeting with management plans individually tailored according to factors relating to both comorbidity and tumour stage. In general, fit patients with tumours of stage T3 and equivocal T4, N0 and N1 were considered for neoadjuvant therapy prior to surgery. Less fit patients and those with T1-2, N0 disease were considered for surgery alone. One hundred and twenty-one patients underwent standard subtotal oesophagectomy as described by Lewis (1946) and Tanner (1947). Transhiatal resection, as described by Orringer (1985), was performed in 81 patients. This was employed selectively in patients with adenocarcinoma of the lower third of the oesophagus who had significant cardiorespiratory co-morbidity. Neoadjuvant chemotherapy or chemoradiotherapy were given to 87 patients and 31 patients respectively.

### **2.3.3 Restaging using TNM7**

All patients were originally staged histopathologically in accordance with TNM6 and then retrospectively re-staged using TNM7. The primary outcome measure was survival.

### **2.3.4 Follow-up**

Patients were followed-up clinically at 3 monthly intervals for the first year following surgery, decreasing to 6 monthly intervals thereafter, for a total of 5 years or until death. One hundred and eighty-seven patients (92.6%) were followed-up for 5 years or until death. Death certification was obtained from the Office for National Statistics (ONS).

The regional ethics committee was contacted regarding this study, but a formal application was deemed unnecessary.

### **2.3.5 Statistical analysis**

Data were expressed as median (range) and non-parametric methods were used. Cumulative survival was calculated according to the life-table method of Kaplan and Meier (1958), and differences in survival between groups of patients were analysed with the log rank test. Multivariate analysis of factors influencing survival was performed using Cox's proportional hazards model (1972). All data analysis was performed using SPSS version 18.0 (Chicago, USA).

## 2.4 RESULTS

### 2.4.1 Stage re-categorisation

The T and N stages, stage groups and prognostic groups of the patients are shown in Table 2.1, and the proportion of patients who changed stages when TNM7 was applied is summarised in Table 2.2. There were no changes observed in oesophageal cancer pT stage, but significant changes were observed in pN stage. Of the 110 patients (54.5%) with lymph node metastases classified as pN1 by TNM6, 56 (27.7%) remained pN1, 35 (17.3%) were re-classified as pN2, and 19 (9.4%) patients were re-classified as pN3 by TNM7. With regard to stage groups, the number of patients with stage I disease almost doubled using TNM7, whilst in contrast the number of patients with stage II tumours was reduced by almost a third. The number of patients with stage III tumours increased slightly when classified by TNM7, whilst the number of patients with stage IV tumours remained unchanged. Down stage re-categorisation occurred in 20 (9.9%) patients when classified by TNM7 (stage II to I). Up stage re-categorisation occurred in 4 (2.0%) patients (stage II to III). When TNM7 prognostic group allocations were compared with TNM6 allocations, fewer were classified as stage I, and more were classified as stage II. The numbers of patients with stages III and IV tumours remained unchanged. Eleven patients from the early period of this series could not be allocated a prognostic group because of pathology reports that failed to comment on tumour grade.

### 2.4.2 Survival

Table 2.3 illustrates median and 5-year survival related to stage. Survival related to TNM7 is shown separately. Figures 2.1 to 2.3 demonstrate Kaplan-Meier survival curves for oesophageal cancer by TNM6 and TNM7 stage groups, and TNM7 prognostic groups.

For stage I oesophageal cancer, 5-year survival by TNM7 was poorer by 16.1% when compared with TNM6. In contrast stage II oesophageal cancer 5 year survival by TNM7 improved by 4.4%, and median survival improved by 17 months. Survival for patients with stage III and IV tumours remained the same. Allocation of TNM7 prognostic groups produced survival plots that were midway between those obtained with TNM6 and TNM7 stage groups for patients with stage I and II tumours, and were unchanged for patients with stage III and IV tumours.

### 2.4.3 Univariate and multivariate analysis

Univariate analysis of the factors associated with survival is shown in Table 2.4. On multivariate analysis including the following variables – tumour grade, pT stage, TNM6 pN stage, TNM7 pN stage, TNM6 stage group, TNM7 stage group, TNM7 prognostic group, and the number of lymph node metastases – only TNM7 prognostic group emerged as significantly and independently associated with survival (Table 2.5).

**Table 2.1 Details of the patients' staging by TNM6 and TNM7**

<b>T Stage (%)</b>	<b>TNM6</b>	<b>TNM7</b>
T1	29 (14.4)	29 (14.4)
T2	29 (14.4)	29 (14.4)
T3	130 (64.4)	130 (64.4)
T4	14 (6.9)	14 (6.9)
<b>N Stage (%)</b>		
N0	92 (45.5)	92 (45.5)
N1	110 (54.5)	56 (27.7)
N2	N/A	35 (17.3)
N3	N/A	19 (9.4)
<b>Stage Groupings (%)</b>		
I	23 (11.4)	43 (21.3)
II	80 (39.6)	56 (27.7)
III	93 (46.0)	97 (48.0)
IV	6 (3.0)	6 (3.0)
<b>Prognostic Groupings (%)</b>		
I	N/A	27 (13.4)
II	N/A	61 (30.2)
III	N/A	97 (48.0)
IV	N/A	6 (3.0)
Not determined	N/A	11 (5.4)

Table 2.2 Stage re-categorisation related to TNM7 classification

		TNM7 Stage			
		I	II	III	IV
TNM6 Stage	I	23	0	0	0
	II	20	56	4	0
	III	0	0	93	0
	IV	0	0	0	6

The shaded boxes represent patients with the same stage group under both TNM 6 and TNM 7

**Table 2.3 Stage-by-stage patient survival**

<b>Survival</b>	<b>TNM6 Stage Groups</b>	<b>TNM7 Stage Groups</b>	<b>TNM7 Prognostic Groups</b>
<b>Stage I</b>			
Median (months)	N/A	111	111
5-year (%)	78.3	62.2	67.7
<b>Stage II</b>			
Median (months)	47	64	48
5-year (%)	46.3	50.7	48.6
<b>Stage III</b>			
Median (months)	23	23	23
5-year (%)	18.3	17.6	17.6
<b>Stage IV</b>			
Median (months)	13	13	13
5-year (%)	0	0	0



**Table 2.4 Univariate analysis of factors influencing survival**

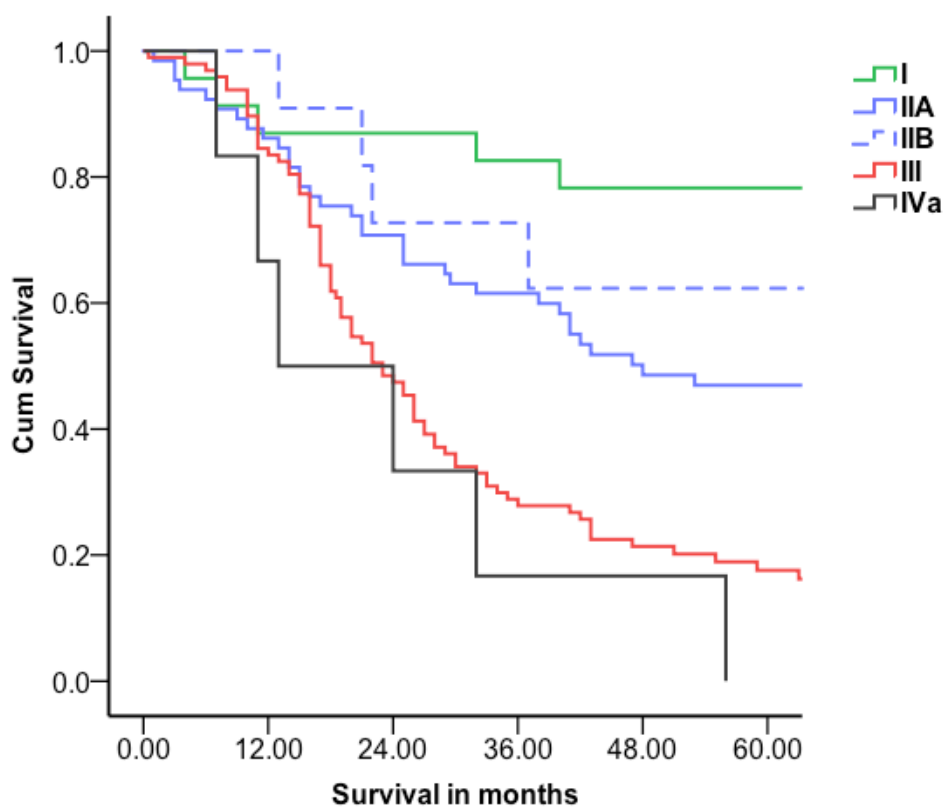
<b>Variable</b>	<b>Chi<sup>2</sup></b>	<b>df</b>	<b>p value</b>
Age	48.020	41	0.210
Gender	1.039	1	0.308
Histological cell type	1.300	1	0.254
Histological tumour grade	10.260	2	0.006
Operative approach (TT vs. TH)	0.795	1	0.373
Neoadjuvant therapy	0.627	1	0.429
T stage (same in TNM6 and TNM7)	21.514	3	<0.0001
N stage (TNM6)	21.499	1	<0.0001
N stage (TNM7)	37.509	3	<0.0001
Number of lymph node metastases	61.677	12	<0.0001
Stage groupings (TNM6)	36.587	4	<0.0001
Stage groupings (TNM7)	50.531	7	<0.0001
Prognostic groupings (TNM7)	47.147	7	<0.0001

TT = trans thoracic, TH = trans hiatal.

**Table 2.5 Multivariate analysis of factors influencing survival**

<b>TNM7 Prognostic Stage</b>	<b>Hazard Ratio</b>	<b>95% CI</b>	<b>p value</b>
Stage IA		Reference group	
Stage IB	3.901	1.034 - 14.721	0.045
Stage IIA	5.994	1.586 - 22.659	0.008
Stage IIB	4.346	1.303 - 14.503	0.017
Stage IIIA	5.734	1.743 - 18.869	0.004
Stage IIIB	10.838	3.244 - 36.211	<0.001
Stage IIIC	13.130	3.873 - 44.511	<0.001
Stage IV	11.565	2.743 - 48.760	<0.001

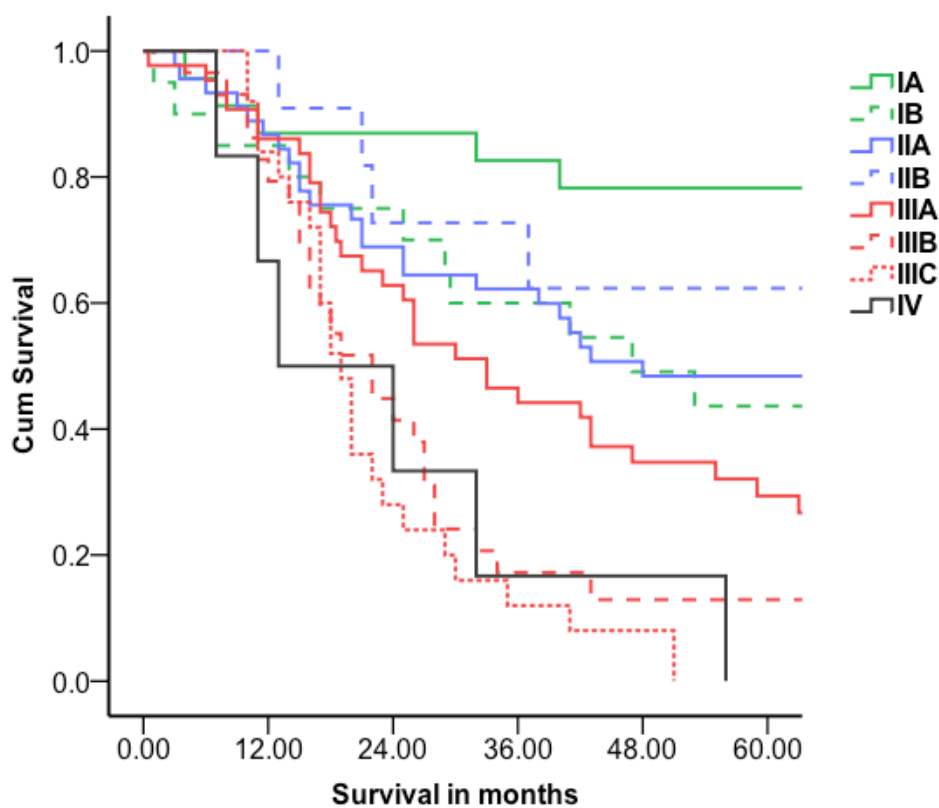
**Figure 2.1 Oesophageal cancer survival related to TNM6 stage groups**



Chi<sup>2</sup> 36.587, df 4, p<0.0001

No. at risk	0m	12m	24m	36m	48m	60m
Stage I	23	20	20	19	16	16
Stage IIA	65	56	46	38	30	26
Stage IIB	11	11	8	7	4	4
Stage III	97	81	46	26	19	13
Stage IVa	6	4	2	1	1	0

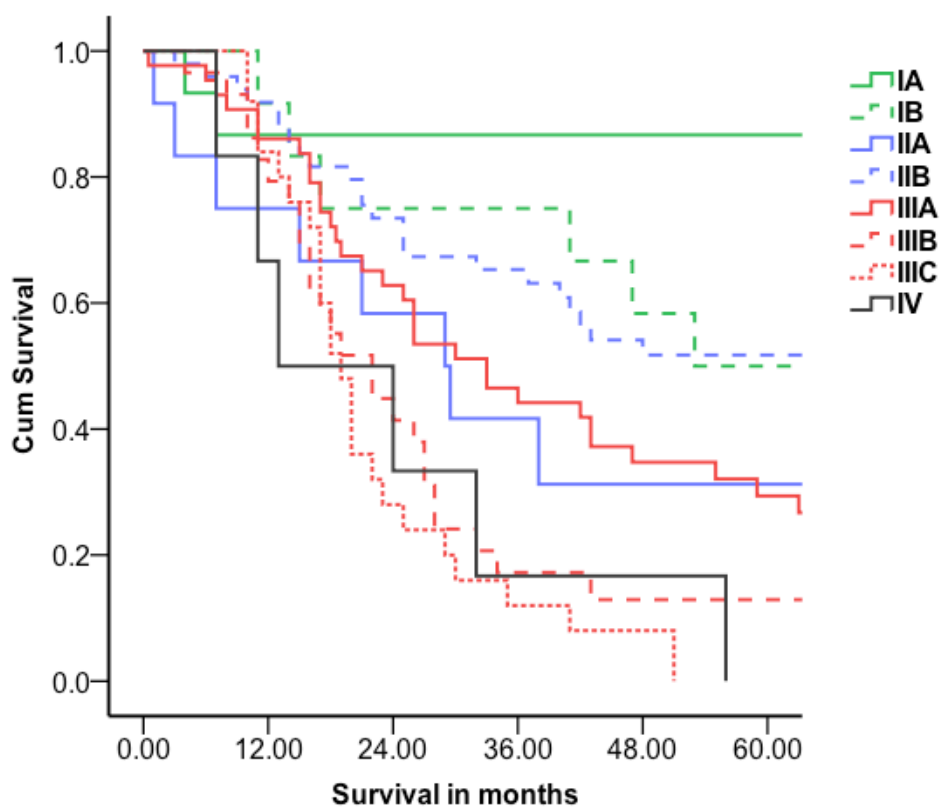
**Figure 2.2 Oesophageal cancer survival related to TNM7 stage groups**



Chi<sup>2</sup> 50.531, df 7, p<0.0001

No. at risk	0m	12m	24m	36m	48m	60m
Stage IA	23	20	20	19	16	16
Stage IB	20	17	15	11	9	7
Stage IIA	45	39	31	27	21	19
Stage IIB	11	11	8	7	4	4
Stage IIIA	43	37	27	19	15	11
Stage IIIB	29	23	12	4	3	2
Stage IIIC	25	21	7	3	2	0
Stage IV	6	4	2	1	1	0

**Figure 2.3 Oesophageal cancer survival related to TNM7 prognostic groups**



Chi<sup>2</sup> 47.147, df 7, p<0.0001

No. at risk	0m	12m	24m	36m	48m	60m
Stage IA	15	13	13	13	12	12
Stage IB	12	11	9	9	7	5
Stage IIA	12	9	7	4	3	3
Stage IIB	49	45	36	30	22	20
Stage IIIA	43	37	27	19	14	11
Stage IIIB	29	23	12	4	3	2
Stage IIIC	25	21	7	3	2	0
Stage IV	6	4	2	1	0	0

## 2.5 DISCUSSION

This study is the first to be carried out in a Westernised country to examine the outcome in patients using the new TNM7 staging system compared with TNM6 for oesophageal cancer. The principal findings were that stage re-categorisation occurred in 11.9% of patients, and this resulted in significant artefactual change in survival rates for early stage disease (I and II), but no change in outcome for more advanced stage disease (III and IV). Prognosis was better predicted by TNM7 when compared with TNM6, and specifically by the new prognostic groups incorporated in TNM7. This data therefore provides strong support for the updated TNM7 staging system for oesophageal cancer, and lends further weight to the validity of the data-driven approach used to derive this radical update (Rice et al 2010).

The study has several strengths. The patient numbers are relatively large by Western standards, and represent a consecutive series treated by a single UK cancer network. All patients received stage-directed treatment by a specialist regional multidisciplinary team with considerable experience in the treatment of oesophagogastric cancer. The surgery was performed by specialist upper GI surgeons whose results have been well audited (Morgan et al 2009) and shown to be equivalent or better than those reported in the UK based MRC OEO2 randomised trial (Morgan et al 2009, MRC Oesophageal Cancer Working Group 2002). The patients resided in a well defined geographical area, and the follow-up data are

especially robust with dates and causes of death obtained from the Office for National Statistics.

Nevertheless, there are potential limitations. Although the numbers of patients were large for a single UK region, they are relatively small when compared to the large multicentre study undertaken to derive TNM7 for oesophageal cancer (Rice et al 2010). However, Rice et al (2010) describe a patient series who underwent surgery alone, whereas our patients were treated with neoadjuvant chemotherapy in line with current UK practice, where neoadjuvant chemotherapy is the standard of care for locoregionally advanced oesophageal cancer (MRC Oesophageal Cancer Working Group 2002). In addition, total lymph node harvests were variable, with a median of 11 nodes (range 1-38) retrieved. We have reported previously that the prognosis of surgically resected oesophageal cancer is highly dependent on the numbers of lymph nodes examined pathologically, again arguably due to stage migration effects (Twine et al 2009b). Hsu et al (2010) from Taiwan have recently reported a comparison of TNM6 vs. TNM7 in surgically resected oesophageal squamous cell carcinoma. Their findings confirmed the predictive value of the new pN and pM stage criteria and they concluded that TNM7 constituted an improvement over TNM6 in terms of informing outcome. However, although their sample size was large (392), as might be expected from its geographical origin, this study consisted exclusively of patients diagnosed with squamous cell cancer, and it is therefore

uncertain how applicable their conclusions are to patients diagnosed with adenocarcinoma, the predominant Western tumour.

Improving the accuracy of any given staging system is a fundamental aim of modifying and upgrading prognostic models, and TNM7 appears to have been successful in this regard in relation to oesophageal cancer. Such a benefit must however be balanced against potential and inherent disadvantages of modifying histopathological staging. The 'Will Rogers Phenomenon' is a perceived paradox named after a quote attributed to the US comedian and social commentator Will Rogers (1879-1935). Referring to migration during the American economic depression of the 1930s, he allegedly said:

“When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.”

An analogous phenomenon is the concept of cancer stage migration, whereby changes in staging result in apparent differences in group outcomes, yet individual patient outcomes remain unchanged. The first report of this phenomenon described a cohort of lung cancer patients that had artefactually better stage specific survival than historical controls from the same institution (Feinstein et al 1985). The difference was explained by the combination of both a prognostically favourable lead time bias, and stage migration, as a result of more advanced imaging techniques (Feinstein et al 1985). Changes in the rules governing the grading of prostate cancer biopsies, and improved histopathological processing of



bladder cancer specimens, have produced similar stage migration effects in urological oncology (Gofrit et al 2008). In the present study, significant yet purely artefactual changes in the survival of early stage oesophageal cancer have been demonstrated, through the application of the TNM7 system, for the same reasons. Such changes may not only be mistakenly attributed to the effects of treatment, but equally importantly they risk preventing meaningful comparison of patient outcomes with historical controls, including those published in clinical trials. Indeed, this study indicates that it is now imperative for the results of clinical trials to be reported in relation to the TNM stage classification used. There is also a responsibility upon the clinicians involved in revising and updating the TNM staging system to ensure that modifications are based on the best available evidence, using pathological criteria that are known to be reproducible, to justify any concomitant problems that an update may bring. In the case of the colorectal cancer TNM staging system, major concerns have been raised within the pathology community regarding modifications incorporated within TNM6 and TNM7 because of a perceived lack of a sound evidence base (Quirke et al 2007, Quirke et al 2010) and because of this, UK colorectal cancer staging continues to be classified by means of TNM5, more than a decade after its publication (Quirke et al 2010).

## **2.6 CONCLUSION**

TNM7 is a better prognostic tool than TNM6 for oesophageal cancer, due predominantly to the inclusion of the lymph node metastases count. Moreover, the new system of prognostic grouping in TNM7, taking account

of tumour grade and site, has further refined staging accuracy when compared with the traditional anatomically based stage grouping. *TNM7* should therefore also form the basis for the radiological reporting and staging of all modalities for oesophageal cancer. Notwithstanding the significant benefit *TNM7* provides, clinicians must be aware of the Will Rogers Phenomenon in the context of cancer staging, and avoid drawing misleading conclusions when comparing current patient outcomes with those of historical controls.

## **Chapter 3**

### **The influence of CT-PET in staging oesophageal cancer**

### 3.1 SUMMARY

The aim was to clarify the additional value of CT-PET imaging over and above CT and EUS in refining stage-directed therapy for oesophageal cancer, with particular emphasis on N and M stage.

One hundred and fifty patients underwent CT, EUS and CT PET followed by multidisciplinary treatment. Fifty-four patients underwent surgery, 40 definitive chemoradiotherapy, 2 endoscopic mucosal resection, 53 palliative therapy, and 1 died during staging. The primary outcome measure was the relative accuracy of each modality in determining the radiological (r) TNM stage.

The rN stage was upstaged by CT-PET in 6 (4.0%) patients, compared with combined CT and EUS. The strength of agreement between radiological and histopathological N stage was fair for EUS (Kw=0.316, 96% CI 0.000-0.591, p=0.044) but there was no agreement for CT-PET (Kw=0.041, 95% CI -0.104-0.211, p=0.604). The sensitivity, specificity, positive predictive value and negative predictive value for CT-PET rN stage were 12.5%, 92.9%, 75.0% and 38.2%. In contrast rM stage was upstaged by CT-PET in 36 (24.0%) patients. Failure of CT-PET to detect distant metastases occurred in 10 (6.7%) patients.

CT PET materially altered the radiological perceived oesophageal tumour stage in 1 in 4 patients, with clear potential economic savings and must therefore become a mainstay of the contemporary pre-operative staging protocol.

### 3.2 INTRODUCTION

Accurate radiological staging of patients with oesophageal cancer is essential if stage directed multimodality treatment regimens are to be used appropriately and optimal outcomes achieved. Staging must be able to identify those patients with distant metastases (M1 stage) at presentation, so that inappropriate aggressive treatment can be avoided. In patients with early tumours, locoregional staging must be able to precisely identify the depth of tumour invasion (rT stage), so that endoscopic resection can be considered where appropriate (Allum et al 2011). In patients with more advanced tumours the lymph node stage (rN stage) and the precise positions of any lymph node metastases proximal or distal to the primary tumour must be identified to establish the full extent of the disease. This information informs not only the feasibility of surgical resection and the need for neoadjuvant therapy, but also facilitates the planning of newer non-surgical treatment options such as definitive chemoradiotherapy (Crosby et al 2004, Gwynne et al 2011).

The principal modalities used in the past were computed tomography (CT), endoluminal ultrasonography (EUS), and where appropriate, staging laparoscopy. Computed tomography is the first line investigation to exclude gross metastatic disease. Computed tomography also provides limited information on rT and rN stage, and it's accuracy in these respects has been reported to vary with body mass index (Twine et al 2009c). Furthermore, the assessment of lymph nodes by CT is entirely dependant on size criteria, with difficulty detecting metastases in lymph nodes of

normal size (van Vliet et al, 2008). Endoluminal ultrasonography is considered the recommended gold standard for defining rT and rN stage (Allum et al 2011), exhibiting superior accuracy over CT in these areas (Kienle et al 2002, Blackshaw et al 2008), although it is constrained in the assessment of distant lymph nodes and viscera by its limited depth of penetration (Kienle et al 2002). FDG-positron emission tomography (PET) provides metabolic tumour information, and has been shown to have superior sensitivity to CT in the detection of distant metastases (van Westreenen et al 2004, van Vliet et al 2008). Integrated CT-PET scanning directly combines this metabolic information with the anatomical detail needed to accurately localise the sites of abnormality, and avoids the possibility of inaccurate co-registration encountered when information from independent PET and CT scans are combined. Funding for integrated CT-PET imaging has been available for patients in S.E. Wales since January 2009. The aim of this study was to assess the additional value of CT-PET in refining oesophageal cancer radiological stage.

### **3.3 METHODS**

#### **3.3.1 Staging and the utilisation of CT-PET**

The first one hundred and fifty consecutive patients to undergo CT-PET imaging in the S.E. Wales cancer network were included in the present study. Patients proceeded to CT-PET imaging only if they were suitable for potentially curative treatment on the grounds of CT stage and performance status, and this was arranged concurrently with endoluminal

ultrasonography (EUS). All CT-PET imaging took place between January 2009 and June 2011. The first 68 studies were performed at the Cheltenham Imaging Centre until August 2010 when the Wales CT-PET scanner became operational. All subsequent imaging was provided at the University Hospital of Wales. All staging investigations were reported in accordance with the UICC Tumour Nodes Metastasis (TNM) 6<sup>th</sup> Edition (Sobin and Wittekind 2002).

### **3.3.2 Treatment modalities**

The algorithm for neoadjuvant and surgical treatment of oesophageal cancer in the S.E. Wales network has been described in Chapter 2. A small number of patients in this study with Siewert type III junctional tumours were treated by means of total D2 gastrectomy. The protocols for definitive chemoradiotherapy (dCRT) have been described previously (Crosby et al 2004, Gwynne et al 2011) and are covered in more detail in Chapter 4.

### **3.3.3 Statistical Analysis**

Grouped data were expressed as median (range) and non-parametric methods were used throughout. The strength of agreement between radiological and histopathological staging was assessed using the weighted Kappa statistic (Kw).

### **3.4 RESULTS**

#### **3.4.1 Radiological stage**

The clinical and radiological details of the patients are provided in Table 3.1. One hundred and forty (93.3%) patients had primary tumours that were demonstrated on CT-PET. There were ten patients whose tumours could not be identified on CT-PET. Of these, four were very early cancers of EUS stage rT1, for which the lack of FDG uptake by the tumour was attributed by the radiologist more to small size, rather than non avid tumours. The remaining six tumours (4.0%) were more bulky yet non avid. All ten non-identified tumours were adenocarcinomas. Details of the treatments prescribed and histopathological staging of the surgical patients are provided in Table 3.2.

#### **3.4.2 Influence of CT-PET on radiological T Stage**

Tumour stage was only reported on CT-PET in ten (6.7%) patients. Of these ten patients 3 were upstaged by CT-PET when compared with the combined CT/EUS rT stage. Two patients were upstaged from rT3 to rT4, and one from rT2 to rT3. The remaining 140 (93.3%) patients had a rT stage that was either not formally assessed or reported as TX on CT-PET.

#### **3.4.3 Influence of CT-PET on radiological N Stage**

Combined CT/EUS N stage was upstaged from rN0 to rN1 in 6 (4.0%) patients by the addition of CT-PET (Table 3.3).



#### 3.4.4 Comparative radiological vs. histopathological N Stage

A comparison of CT, EUS and CT-PET perceived N stage with pathologically defined N stage, in a subgroup of 38 patients who had tumours crossed at EUS, and who underwent surgical resection is shown in Table 3.4. The overall strength of agreement was fair for EUS (Kw=0.316, 95% CI 0.000-0.591, p=0.044). In contrast there was poor agreement for both CT (Kw=0.064, 95% CI -0.156-0.304, p=0.601) and CT-PET (Kw=0.041, 95% CI -0.104-0.211, p=0.604). Sensitivity, specificity, positive predictive value and negative predictive value, for the three staging modalities in terms of perceived rN stage are shown in Table 3.5. The number of lymph node metastases identified by EUS was not significantly different from the histopathological count [median 1 (0-18) vs. 1 (0-11), p=0.095]. In contrast, the number of lymph node metastases identified by CT-PET was significantly lower than that reported histopathologically [median 0 (0-2) vs. 1 (0-11), p<0.0001].

#### 3.4.5 Influence of CT-PET on M stage

The rM stage was upstaged by CT-PET to rM1 in 36 (24.0%) patients. The sites of CT-PET identified metastases are listed in Table 3.6. In 21 patients (14.0%) the CT scan failed to identify distant metastases (M0). In the remaining 15 patients (10%) CT had identified lesions that were equivocal for metastases (MX) and without the confirmation afforded by CT-PET, there would have been insufficient evidence to allow the MDT to deviate from potentially curative to palliative treatment intent. The

treatment intent for all 36 patients changed to palliative as a direct result of the CT-PET. False negative CT-PET rM0 stage occurred in 10 (6.7%) patients. Four patients had peritoneal or liver metastases detected on staging laparoscopy and four had liver metastases apparent on laparotomy. The remaining two patients had cervical lymph node metastases (M1a) outside the surgical field identified on EUS, but not seen on CT-PET, both of which were confirmed by fine needle aspiration cytology. The overall negative predictive value for CT-PET M stage was therefore 90.4%.

#### **3.4.6 Additional diagnostic workload**

A summary of the additional diagnostic workload generated as a consequence of the CT-PET imaging findings is shown in Table 3.7. Twenty-two patients (14.7%) underwent further investigations, most of which confirmed that the FDG uptake on CT-PET was physiological, or indicative of benign pathology. One patient was subsequently diagnosed with a previously undetected early invasive breast cancer.

#### **3.4.7 Treatment**

Potentially curative treatment was attempted in 96 (64.0%) patients. The reasons for palliative treatment, other than for those patients upstaged by CT-PET, included disease lengths considered too extensive for surgery or curative dCRT (5 patients), deterioration in performance status during staging (4), demonstration of direct liver infiltration on staging laparoscopy (1), and a patient declining potentially curative treatment (1).

**Table 3.1 Clinical and radiological details of the patients**

Number	150
Age (Y)	67 (36-82)
Gender M:F	111:39
ACA : SCC : neuroendocrine	115 : 33 : 2
<b>Anatomical site (%)</b>	
Upper third	3 (2.0)
Middle third	33 (22.0)
Lower third inc Siewert I	80 (53.3)
Siewert II junctional	13 (8.7)
Siewert III junctional	21 (14.0)
<b>CT T Stage (%)</b>	
T1	10 (6.7)
T2	20 (13.3)
T3	99 (66.0)
T4	21 (14.0)
<b>CT N Stage (%)</b>	
N0	74 (49.3)
N1	76 (50.7)
<b>CT M Stage (%)</b>	
M0	122 (81.3)
MX	28 (18.7)
EUS attempted (%)	126 (84.0)
EUS tumour crossed (%)	107 (71.3)
<b>EUS T Stage (%)</b>	
T1	9 (6.0)

T2	7 (4.7)
T3	75 (50.0)
T4	16 (10.7)
<b>EUS N stage (%)</b>	
N0	38 (25.3)
N1	69 (46.0)
EUS M1a stage (%)	2 (1.3)
<b>CT-PET T stage (%)</b>	
T3	6 (4.0)
T4	4 (2.7)
TX or not reported	140 (93.3)
<b>CT-PET N stage (%)</b>	
N0	97 (64.7)
N1	53 (35.3)
<b>CT-PET M stage (%)</b>	
M0	103 (68.7)
M1	36 (24.0)
MX	11 (7.3)

ACA – adenocarcinoma, SCC – squamous cell carcinoma,  
Age is median (range).

**Table 3.2 Details of treatment and histopathological staging****Treatment (%)**

Surgery	54 (36.0)
Neoadjuvant chemotherapy	40 (26.6)
Surgery alone	14 (9.3)
Transthoracic oesophagectomy	21 (14.0)
Transhiatal oesophagectomy	14 (9.3)
Total D2 gastrectomy	10 (6.7)
Open and close laparotomy	9 (6.0)
Resection completed	45 (30.0)
Definitive chemoradiotherapy	40 (26.7)
EMR	2 (1.3)
Palliation	53 (35.3)
Died during staging	1 (0.7)

**Resected patients****Histopathological T stage (%)**

CPR	1 (0.7)
T1	5 (3.3)
T2	14 (9.3)
T3	24 (16.0)
T4	1 (0.7)

**Histopathological N stage (%)**

N0	17 (11.3)
N1	28 (18.7)

EMR – endoscopic mucosal resection, CPR – complete pathological response.

**Table 3.3 Combined CT/EUS vs. CT-PET perceived N stage**

		Stage by CT-PET	
		N0	N1
Stage by combined	N0	45	6
CT EUS	N1	52	47

Table 3.4 Radiological vs. histopathological N stage

		Stage by histopathology	
		N0	N1
Stage by CT	N0	11	17
	N1	3	7

		Stage by histopathology	
		N0	N1
Stage by EUS	N0	10	9
	N1	4	15

		Stage by histopathology	
		N0	N1
Stage by CT-PET	N0	13	21
	N1	1	3

**Table 3.5 Radiological N stage sensitivity, specificity, PPV, NPV**

	<b>CT</b>	<b>EUS</b>	<b>CT-PET</b>
<b>Sensitivity</b>	29.2	62.5	12.5
<b>Specificity</b>	78.6	71.4	92.9
<b>PPV</b>	70.0	78.9	75.0
<b>NPV</b>	39.3	52,6	38.2

PPV – positive predictive value, NPV – negative predictive value.

**Table 3.6 Sites of CT-PET detected occult metastases**

<b>Site of metastasis</b>	<b>Number (%)</b>
Lymph nodes outside surgical field	25 (16.7)
Liver	9 (6.0)
Musculoskeletal	6 (4.0)
Lung / pleural	5 (3.3)
Renal	3 (2.0)
Adrenal	2 (1.3)
Peritoneal	2 (1.3)
Ocular	1 (0.7)
Tongue / pharynx	1 (0.7)

Some patients had metastases at more than one site.



**Table 3.7 Additional diagnostic workload generated by CT-PET**

<b>Site of FDG uptake</b>	<b>Number (%)</b>	<b>Outcome</b>
Large bowel / rectum	9 (6.0)	5 polyps, 4 normal
Pharynx / vocal cords	4 (2.7)	All normal
Prostate	4 (2.7)	3 benign, 1 not formally investigated
Adrenal	3 (2.0)	All benign
Breast	1 (0.7)	Breast cancer
Hip joint capsule	1 (0.7)	Normal
Parotid gland	1 (0.7)	Benign tumour

### 3.5 DISCUSSION

This study investigated the contribution of CT-PET in the staging and treatment of a consecutive cohort of patients with oesophageal cancer. The principal finding was that CT-PET upstaged twenty-four patients to stage rM1 and consequently avoided inappropriate aggressive radical treatment with no prospect of cure. Twenty-two (14.7%) patients required further, sometimes invasive, diagnostic testing on the basis of incidental CT-PET findings.

There are major pitfalls associated with the use of FDG-PET in the assessment of rN stage. Principally FDG uptake in perioesophageal lymph nodes that are anatomically close to the primary tumour is difficult to differentiate from uptake originating from the oesophagus itself, due to the limited spatial resolution of PET (Rice 2000, Chowdhury et al 2008). Indeed, it has been demonstrated that PET has greater accuracy in the identification of regional and distant nodal involvement, than in local lymph nodes (Flamen et al 2000, Yoon et al 2003). In addition FDG uptake within lymph nodes can occur in benign disease, including granulomatous infection (Mackie and Pohlen 2005) and sarcoidosis (Maeda et al 2005) and in many cases this cannot be confidently distinguished from malignant disease.

Numerous studies have examined the individual accuracy of EUS and PET in terms of oesophageal rN stage. Radiological stage sensitivity and specificity for EUS range from 45% to 97% and 33% to 100%, and for PET

range from 22% to 82% and 60% to 100% (van Vliet et al 2008). Very few studies have examined the accuracy of integrated CT-PET compared with separate CT and PET, although Yuan et al (2006) identified small improvements in rN stage sensitivity and specificity for integrated CT-PET compared with separate CT and PET. Meta-analysis derived pooled sensitivity and specificity for EUS are 80% and 70%, and for PET 57% and 85% (van Vliet et al 2008). The results of this study demonstrate rN stage sensitivity for EUS (62.5%) and CT-PET (12.5%) fall short of these, however the trend of greater sensitivity with EUS compared with PET holds true. In contrast rN stage specificity for EUS (71.4%) and CT-PET (92.9%) in this study are equivalent to reported meta-analysis figures for EUS, and are indeed better for PET. However, the patient numbers in this study were relatively small and care must therefore be taken in the analysis of small differences in sensitivity and specificity. It would appear reasonable though to suggest the results concur with the meta-analysis findings of greater sensitivity for EUS, yet greater specificity for PET, in the assessment of rN stage.

The principal strength of PET based imaging is in the detection of occult distant metastases. Meta-analysis derived pooled sensitivity and specificity rM stage for CT are 52% and 91%, and for PET 71% and 93%. A comparison of the results of the present study with these published sensitivity and specificity figures cannot be made as CT-PET imaging was not performed on all patients undergoing staging, but rather reserved only for a select cohort potentially suitable for curative treatment based on CT

stage. However, the CT-PET influence in refining M stage in almost a quarter of patients in this study clearly demonstrates its superiority over CT in this regard. The 6.7% of patients in this cohort with metastases undetected by both CT and CT-PET is comparable to a published rate of 5% from a recent prospective trial (Meyers et al 2007), and therefore this modality is not without limitations in terms of rM stage. One patient (0.7%) in this series had an unrelated synchronous cancer diagnosed on CT-PET, although a further patient had a suspected prostatic carcinoma that was not formally investigated due to extensive oesophageal metastases. The identification of synchronous cancers is well documented for PET-based imaging and has been reported in as many as 5.5% of patients, of which the majority have malignant or premalignant colorectal lesions (van Westreenen et al 2005).

The study has potential limitations. The total number of patients was relatively high, yet the numbers who underwent surgical resection relatively small, limiting the accuracy of the radiological vs. pathological N stage comparison. The accuracy of the EUS examinations was a little disappointing, and indeed higher strengths of agreement with pathological N stage have previously been reported in our unit (Kw=0.639 95% CI 0.576-0.702, p = 0.0001, Twine et al 2009c). The reasons for this are unclear but it may relate to the small numbers, and the use of neoadjuvant therapy. However, it must be acknowledged that the predominant pattern of EUS inaccuracy in this series was in under, rather than over, staging N stage.

Aside from the obvious benefits for those patients avoiding inappropriate radical surgery, there will clearly be a substantial associated cost saving. However a formal cost analysis was not within the remit of this study. There is scope for further research, with larger patient numbers, to evaluate the differing accuracy of EUS and PET in identifying peritumoural vs. more distant regional lymph node metastases, and also to assess this within the framework of TNM7 defined N1, N2 and N3 subgroups.

In contrast the study has several strengths. The patients were a consecutive series. All data were collected prospectively, and treatment was provided by an experienced MDT. All imaging was carefully reviewed in a regional MDT setting, and the reasons for differing treatment decisions were clearly defined.

### **3.6 CONCLUSION**

The addition of CT-PET to the staging algorithm for oesophageal cancer resulted in the upstaging of 24% of patients, in whom inappropriate aggressive curative treatment was avoided. The principal strength of CT-PET was in the assessment of M stage, with a very limited role in N stage. The roles of CT, EUS and CT-PET are complementary, and a combined staging approach utilising all three will optimise treatment decisions in oesophageal cancer.

## **Chapter 4**

**The relative incidence and pattern of oesophageal cancer recurrence  
following definitive chemoradiotherapy and surgery**

#### 4.1 SUMMARY

The aim of this study was to determine the relative incidence and pattern of oesophageal cancer recurrence following definitive chemoradiotherapy and surgery.

Three hundred and eleven consecutive patients unsuitable for surgery on the grounds of performance status (n=137), bulky local disease (n=121) or personal choice (n=53) received definitive chemoradiotherapy (164 ACA, 147 SCC), and 312 surgery (252 ACA, 60 SCC) (200 neoadjuvant chemotherapy). The primary outcome measure was disease-free survival.

Oesophageal cancer recurrence was diagnosed in 44.1% after definitive chemoradiotherapy compared with 40.7% after surgery (p=0.222). Locoregional recurrence was commoner after definitive chemoradiotherapy than surgery (24.1% vs. 9.3%, p<0.0001). Distant metastases were commoner after surgery than definitive chemoradiotherapy (22.8% vs. 12.9%, p=0.001). The median times to recurrence after definitive chemoradiotherapy and surgery were 15 and 17 months respectively (p=0.052). Stage related disease-free 2-year survival after definitive chemoradiotherapy vs. surgery was: stage I (68.6 vs. 85.6%, p=0.069), II (36.9 vs. 47.4%, p=0.011), III (31.0 vs. 28.6, p=0.878), IVa (21.4 vs. 26.3%, p=0.710).

These findings support the need for a randomised trial of definitive chemoradiotherapy vs. surgery in oesophageal cancer irrespective of histopathological cell type.

## 4.2 INTRODUCTION

Oesophageal carcinoma is the 9<sup>th</sup> most common cancer in the UK, and has increased in incidence by more than 60% in males over the past 30 years (Cancer Research UK 2007). The optimum contemporary treatment in the UK is considered to be neoadjuvant chemotherapy followed by surgery (Medical Research Council Oesophageal Cancer Working Party 2002), but the recent UK national audit suggested that fewer than 30% of all cases of oesophageal cancer undergo surgery (National Oesophago-gastric Cancer Audit 2010). Despite recent advances in physiological and radiological staging, anaesthesia and surgical techniques, outcomes remain poor, with operative morbidity and mortality rates of 30% and 4.5 to 10.1% respectively, 2-year survival rates of 34 to 43%, and overall 5 year survival of 17 to 23% (Medical Research Council Oesophageal Cancer Working Party 2002, National Oesophago-gastric Cancer Audit 2010, Kelson et al 1998, Al-Sarira et al 2007). Moreover surgery has a major detrimental impact on short term health-related quality of life, that persists at least six months following oesophagectomy (Avery et al 2007).

Definitive chemoradiotherapy (dCRT) has been reported to result in long term survival of patients with both squamous cell carcinoma and adenocarcinoma of the oesophagus and championed as an alternative treatment for patients with squamous cell carcinoma (Cooper et al 1999, Crosby et al 2004, Gwynne et al 2011, Bedenne et al 2007, Stahl et al 2005, Chan et al 1999, Coia et al 2000, Kaneko et al, 2003, Geh 2001, Chiu et al 2005). Three randomised trials have compared dCRT to



surgery with or without neoadjuvant therapy for patients with squamous cell carcinoma, all of which reported similar overall survival rates (Bedenne et al 2007, Stahl et al 2005, Chiu et al 2005). However, the trials were underpowered to examine the possible equivalence of dCRT compared to surgery and limited HRQL data were reported. No well designed and conducted randomised trial has yet compared dCRT to surgery based treatment for oesophageal adenocarcinoma, and as such the role of dCRT in treating fit patients with potentially operable adenocarcinoma remains uncertain.

A stage-for-stage comparison of dCRT and surgery for oesophageal cancer irrespective of pathological cell type, from the S.E. Wales regional cancer network, has demonstrated similar overall 2-year survival for patients treated with dCRT, surgery alone and neoadjuvant therapy followed by surgery (Morgan et al 2009). However, criticism was received following publication for suspected poorer locoregional disease control after dCRT, relative to surgery (Clark et al 2010) and the lack of recurrence data in this study left this open to question.

The aim of this study therefore was to determine the relative incidence and pattern of oesophageal cancer recurrence following dCRT and surgery in patients receiving stage directed therapy with curative intent.

## 4.3 METHODS

### 4.3.1 Patient selection and radiological staging

The study included consecutive patients diagnosed with potentially curable oesophageal carcinoma of any cell type between 1 January 1998 and 31 October 2010, by a regional cancer network multidisciplinary team serving a population of 1.4 million. Clinical and pathological information was collected on a prospectively maintained database. Pre-operative staging involved computed tomography (CT), endoluminal ultrasonography (EUS) and if appropriate, laparoscopy. More recently CT-PET imaging has been incorporated into the staging protocol, for patients diagnosed from early 2009 onwards. All staging was in accordance with the UICC Tumour Nodes Metastasis Classification (TNM) 6<sup>th</sup> Edition (Sobin et al 2002). The EUS examinations were either performed or supervised by a single radiologist. In addition to standard TNM criteria, and the primary tumour length, EUS examinations also reported the lymph node metastasis count (LNMC) and the EUS defined total length of disease (ELOD). The latter was equal to the tumour length for patients staged N0. However, for patients with suspicious lymph node metastases ELOD was calculated according to the distance between the most proximal lymph node or tumour extent and the most distal lymph node or tumour extent. Sixteen patients (2.5%) were excluded because their tumours were too stenotic to be crossed at EUS, and therefore a full and accurate radiological stage was not available. Ethical approval was sought from the regional ethics committee, but the chair confirmed that individual patient consent was not

required to report clinical outcomes alone and as such no formal approval was necessary.

#### **4.3.2 Surgery +/- neoadjuvant therapy**

Management plans were individually tailored according to patient factors and disease stage. In general, fit patients with tumours of stage T3 and equivocal T4, N0 and N1 were considered for neoadjuvant therapy prior to surgery. Prior to 2002 patients were treated with neoadjuvant chemoradiotherapy. Following the publication of the MRC OE02 trial (Medical Research Council Oesophageal Cancer Working Party, 2002) patients received neoadjuvant chemotherapy. Less fit patients and those with T1-T2, N0 disease were considered for surgery alone. Most patients underwent standard subtotal oesophagectomy as described by Lewis and Tanner (Lewis 1946, Tanner 1947). Transhiatal resection, as described by Orringer (Orringer 1985), was used selectively in patients with adenocarcinoma of the lower third of the oesophagus who had significant cardiorespiratory co-morbidity. Oesophageal resection was defined as potentially curative when all visible tumour had been removed and both proximal and distal resection margins were free from tumour on histological examination. Involvement of the circumferential resection margin was defined as the presence of tumour within 1mm of the circumferential margin.

### **4.3.3 Definitive chemoradiotherapy**

Patients deemed unsuitable for surgery on grounds of co-morbidities and/or performance status, locoregional disease considered too extensive for curative resection or personal choice received dCRT. They received four cycles of cisplatin (60 mg/m<sup>2</sup>) and a fluoropyrimidine over 12 weeks, with cycles 3 and 4 given concurrently with 50 Gy conformal radiotherapy delivered in a single phase in 25 fractions. The dCRT protocol which has evolved over time has been described in detail previously (Crosby et al 2004, Gwynne et al 2011, Morgan et al 2009). Toxicity related to oncological therapy was graded using the National Cancer Institute common criteria for adverse events (National Cancer Institute, 2003).

### **4.3.4 Follow-up and Disease Recurrence**

After completion of dCRT a CT scan was carried out to assess the response and to establish a baseline after treatment. Repeat endoscopy was not routinely carried out after treatment. All patients were reviewed every 3 months for the first year after dCRT or oesophagectomy, and every 6 months thereafter. Definitive chemoradiotherapy patients were deemed to have progressive local disease where there was a failure to respond to treatment, defined as disease progression within 6 weeks from the date of completion of treatment. Disease recurrence was suspected clinically and confirmed with investigations, usually CT or endoscopy. Patterns of recurrence were defined as locoregional (L), distant (D) (metastatic) or both locoregional and distant (L and D), when both were

diagnosed at the same time. The time of recurrence was taken as the date of the confirmatory investigation. Follow-up until 5 years or death was available for 539 (86.5%) patients. Death certification was obtained from the Office for National Statistics.

#### **4.3.5 Statistical Analysis**

Analysis was based on intention to treat. The primary outcome measures were oesophageal cancer recurrence, disease-free survival and overall survival. Grouped data were expressed as median (range) and non parametric methods were used. Disease-free survival for all patients was calculated using similar methodology to both the MRC OEO2 (Medical Research Council Oesophageal Cancer Working Party, 2002) and US Intergroup (Kelson, 1998) randomised trials, by measuring the period from a landmark time of 6 months after diagnosis (6 months from time of randomisation in the trials) to the date of recurrence. This approach was adopted for the trials, to allow for the variable interval to surgery following diagnosis, depending on whether neoadjuvant therapy was prescribed. As in the randomised trials, events resulting in a failure to complete curative treatment such as not proceeding to surgery, open and close laparotomy, palliative resection, in-hospital mortality, and disease progression during dCRT, were assumed to have occurred at this landmark time, to maintain the intention to treat analysis. Overall survival was measured from the date of diagnosis. Cumulative survival was calculated according to the life-table method of Kaplan and Meier, and differences between groups were analysed with the log rank test. Univariate analyses examining

factors influencing survival were initially examined, and those with associations found to be significant retained in a Cox's proportional hazards model. The final multivariate model also included gender, age and histological cell type, to correct for baseline differences between the groups.

#### **4.4 RESULTS**

##### **4.4.1 Details of the patients and treatment prescribed**

Six hundred and twenty-three patients were included in the study, and their details related to treatment modality are shown in Table 4.1. Of the 623 patients, 311 were deemed unsuitable for surgery on the basis of co-morbidity and/or performance status (137, 44.1%), extensive locoregional disease (121, 38.9%) or personal choice (53, 17.0%) and received dCRT. Of these 311 patients, 70 (22.5%) had disease that progressed despite dCRT treatment. No patients died during treatment with dCRT. The remaining 312 patients were deemed suitable for surgical treatment. Neoadjuvant chemotherapy and chemoradiotherapy was given to 150 (48.9%) and 50 (16.3%) patients respectively.

##### **4.4.2 Details of the surgery**

The operative approach was trans thoracic in 167 (53.5%) and transhiatal in 107 (34.3%). Six patients (1.9%) failed to proceed to surgery following neoadjuvant therapy due to disease progression. Resection was potentially curative (R0) in 254 (81.7%) and palliative (R1 or R2) in 20 (6.4%). Circumferential resection margin (CRM) status was negative in

155 (49.7%), involved in 99 (31.7%) and not reported in 20 patients (6.4%) from early in the series. Thirty-two patients (10.3%) underwent open and close laparotomy. The operative mortality (deaths within 30 days) was 12 (3.8%) and the in-hospital mortality rate was 14 (4.5%). In total 72 patients (23.1%) failed to complete potentially curative surgical treatment for these reasons.

#### **4.4.3 Treatment related morbidity**

The overall rate of operative morbidity in the surgical group was 38.5% (120 patients). In comparison the rates of grade III and IV toxicity in the dCRT patients were 42.1% (131 patients) and 7.1% (22 patients).

#### **4.4.4 Disease recurrence**

Data on cancer recurrence related to treatment type are shown in Table 4.2. There was no significant difference in the overall rate of recurrence. Locoregional recurrence was two and half times commoner after dCRT than surgery. In contrast distant recurrence was nearly twice as common after surgery. Definitive chemoradiotherapy was associated with a trend towards a 2 month reduction in time to recurrence ( $p=0.052$ ), and non-significant 3 and 4 month reductions in time to locoregional and distant recurrence respectively, when compared with surgery.

#### **4.4.5 Disease-free and overall survival**

For patients with all stages of disease, surgery was associated with significantly better disease-free survival (median 14 vs. 9 months, 2-year

39.8 vs. 33.0%,  $p=0.003$ ) and overall survival (median 28 vs. 22 months, 2-year 56.2 vs. 45.4%,  $p=0.001$ ) than dCRT. Stage-for-stage median and 2-year disease-free survival for surgery versus dCRT was: stage I (n/a vs. 59 months, 85.6 vs. 68.6%,  $p=0.069$ ), stage II (24 vs. 12 months, 47.4 vs. 36.9%,  $p=0.011$ ), stage III (9 vs. 6 months, 28.6 vs. 31.0%,  $p=0.878$ ) and stage IVa (0 vs. 3 months, 26.3 vs. 21.4%,  $p=0.710$ ). (See Figures 4.1 - 4.4) Stage-for-stage median and 2-year overall survival for surgery versus dCRT was: stage I (n/a vs. 68 months, 85.6 vs. 68.6%,  $p=0.236$ ), stage II (41 vs. 26 months, 67.2 vs. 51.3%,  $p=0.013$ ), stage III (22 vs. 17 months, 46.2 vs. 41.8%,  $p=0.377$ ) and stage IVa (19 vs. 15 months, 31.6 vs. 42.9%,  $p=0.665$ ).

A subanalysis of the same parameters including only patients with oesophageal ACA demonstrated broadly similar results for patients with SCC and ACA. Disease-free survival was significantly better following surgery than dCRT for stage I (n/a vs. 45 months, 88.1 vs. 68.6%,  $p=0.008$ ) and stage II (24 vs. 14 months, 2-year 48.0 vs. 33.7%,  $p=0.036$ ), but comparable to dCRT for stage III (8 vs. 5 months, 24.3 vs. 30.5%,  $p=0.593$ ) and stage IVa (0 vs. 3.0 months, 20.0 vs. 20.0%,  $p=0.915$ ). Overall survival was better following surgery than dCRT for stage I (n/a vs. 68 months, 88.1 vs. 68.6%,  $p=0.078$ ) and non significantly better for stage II (34 vs. 25 months, 66.8 vs. 50.0%,  $p=0.062$ ), but comparable to dCRT for stage III (22 vs. 17 months, 43.9 vs. 41.2%,  $p=0.721$ ) and stage IVa (19 vs. 12 months, 26.7 vs. 33.3%,  $p=0.577$ ).



#### 4.4.6 Influence of histological cell type

The patients were analysed in relation to histological cell type, irrespective of the treatment modality prescribed. Patients with SCC had significantly more advanced stages of disease than patients with ACA (stage I: 3.4 vs. 6.0%, stage II: 27.1 vs. 37.5%, stage III: 61.4 vs. 49.3%, stage IV: 8.2 vs. 7.2%,  $p=0.017$ ), and a greater proportion received dCRT than surgery (71.0 vs. 39.4%,  $p<0.0001$ ). Recurrence occurred in 85 (41.1%) patients with SCC and 179 (43.0%) patients with ACA ( $p=0.860$ ). There was a greater incidence of locoregional recurrence in patients diagnosed with SCC compared with patients diagnosed with ACA (46 vs. 58, 22.2 vs. 13.9%,  $p=0.009$ ). In contrast, distant recurrence was more common for patients with ACA than patients with SCC (85 vs. 26, 20.4 vs. 12.6%,  $p=0.016$ ). Disease-free survival was comparable for patients with ACA and SCC (12 vs. 11 months, 35.6 vs. 38.0%,  $p=0.847$ ). Overall survival was also comparable for patients with ACA and SCC (25 vs. 25 months, 50.7% vs. 50.8%,  $p=0.817$ , respectively).

#### 4.4.7 Influence of neoadjuvant therapy

One hundred and twelve patients underwent surgery alone (S), and 200 patients underwent surgery following neoadjuvant therapy (CS, 50 chemoradiotherapy, 150 chemotherapy). Surgery following neoadjuvant therapy was associated with poorer disease-free survival (median 12 vs. 24 months, 2 year 34.2 vs. 49.4%,  $p=0.039$ ) and overall survival (median 25 vs. 41 months, 2 year 50.8 vs. 65.6%,  $p=0.049$ ) than surgery alone.

There was a trend towards failure to complete curative treatment for the CS patients when compared with S (53 vs. 19 patients, 26.5% vs. 17.0%,  $p=0.068$ ). There was no significant difference in the incidence of cancer recurrence following CS when compared with S (82 vs. 45 patients, 41.0% vs. 40.2%,  $p=0.887$ ). Similarly, there were no significant differences in the patterns of cancer recurrence following CS and S [local recurrence 20 (10.0%) vs. 9 (8.0%), distant recurrence 48 (24.0%) vs. 23 (20.5%), both local and distant 13 (6.5%) vs. 12 (10.7%) and site unspecified 1 (0.5%) vs. 1 (0.9%), overall  $p=0.486$ ]

#### **4.4.8 Univariate and multivariate analysis**

A univariate analysis of factors influencing disease-free survival is shown in Table 4.3. A multivariate analysis of the factors significant on univariate analysis, and corrected for gender, age and histological cell type, identified EUS T stage and EUS defined LNMC to be independently and significantly related to disease-free survival (Table 4.4).

**Table 4.1 Details of the patients**

	<b>Surgery</b>	<b>dCRT</b>	<b>p value</b>
Number	312	311	
Gender M:F	244:68	172:139	<0.0001
Median Age (Y) (range)	62 (31-79)	69 (39-85)	<0.0001
Age <70:≥70	242:70	159:152	<0.0001
Histology ACC:SCC	252:60	164:147	<0.0001
<b>Site of Tumour (%)</b>			<0.0001
Upper third	0	12 (3.9)	
Middle third	53 (17.0)	123 (39.5)	
Lower third & GOJ	259 (83.0)	173 (55.6)	
Unknown	0	3 (1.0)	
<b>Radiological Stage (%)</b>			<0.0001
I	22 (7.1)	10 (3.2)	
II	126 (40.4)	86 (27.7)	
III	145 (46.5)	187 (60.1)	
IVa	19 (6.1)	28 (9.0)	
<b>EUS T Stage (%)</b>			<0.0001
T1	26 (8.3)	12 (3.9)	
T2	52 (16.7)	39 (12.5%)	
T3	209 (67.0)	178 (57.2)	
T4	25 (8.0)	82 (26.4)	
<b>EUS N Stage (%)</b>			<0.0001
N0	128 (41.0)	85 (27.3)	
N1	184 (59.0)	226 (72.7)	
<b>EUS M1a (%)</b>	19 (6.1)	28 (9.0)	0.169

#### 4 Recurrence Patterns

Median ELOD (range)	6 (0-20)	7 (0-26)	<0.0001
ELOD ≤ 5cm (%)	116 (37.2)	92 (29.6)	0.017
ELOD ≤ 7cm (%)	173 (55.4)	138 (44.3)	0.011
ELOD ≤ 10cm (%)	226 (72.4)	192 (61.7)	<0.0001
ELOD not reported (%)	51 (16.3)	43 (13.8)	0.380

ELOD – EUS defined total disease length in cm

**Table 4.2 Outcomes related to treatment type**

	<b>Surgery</b>	<b>dCRT</b>	<b>p value</b>
Progressive disease despite dCRT (%)	-	70 (22.5)	-
No surgery / palliative resection / in hospital mortality (%)	72 (23.1)	-	-
Disease free (%)	113 (36.2)	104 (33.4)	0.467
Recurrence (%)	127 (40.7)	137 (44.1)	0.222
<b>Site of recurrence (%)</b>			
Locoregional	29 (9.3)	75 (24.1)	<0.0001
Distant	71 (22.8)	40 (12.9)	0.001
Both	25 (8.0)	22 (7.1)	0.657
Unspecified	2 (0.6)	0	0.157
Median time to recurrence (range)	17 (2-74)	15 (5-162)	0.052
Median time to locoregional recurrence (range)	18 (7-50)	15 (6-65)	0.134
Median time to distant recurrence (range)	16 (2-74)	12 (5-162)	0.175

Time to recurrence in months.

**Table 4.3 Univariate analysis of factors influencing disease-free survival**

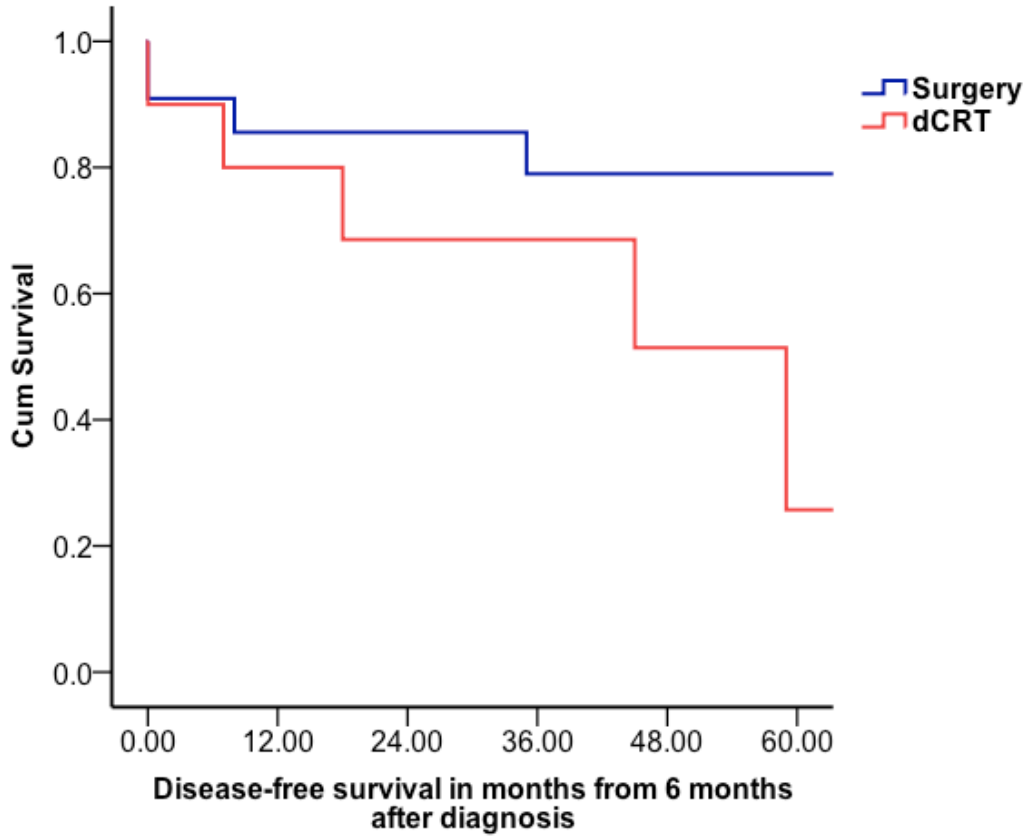
<b>Factor</b>	<b>Chi<sup>2</sup></b>	<b>df</b>	<b>p value</b>
Age	58.251	50	0.198
Age group (10 years)	3.190	3	0.363
Gender	1.510	1	0.219
Histological cell type	0.037	1	0.847
EUS T stage	34.543	3	<0.0001
EUS N stage	30.800	1	<0.0001
EUS defined tumour length	26.934	16	0.042
EUS defined disease length	41.198	24	0.016
EUS defined LNMC	36.711	11	<0.0001

LNMC – lymph node metastasis count

**Table 4.4 Multivariate analysis of factors influencing disease-free survival**

	<b>Hazard Ratio</b>	<b>95% CI</b>		<b>p value</b>
EUS defined LNMC	1.066	1.022	1.112	0.003
EUS T Stage				
T1		Reference group		
T2	1.959	1.017	3.774	0.044
T3	2.477	1.343	4.567	0.004
T4	2.566	1.304	5.050	0.006

Figure 4.1 Stage I disease-free survival related to treatment

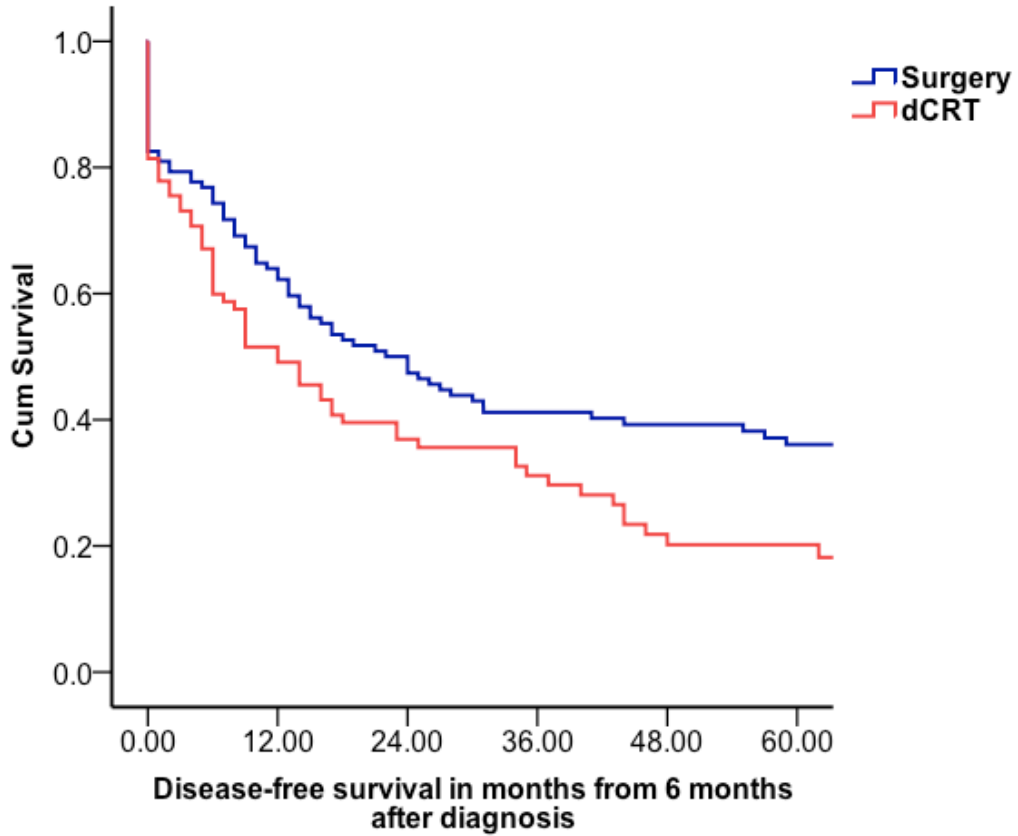


Chi<sup>2</sup> 3.316, df 1, p=0.069

No. at risk	0m	12m	24m	36m	48m	60m
Surgery	22	15	15	12	11	11
dCRT	10	8	6	4	3	1



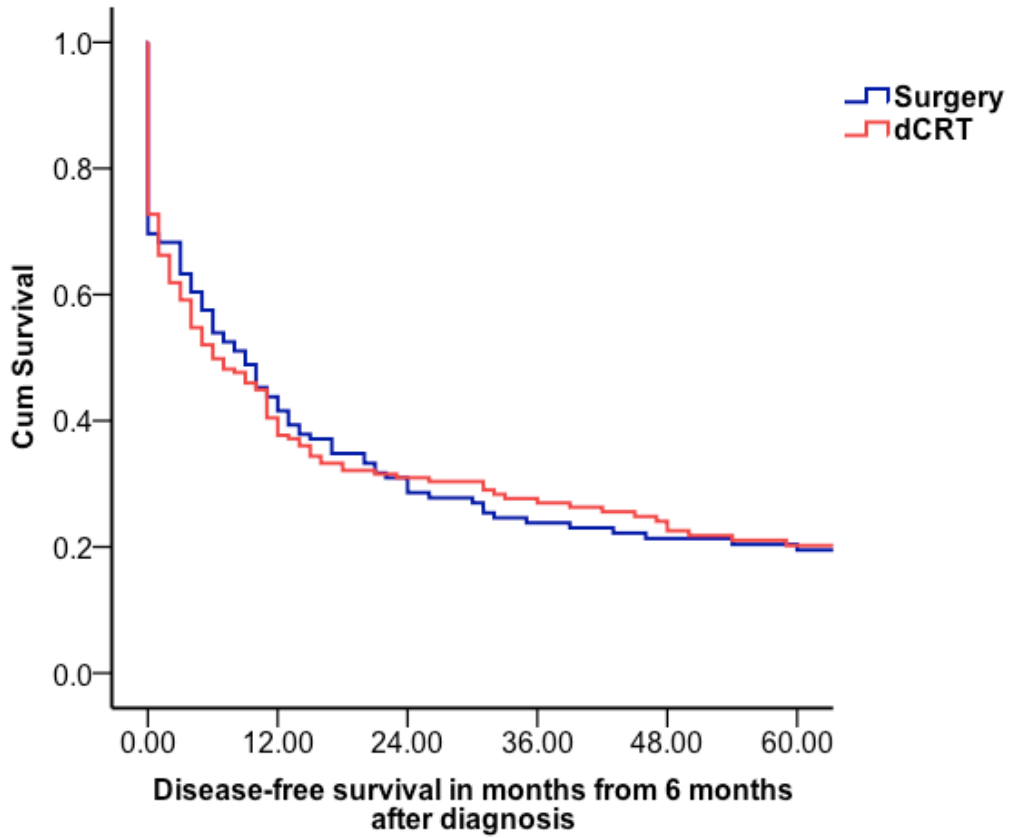
Figure 4.2 Stage II disease-free survival related to treatment



Chi<sup>2</sup> 6.535, df 1, p=0.011

No. at risk	0m	12m	24m	36m	48m	60m
Surgery	126	72	54	44	39	34
dCRT	86	41	28	21	12	10

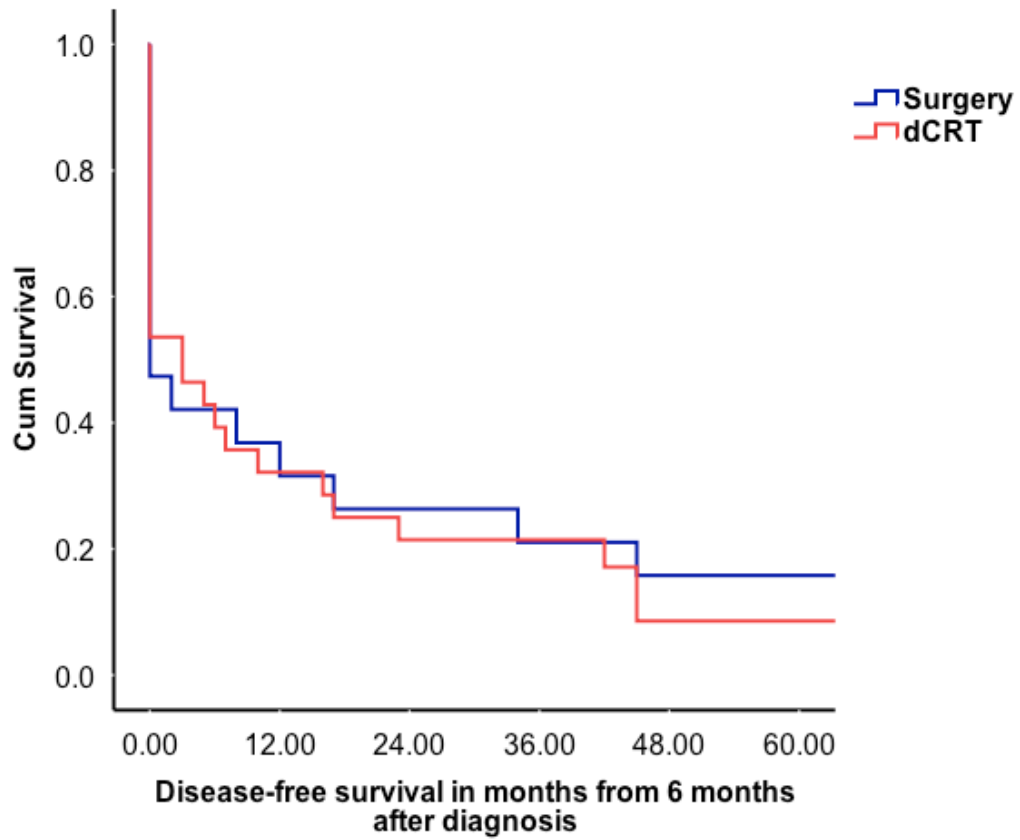
Figure 4.3 Stage III disease-free survival related to treatment



Chi<sup>2</sup> 0.023, df 1, p=0.878

No. at risk	0m	12m	24m	36m	48m	60m
Surgery	145	56	36	30	25	21
dCRT	187	68	51	39	30	24

Figure 4.4 Stage IV disease-free survival related to treatment



Chi<sup>2</sup> 0.138, df 1, p=0.710

No. at risk	0m	12m	24m	36m	48m	60m
Surgery	19	6	5	4	3	3
dCRT	28	9	6	5	2	2

## 4.5 DISCUSSION

This study represents the largest single centre prospective cohort comparative series of dCRT and surgery for oesophageal cancer in the United Kingdom. The principal finding was that overall rates of oesophageal cancer recurrence were comparable for surgery and dCRT, but the patterns and distribution of recurrence differed in relation to treatment type. Chemoradiotherapy was associated with rates of locoregional recurrence that were two and a half times more common than after surgery, but in contrast distant metastatic recurrence was more than one and a half times commoner after surgery than dCRT. Disease-free and overall survival were better following surgery than dCRT for patients diagnosed with early stage (I and II) oesophageal cancer, but were similar for patients with advanced stage (III and IVa) cancer. The 311 patients undergoing dCRT were significantly older with associated cardiorespiratory comorbidities, were more likely to have squamous cell carcinomas, and had longer and more locally advanced tumours than patients undergoing surgery. Nevertheless these patients had an overall median survival of 22 months, with 45.4% and 23.9% of patients being alive at 2 and 5 years respectively. Even patients with T4 disease survived for a median of 13 months, with a 2 year survival of 32.6%. Based on historical control data, such patients in the past would have been offered only palliative therapy with a likely 2 year survival of some 5 to 10%.

Relatively few randomised control trials have directly compared dCRT with surgery in the management of oesophageal cancer and definitive conclusions are therefore uncertain. Chiu et al from China (2005) randomised 80 patients with SCC to dCRT or surgery and found little difference in disease-free survival (54.5 vs. 58.3 after S or dCRT respectively,  $p=0.45$ ). Patients treated with S had a slightly higher proportion of recurrence in the mediastinum whereas patients treated with dCRT sustained a higher proportion of recurrence in the cervical or abdominal regions (Chiu et al 2005). Similarly, Carstens et al (2007) from Sweden randomised 91 patients with both ACA and SCC to dCRT or S and reported 4 year survival of 29% and 23% respectively (not significant, no recurrence data quoted, no p value quoted). Conversely, Badwe et al (1999) from India randomised 99 patients with SCC to radiotherapy alone (50 Gy in 25 fractions with a 15 Gy boost to the tumour bed) versus S alone and reported a significant survival advantage in favour of surgery ( $p=0.002$ ), but again no recurrence data was quoted. Two further randomised trials have compared dCRT alone with neoadjuvant chemoradiotherapy (CRT) followed by surgery, in patients with exclusively oesophageal squamous cell carcinomas (Bedenne et al 2007, Stahl et al 2005). Neither demonstrated significant differences in overall survival between treatment types. Stahl et al reported 2-year locoregional disease-free rates of 64.3% for CRT followed by surgery and 46.7% for dCRT, commenting that the addition of surgery improved local disease control but not overall survival (Stahl et al 2005). This is similar to the

findings of this study but Stahl et al do not provide any data on recurrence at other sites, namely distant metastases. Bedenne et al (2007) reported comparable 2-year recurrence rates of 56.7% for CRT followed by surgery and 59.6% for dCRT. Local recurrence was significantly more frequent after dCRT, but there was no significant difference in the rate of distant recurrence between the groups (Bedenne et al 2007). A British feasibility study of patients is currently underway to establish whether a full multicentre randomised trial of dCRT versus surgically based treatment is possible in the UK, although only patients with squamous cell carcinoma will be studied (Blazeby 2011).

The study has several potential limitations. This was a non-randomised, observational comparison of two treatment modalities allocated on a per patient basis, and therefore is potentially vulnerable to selection bias. Consequently the groups were unbalanced in terms of age, performance status, histopathological cell type, and length and stage of disease. Furthermore, there was a predominance of squamous cell carcinoma in the dCRT cohort, which is perceived to have greater radiosensitivity than the predominant adenocarcinoma, and these patients are less likely to be surgical candidates due to a combination of the site of the oesophageal tumour (high oesophagus) and co-morbidity related to aetiological factors that are in common with the cancer. Nevertheless, comparable long term survival has been reported with dCRT for adenocarcinoma (Geh 2001). However, histopathological cell type was not found to be associated with disease-free survival on univariate analysis. Moreover, the stage-for-

stage subanalysis of the patients with oesophageal adenocarcinoma found that surgery and dCRT remained associated with comparable disease-free, and overall survival rates, for stage III and IV cancers, after exclusion of the data related to squamous carcinomas. However, such subgroup analysis can introduce further bias, and a consequence of reducing patient numbers is the possibility of inadequate statistical power to detect real differences. Of the patients receiving neoadjuvant chemotherapy and failing to progress to surgery (1.9%); the current series included a number of borderline resectable patients at diagnosis, in whom it was hoped that neoadjuvant chemotherapy might result in down staging, facilitating surgery. In the course of neo-adjuvant treatment, there always exists a proportion of patients whose disease progresses, or who become physiologically too unwell for surgery. In the US Intergroup 0116 (Kelson et al 1998) and the MRC OE02 (Medical Research Council Oesophageal Cancer Working Party 2002) trials, the corresponding numbers of patients randomised to pre-operative therapy that underwent resection were 180 of 213, and 360 of 401, respectively. Data was not available on quality of life, as this is not usually recorded in routine clinical practice.

In contrast, the present study has several strengths in that it represents the largest series of consecutive patients treated over 12 years in a single upper gastrointestinal cancer network, by an experienced multidisciplinary team based on state of the art radiological staging in each patient, with the surgery performed by specialist surgeons (Morgan et al 2007b and 2009 and Adams et al 2007). The integrity of a stage-for-stage approach to

analysis, with the inclusion of patients treated non-surgically, is highly dependant on accurate radiological staging. All patients included in this study had complete EUS examinations, with well documented radiological expertise and user reliability (Weaver et al 2004). The patients reside in a stable and well defined geographical area, and consequently the follow-up data is particularly robust. The findings of this study cannot be explained on the basis of poorer than expected results from the surgery. The in-hospital mortality rate (4.5%) is comparable to large trial data (6-10%) (Kelson et al 1998, Medical Research Council Oesophageal Cancer Working Party, 2002) and the 2010 UK National Audit (4.5%) (National Oesophago-gastric Cancer Audit 2010). The overall survival rates following surgery (median 28 months, 2 year 56.2%) compare favourably with the results from both the MRC OE02 (median 13.3 to 16.8 months, 2 year survival 34 to 43%) (Medical Research Council Oesophageal Cancer Working Party, 2002) and the US Intergroup (median 14.9 to 16.9 months, 2 year survival 35 to 37%) (Kelson et al 1998) trials. Disease-free survival can also be directly compared to these trials, given the similar statistical methodology employed in this study. Whilst neither trial presents detailed data on disease-free survival, median and 2 year disease-free survival can be extrapolated from the published Kaplan-Meier plots (Medical Research Council Oesophageal Cancer Working Party 2002, Kelson et al 1998). The disease-free survival in the surgical patients in this study (median 14 months, 2 year 39.8%) compares very favourably to both OE02 (0 to 6 months, 20%, Medical Research Council Oesophageal Cancer Working



Party 2002) and the US Intergroup trial (0 months, 22%, Kelson et al 1998). The overall survival rates following dCRT (median 22 months, 2-year 45.4%) compare favourably with other published series, which have shown consistent overall survival (median 14-18 months, 2-year 35-40%) in both SCC and ACA (Cooper et al 1999, Bedenne et al 2007, Stahl et al 2005, Chan et al 1999, Coia et al 2000, Kaneko et al 2003, Geh 2001).

#### **4.6 CONCLUSION**

In conclusion, the results of this study have again shown that dCRT is an effective and well tolerated treatment for patients diagnosed with oesophageal cancer of any histopathological cell type. Survival rates were similar to those reported in surgical series; supporting the view that dCRT should be considered in all patients, particularly those at higher risk from surgery due to co-morbidity and stage III disease in whom an R0 resection is less likely. Relapses were predominantly local after dCRT but metastatic after surgery. Indeed, locoregional disease was a component of treatment failure in 70.8% of cases after dCRT compared with 42.5% after surgery, whereas metastases were a component in 45.3% of cases after dCRT compared with 75.6% after surgery. The overall local failure rate after dCRT of 31.2% is similar to other studies but seems higher than that reported after surgery. Most sites of first recurrence after dCRT were within the radiation field, suggesting a need for intensifying local therapy allied to improving systemic therapy. Further research to optimise dCRT technique, focusing on recent advances such as intensity-modulation radiotherapy may allow safe dose escalation. Improved systemic therapy

with targeted agents such as anti-epidermal growth factor receptor inhibitors have shown promise when combined with radiotherapy in other tumour sites (Bonner et al, 2006) and are currently under investigation in the UK National Cancer Research Institute SCOPE 1 study of dCRT for oesophageal cancer (Crosby 2009). A prospective randomised trial is needed to directly compare outcomes after dCRT and surgically based therapy for oesophageal cancer, but the difficulties of satisfying both patient and surgeon preferences would be considerable (Blazeby 2011). The feasibility study underway at present is examining whether it is possible to recruit patients into a randomised control trial comparing diverse treatments (Blazeby et al 2011). The above trial is proposed in oesophageal SCC but the data from this study suggest that it may also be able to incorporate patients diagnosed with ACA, making the feasibility of such a trial more likely.

## **Chapter 5**

**The prognostic significance of involvement of the circumferential  
resection margin following oesophagectomy and influence of  
differing neoadjuvant therapy regimens**

## 5.1 SUMMARY

The optimum multimodal treatment for oesophageal cancer, and the prognostic significance of histopathological tumour involvement of the circumferential resection margin (CRM+) are uncertain. The aims of this study were to determine the prognostic significance of CRM+ after oesophagectomy and to identify endosonographic (EUS) features that predict CRM+.

Two hundred and fifty six consecutive patients underwent potentially curative oesophagectomy [118 neoadjuvant chemotherapy (CS) and 42 chemoradiotherapy (CRTS)]. The primary outcome measures were overall and disease-free survival (DFS).

A positive CRM was reported in 93 (38.0%) of all patients, and in 85 (62.4%) of the pT3 patients. Multivariate analysis of pathological factors revealed: lymphovascular invasion (HR 2.437, 95%CI 1.633-3.636,  $p < 0.0001$ ) and CRM+ (HR 1.878, 95%CI 1.266-2.785,  $p = 0.002$ ) to be independently and significantly associated with DFS. Multivariate analysis revealed EUS T stage (T3 or T4, OR 34.560, 95%CI 9.032-132.241,  $p < 0.0001$ ) and the use of CRTS (OR 0.099, 95% CI 0.029-0.334,  $p < 0.0001$ ) to be independently and significantly associated with CRM+.

A positive CRM was a better predictor of disease-free survival than standard pTNM stage, and these results support the need for a randomised trial of CRTS vs. CS in patients with oesophageal cancer of radiological T3 or T4 stage.

## 5.2 INTRODUCTION

The significance of pathological involvement of the circumferential resection margin (CRM) following surgery for rectal cancer is well established. An involved rectal CRM has a proven association with local recurrence and poor survival (Quirke et al 1986, Adam et al 1994, Birbeck et al 2002), and as such patients deemed radiologically to be at high risk are offered pre-operative chemoradiotherapy (Theodoropoulos et al 2002, Klautke et al 2005). In contrast, the significance of pathological CRM involvement in oesophageal cancer is far less certain. Sagar et al (1993) first demonstrated an association between an involved CRM and local recurrence after oesophagectomy. A number of heterogeneous studies have since sought to further illuminate this issue and investigate the influence of oesophageal CRM involvement on survival (Dexter et al 2001, Khan et al 2003, Griffiths et al 2006, Sujendran et al 2008, Scheepers et al 2009, Saha et al 2009, Mirnezami et al 2010). Many have demonstrated CRM involvement to impact negatively on overall survival (Dexter et al 2001, Sujendran et al 2008, Scheepers et al 2009, Saha et al 2009), although other studies have found no association with survival at all (Khan et al 2003), no influence on survival when only T3 tumours were analysed (Griffiths et al 2006), and no independent association with survival (Mirnezami 2010). The relevance of an involved CRM therefore remains uncertain.

The majority of patients with oesophageal cancer in the UK present with locoregionally advanced disease. The aims of neoadjuvant treatment in

this patient cohort are to increase the probability of a complete (R0) resection and to improve survival. Since the publication of the MRC OE02 randomised trial almost a decade ago, neoadjuvant chemotherapy followed by surgery has remained the mainstay of contemporary treatment in the UK (MRC Oesophageal Cancer Working Group 2002). However, less than 30% of patients in the UK are suitable for this treatment (NHS Information Centre 2010), and even for those that are, 5-year survival is poor at just 23% (Allum et al 2009). Few studies have examined the influence of different neoadjuvant treatment regimes on oesophageal CRM involvement rates specifically. Sujendran et al (2008) report a significant reduction in CRM involvement rate associated with neoadjuvant chemotherapy compared with surgery alone for T3 tumours, yet even after this reduction, 31% still had a positive CRM. The overall incidence of CRM involvement is 29% in the 2010 UK National Oesophago-gastric Audit (NHS Information Centre 2010), and ranges from 20 to 47% in the published series (Sagar et al 1993, Dexter et al 2001, Khan et al 2003, Griffiths et al 2006, Sujendran et al 2008, Scheepers et al 2009, Saha et al 2009, Mirnezami et al 2010).

Neoadjuvant chemoradiotherapy can result in tumour downstaging in more than 90% of patients, (Reynolds et al 2007) and complete pathological response in 15 to 29% (Rohatgi et al 2005, Reynolds et al 2007, Stahl et al 2009, Donahue et al 2009, Courrech Staal et al 2010), offering the possibility of increased R0 resection rates. However, this treatment modality has fallen out of favour in the UK due to a combination of

concerns about increased surgical morbidity and mortality, the publication of the results of the OE02 trial promoting neoadjuvant chemotherapy, and on going patient recruitment into the MRC OE05 trial. The use of EUS criteria to pre-operatively estimate the risk of a circumferentially incomplete resection (R1) has the potential to guide the choice of neoadjuvant therapy prescribed. However, this possibility has not been studied to date.

The aims of this study were three-fold:

1. To identify the relative prognostic significance of CRM involvement after potentially curative oesophagectomy.
2. To assess the strength of pre-operative EUS derived factors in predicting subsequent CRM involvement.
3. To identify the influence of differing neoadjuvant modalities on CRM involvement rates.

## **5.3 METHODS**

### **5.3.1 Patient selection and staging**

Consecutive patients treated for oesophageal cancer between 1 January 1998 and 31 October 2010 by the regional S.E. Wales upper GI cancer network were studied. Patient exclusion criteria were as follows: 1. Treatment for high grade dysplasia in the absence of invasive malignancy. 2. Open and close surgery. 3. Pathological involvement of the longitudinal resection margins. 4. Missing pathological TNM stage information. Consequently, 256 patients underwent potentially curative oesophagectomy and were included in the study. Clinical, radiological and pathological information was collected on a prospectively maintained database. Pre-operative staging was in accordance with the UICC Tumour Nodes Metastasis (TNM) 6<sup>th</sup> Edition (Sobin and Wittekind 2002), using the algorithm described in Chapter 4. All EUS examinations were either performed or supervised by a single radiologist (Weaver et al 2004).

### **5.3.2 Surgery +/- neoadjuvant therapy**

All patients had individually tailored management plans. In general, fit patients with tumours of stage T3 and equivocal T4, N0 and N1 were considered for neoadjuvant therapy. Prior to 2002 patients were treated with neoadjuvant chemoradiotherapy. They received two cycles of cisplatin (60mg/m<sup>2</sup>) with 300mg/m<sup>2</sup> per day of infusional 5-fluorouracil (5-FU) before 45Gy radiotherapy delivered in 25 fractions. Following the publication of the OE02 trial, patients were treated with neoadjuvant



chemotherapy. They received either two cycles of cisplatin (80mg/m<sup>2</sup>) and 5-FU (1000mg/m<sup>2</sup>) or four cycles of epirubicin (50mg/m<sup>2</sup>), cisplatin and 5-FU (200mg/m<sup>2</sup>). The operative approach was transthoracic for 152 (59.4%) patients, and transhiatal for 104 (40.6%). All surgery was performed by specialist upper GI surgeons. Oesophageal resection was defined as potentially curative when all visible tumour had been removed and both proximal and distal resection margins were free from tumour on histological examination. Operative mortality was defined as death occurring within 30 days of surgery.

### **5.3.3 Circumferential margin assessment**

Pathological involvement of the circumferential resection margin was defined according to the Royal College of Pathologists, as the presence of tumour within 1mm of the circumferential margin (Mapstone 1998).

### **5.3.4 Follow-up**

All patients were reviewed every 3 months for the first year and then 6 monthly. Suspected disease recurrence was investigated with CT and/or endoscopy. The time of recurrence was taken as the date of the confirmatory investigation. Follow-up until 5 years or death was available for 210 (82%) patients. Death certification was obtained from the Office for National Statistics.

### **5.3.5 Statistical analysis**

Grouped data were expressed as median (range) and non-parametric methods were used. Overall survival was calculated in months from the date of diagnosis. Disease-free survival was also calculated in months from the date of diagnosis, with either the confirmation of disease recurrence or death constituting the end point. Cumulative survival was calculated according to the life-table method of Kaplan and Meier, and differences between groups were analysed with the log rank test. Multivariate analysis of factors found to be significant on univariate analysis was performed with Cox regression. Analysis of pre-operative factors influencing CRM status was performed using binary logistic regression.

## **5.4 RESULTS**

### **5.4.1 Clinical, radiological and pathological details of the patients**

The clinical and radiological details of the patients related to neoadjuvant treatment type are shown in Table 5.1, and pathological details in Table 5.2. There were progressive increases in the radiological T and N stages of the patients treated with surgery alone, neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy. A complete pathological response occurred in more than one third of patients who received chemoradiotherapy, but was a relatively rare event in those treated with chemotherapy. CRM status was reported in 245 (95.7%) patients, of which 93 (38.0%) had an involved CRM.

#### **5.4.2 Overall and disease-free survival**

Figures 5.1 and 5.2 show Kaplan-Meier survival curves for overall and disease-free survival related to CRM status, for all patients included in this study. A negative CRM was associated with significantly better overall survival (median 66 vs. 25 months, 2-year 70.5 vs. 53.2%,  $p < 0.0001$ ) and disease-free survival (median 52 vs. 18 months, 2-year 65.7 vs. 34.5%,  $p < 0.0001$ ). Figures 3 and 4 show similar survival curves for overall and disease-free survival related to CRM status, for patients of pT3 stage. In this pT3 subgroup a negative CRM was associated with significantly better overall survival (median 36 vs 26 months, 2-year 65.1 vs 57.4%,  $p = 0.025$ ) and disease-free survival (median 30 vs 19 months, 2-year 59.1 vs 37.1,  $p = 0.013$ ) when compared with a positive CRM.

A univariate analysis of clinical and pathological factors influencing both overall and disease-free survival is shown in Table 5.3. The same six factors were identified as significant for both measures of survival, and were entered into multivariate analyses, with individual models for overall and disease-free survival (Table 5.4). Lymphovascular invasion retained an independent association with both survival measures, but CRM+ was only independently associated with disease-free survival.

#### **5.4.3 CRM status related to radiological T stage**

The overall rates of CRM involvement related to EUS defined T stage were T1 (0), T2 (6 of 43, 14.0%), T3 (78 of 159, 49.1%) T4 (6 of 16, 37.5%). For patients treated with surgery alone these CRM involvement

rates were T1 (0), T2 (2 of 31, 6.5%), T3 (27 of 37, 73.0%) and T4 (N/A). For patients treated with neoadjuvant chemotherapy the equivalent rates were T1 (0), T2 (4 of 11, 36.4%), T3 (47 of 89, 52.8%) and T4 (5 of 9, 55.6%). For patients treated with neoadjuvant chemoradiotherapy the rates were T1 (N/A), T2 (0), T3 (4 of 33, 12.1%) and T4 (1 of 7, 14.3%). The reduced CRM involvement rate for EUS T3 tumours following chemoradiotherapy (12.1%) compared with surgery alone (73.0%) and chemotherapy (52.8%) was highly statistically significant ( $p < 0.0001$ ).

#### **5.4.4 CRM status related to pathological T stage**

The overall rates of CRM involvement related to pT stage were T1 (0), T2 (4 of 43, 9.3%), T3 (85 of 135, 63.0%), T4 (4 of 5, 80%). The rates of CRM involvement in the 135 patients with pT3 tumours related to neoadjuvant treatment type were surgery (27 of 41, 65.9%), neoadjuvant chemotherapy (54 of 80, 67.5%) and neoadjuvant chemotherapy (4 of 14, 28.6%,  $p = 0.022$ ).

#### **5.4.5 Influence of EUS derived factors on CRM involvement**

The results of univariate and multivariate binary logistic regression analysis of the association between various EUS derived factors and subsequent CRM involvement are presented in Table 5.5. Neoadjuvant treatment type was also included in this analysis because of its significant influence on CRM outlined above. The multivariate model included all factors significant on univariate analysis. The only EUS variable that retained an independent association with CRM involvement was EUS T

stage, with an almost 35-fold increased risk of CRM involvement once a tumour was T stage T3 or greater by EUS criteria. Neoadjuvant treatment type also emerged as independently significant on multivariate analysis. There was a non-significant trend towards a reduced risk of CRM involvement associated with neoadjuvant chemotherapy compared with surgery alone, but a highly significant reduction in risk conferred by neoadjuvant chemoradiotherapy.

#### **5.4.6 Operative morbidity and mortality**

The overall rates of all operative morbidity after surgery alone, neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy were 42 (47.7%), 51 (46.8%) and 21 (50.0%) respectively (p=0.939). The equivalent operative mortality was 5 (5.2%), 1 (0.8%) and 5 (11.9%) respectively (p=0.009). The overall operative mortality rate was 11 (4.3%).

**Table 5.1 Details of the patients**

	<b>S</b>	<b>CS</b>	<b>CRTS</b>	<b>p value</b>
Number	96	118	42	
Gender M:F	75:21	92:26	31:11	0.836
Median age (Y) (range)	66 (35-79)	62 (36-74)	55 (31-71)	<0.0001
Histology ACC:SCC	73:23	98:20	30:12	0.219
<b>EUS T Stage (%)</b>				<0.0001
T1	23 (24.0)	2 (1.7)	0	
T2	31 (32.3)	11 (9.3)	1 (2.4)	
T3	41 (42.7)	92 (78.0)	34 (81.0)	
T4	1 (1.0)	10 (8.5)	7 (16.7)	
Not crossed	0	3 (2.5)	0	0.169
<b>EUS N Stage (%)</b>				<0.0001
N0	63 (65.6)	42 (36.0)	10 (23.8)	
N1	33 (34.4)	73 (62.0)	32 (76.2)	
Not crossed (%)	0	3 (2.5)	0	0.169
EUS M1a (%)	2 (2.1)	5 (4.2)	3 (7.1)	0.358
EUS tumour length (range)	3 (0-15)	5 (1-12)	5 (1-11)	<0.0001
EUS disease length (range)	3 (0-15)	7 (1-19)	5 (1-16)	<0.0001
EUS tumour thickness in (range)	0.9 (0-1.7)	1.3 (0.5-3.0)	1 (0.5-2.0)	<0.0001

Length and thickness parameters are median cm (range). S – surgery alone, CS – neoadjuvant chemotherapy, CRTS – neoadjuvant chemoradiotherapy.

Table 5.2 Pathological details of the patients

	<b>S</b>	<b>CS</b>	<b>CRTS</b>	<b>p value</b>
CPR (%)	n/a	3 (2.5)	15 (35.7)	<0.0001
<b>pT stage (%)</b>				<0.0001
T1	31 (32.3)	9 (7.6)	4 (9.5)	
T2	17 (17.7)	20 (17.0)	6 (14.3)	
T3	47 (50.0)	82 (69.5)	15 (35.7)	
T4	1 (1.0)	4 (3.4)	2 (4.8)	
<b>pN stage (%)</b>				<0.0001
N0	49 (51.0)	40 (33.9)	30 (71.4)	
N1	47 (49.0)	78 (66.1)	12 (28.6)	
<b>Tumour grade (%)</b>				0.075
Well	13 (13.5)	7 (5.9)	1 (2.4)	
Moderate	47 (49.0)	52 (44.1)	9 (21.4)	
Poor	27 (28.1)	51 (43.2)	11 (26.2)	
Not reported	9 (9.4)	5 (4.2)	6 (14.3)	
<b>CRM (%)</b>				<0.0001
Negative	61 (63.5)	55 (46.6)	36 (85.7)	
Positive	29 (30.2)	59 (50.0)	5 (12.0)	
Not reported	6 (6.3)	4 (3.4)	1 (2.4)	
<b>LV invasion (%)</b>				0.023
Yes	43 (44.8)	56 (47.5)	27 (64.3)	
No	30 (31.3)	50 (42.4)	7 (16.7)	
Not reported	23 (24.0)	12 (10.2)	8 (19.0)	

S – surgery alone, CS – neoadjuvant chemotherapy, CRTS – neoadjuvant chemoradiotherapy, CPR – complete pathological response to neoadjuvant therapy, LNMC – lymph node metastasis count, CRM – circumferential resection margin, LV – lymphovascular.

**Table 5.3 Univariate analysis of factors influencing survival**

Factor	Disease-free survival			Overall survival	
	Chi <sup>2</sup>	df	p value	Chi <sup>2</sup>	p value
Age	50.786	42	0.166	41.108	0.510
Gender	1.408	1	0.235	1.767	0.184
Path cell type	1.089	1	0.297	1.034	0.309
Neo treatment type	0.950	2	0.622	0.892	0.604
pT stage	27.963	4	<0.0001	23.164	<0.0001
pN stage	27.161	1	<0.0001	24.060	<0.0001
Tumour grade	12.526	2	0.002	13.208	0.001
CRM involvement	26.212	1	<0.0001	21.004	<0.0001
LV invasion	38.257	1	<0.0001	31.757	<0.0001
LNMC	70.308	14	<0.0001	68.184	<0.0001

Path – pathological, Neo – neoadjuvant, LV – lymphovascular, LNMC – lymph node metastasis count.



**Table 5.4 Multivariate analysis of factors influencing survival**

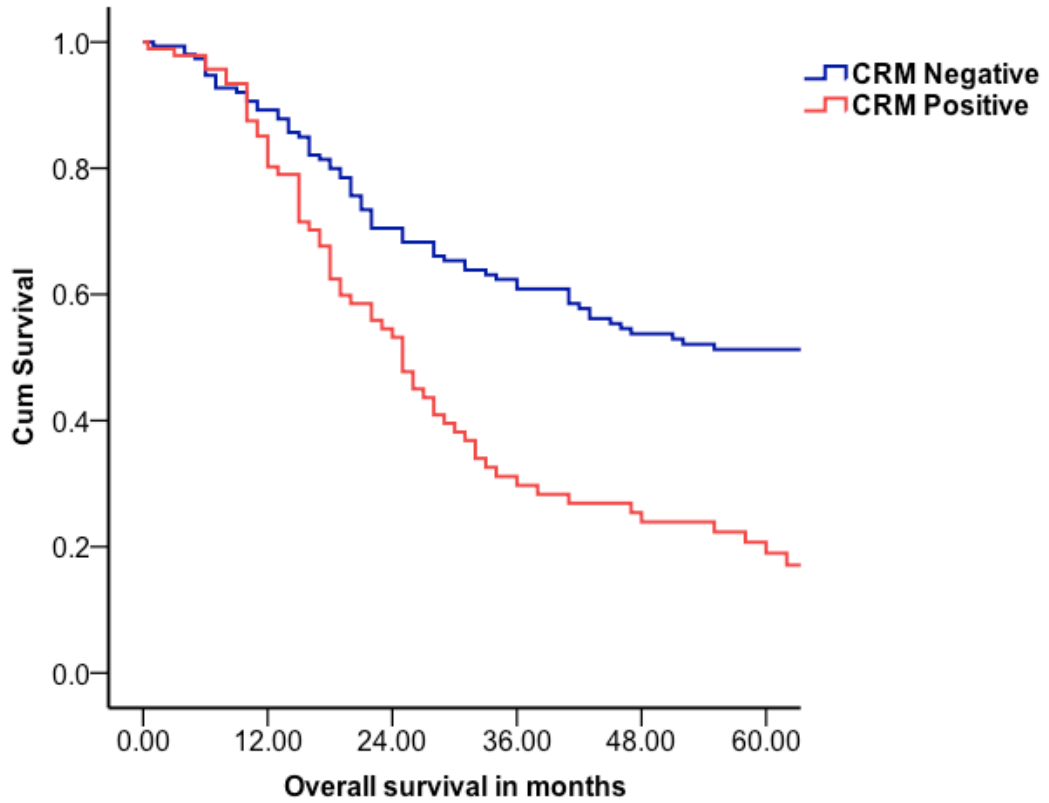
	<b>Hazard Ratio</b>	<b>95% CI</b>	<b>p value</b>
<b>Overall Survival</b>			
Lymphovascular invasion	2.184	1.428 - 3.342	<0.0001
LNMC	1.082	1.024 - 1.143	0.005
<b>Disease-free Survival</b>			
Lymphovascular invasion	2.437	1.633 - 3.636	<0.0001
CRM involvement	1.878	1.266 - 2.785	0.002

LNMC – lymph node metastasis count

**Table 5.5 Binary logistic regression analysis of pre-operative factors associated with an involved circumferential margin**

Factor		Odds Ratio	95% CI	p value
<b>Univariate analysis</b>				
EUS T stage	T1/T2	Reference group		
	T3/T4	9.385	3.856 - 22.841	<0.0001
EUS N stage	N0	Reference group		
	N1	1.773	1.040 - 3.024	0.035
EUS tumour length		1.165	1.045 - 1.299	0.006
EUS disease length		1.077	1.020 - 1.158	0.043
EUS tumour thickness		1.869	0.993 - 3.516	0.053
EUS LNMC		1.169	1.040 - 1.313	0.009
Neoadj Rx	S	Reference group		
	CS	2.256	1.270 - 4.009	0.006
	CRTS	0.292	0.104 - 0.822	0.020
<b>Multivariate analysis</b>				
EUS T stage	T1/T2	Reference group		
	T3/T4	34.560	9.032 - 132.241	<0.0001
Neoadj Rx	S	Reference group		
	CS	0.529	0.227 - 1.232	0.140
	CRTS	0.099	0.029 - 0.334	<0.0001

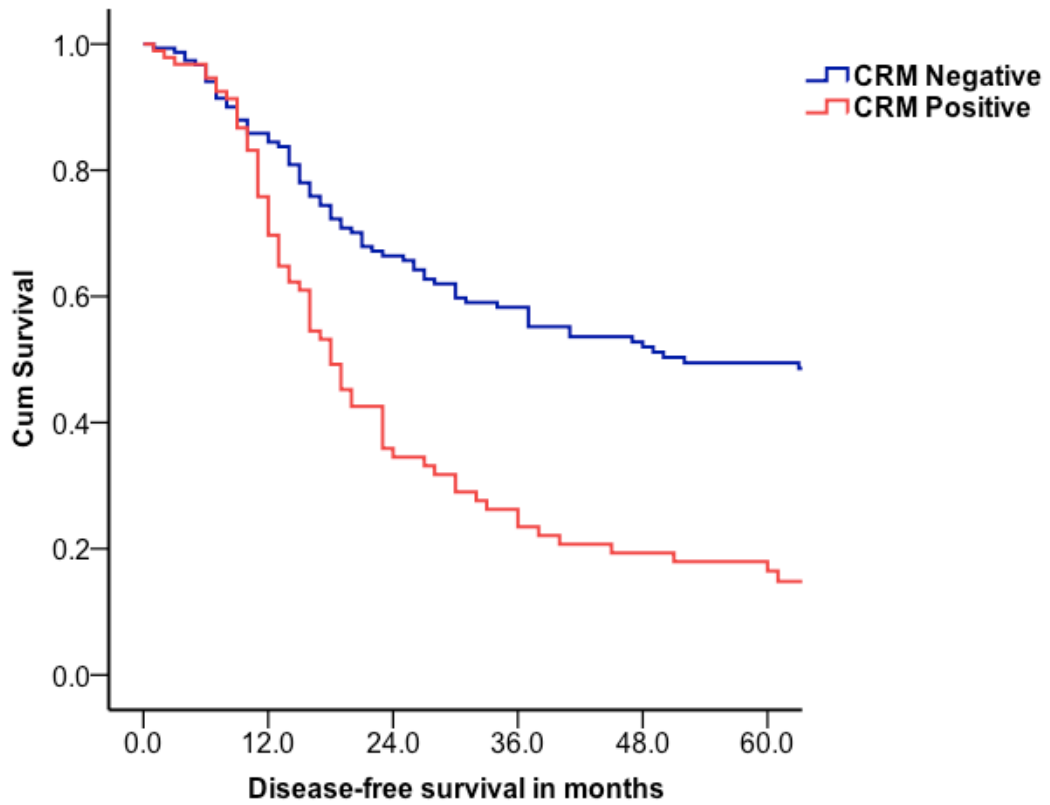
Figure 5.1 Overall survival related to CRM status for all patients



Chi<sup>2</sup> 21.004, df 1, p<0.0001

No. at risk	0m	12m	24m	36m	48m	60m
CRM -ve	152	125	96	80	66	58
CRM +ve	93	66	39	21	16	11

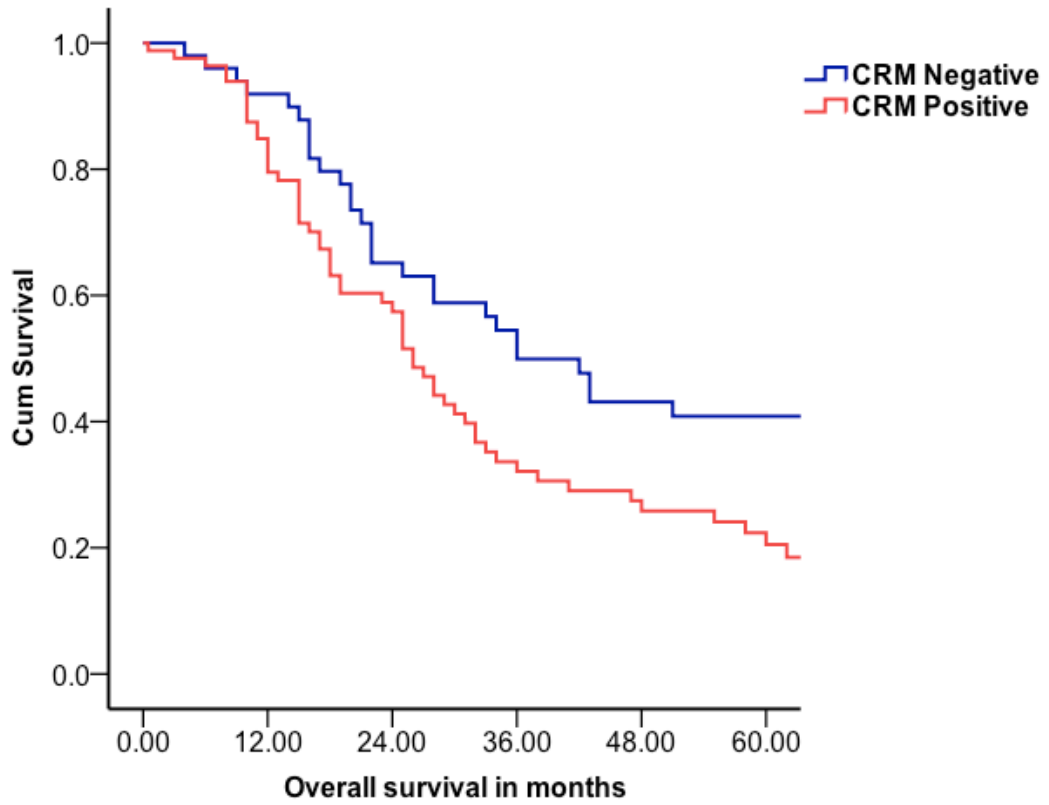
Figure 5.2 Disease-free survival related to CRM status for all patients



Chi<sup>2</sup> 26.212, df 1, p<0.0001

No. at risk	0m	12m	24m	36m	48m	60m
CRM -ve	152	118	90	76	63	56
CRM +ve	93	57	25	17	14	10

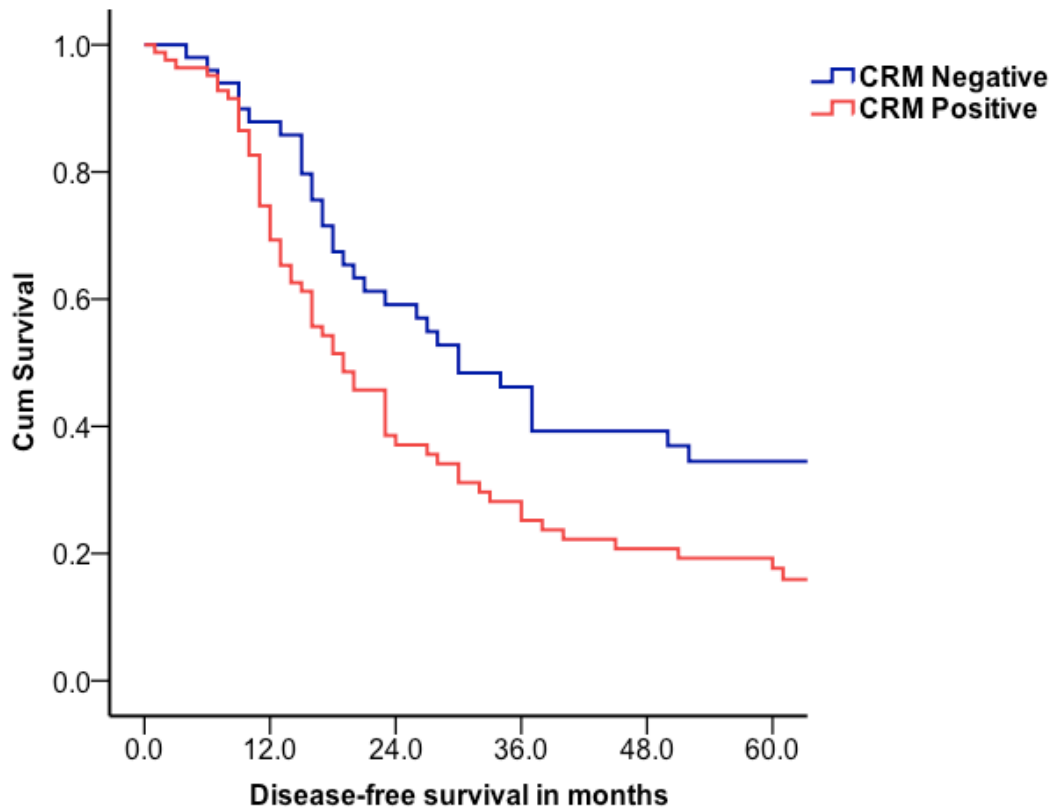
Figure 5.3 Overall survival related to CRM status for pT3 patients



Chi<sup>2</sup> 5.058, df 1, p=0.025

No. at risk	0m	12m	24m	36m	48m	60m
CRM -ve	50	45	31	22	19	15
CRM +ve	83	60	39	21	16	10

**Figure 5.4 Disease-free survival related to CRM status for pT3 patients**



Chi<sup>2</sup> 6.229, df 1, p=0.013

<b>No. at risk</b>	<b>0m</b>	<b>12m</b>	<b>24m</b>	<b>36m</b>	<b>48m</b>	<b>60m</b>
CRM -ve	50	43	28	20	17	13
CRM +ve	83	52	25	17	14	10

## 5.5 DISCUSSION

This work represents the third largest study of the prognostic significance of CRM following oesophagectomy, and one of only two that assess disease-free survival. Furthermore, it is the only study to date to examine the value of EUS factors in predicting subsequent CRM involvement. The principal findings were that a positive CRM is associated with poorer overall and disease-free survival, for patients of all pT stages, as well as for those with only pT3 stage tumours, and is independently associated with disease-free survival. A number of EUS factors predicted a positive CRM, but EUS T stage was the strongest, with half of all patients with EUS defined T3 tumours subsequently having a positive CRM. A positive CRM was significantly less common after neoadjuvant chemoradiotherapy than chemotherapy for EUS stage T3 tumours, on a stage for stage basis.

The significance of involvement of the oesophageal CRM is crucial in making treatment decisions, and informing prognosis, yet remains poorly understood, due largely to the relative lack of contemporary literature, and inconsistency therein. The eight published studies on this subject vary in many regards, including study design, the use of neoadjuvant therapy, surgical techniques, differences in pathological specimen handling and processing, and the rates of CRM involvement quoted (Sagar et al 1993, Dexter et al 2001, Khan et al 2003, Griffiths et al 2006, Sujendran et al 2008, Scheepers et al 2009, Saha et al 2009, Mirnezami et al 2010). Despite these differences only two of the studies have failed to demonstrate any independent survival association with CRM status, both

of which had the largest sample sizes of all those published. Khan et al (2003) found no association between CRM and survival in 329 patients. However, their series of patients were treated between 1987 and 1996, with none receiving any form of neoadjuvant treatment, yet despite this their reported CRM positivity rate was only 20%, the lowest of all the published series. This calls into question the accuracy of the histological assessment of the CRM in this study. More recently, a series of 314 patients (Mirnezami et al 2010) identified CRM status to be positively associated with survival on univariate testing, but not independently significant. However, this series differed from most in that it included patients with positive longitudinal resection margins, and this latter factor consequently emerged as one of the factors independently associated with survival on multivariate analysis. Several studies have demonstrated that a positive CRM had a greater influence on survival for tumours with a low lymph node burden (Dexter et al 2001, Griffiths et al 2006), whilst another demonstrated an adverse influence on survival for T3 tumours irrespective of nodal stage (Sujendran et al 2008). Subanalysis of pT3 tumours in this study on the basis of pathological nodal stage, identified definite trends towards poorer overall and disease-free survival with a positive CRM, with and without lymph node metastases, but these didn't reach significance, possibly due to underpowered sample sizes.

The reasons for the stronger prognostic influence of CRM status on disease-free survival than overall survival in this study are unclear. For a tumour such as oesophageal carcinoma, where relapse following surgery



is common, and for which there is little or no prospect of further curative treatment, it is logical to consider disease-free and overall survival to be very closely related. Clearly both are clinically important outcome measures. However, disease-free survival takes into account both the physical and psychological burden of tumour recurrence, and subsequent associated palliative treatment. In the present study, lymphovascular invasion was the strongest prognostic factor for both overall and disease-free survival, which is in keeping with the literature which recognises both venous and lymphatic invasion to be highly significant prognostic markers (Theunissen et al 1991, Paraf et al 1995, Zafirellis et al 2002, von Rahden et al 2005).

From a histopathology perspective the assessment of the oesophageal CRM is controversial. Whilst the debate continues as to the significance of CRM, pathological lymph node stage is an established prognostic factor (Theunissen et al 1991, Kawahara K 1998, Khan et al 2003). It has been said that accurate assessment of both lymph node stage and CRM status are incompatible, and therefore a compromise is required to satisfy both requirements (Mapstone et al 2007). In particular, the dissection of lymph nodes from the resected specimen by some surgeons renders meaningful assessment of the CRM impossible (Mapstone et al 2007). The precise definition used to define a positive CRM is yet another issue of uncertainty. In the UK, a positive CRM is defined as tumour within 1mm of the CRM by the Royal College of Pathologists (Mapstone et al 1998), whilst the American College of Pathologists use a definition of tumour present at the

margin itself (Washington et al 2009). Comparative studies have identified differences in the relative prognostic value of CRM status, depending on the definition used, in favour of the American system (Deeter et al 2009, Verhage et al 2011, Chao et al 2011).

This study reinforces the substantial incidence of positive CRMs after potentially curative oesophagectomy. Most patients in the UK present with T3 disease, for which neoadjuvant chemotherapy followed by surgery is the current standard of care. Based on these results such patients have a 52.8% chance of having a circumferentially incomplete (R1) resection. The results of this study also suggest the possibility of significantly improved odds (87.5%) of a circumferentially complete (R0) resection when treated with neoadjuvant chemoradiotherapy, a treatment which is considered the neoadjuvant modality of choice in the USA (Hingorani et al 2011). Provided acceptable toxicity, morbidity and mortality can be achieved with this aggressive treatment, there exists the possibility of improved outcomes. A complete pathological response is known to occur in up to a third of patients treated with chemoradiotherapy prior to surgery and this provides a well established survival advantage. (Courrech Staal et al 2010). Neoadjuvant chemotherapy and chemoradiotherapy have each been extensively compared with surgery alone in a number of meta-analyses (Urschel et al 2003, Sjoquist et al 2011), yet there is little high quality data comparing these two modalities with each other. Only two randomised trials, one German (Stahl et al 2009) and the other Australian (Burmeister et al 2011) have addressed this question. Meta-analysis of

both showed a trend towards improved survival with chemoradiotherapy but this was not significant (Sjoquist et al 2011). Both trials closed early and were underpowered. There was no association between the type of neoadjuvant treatment and the risk of post-operative mortality (Sjoquist et al 2011). The clear need exists for an adequately powered randomised trial of these two neoadjuvant regimes, and this has recently been proposed in the UK (Hingorani et al 2011). The results of the present study lend further support to this, and suggest that such a trial should focus on patients with EUS T3 tumours.

The present study has several weaknesses. The reporting of histological factors was undertaken by three separate pathology departments within the cancer network, and there could therefore be discrepancies in the reporting of CRM, particularly considering the many difficulties already discussed in relation to this. However, the rates of CRM involvement lie within the range reported in published series, and it therefore seems unlikely that CRM involvement has been substantially under-reported. The number of patients in this study are relatively large, yet are not sufficient to enable a meaningful subgroup analysis of exclusively patients with EUS T3 tumours. Such a subgroup analysis would be of value in establishing the relative influence of the radiological factors other than EUS T stage that were predictive of CRM involvement on univariate analysis. The comparison of different neoadjuvant modalities is open to bias, as these treatments were allocated on a non-randomised, per patient basis, and based on MDT practice at the time.

In contrast, the present study has several strengths. All the treatment was provided by an MDT experienced in the management of oesophageal cancer, and whose results have been well audited (Morgan et al 2007b). The EUS part of the study is particularly original work, and the only study yet to compare EUS factors with CRM status, and to relate this to the effects of differing neoadjuvant treatments. All EUS examinations were performed or supervised by a radiologist with considerable experience and expertise in this staging technique. The follow-up data is robust for the reasons discussed in Chapter 4.

## **5.6 CONCLUSION**

Involvement of the oesophageal CRM is an independently significant predictor of disease-free survival. Its occurrence can be estimated from several EUS variables, but T stage is the strongest predictor. Its incidence can be reduced by neoadjuvant chemoradiotherapy. There is an urgent need for a trial of chemoradiotherapy vs. chemotherapy in operable oesophageal cancer and the results of this study suggest T3 and T4 tumours should be targeted.

## **Chapter 6**

### **Early enteral nutrition following upper gastrointestinal surgical resection**

## 6.1 SUMMARY

The aim of this study was to determine if early enteral nutrition (EEN) improved clinical outcomes and shortened length of hospital stay.

This was a prospective multicentre randomised controlled trial within the S.E. Wales cancer network. One hundred and twenty-one patients with suspected operable upper gastrointestinal cancer (54 oesophageal, 38 gastric, 29 pancreatic) were studied. Patients were randomised to receive EEN (n=64) or standard care post-operatively (nil by mouth and IV fluid, n=57). Analysis was based on intention to treat and the primary outcome measure was length of hospital stay.

Operative morbidity was less common after EEN (32.8%) than Control management (50.9%,  $p=0.044$ ), due to fewer wound infections ( $p=0.017$ ), chest infections ( $p=0.036$ ) and anastomotic leaks ( $p=0.055$ ). Median length of hospital stay was 16 days (IQ=9) after EEN compared with 19 (IQ=11) days after Control management ( $p=0.023$ ).

EEN was associated with significantly shortened length of hospital stay and improved clinical outcomes. These findings reinforce the potential benefit of early oral nutrition as evidenced by enhanced recovery after surgery programmes, and such strategies deserve further research in upper GI surgery.

## 6.2 INTRODUCTION

Gastrointestinal surgery involving intestinal resection and anastomosis commonly entails long periods of starvation or “nil by mouth”, while new anastomoses heal. This strategy is designed to allow time for intestinal motility to return to normal, and to protect anastomoses from the stress of introducing oral fluids and diet (Lewis et al 2009). Upper gastrointestinal cancer surgery in particular, is frequently performed in malnourished patients (Nygren et al 2003) which if severe, can be associated with a higher incidence of post-operative complications, which may in turn impede recovery (Weimann et al 2006).

Oesophageal, gastric and pancreatic cancer represent the 7th, 8th and 10th commonest causes of death from cancer in the UK, accounting for approximately 19,000 deaths per annum (Cancer Research UK). Surgical resection remains the mainstay of curative treatment (Allum et al 2011) but is complex in nature and frequently associated with post-operative morbidity and mortality, even in well nourished patients (NHS Information Centre 2010). Traditional post-operative management often involves intravenous fluids for 7 to 10 days, with ad hoc additional nutritional support, often delayed, and frequently utilising parenteral nutrition (PN). Enteral nutrition (EN) has been reported to preserve gut structure and function (Maxton et al 1989), enhance gut mediated immunity (Kudsk et al 2002) and to be feasible in over 90% of patients undergoing gastrointestinal surgery (Braga et al 2002). Moreover randomised comparisons have reported that EN is superior to PN with regard to clinical

outcomes (Bozzetti et al 2001) because of fewer associated septic complications (Moore et al 1986, Mochizuki et al 2000) and shorter lengths of hospital stay (Aiko et al 2001).

However, contemporary opinion is that EEN should not be recommended for routine clinical practice because firstly the above benefits remain unproven (Lewis et al 2009) and secondly because the method of enteral delivery is controversial. Nasojejunal tubes may be unreliable and poorly tolerated by patients (Hoffmann et al 2001) and surgical jejunostomy placement is not only invasive, but also associated with major complications (Hoffman et al 2001). Nevertheless, a recent meta-analysis concluded that early feeding may be beneficial after elective gastrointestinal resection, but emphasised the need for an adequately powered trial to confirm or refute the findings observed in previous small trials (Lewis et al 2009).

The aim of this study was to determine if EEN was well tolerated, safe and whether or not it improved clinical outcomes in terms of post-operative morbidity, mortality, fluid balance and length of hospital stay. The setting was a UK regional upper GI cancer network serving a population of 1.4 million.

## **6.3 METHODS**

### **6.3.1 Study design**

This open, prospective, pragmatic RCT was conducted in three NHS hospitals, which were part of the S.E. Wales upper gastrointestinal cancer



network. Data were collected over 30 months, and the trial closed in July 2006. All adult patients admitted with a suspected upper gastrointestinal malignancy and referred for major elective surgery, were eligible for participation. Exclusion criteria were: age under 18 years; unable or unwilling to give informed consent; pregnancy; pre-operative infection; previous intestinal surgery resulting in residual small intestine length of less than 100cm.

Approval was obtained from the S.E. Wales NHS Ethics Committee, and the trial was registered with the National Research Register and UK Clinical Research Network (UKCRN ID: 1730). All trial participants provided written informed consent. Copies of the Ethics Committee approval letter and the consent form used are presented in Appendix 3. All surgical and nursing staff associated with patient care were given detailed information about the study protocol. Outcome data were assessed and collected by two members of the research team who were trained in the details of the data collection requirements.

After the operating surgeon had confirmed that a potentially curative operative procedure had been performed, patients were randomised to receive either Early Enteral Nutrition (EEN) or Control (CON). Randomisation was stratified within each centre, and the randomisation sequence was generated by computer in permuted blocks of 30. The code was kept in opaque, sealed envelopes labelled with sequential study numbers in a locked box at the co-ordinating research site.

This was an unblinded study. Placebo was considered, but for the purpose of this study was not used. One study (Schloerb et al 2004) attributed major and even fatal complications when hypotonic solutions were delivered via jejunostomies and therefore this placebo was considered by research team to have a potential biological effect. It was considered difficult to conceal treatment allocation by any practical means, given the nature of the intervention. However, data entry was completed blinded to group allocation.

### **6.3.2 Baseline evaluation and general management**

After patients consented to participate in the trial, a pre-operative baseline medical, physiological and nutritional assessment was completed. Pre-operative staging was in accordance with TNM and as described in earlier chapters.

### **6.3.3 Details of post-operative nutritional support**

All patients in the study had a needle catheter feeding jejunostomy (Freka Fresnius, Cheshire, UK) inserted at operation.

Control management consisted of patients being kept nil by mouth, with hydration maintained by means of intravenous fluids, which continued until the introduction of oral fluids and diet. These patients also received 10ml/hour of sterile water via the jejunostomy, and this was continued until the introduction of oral fluids. Patients who had undergone oesophagectomy or total gastrectomy underwent a radiological contrast swallow between day 7 and 10 after surgery, and provided this

demonstrated no anastomotic dehiscence, oral fluids and diet were introduced gradually over 2 to 5 days. After the radiological contrast swallow, if patients were diagnosed with radiological anastomotic leaks, they received either enteral or parenteral nutritional support at the discretion of the consultant surgeon until deemed safe to commence oral fluids. Nutritional requirements were calculated based on 30 kcal per kg per day (Elwyn et al 1980).

Early Enteral Nutrition was delivered via the jejunostomy. Nutritional support was commenced within 12 hours of surgery at 20ml/hour of a standard 1 kcal/ml commercial whole protein enteral feed for the first 24 hours in patients undergoing oesophagogastric resection, with the rate increasing as tolerated by 10ml/hour every 12 hours, until the maximum feed target rate of 80ml/hour was achieved. Patients undergoing pancreatic resection were commenced on 10ml/hours of a 1.3kcal/ml commercial semi-elemental enteral feed on the first post-operative day, which was then steadily increased as for the oesophagogastric patients. The aim was to achieve a minimum of half of nutritional requirements (Elwyn et al 1980) by the fifth post-operative day. Intravenous fluids were administered in addition to the enteral feeding, as necessary to maintain fluid balance. Once oral intake was established, patients commenced a 1.5 kcal/ml enteral feed and converted to overnight enteral nutrition via the jejunostomy over 12 hours. This continued until it was deemed that 75% of nutritional requirements were being achieved orally. Nutritional requirements were calculated as for control patients (Elwyn et al 1980).

Patients allocated EEN also underwent radiological contrast swallow between day 7 and 10 after surgery.

#### **6.3.4 Details of the surgery**

##### **Oesophagectomy**

Fifty-four patients underwent oesophageal resection, with the choice of operative approach and use of neoadjuvant chemotherapy as described in Chapters 3, 4, and 5. Thirty patients underwent standard subtotal oesophagectomy (Lewis 1946, Tanner 1947). Transhiatal resection (Orringer 1985) was performed in 24 patients. Neoadjuvant chemotherapy with 5-FU and Cisplatin was given to 34 patients.

##### **Gastrectomy**

Thirty-eight patients underwent gastric resection. The type of surgery was determined by the anatomical location of the tumour. Subtotal gastrectomy was performed in patients with antral tumours and total gastrectomy was performed for tumours of the cardia (Siewert type III), body and linitis plastica. Thirty patients underwent modified radical D2 resection (preserving the pancreas and the spleen where possible) as originally described by Sue-Ling et al (1993). Eight patients underwent a selective D1 lymphadenectomy as chosen by individual surgeons for elderly patients with medical co-morbidities or patients with early tumours on CT criteria, who it was considered would benefit from a quicker, simpler operation.

## **Pancreatectomy**

Twenty-nine patients underwent pancreatic resection. Twenty-six patients underwent Pylorus Preserving Pancreaticoduodenectomy as described by Transverso and Longmire (1978), and 3 patients underwent total pancreatectomy as described by Rockey (1943).

### **6.3.5 End points**

The primary endpoint for the study was length of hospital stay (LOHS), which was defined as the time from the date of the index operation to the date the operating surgeon assessed that the patient was medically fit for discharge, or death. This definition controlled for any administrative factors that may prolong discharge, for example, waiting for social support packages. Strict and precise criteria were used to define when patients were fit for discharge. These criteria included the ability to: mobilise out of bed and ambulate, prepare a drink or food and get to the lavatory in their home. Secondary endpoints were operative morbidity, operative mortality and fluid balance. Patients were reviewed at 6 and 12 weeks post-discharge, and readmission rates during that period were documented.

### **6.3.6 Sample Size**

The study hypothesised that a mean reduction in length of hospital stay of 3 days, without any deterioration in clinical outcomes, would constitute a clinically important difference in outcome (Aiko et al 2001). Fifty-five patients per group were needed to detect such a difference based on a power calculation with alpha set at 0.05 and 80% power.

### **6.3.7 Statistical analysis**

All data were presented as median and interquartile range (IQR), and non-parametric tests were used throughout. Overall survival was analysed according to Kaplan and Meier, and differences assessed with the log rank test. Overall survival was calculated in months from the date of diagnosis. The data were analysed on an intention to treat basis.

## **6.4 RESULTS**

From 192 consecutive recruited patients, 34 declined participation (Table 6.1). In general there were no striking differences between the patients who provided consent and the patients who declined to consent. However, patients with more advanced disease were more likely to opt for participation. An additional 37 patients were excluded as they were found to have disseminated disease at the time of laparotomy. The study was intended to include only patients who underwent potentially curative surgery for randomisation (CONSORT diagram, Figure 6.1). The details of the patients related to treatment allocation and baseline nutritional parameters are shown in Table 6.2. The groups were deemed comparable at baseline other than the discrepancy regarding ASA grade.

### **6.4.1 Length of hospital stay and readmission**

The median LOHS for patients after EEN was 16 days (IQR 9 days) compared with 19 days (IQR 11 days) after CON therapy ( $p = 0.023$ ). These data are presented in Figure 6.2, which demonstrates a clear advantage for EEN for the first 30 days. Intention to treat analysis with the

operative deaths removed, did not alter the primary outcome (EEN group 16 days vs. CON 19 days,  $p=0.039$ ). There were no statistically significant differences between the two groups for hospital readmissions after EEN within 6 weeks of discharge (EEN 4 patients, vs. CON 6 patients,  $p=0.501$ ), or between 6 and 12 weeks after discharge (EEN 1 patient vs. CON 2 patients,  $p=0.237$ ).

#### **6.4.2 Operative morbidity and mortality**

Details of the operative morbidity are shown in Table 6.3. Operative morbidity occurred in 50 patients (41.3%) of the total population, and was less common after EEN therapy (21 patients, 32.8%) compared with CON therapy (29 patients, 50.9%,  $p=0.044$ , Table 6.3). There were 3 operative deaths (within 30 days of surgery, 2.4%). All deaths (3 patients, 4.7%) occurred in patients randomised to receive EEN. One patient died on the first post-operative day following portal vein haemorrhage after pancreatic resection, prior to commencing EEN. The other two patients died after oesophagectomy; one on the 8th post-operative day as a result of chest sepsis and respiratory failure, and the other on the 20th post-operative day as a result of anastomotic leak followed by chest sepsis and respiratory failure. Neither of these deaths were attributed to the enteral nutrition, and the complications developed on the second and third post-operative days respectively.

Fewer EEN patients were discharged on continuing enteral nutrition, but this difference was not statistically significant (EEN 5 patients (7.8%) vs.

12 patients (21.1%) after CON,  $p=0.092$ ). These patients were not achieving their target nutritional requirements orally.

#### **6.4.3 Jejunostomy complications**

There were no reported major jejunostomy related complications, such as catheter site infections, leakage or displacement. Although there were several reports of transient catheter occlusions, these did not interfere with feed delivery for more than 24 hours. Fifty-four patients randomised to EEN (84.3%) had uninterrupted enteral feeding during the 1<sup>st</sup> post-operative week.

#### **6.4.4 Nutritional intake**

The median percentage daily nutritional requirement achieved by the end of the first post operative week in patients receiving EEN was 69% (IQR 53) compared with zero % (IQR 0) in control patients. The median calorie intake during the first post-operative week was 7627kcal (IQR 4123) for patients receiving EEN compared with zero kcal (IQR 0) in control patients. The median protein intake during the first post-operative week was 328g (IQR 175) for patients receiving EEN compared with zero g (IQR 0) in control patients.

#### **6.4.5 Fluid balance**

The median IV fluid intake during the first post-operative week was 12125ml (IQR 6791) for patients receiving EEN compared with 19210ml (IQR 4150) in control patients ( $p<0.0001$ ). The median volume of feed



administered during the first post-operative week was 7260ml (IQR 4488) for patients receiving EEN compared with 0ml (IQR 0) in control patients. ( $p < 0.0001$ ). The total fluid intake of the patients, by all routes of administration, during the first post-operative week was 20383ml (IQR 5132) for patients receiving EEN compared with 21180ml (IQR 4270) for control patients ( $p = 0.673$ ). The median cumulative fluid balance at the end of the first post-operative week was 4213ml positive (IQR 3438) for patients receiving EEN compared with 4464ml positive (IQR 4978) for control patients ( $p = 0.935$ ). Peripheral oedema during the first post-operative week was identified in 4 (6.3%) patients receiving EEN compared with 15 (26.3%) control patients ( $p = 0.002$ ).

#### **6.4.6 Overall survival**

There was no significant difference in long term survival for the patients who received EEN compared with the control patients. Median, 2-year and 5-year overall survival were 41 months, 60.6% and 36.4% for the patients who received EEN, compared with 33 months, 61.2% and 41.4% for the control patients ( $p = 0.807$ ).

**Table 6.1 Details of the patients related to consent to randomisation**

	<b>Consent declined</b>	<b>Consent to randomisation</b>
Number	34	121
Median age (IQR)	62.5 (18)	64 (15)
Gender M:F	16:18	83:38
<b>Site of tumour (%)</b>		
Oesophageal	10 (29.4)	54 (44.6)
Gastric	14 (41.2)	38 (31.4)
Pancreatic	10 (29.4)	29 (23.9)
<b>Radiological TNM stage (%)</b>		
I	10 (29.4)	12 (9.9)
II	17 (50.0)	55 (45.5)
III	7 (20.6)	51 (42.1)
IVa	0	3 (2.5)

**Table 6.2 Details of the patients and surgery**

	<b>CON</b>	<b>EEN</b>	<b>Total</b>
Median age (Y) (IQR)	63 (16)	64.5 (14)	64 (15)
Gender M:F	40:17	43:21	83:38
<b>Pathological TNM stage (%)</b>			
<b>0</b>	5 (8.8)	5 (7.8)	10 (8.3)
<b>I</b>	14 (24.6)	17 (26.6)	31 (25.6)
<b>II</b>	15 (26.3)	19 (29.7)	34 (28.1)
<b>III</b>	20 (35.1)	23 (35.9)	43 (35.6)
<b>IVa</b>	3 (5.3)	0	3 (2.5)
<b>Histological diagnosis</b>			
<b>Oesophageal (%)</b>			
ACA	19 (33.3)	23 (35.9)	42 (34.7)
SCC	4 (7.0)	4 (6.3)	8 (6.6)
Carcinosarcoma	0	1 (1.6)	1 (0.8)
Anaplastic carcinoma	1 (1.8)	0	1 (0.8)
High grade dysplasia	1 (1.8)	1 (1.6)	2 (1.7)
<b>Gastric (%)</b>			
ACA	15 (26.3)	21 (32.8)	36 (29.8)
GIST	1 (1.8)	0	1 (0.8)
Benign ulcer	0	1 (1.6)	1 (0.8)
<b>Pancreatic (%)</b>			
ACA	7 (12.3)	7 (10.9)	14 (11.6)
Cholangiocarcinoma / ampullary tumour	4 (7.0)	2 (3.1)	6 (5.0)
Neuroendocrine	0	1 (1.6)	1 (0.8)

Intraductal papillary mucinous tumour	1 (1.8)	0	1 (0.8)
Adenoma	0	1 (1.6)	1 (0.8)
Chronic pancreatitis	2 (3.5)	2 (3.1)	4 (3.3)
Duodenal adenoma	2 (3.5)	0	2 (1.7)
<b>Surgical procedure (%)</b>			
Transhiatal oesophagectomy	10 (17.5)	14 (21.9)	24 (19.8)
Ivor Lewis oesophagectomy	15 (26.3)	15 (23.4)	30 (24.8)
Subtotal D1 gastrectomy	2 (3.5)	4 (6.3)	6 (5.0)
Subtotal D2 gastrectomy	6 (10.5)	6 (9.4)	12 (9.9)
Total D1 gastrectomy	0	2 (3.1)	2 (1.7)
Total D2 gastrectomy	8 (14.0)	10 (15.6)	18 (15.0)
PPPD	15 (26.3)	11 (17.2)	26 (21.5)
Total pancreatectomy	1 (1.8)	2 (3.1)	3 (2.5)
<b>ASA grade (%)</b>			
I	0	1 (1.6)	1 (0.8)
II	39 (68.4)	25 (39.1)	64 (52.5)
III	18 (31.6) *	38 (59.4) *	56 (46.0)
Pre-operative BMI Kg/m <sup>2</sup> (IQR)	24.4 (5.7)	25.6 (4.9)	25.4 (5.4)
Pre-operative weight Kg	70 (17)	76 (18)	73 (18)
Unintentional weight loss % (IQR)	6.1 (10.1)	5.6 (11.6)	6.1 (11.1)
<b>Pre-op NRI (%)</b>			
Borderline malnutrition	43 (75.5)	47 (73.4)	90 (74.4)
Moderate malnutrition	8 (14.0)	8 (12.5)	16 (13.2)

Severe malnutrition	6 (10.5)	9 (14.0)	15 (12.4)
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ACA – adenocarcinoma

SCC – squamous cell carcinoma

GIST – gastro intestinal stromal tumour

PPPD – pylorus preserving pancreaticoduodenectomy

ASA – American Society of Anaesthesiologists

\*p=0.004

BMI – body mass index

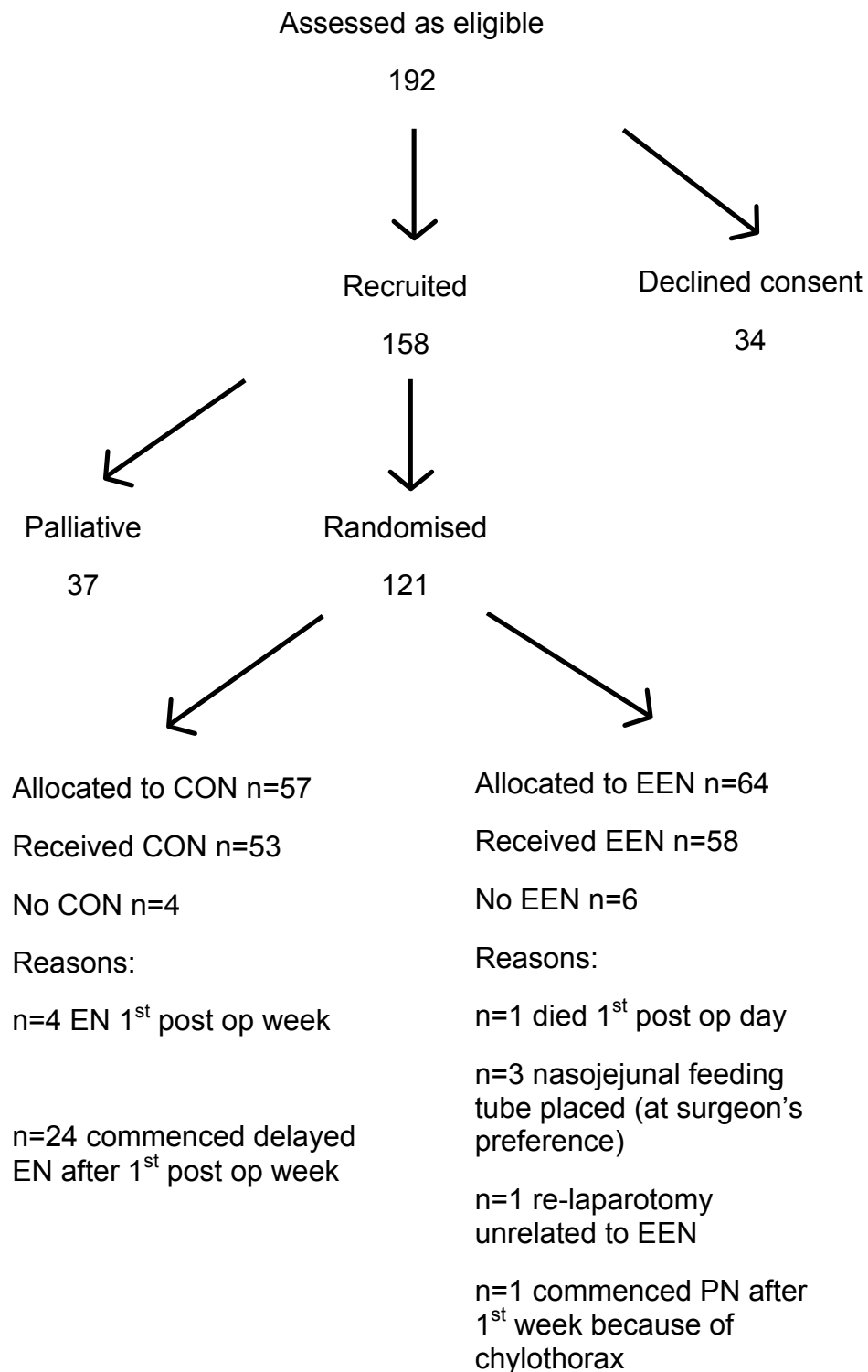
NRI – nutritional risk index (Veterans Affair, 1991)

Unintentional weight loss was during 6-12 weeks prior to admission for surgery.

**Table 6.3 Details of operative morbidity**

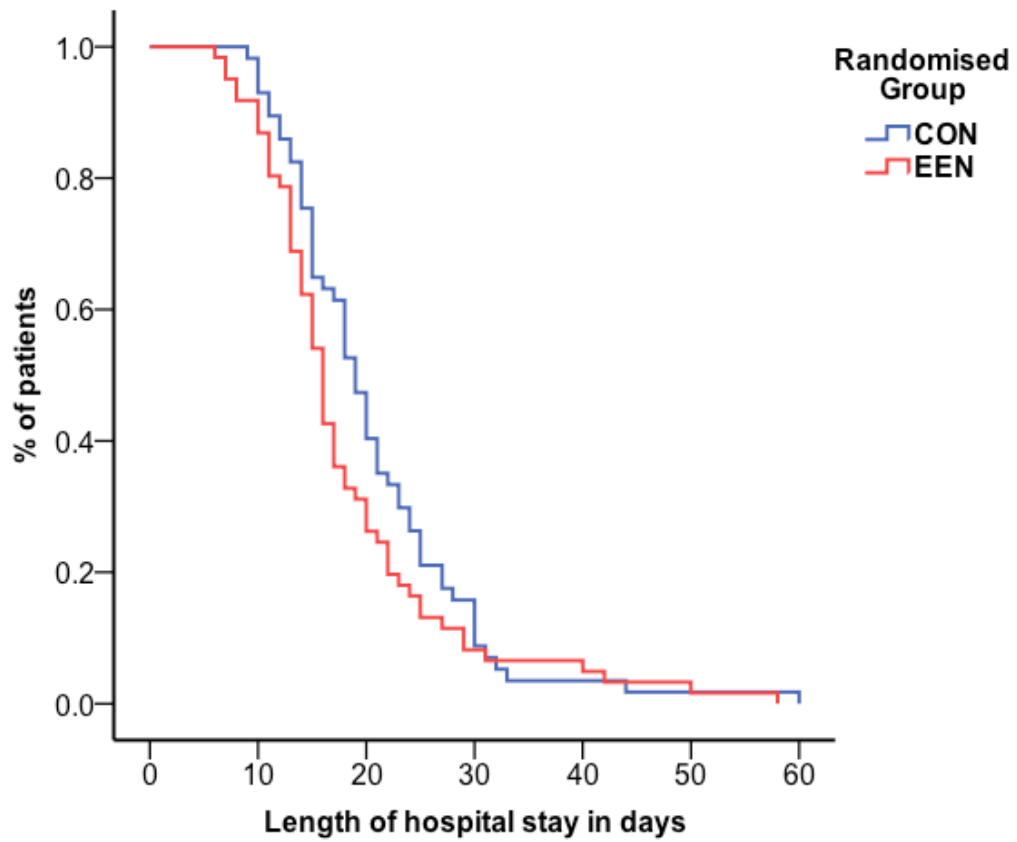
<b>Complication</b>	<b>CON</b>	<b>EEN</b>	<b>p value</b>
<b>Infective Complications (%)</b>			
Wound infection	16 (28.1)	7 (10.9)	0.017
Chest infection	12 (21.1)	5 (7.8)	0.036
Anastomotic leak	7 (12.2)	2 (3.1)	0.055
Urinary tract infection	3 (5.3)	1 (1.6)	
Bacteramia	3 (5.3)	2 (3.1)	
<b>Non Infective Complications (%)</b>			
Pleural effusion	10 (17.5)	10 (15.6)	
Myocardial infarction	1 (1.8)	0	
Major haemorrhage	2 (3.5)	0	
Chylothorax	0	1 (1.6)	
Rec. laryngeal nerve palsy	0	1 (1.6)	

Figure 6.1 CONSORT diagram



**All patients included in ITT analysis**

Figure 6.2 Length of hospital stay related to randomisation



Log Rank  $\chi^2$  2.386, df 1,  $p=0.122$



## 6.5 DISCUSSION

This study represents the first adequately powered prospective randomised control trial of early enteral nutrition versus standard care in patients undergoing upper gastrointestinal resectional surgery in the UK. The principal findings were that EEN delivered within 12 hours of leaving the operating theatre was feasible, safe, and associated with significantly better clinical outcomes. Post-operative morbidity was far less common, and septic and anastomotic complications in particular, were on average less than half and one third as common respectively after EEN. These findings resulted in durations of hospital stay that were strikingly different for the two randomised groups. Patients who received EEN had hospital stays that were three days shorter than those of the control patients, despite the fact that the EEN patients were of significantly poorer performance status. Moreover, peripheral oedema was less than one quarter as common after EEN compared with CON, despite the two groups having seemingly comparable total fluid intake and cumulative fluid balance.

Preventing complications after oesophagectomy, gastrectomy and pancreatectomy is as important, if not more so, than the rapid and proactive management of complications which do occur, if outcomes are to be improved. Enteral nutrition has been reported in a number of randomised control trials to be associated with fewer septic complications than standard care (Kudsk et al 1996, Aiko et al 2001) and shorter LOHS, but none have had the statistical power to prove benefit. Consequently Koretz

et al (2009) reported that EN has been accepted and implemented into clinical practice without convincing scientific support. Designing and conducting pragmatic clinical trials, particularly in surgical patients with complex and diverse needs, are fraught with limitations and this study is typical in this regard. Precise definition of the primary outcome measure (LOHS) is crucial but controversial. LOHS is influenced by many factors including patient age and performance status, and intra-operative factors such as type of surgical procedure, level of lymphadenectomy and blood loss (Clearly et al 1991, Greenfield et al 1993). In the few previous RCTs which included clear definitions of LOHS, emphasis has focused on the time from index operation to hospital discharge, which may be criticised unless robust discharge criteria are agreed because patients often remain in hospital for non-medical reasons. In the UK, delays in agreeing social care packages frequently cause delays in hospital discharge. The cumulative LOHS curve (Figure 6.2) demonstrates an early EEN associated benefit until 30 days after surgery. Any benefit beyond this is difficult to assess, because durations of stay over 30 days, by definition occurred in patients who had suffered serious complications and would consequently have received therapeutic EN irrespective of randomisation. Furthermore, a major criticism of studies which report length of hospital stay as a primary outcome is the failure to address the issue of rates of hospital readmission. One of the strengths of this study is that hospital readmission rates were similar regardless of randomisation during the initial 3-month follow up period.

There are several potential criticisms of this study. Firstly, the patients studied had heterogeneous diagnoses and underwent different surgical procedures. However, this may suggest that the benefit of EEN was independent of the cancer site and type of operation. Oesophagectomy, gastrectomy and pancreatectomy clearly differ, but the complexity and duration of the surgery, and the subsequent risk of morbidity and mortality were comparable (Allum et al 2011, Kotwall et al 2002). Treatment allocation was not concealed, and this approach has been reported to exaggerate treatment effects. No placebo was used because of the risk of placebo associated physiological effect, producing false atypical results, and possible detrimental risk to control patients. Beier-Holgersen et al (1996) reported a study of saline placebo vs. enteral feeding after major elective gastrointestinal surgery. Enterally fed patients had improved outcomes, but placebo patients had unusually high complication rates, possibly associated with either the lack of enteral feed or saline use.

With regard to post-operative fluid therapy, EEN patients received on average 7 litres less intravenous fluid (37%) than control patients over the first post-operative week, but the total fluid therapy received (including enteral feed) was comparable (3.9% greater volume after CON,  $p=0.673$ ). Moreover, the cumulative fluid balance over the entire first post-operative week was also similar (6.0% greater volume after CON,  $p=0.935$ ). GIFTASUP consensus guidance (Powell-Tuck et al 2009) suggests that adult maintenance fluid requirements should be approximately 1.5 to 2.5 litres per 24 hours (25 to 35 ml/Kg/24h). Control patients in this study

received on average 2800ml of IV fluid per 24/h, which is some 12% greater than the maximum guidance. However these patients had all undergone complex upper GI resectional surgery for cancer and would arguably have therefore required replacement of extra fluid losses. Data regarding the types of intravenous fluids administered to patients was not collected prospectively. The possibility therefore exists that some of the benefits witnessed after EEN may have been derived from them receiving less sodium, as a consequence of lower intravenous fluid intakes, than control patients. The adverse effects of excess sodium administration are well documented (Lobo 2004, Allison 2004, Powell-Tuck et al 2009). The four-fold higher rate of peripheral oedema in CON patients compared with EEN, is highly relevant, as peripheral oedema is known to correlate with delayed return of gut function, prolonged hospital stay and post-operative complications after major abdominal surgery (Itobi et al 2006).

Complications related to the feeding jejunostomy were conspicuous by their absence in this study. In contrast, the National Oesophago-Gastric Cancer Audit 2010 reported complications such as chest sepsis (15.1%), wound sepsis (4.7%), and anastomotic leaks (8.3%) to occur more frequently in patients receiving a feeding jejunostomy, necessitating re-operation in 11.7% of patients (NHS Information Centre 2010). However, this data must be interpreted with caution as patients receiving feeding jejunostomies in the above audit may have been more malnourished and no data were provided as to whether the jejunostomies were actually utilised for feeding purposes. The operative morbidity reported in this

study is high, certainly when compared with the above national oesophagogastric audit; although anastomotic leak rates were comparable (oesophagectomy 9.3% vs. 8.3%; gastrectomy 2.6% vs. 5.9%). For wound (oesophagectomy 20% vs. 3.9%, gastrectomy 10.5% vs. 3.3%) and respiratory infection (oesophagectomy 24.1% vs. 12.9%, gastrectomy 7.9% vs. 7.3%) the rates in this study are higher than the national UK figures (NHS Information Centre 2010). However, this study used broad and inclusive definitions of complications. Furthermore, the patients in this trial were very carefully scrutinised for complications, in contrast to third person audit data collection (contributed in part by Cancer Networks, and cross-referenced with other databases, such as Hospital Episode Statistics in England) used to compile the national audit, and this may help to explain some of these differences. In contrast, overall oesophagectomy and gastrectomy operative mortality in this study compared favourably with national data (3.7% vs. 3.8% and 0 vs. 4.5% respectively, NHS Information Centre 2010).

## **6.6 CONCLUSION**

This randomised clinical trial has shown an important and clinically significant improvement in outcomes associated with EEN by means of feeding jejunostomy in patients undergoing major upper gastrointestinal surgical resection. This is associated with major clinical implications for individual tailored integrated care pathways and broader economic implications for healthcare systems. The findings are also in keeping with the conclusions of both Lewis et al (2001 and 2009) meta-analyses.

Recent discussion has focused on early volitional oral intake in the first few post-operative days following upper gastrointestinal surgery (Lassen et al 2008) and this again reinforces the argument to abandon the traditional nil by mouth strategy. Certainly, contemporary enhanced recovery after surgery programmes no longer prescribe prolonged periods of post-operative starvation, and the effect of this may in itself contribute to reductions in length of hospital stay equivalent to those described in this study. The advantageous shorter length of stay associated with EEN might not therefore be as marked, if a more contemporary comparison was made between EEN and early oral introduction of feed, such as sip feeds, and early free diet. However, such an approach is not always appropriate in patients who have undergone oesophagectomy or total gastrectomy and who require contrast swallows to check on the integrity of the anastomosis prior to commencing oral intake. Huge scope remains for refining peri-operative nutritional intervention to maximise the benefits for patients, allied to minimising risk and cost. Furthermore, increased research efforts are required into the complex and interdependent mechanisms whereby nutritional interventions enhance recovery after surgery.

## **Chapter 7**

### **Upper gastrointestinal cancer surgery centralisation in South East Wales**

## 7.1 SUMMARY

The aim of this study was to determine the influence of a reconfigured centralised surgical model of care allied to an ERAS programme, when compared with historical control outcomes.

The details of 664 consecutive patients diagnosed with UGI cancer over a 2 year period were collected prospectively and the outcomes before (n=266) and after centralisation (n=398) inception compared. The primary outcome measure was length of hospital stay (LOHS).

Following centralisation, the proportion of patients treated with potentially curative intent increased from 63 (23.7%) to 152 (38.2%),  $p < 0.0001$ . The critical care (CC) cancellation rate fell from 15.7% to 2.3% ( $p = 0.003$ ), and CC bed usage fell from a median and total of 1 and 250 to 1 and 152. UGI cancer operative mortality and morbidity (Clavien-Dindo >III) were 3.0 and 33.3% before compared with 1.7 and 16.7% after centralisation respectively. Total length of hospital stay (LOHS) shortened from 17.5 to 14 days,  $p = 0.037$ . On multivariate analysis, ERAS (HR 2.485, 95% CI 1.499 to 4.122,  $p < 0.0001$ ), operative morbidity (HR 0.260, 95% CI 0.156 to 0.432,  $p < 0.0001$ ), and operation type (overall  $p < 0.0001$ ) were independently associated with LOHS.

These outcomes demonstrate the potential patient safety and quality improvements achievable by compliance with NHS executive commissioning guidelines.



## 7.2 INTRODUCTION

Upper gastrointestinal cancer service reconfiguration and centralisation consistent with the guidelines for commissioning cancer services (Department of Health 2001), strongly supported and largely achieved in England, has received lesser resource and support in Wales. Indeed the most recent audit of activity related to oesophagogastric management demonstrated that many surgeons' case loads remained small, staging strategies were idiosyncratic, open and close operations were performed in 23% of cases, operative mortality was 12%, and 2-year survival was 42% following oesophagectomy and 43% following gastrectomy (Pye et al 2001).

Upper gastrointestinal surgery has, by tradition, been within the domain of the general surgeon and historically, a notional district general surgeon might expect to deal with fewer than 25 people with oesophageal cancer and 40 with gastric cancer per year (Pye et al 2001). The last decade, however, has witnessed significant changes in practice in general surgery and sub-specialisation for major oncological work is now the accepted routine. This is in keeping with NHS published guidance, one of whose key recommendations was that specialist teams be established, serving populations of greater than one million (Department of Health 2001). Moreover, Enhanced Recovery After Surgery (ERAS) protocols have also recently been championed to improve outcomes after major colorectal surgery but have not been tested in the surgical management of upper GI cancers (Basse et al 2000).

Specialist multidisciplinary team expertise has been described to improve outcomes for patients in sporadic reports (Siewert and Roder 1992, Sue-Ling et al 1993, McCulloch 1994, Stephens et al 2006), but these hypotheses have not been tested by means of randomised control trials. In addition, case volume per surgeon or per unit has also been reported to be an important factor determining outcome of treatment of a raft of cancers (Matthews et al 1986, McCulloch 1994, Steele 1996, Swisher et al 2000, Van Lanshot et al 2001, Bachmann et al 2002, Birkmeyer et al 2003, Skipworth et al 2010, Anderson et al 2011), yet data regarding the factual impact of reconfiguring and centralising cancer surgery is scarce, if not absent altogether.

The aim of this study, therefore, was to determine the influence of a new clinical model comprising reconfigured centralised surgery encompassing a revised critical care admission protocol (commenced August 2010) and allied to ERAS (commenced October 2010), when compared with the historical control outcomes of three local hospital sites over the previous year. The setting was a UK regional cancer network serving a population of 1.4 million.

### **7.3 METHODS**

#### **7.3.1 S.E. Wales service reconfiguration**

The S.E. Wales region has a population of approximately 1.4 million, which is served by three NHS Health Boards. These are Cardiff and Vale University Health Board (catchment population 450,000), Aneurin Bevan

Health Board (catchment population 600,000) and Cwm Taf Health Board (catchment population 325,000). Together these health boards run six acute hospitals: four district general hospitals and two teaching hospitals, and this area constitutes the South East Wales Upper GI cancer network. Prior to August 2010 the surgical care of patients with oesophagogastric cancer was delivered by 8 surgeons undertaking surgery at 4 different hospital sites. After a protracted period of negotiation between health care commissioners, health board management, involved clinicians and other stakeholders, an agreement was reached in December 2009 to reconfigure and centralise the upper GI surgical service on a single site at the University Hospital of Wales (UHW), in Cardiff, with an agreed start date of August 2010. The new model was based on 5 specialist upper gastrointestinal surgeons performing all the resectional surgery; three of the surgeons were based at the surgical centre, whilst the other two were to operate on an in-reach basis. One of the Cardiff based surgeons provided an outreach MDT and outpatient service at the Royal Gwent Hospital, Newport, for the Aneurin Bevan Health Board catchment population. The facility existed for joint consultant operating, where necessary. Diagnosis and staging continued to be undertaken locally within each health board, coordinated via three local weekly MDTs, and all cases deemed suitable for curative treatment were discussed at the existing weekly regional S.E. Wales MDT. The new surgical service commenced on 1<sup>st</sup> August 2010.

### **7.3.2 Enhanced recovery after surgery**

Allied to the new surgical configuration was the establishment of an enhanced recovery after surgery (ERAS) programme in October 2011, based on the well established principles introduced by Kehlet and colleagues in the arena of colorectal surgery (Basse et al 2000). In addition policies regarding the planned admission of patients to critical care post-operatively were updated, and took account of the results of cardiopulmonary exercise testing (CPET), which was performed in all patients proceeding to surgery following centralisation. Provided CPET was satisfactory, patients due to undergo oesophagectomy were booked into the high dependency unit (HDU), rather than intensive care (ITU), and patients due to undergo gastrectomy were booked to return to the ward, rather than HDU.

### **7.3.3 Data collection**

The oesophageal and gastric cancer caseload referred to the MDTs during the year preceding the start of centralisation (August 2009 to July 2010) was compared with the following year (August 2010 to July 2011). The pre-centralisation year data across the three health boards was collected using a combination of a prospectively maintained database (for two of the three health boards) in combination with MDT records and retrospective review of hospital records. The post-centralisation year data was collected prospectively. Measures of outcome included numbers of new patients diagnosed with oesophagogastric cancer and gastrointestinal stromal

tumours (GISTs), the numbers treated with curative intent, details of the surgery, post operative morbidity and mortality, theatre utilisation, critical care bed occupancy, length of hospital stay and readmission rates following discharge.

#### **7.3.4 Surgical treatment +/- neoadjuvant therapy**

Management plans were individually tailored according to patient related factors and their stage of disease. The tumours were staged using computed tomography (CT), endoscopic ultrasound (EUS), computed tomography positron emission tomography (CT-PET) and staging laparoscopy as appropriate. The S.E. Wales MDT treatment algorithms for oesophageal and gastric cancer have been described in Chapter 6. Recent changes in gastric cancer management have included the increased use of peri-operative chemotherapy in patients with locoregionally advanced tumours. The surgery for gastric GISTs included local resection, sleeve gastrectomy or partial gastrectomy, as deemed appropriate.

Operative morbidity was graded in accordance with the Dindo-Clavien classification (Dindo and Clavien 2004). Particular emphasis was placed on the incidence of morbidity of Dindo-Clavien grade III or higher, as this represented a complication that required an endoscopic, radiological or surgical intervention. In contrast, morbidity of Dindo-Clavien grade I or II required only pharmacological treatment.

### 7.3.5 Statistical analysis

Surgical outcomes were analysed in two ways. Firstly, outcomes were analysed on an intention to treat basis in the two cohorts. Secondly the patients who completed potentially curative surgery for oesophagogastric cancer (excluding open and close, palliative surgery and GIST surgery) were analysed separately. Grouped data were expressed as median (range) and non-parametric methods were used throughout. Univariate and multivariate analyses of factors influencing length of hospital stay were performed using the log rank test and Cox regression respectively.

## 7.4 RESULTS

### 7.4.1 Details of the patients

The global caseloads presented to the regional MDTs were 271 and 425 patients for the years pre and post centralisation respectively. Table 7.1 shows the details of the patients. The perceived radiological stage groups of the patients pre and post centralisation were: Stage I, 24 (9.0%) and 33 (8.3%), Stage II, 40 (15.0%) and 53 (13.3%), Stage III, 75 (28.2%) and 110 (27.6%) and Stage IV, 105 (39.5%) and 144 (36.2%). The remaining patients [22 (8.3%) and 58 (14.6%)] were not formally staged radiologically, either because of advanced age such that the MDT group felt their management would be palliative irrespective of stage, or because of diagnoses such as high grade dysplasia, GIST or lymphoma, for which a TNM stage is not appropriate.

#### 7.4.2 Details of treatment

Treatment was potentially curative in 63 (23.7%) and 152 (38.2%) patients pre and post centralisation respectively ( $p < 0.0001$ ). Potentially curative treatment consisted of surgery [51 (19.1%) vs. 87 (21.9%)], definitive chemoradiotherapy [12 (4.5%) vs. 31 (7.8%)], endoscopic mucosal resection [0 vs. 12 (3.0%)], and haematological chemotherapy for lymphoma (1 patient post centralisation). In addition 21 (5.3%) patients with oesophagogastric cancer were either awaiting a date for surgery, or receiving neoadjuvant therapy, with the probability of subsequent surgery, at the end of July 2011.

The details of the surgery are shown in Table 7.2. The rates of open and close laparotomy for oesophagogastric cancer were similar at 13.7% and 13.6% pre and post centralisation respectively ( $p = 0.988$ ).

#### 7.4.3 Operative morbidity and mortality

Surgical outcome and length of stay data are presented in Table 7.3, both for the surgical cohorts from each year as a whole, and as a subgroup analysis of the patients who completed a potentially curative resection for oesophagogastric cancer (excluding open and close, palliative surgery and GISTs). The cause of the in-hospital death pre centralisation was myocardial infarction following total gastrectomy. The causes of the two in hospital deaths post centralisation were multi-organ failure secondary to conduit necrosis following Ivor Lewis oesophagectomy, and sepsis secondary to abdominal collections following subtotal gastrectomy.

Morbidity was classified according to the Dindo-Clavien classification (2004). There were non-significant 50% reductions in the incidence of serious (Dindo-Clavien  $\geq$  III) morbidity for all the surgical patients and the oesophagogastric cancer resection group. Anastomotic leaks occurred in 3 (9.1%) and 5 (7.5%) of the cancer resection patients pre- and post-centralisation respectively ( $p=0.910$ ).

The morbidity rates were also analysed according to whether or not patients were treated within the ERAS program. Enhanced recovery was associated with non-significant 50% reductions in the incidence of serious (Dindo-Clavien  $\geq$  III) morbidity for all the patients (20.3% vs. 10.7%,  $p=0.089$ ) and for the oesophagogastric cancer resection group (31.0% vs. 15.7%,  $p=0.067$ ).

### **7.4.4 Critical care utilisation and length of hospital stay**

For all patients centralisation resulted in a significant reduction in ITU ( $p<0.0001$ ) and critical care ( $p=0.038$ ) stays. For the oesophagogastric cancer resection patients the same pattern remained (ITU stay  $p<0.0001$ , critical care stay  $p<0.0001$ ), but in addition, median length of total hospital was significantly shortened by 3.5 days ( $p=0.037$ ). The total ITU and HDU bed days utilised were 166 vs. 39 and 84 vs. 113 pre and post centralisation respectively. The overall critical care bed days utilised were 250 and 152 pre and post centralisation respectively. The 30-day hospital readmission rates were 5.9% and 9.1% pre- and post- centralisation respectively ( $p=0.499$ ).



The influence of ERAS on the lengths of stay was also examined. For all patients ERAS was associated with a significant reduction in ITU stay [median 0 (0-70) vs. 0 (0-12),  $p=0.003$ ]. There were non significant differences in HDU stay [median 1 (0-11) vs. 1 (0-9),  $p=0.400$ ], critical care stay [median 1 (0-70) vs. 1 (0-20)] and overall hospital stay [median 14 (2-72) vs. 12 (3-36),  $p=0.131$ ]. For the oesophagogastric cancer resection patients ERAS was associated with significant reduction in ITU stay [median 0 (0-70) vs. 0 (0-12),  $p=0.002$ ] and critical care stay [median 2 (0-70) vs. 1 (0-20),  $p=0.035$ ] but non-significant reductions in HDU stay [median 1 (0-11) vs. 1 (0-9),  $p=0.304$ ] and overall hospital stay [median 16 (5-72) vs. 14 (7-36),  $p=0.056$ ]. Thirty day hospital readmission rates were 6.3% and 9.3% pre and post ERAS respectively ( $p=0.603$ ).

### **7.4.5 Additional surgical workload**

In addition to the major resectional surgery, staging laparoscopy and the insertion of feeding jejunostomies, to facilitate nutrition during neoadjuvant therapy, placed an additional burden on the surgical service at the main centre (UHW). During the year following centralisation, 69 staging laparoscopy procedures and 15 feeding jejunostomies were performed across the network, of which 39 and 11 respectively were undertaken at UHW.

### **7.4.6 Operating theatre list utilisation and cancellation**

In terms of surgical resources, after taking into account bank holidays and consultant leave, a total of 120 all day upper GI theatre lists were available

during the year following centralisation at UHW. Of these 78 (65.0%) were used for at least one, and in some cases two, major cancer resections. Cancellation of major resection cases in the post centralisation year occurred on only two occasions (2.2%) due to lack of an ITU bed, and both patients underwent surgery the following week. In comparison cancellation during the pre centralisation period occurred on eight occasions (15.6%,  $p=0.005$ ).

#### **7.4.7 Univariate and multivariate analysis**

A univariate analysis of factors influencing length of hospital stay, for the oesophagogastric cancer resection subgroup of patients, is shown in Table 7.4. A multivariate analysis, with the model incorporating all factors significant on univariate analysis, is shown in Table 7.5.

Table 7.1 Details of the patients

	Pre Centralisation	Post Centralisation
Patients Referred to MDT	271	425
New diagnoses	266	398
Recurrent disease	5	27
	<b>New Diagnoses (%)</b>	
Cardiff and Vale Health Board	92 (34.6%)	126 (31.7%)
Aneurin Bevan Health Board	120 (45.1%)	177 (44.5%)
Cwm Taf Health Board	54 (20.3%)	95 (23.9%)
Median age (Y) (range)	73 (32-97)	71 (32-95)
Male : Female	175:91	257:141
<b>Oesophageal</b>	<b>139</b>	<b>225</b>
HGD	0	8
ACA	87	152
SCC	50	56
Neuroendocrine tumour	1	1
Undifferentiated carcinoma	0	6
Small cell carcinoma	1	1
Lymphoma	0	1
<b>Gastric</b>	<b>112</b>	<b>144</b>
HGD	0	2
ACA	109	137
Undifferentiated carcinoma	1	1
Neuroendocrine tumour	1	1
Small cell carcinoma	1	0

Lymphoma	0	3
<b>GIST</b>	<b>13</b>	<b>24</b>
Gastric	10	20
Oesophageal	1	1
Jejunal	2	3
<b>Duodenal</b>	<b>2</b>	<b>5</b>
ACA	2	4
Adenoma with HGD	0	1

HGD – high grade dysplasia, ACA – adenocarcinoma, SCC – squamous cell carcinoma

Table 7.2 Details of the surgery

	<b>Pre Centralisation</b>	<b>Post Centralisation</b>	<b>p value</b>
<b>Overall Number (%)</b>	<b>51</b>	<b>88</b>	
Ivor Lewis Oesophagectomy	14 (27.5)	11 (12.5)	
Trans Hiatal oesophagectomy	4 (7.8)	14 (15.9)	
Three stage oesophagectomy	0	3 (3.4)	
Total gastrectomy	7 (13.7)	16 (18.2)	
Subtotal gastrectomy	9 (17.6)	16 (18.2)	
Palliative bypass	1 (2.0)	5 (5.7)	
Open and close	7 (13.7)	12 (13.6)	0.988
<b>GIST Surgery (%)</b>			
Distal or sleeve gastrectomy	5 (9.8)	5 (5.7)	
Local gastric excision	3 (5.9)	3 (3.4)	
Small bowel resection	1 (2.0)	1 (1.1)	
Omentectomy	0	1 (1.1)	
Open and close	0	1 (1.1)	

**Table 7.3 Surgical outcomes and length of stay**

	<b>Pre Centralisation</b>	<b>Post Centralisation</b>	<b>p value</b>
<b>ALL PATIENTS (%)</b>			
Number	51	88	
Operative (30 day) mortality	1 (2.0)	1 (1.1)	0.694
In hospital mortality	1 (2.0)	2 (2.3)	0.903
Any morbidity	16 (31.4)	35 (39.8)	0.220
Morbidity of Dindo- Clavien Grade $\geq$ 3	11 (21.5)	10 (11.4)	0.105
<b>Dindo-Clavien grades of morbidity (%)</b>			<b>0.015</b>
No morbidity	35 (68.6)	53 (60.3)	
Grade I	0	5 (5.7)	
Grade II	5 (9.8)	20 (22.7)	
Grade IIIa	3 (5.9)	0	
Grade IIIb	0	3 (3.4)	
Grade IVa	3 (5.9)	4 (4.5)	
Grade IVb	4 (7.8)	1 (1.1)	
Grade V	1 (2.0)	2 (2.3)	
<b>Length of stay</b>			
ITU stay	0 (0-70)	0 (0-12)	<0.0001
HDU stay	1 (0-11)	1 (0-9)	0.233
Critical care stay	1 (0-70)	1 (0-20)	0.038
Total hospital stay	14 (2-72)	12.5 (3-49)	0.238
<b>CURATIVE OESOPHAGOGASTRIC CANCER RESECTION (%)</b>			
Number	33	60	

Operative (30 day) mortality	1 (3.0)	1 (1.7)	0.664
In hospital mortality	1 (3.0)	2 (3.3)	0.937
Any morbidity	16 (48.4)	29 (48.3)	0.989
Morbidity of Dindo-Clavien Grade $\geq$ 3	11 (33.3)	10 (16.7)	0.066
<b>Dindo-Clavien grades of morbidity (%)</b>			<b>0.043</b>
No morbidity	17 (51.5)	31 (51.7)	
Grade I	0	3 (5.0)	
Grade II	5 (15.2)	16 (26.7)	
Grade IIIa	3 (9.1)	0	
Grade IIIb	0	3 (5.0)	
Grade IVa	3 (9.1)	4 (6.7)	
Grade IVb	4 (12.1)	1 (1.7)	
Grade V	1 (3.0)	2 (3.3)	
<b>Length of stay</b>			
ITU stay	0 (0-70)	0 (0-12)	<0.0001
HDU stay	2 (0-11)	1 (0-9)	0.108
Critical care stay	2 (0-70)	1 (0-20)	<0.0001
Total hospital stay	17.5 (5-72)	14 (7-49)	0.037

Lengths of stay are median in days (range)

**Table 7.4 Univariate analysis of factors influencing length of hospital stay**

<b>Variable</b>	<b>Chi2</b>	<b>df</b>	<b>p value</b>
Age	83.890	37	<0.0001
Cancer site (oesophageal vs gastric)	16.803	1	<0.0001
Radiological stage group of cancer	3.948	4	0.413
Operation type	34.229	3	<0.0001
Unit surgery performed in	5.803	2	0.055
Centralisation	7.006	1	0.008
ERAS program	6.491	1	0.011
Operative morbidity	34.916	1	<0.0001

**Table 7.5 Multivariate analysis of factors influencing length of hospital stay**

<b>Variable</b>	<b>Hazard Ratio</b>	<b>95% CI</b>		<b>p value</b>
Operative morbidity	0.260	0.156	0.432	<0.0001
ERAS program	2.485	1.499	4.122	<0.0001
<b>Operation type</b>				
Subtotal gastrectomy	Reference group			
Total gastrectomy	0.281	0.147	0.535	<0.0001
Trans hiatal oesophagectomy	0.194	0.092	0.409	<0.0001
Trans thoracic oesophagectomy	0.207	0.108	0.396	<0.0001



## 7.5 DISCUSSION

The organisation of oesophagogastric cancer surgery services in the UK remains a subject of considerable controversy. In 2001, in recognition of traditionally poor short and long term outcomes, the Department of Health recommended that the surgical treatment of oesophageal and gastric cancer be centralised in units serving populations of at least 1 million (Department of Health 2001). A wealth of evidence now exists internationally to support the inverse relationship between hospital and surgeon volumes and short term outcomes, particularly operative mortality, following oesophagogastric resection (Matthews et al 1986, Swisher et al 2000, Van Lanshot et al 2001, Bachmann et al 2002, Birkmeyer et al 2003, Skipworth et al 2010, Anderson et al 2011). There is also recent evidence of the positive impact of concentrating oesophagogastric surgery on long term survival (Birkmeyer et al 2007, Van de Poll-Franse et al 2011). Nevertheless, opinions regarding the optimum service configuration remain divided in the UK, with Gillison et al (2002) finding no evidence of improved short or long term survival related to higher surgeon operative caseloads. Dickson et al (2001) have highlighted the disadvantages of centralising oesophageal surgery, most notably the deterioration of surgical services and capabilities in district general hospitals, potentially disadvantaging patients with other surgical diagnoses requiring upper GI expertise. Furthermore, there is no agreed threshold for defining what constitutes a high workload volume.

Most published studies on volume/outcome interactions are population based, with very few demonstrating actual improvements after centralisation of surgery (Birkmeyer et al 2007). The principal finding of this study was that the centralisation of upper GI cancer surgery at the University Hospital of Wales was feasible, safe and resulted in significant reductions in the use of critical care resources.

There are limitations to this study. The data on the control year prior to centralisation was collected largely retrospectively, relies to a large extent on the accurate identification of patients from MDT records, and therefore will inevitably be less robust than the prospective data from the following year. This may partly explain both the lower number of patients identified from the year preceding centralisation and the lower number of patients with recurrent disease identified relative to the following year. Therefore, some caution must be exercised in over-interpretation of the absolute numbers prior to centralisation. However, to a degree this method of data collection for the surgical patients is mitigated by two factors. Firstly, all the patients who underwent surgery prior to centralisation from two of the three local health boards, and therefore the majority of the surgical patients, had been entered into a prospectively maintained database which included surgical outcomes. Secondly, computerised records at the three health boards accurately record dates of hospital stay on different wards, operation notes, discharge documentation and all radiological and pathological test results. It is therefore unlikely that any surgical patients

have been missed or that any major errors exist in terms of outcomes and particularly length of stay.

The reconfigured surgical service and the introduction of an ERAS programme are inextricably linked in the results of this study and it is difficult to be certain of the relative influence of each on the outcomes studied. In the present study, multivariate analysis identified ERAS to be independently related to the length of hospital stay, whilst the effect of centralisation was highly significant on univariate analysis. There is considerable evidence from colorectal surgery which suggests ERAS is likely to contribute to reduced complication rates and shortened hospital stay. Key input from the Intensive Care Department to update the new surgical model with a critical care admission protocol had an impact on ITU bed utilisation and this was independent of ERAS. Moreover, the well documented effects of increased surgical volume on outcomes in the literature offer a further possible explanation for the improved outcomes demonstrated. Specifically, the possibility of joint consultant operating, whilst possible pre-centralisation, has been made more accessible within the centralised service, and this may have delivered its own benefits in particularly difficult cases. It is likely that the reasons for the demonstrated improvements are multifactorial, and further work is warranted to establish the influence of ERAS, and refine its application in upper GI surgery.

The significant reductions in ITU and overall critical care bed occupancy are certain to have resulted in considerable financial cost savings to the

cancer network. However, it was not within the remit of this study to formally assess cost effectiveness.

It is generally accepted that most patients prefer to undergo medical treatment in their local hospital where possible. It is therefore important to assess patient satisfaction when introducing a centralised clinical service. Whilst the results of this survey are awaited at present, patient feedback has been very favourable, no complaints have been received, and patients continue to undergo their diagnostic and staging investigations at their local hospitals.

The present study has several strengths. It is one of very few UK reports of outcomes following centralisation of oesophagogastric surgery. The data for the year following centralisation was collected prospectively by the author. This involved attendance at almost all MDT meetings and prospective review of all surgical patients during their hospital admission, and for these reasons the data is highly robust.

At the time of writing, only two other UK studies have reported outcomes after centralising oesophagogastric cancer surgery. In 2004 Branagan et al reported the early impact of centralisation within Wessex, and found similar overall complication rates but a significant reduction in operative mortality (5 of 33 vs 0 of 40,  $p=0.022$ ). Pathology reporting and mean lymph node harvest were also noted to have improved in the centralised unit. The patient numbers treated were relatively small, and the operative mortality prior to centralisation (5 of 33, 15.2%) would be considered

excessive today. These findings contrast to our experience, where operative mortality rates were low before centralisation, making such a dramatic improvement unlikely to be realised in S.E. Wales. In 2006, Forshaw et al reported their experience of oesophagogastric resection within an efficient high volume unit in London. They reported good cancer-related results, without a detrimental impact on the benign elective workload, although they do not present a historical control group for comparison. Our experience in terms of cancer management is in many ways in common with this. However, in contrast to Forshaw et al, there will have almost certainly been an adverse impact on local benign upper GI waiting times, as 65.0% of theatre lists were utilised wholly or in part for cancer surgery. This effect was not examined as part of this study.

The Association of Upper Gastrointestinal Surgeons (2010) has recently recommended that an ideal oesophagogastric unit would consist of 4-6 surgeons, each performing a minimum of 15-20 resections per year and serving a population of 1-2 million. The reconfigured service in S.E. Wales is in line with all of these recommendations.

### **7.6 CONCLUSION**

Centralisation of oesophagogastric cancer surgery, allied to ERAS, is feasible in S.E. Wales within the limited resources available, and demonstrates the patient safety and quality improvements achievable by compliance with NHS guidelines.

## **Chapter 8**

### **General discussion and future studies**

## GENERAL DISCUSSION AND FUTURE STUDIES

This thesis is concerned with examining key areas of the treatment of oesophagogastric cancer where uncertainty exists. These include:

1. Whether the latest update of TNM represents an advance in oesophageal cancer stage categorisation.
2. Whether CT-PET imaging contributes to the contemporary staging algorithm.
3. Whether definitive chemoradiotherapy and surgery are associated with differing rates and patterns of oesophageal cancer recurrence.
4. Whether an involved oesophageal circumferential resection margin has prognostic significance and how neoadjuvant therapy regimes impact on this.
5. Whether early enteral nutrition following resectional surgery improves clinical outcomes.
6. Whether centralisation of surgical services is feasible and improves clinical outcomes.

Despite contemporary multidisciplinary, stage-directed treatment of oesophagogastric cancer, outcomes remain poor when compared with many other malignancies, and this relates largely to late presentation with advanced stage disease. However, the treatments themselves are associated with substantial morbidity and mortality. Chemotherapy and

chemoradiotherapy regimes are associated with significant toxicity, whilst surgical approaches for oesophagogastric cancer are among the most physiologically stressful of all operations.

The treatment of oesophageal cancer must provide the best chance of cure, the lowest risk of morbidity and mortality, and the smallest impact on health related quality of life. Accurate radiological staging is fundamental in determining the most appropriate multimodal treatment option where the possibility of cure exists, and avoiding inappropriate aggressive treatment in those patients with disseminated disease. Successful staging relies on knowledge of the relative strengths and weaknesses of emerging staging modalities, and how such modalities are best incorporated into existing staging algorithms. Furthermore, the TNM criteria used to define stage must be able to accurately predict prognosis, and evolve with the evidence base. The morbidity of surgically based treatment continues to stimulate the search for refinement of potentially curative non-surgical options. The limits of surgery alone in curing oesophageal cancer must be appreciated, neoadjuvant therapy used where appropriate and optimum regimes defined. Principles of peri-operative care and surgical service configuration must continue to develop.

### **8.1 TNM7**

The development of the 7<sup>th</sup> edition of TNM introduced major changes for oesophageal cancer staging, particularly with regard to stratified nodal staging. The updates were not only evidence-based, but a novel data



driven approach was used to accurately redefine stage groupings (Rice et al 2010). The findings reported in Chapter 2 demonstrated that the utilisation of TNM7 to redefine histopathological stage resulted in stage re-categorisation and provided a more accurate determination of prognosis.

The benefits of TNM7 are equally applicable to clinical stage as well as final pathological stage. It is now vital that all radiological modalities report stage in accordance with TNM7, particularly with regard to the number of lymph node metastases. Furthermore, published research must be interpreted in the context of the edition of TNM used, as the stage re-categorisation effect demonstrated prevents meaningful comparison with data derived from an outdated edition of TNM. Correct interpretation of published data is particularly important in the context of large randomised trials where the time interval from study development through to publication of results can be considerable, and there is the possibility of TNM revision during this period.

## **8.2 STAGING CT-PET**

The incorporation of CT-PET in the staging algorithm for oesophageal cancer upstaged a quarter of patients and prevented inappropriate treatment (Chapter 3). This benefit alone justifies the on-going routine use of CT-PET. However, the accuracy of CT-PET in determining N stage was disappointing when compared with EUS, particularly in terms of sensitivity. Further work is needed to establish the reasons for the poor N stage accuracy, so that multidisciplinary teams can be aware of specific

situations in which CT-PET N stage may be particularly inaccurate. Specifically, further studies should define the relative accuracy of peritumoural vs. more distant regional lymph node assessment, compared with histopathological N stage, with large numbers of patients. Such a study would require accurate prospective reporting of the precise location of lymph node metastases identified on CT-PET, in combination with more detailed pathological reporting of lymph node sites, in order to allow comparison. In the future it may be the case that EUS is taken as the definitive assessment of peritumoural lymph nodes, whilst CT-PET is used specifically to refine examination of more distant regional nodes.

Furthermore, the influence of CT-PET in the determination of total disease length must be investigated, as this is crucial for the planning of both surgery and chemoradiotherapy, and may have prognostic value. In particular the relative prognostic value of EUS and CT-PET defined length of disease remains to be identified. The impact of SUV of the primary tumour on overall accuracy of all aspects of CT-PET staging remains to be determined. There may exist a critical SUV level, below which CT-PET staging should be interpreted with caution, or even disregarded completely. Finally the influence of CT-PET on oesophageal cancer survival should be studied, as the up-stage re-categorisation demonstrated in this thesis would be expected to result in improved stage specific survival.

The centralisation of resectional surgery in the S.E. Wales network will facilitate such research, as large numbers of oesophageal resections will

be undertaken and standardised histopathology provided by a single department.

### **8.3 OESOPHAGEAL CANCER RECURRENCE PATTERNS**

Stage for stage examination of long term outcomes following definitive chemoradiotherapy and surgery for oesophageal cancer in Chapter 4 demonstrated similar overall rates of disease recurrence, but very different patterns of relapse. Furthermore, survival was better following surgery than dCRT for early stage disease, but similar for more advanced stage III and IV tumours, with which the majority of patients present in the UK. Some surgeons continue to advocate surgically based treatment for advanced stage oesophageal cancer, largely on the basis of improved locoregional control (Stahl et al 2005, Clark et al 2010), yet the findings in this thesis demonstrate this cannot be justified, as any such benefit in surgically treated patients is offset by the two-fold increased rate of distant recurrence.

The next major goal with regard to the role of dCRT is a randomised controlled trial of this treatment modality compared to surgically based treatment in fit patients with stage III oesophageal cancer of any cell type. However, the potential difficulties in running such a trial are considerable. Early results from a 3 centre feasibility trial (Blazeby 2011) confirm that the proportion of patients with squamous cell carcinoma recruited are small, and therefore running a full trial, although theoretically feasible, would require participation from a large number of centres (Strong et al 2011).

Further research will undoubtedly refine dCRT techniques. Radiotherapy techniques continue to evolve, and in tandem with improved disease localisation radiologically, may enable better local disease control. Radiotherapy targeting is particularly difficult in patients where EUS has failed to cross the primary tumour, and CT-PET may enhance disease localisation in this situation. As knowledge of tumour biology expands on a molecular level, the use of novel monoclonal antibodies, such as Trastuzumab and Cetuximab, allied to conventional chemotherapy agents, may improve the systemic effects of dCRT treatment. Targeted molecular therapies, tailored to individual patients, are likely to form a mainstay of treatment for many cancers in the future, and may eventually replace conventional cytotoxic chemotherapy. Patients with oesophageal cancer, who frequently present with advanced disease, for whom surgical treatment is unsuitable in the majority, may benefit substantially from such developments.

#### **8.4 CIRCUMFERENTIAL RESECTION MARGIN**

The results reported in Chapter 5 demonstrated that involvement of the CRM following oesophagectomy was an independently significant prognostic marker, and of stronger prognostic value than pathological lymph node stage for disease-free survival. The majority of published studies on CRM status report an association with survival, in common with this thesis, although in contrast two of the largest studies failed to identify any such independent survival association. Involvement of the CRM is likely therefore to be one of a number of important pathological prognostic

markers following oesophagectomy. The pathological processing of oesophagectomy specimens is controversial, but irrespective of this, a positive CRM is a common occurrence in contemporary UK practice, occurring in 29% of patients (NHS Information Centre 2010). Assuming appropriately radical surgery has been performed by specialist surgeons, it is reasonable to consider a positive CRM as more a reflection of locally advanced disease than suboptimal surgery. The only conceivable means of significantly reducing CRM positive rates are through the use of more aggressive neoadjuvant therapy regimes. Although Sujendran et al (2007) have shown neoadjuvant chemotherapy reduces the incidence of CRM involvement, the finding reported in this thesis was only a non-significant trend towards the same on multivariate analysis. However, neoadjuvant chemoradiotherapy substantially reduced CRM positive rates in this study, and therefore the issue of CRM status is an integral part of the much wider argument regarding the optimum neoadjuvant therapy regime in oesophageal cancer. High complete resection rates are a feature of many studies of neoadjuvant chemoradiotherapy, including the most recent randomised trial, in which 92.3% of patients treated with chemoradiotherapy had an R0 resection (Gasst et al 2010).

The next major research goal must therefore be a randomised trial of neoadjuvant chemoradiotherapy vs. chemotherapy prior to surgery for T3+ tumours, with close scrutiny of treatment safety, R0 resection rates, survival and health related quality of life. Treatment safety is of paramount concern in this context. Chemoradiotherapy is arguably more

physiologically stressful and toxic than chemotherapy alone, and this has a potential knock-on effect on both the chances of patients remaining fit enough to proceed to surgery, and on maintaining sufficient physiological reserve to proceed to oesophagectomy with acceptable morbidity and mortality. Such a trial must utilise standardised physiological assessment, ideally incorporating cardiopulmonary exercise testing before and after neoadjuvant treatment. This will enhance patient selection and provide objective evidence of the relative impact of chemoradiotherapy and chemotherapy regimes.

A further question that remains to be answered is the need for surgery in the one third of patients who have a complete pathological response to neoadjuvant chemoradiotherapy. Clearly, identification of a complete response radiologically is difficult, as EUS has been shown to be unreliable following radiotherapy, even in complete pathological response (Bowrey et al 1999) and the role of CT-PET in this regard is yet to be defined. Nevertheless, if radiological staging evolves to the point where the degree of pathological response can be accurately determined, this is an issue that will need to be addressed.

### **8.5 EARLY ENTERAL NUTRITION**

The principal findings of Chapter 6 were that early enteral nutrition (EEN) within 12 hours of surgery, delivered via a feeding jejunostomy, was safe and associated with improved clinical outcomes. Concerns remain regarding the safety of feeding jejunostomy placement (NHS Information

Centre 2010), and sceptics feel the only material benefit is the facility to enterally feed patients who develop serious post-operative complications. For these reasons early jejunostomy feeding is not routine practice in all UK centres (Allum et al 2011). The most recent UK oesophagogastric cancer guidelines recommend that some form of nutrition be provided in line with National Institute for Health and Clinical Excellence (2006) guidance, and that preferably this should be enteral where possible. Early enteral nutrition makes sense as a concept, when considered within the wider framework of Enhanced Recovery After Surgery (ERAS). The principles of ERAS, widely advocated and well accepted in patients undergoing colorectal surgery, must now be tested as a complete package in upper gastrointestinal surgery. Arguably there are even greater potential gains for patients undergoing oesophagogastric resection within an ERAS protocol, given the greater magnitude of physiological stress and more prolonged deficit of gut and body function, when compared with colorectal resection. There is enormous scope for refining the ERAS protocol to make it applicable for patients with upper gastrointestinal anastomoses, for whom early oral intake may not be appropriate. The enteral feeding regime studied in Chapter 6 aimed to provide 50% of nutritional requirements by day 5, yet it may be feasible to aim for greater provision, and consequently further reduce the need for intravenous fluids, with the attendant risk of volume and electrolyte imbalances. The significant reduction in peripheral oedema reported in Chapter 6 in patients randomised to EEN occurred despite no significant difference in

overall cumulative fluid balance, suggesting the route of fluid administration is important. Further studies in the context of EEN, within an ERAS protocol, are needed to more accurately quantify the interplay between enteral nutrition and fluid balance. Sophisticated research techniques, such as bioimpedance analysis, have been shown to accurately predict the development of oedema following major abdominal surgery, and consequently identify those at risk of delayed return of gut function, prolonged hospital stay and post-operative morbidity (Itobi et al 2006). Clearly the application of such techniques in the clinical setting warrants further research, ideally within the context of an ERAS protocol. Ultimately the traditional period of nil by mouth for 5 to 7 days, prior to routine contrast radiography for all patients following oesophagectomy and total gastrectomy may be questioned, raising the possibility of early oral fluid and feed intake in selected patients.

## **8.6 CENTRALISATION OF SURGERY**

Subspecialisation of general surgery in the UK has developed rapidly over the last decade, and is now the accepted routine for major oncological surgery. The move towards centralisation of low volume but high complexity cancer surgery was recommended by NHS Executive guidance, but progress has been sporadic and slow. The results of centralisation of surgery in S.E. Wales, reported in Chapter 7, demonstrated that such reconfiguration was feasible and associated with improvements in clinical outcomes. This stands alone as the only large scale comparison of the outcomes before and after service



reconfiguration, in a UK regional cancer network, and will lend support to reconfiguration efforts in other geographical areas and surgical specialities.

The establishment of a high volume surgical centre will facilitate high quality prospective research in all areas of oesophagogastric practice. Specifically, further research effort is needed to establish if centralisation of oesophagogastric surgery is associated with any survival benefit, and to further clarify the individual influences of surgery in a high volume centre and an ERAS protocol. Furthermore, accurate physiological staging for patients suitable for curative treatment is now at a critical juncture, with the increasing availability of cardiopulmonary exercise testing (CPET), the prospect of ever more intensive neoadjuvant chemoradiotherapy regimes on the horizon, and the emerging role of non-surgical curative treatment options for high risk patients. A prospective study of CPET in relation to treatment decisions and oesophagogastric surgical outcomes is urgently needed, and the centralised unit would form an ideal setting for such work.

Finally, the centralisation of regional oesophagogastric surgery in a single high volume centre has major potential benefits for specialist training for the full spectrum of multidisciplinary team members and facilitates national randomised trial recruitment.

## **8.7 CONCLUSION**

Oesophagogastric cancer is still considered by many clinicians to be a “sentence of death”. However, all aspects of staging, physiological

assessment, oncological treatment, surgery and peri-operative care are constantly improving, and this view must be challenged. The cornerstone of oesophagogastric cancer management will continue to be accurate stage-directed treatment, specifically tailored to individual patients. Further research must strive to improve outcomes for patients diagnosed with the most rapidly increasing cancer in the Western world.

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Adjuvant chemotherapy in oesophageal cancer: a meta-analysis and experience from the Shanghai Cancer Hospital.  
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## Appendices

## APPENDIX 1

### Publications and communications derived from work in this thesis

#### 1.1 Published articles

**Reid TD**, Sanyaolu L, Chan D, Williams GT, Lewis WG.  
Relative prognostic value of TNM7 vs. TNM6 in staging oesophageal cancer.  
*Br J Cancer* 2011; 105(6):842-846.

**Reid TD**, Davies IL, Mason J, Roberts SA, Crosby TDL, Lewis WG.  
Stage-for-stage comparison of recurrence patterns after definitive chemoradiotherapy and surgery for oesophageal carcinoma.  
*Clin Oncol* 2012; in press

Barlow R, Price PE, **Reid TD**, Hunt S, Clark GW, Havard TJ, Puntis MC, Lewis WG.  
Prospective multicentre randomised controlled trial of early enteral nutrition for patients undergoing major upper gastrointestinal surgical resection.  
*Clin Nutr* 2011; 30:560-566.

#### 1.2 Published abstracts

**Reid TD**, Barlow R, Davies LL, Price P, Lewis WG.  
Early enteral nutrition improves fluid management in patients undergoing major resection for upper gastrointestinal cancer.  
*Br J Surg* 2010; 97(S2):2-3.  
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**Reid TD**, Chan DSY, Sanyaolu L, Williams GT, Lewis WG.  
The Will Rogers phenomenon. Artifactual statistical effects of the new TNM7 staging system in oesophageal and gastric cancer.  
*Br J Surg* 2011; 98(S3).

**Reid TD**, Davies IL, Mason J, Crosby TD, Lewis WG.  
Stage-for-stage comparison of recurrence patterns after definitive chemoradiotherapy and surgery for oesophageal carcinoma.  
*Br J Surg* 2011; 98(S3).

**Reid TD**, Davies LL, Ellis-Owen R, Roberts SA, Lewis WG.  
Prospective comparison of Computed Tomographic Positron Emission Tomography (CT PET), CT and endosonography (EUS) in the stage directed management of oesophageal cancer.

*Br J Surg* 2011; 98(S3).

### **1.3 Oral Presentations to learned societies**

**Reid TD**, Barlow R, Davies IL, Price PE, Lewis WG.  
Early Enteral Nutrition improves fluid management in patients undergoing major resection for upper gastrointestinal cancer.

*United European Gastroenterology Week, Barcelona, 2010.*

*Association of Surgeons of Great Britain and Ireland, Liverpool, 2010.*

*Welsh Surgical Society, Abergavenny, 2010*

**Reid TD**, Davies LL, Mason J, Crosby TDC, Lewis WG.  
Stage-for-stage comparison of recurrence patterns after definitive chemoradiotherapy and surgery for oesophageal carcinoma.

*European Society of Esophagology, Newcastle upon Tyne, 2011.*

*Association of Surgeons of Great Britain and Ireland, Bournemouth, 2011.*

**Reid TD**, Chan D, Sanyaolu L, Williams GT, Lewis WG.  
The Will Rogers Phenomenon. Artifactual statistical effects of the new TNM7 staging system in oesophageal and gastric cancer.

*Association of Surgeons of Great Britain and Ireland, Bournemouth, 2011.*

**Reid TD**, Roberts SA, Crosby TD, Lewis WG.  
Prognostic significance of circumferential resection margin positivity in oesophageal cancer.

*Welsh Association of Gastroenterology and Endoscopy (WAGE), Llandrindod Wells, 2011*

#### 1.4 Poster Presentations to learned societies

**Reid TD**, Davies LL, Ellis-Owen R, Roberts SA, Lewis WG.  
Prospective comparison of Computed Tomographic Positron Emission Tomography (CT PET), CT and endosonography (EUS) in the stage directed management of oesophageal cancer.

*Association of Surgeons of Great Britain and Ireland, Bournemouth, 2011.*

**Reid TD**, Roberts SA, Crosby TD, Lewis WG.  
Prognostic significance of circumferential resection margin positivity in oesophageal cancer.

*European Society of Esophagology, Newcastle upon Tyne, 2011.*

**Reid TD**, Chan DS, Beamish AJ, Tanner N, Havard TJ, Blackshaw G, Excofet X, Crosby TD, Lewis WG.  
Multidisciplinary upper gastrointestinal cancer team centralization and enhanced recovery improve patient safety, outcome quality and survival significantly.

*Digestive Disease Week, San Diego, 2012.*

## **APPENDIX 2**

### **2.1 TNM7 for oesophageal cancer**

#### **Tumour stage**

- Tis Carcinoma in situ / high grade dysplasia
- T1a Invasion of lamina propria or muscularis mucosae
- T1b Invasion of submucosa
- T2 Invasion of muscularis propria
- T3 Invasion of adventitia
- T4a Invasion of pleura, pericardium, diaphragm or adjacent peritoneum
- T4b Invasion of other structures e.g. aorta, vertebral body, trachea

#### **Nodal stage**

- N0 No regional lymph node metastases
- N1 1 to 2 regional lymph node metastases
- N2 3 to 6 regional lymph node metastases
- N3 >6 regional lymph node metastases

#### **Metastasis stage**

- M0 No distant metastases
- M1 Distant metastases



**2.2 TNM7 anatomical stage groups for oesophageal cancer**

	<b>T</b>	<b>N</b>	<b>M</b>
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2	N1	M0
Stage IIIA	T4a	N0	M0
	T3	N1	M0
	T1, T2	N2	M0
Stage IIIB	T3	N2	M0
Stage IIIC	T4a	N1, N2	M0
	T4b	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

**2.3 TNM7 prognostic stage groups for oesophageal squamous cell carcinoma**

	<b>T</b>	<b>N</b>	<b>M</b>	<b>Grade</b>	<b>Location</b>
Stage IA	T1	N0	M0	1,X	Any
Stage IB	T1	N0	M0	2,3	Any
	T2,T3	N0	M0	1,X	Lower
Stage IIA	T2,T3	N0	M0	1,X	Upper, Middle
	T2,T3	N0	M0	2,3	Lower
Stage IIB	T2,T3	N0	M0	2,3	Upper, Middle
	T1,T2	N1	M0	Any	Any

**Stages IIIA, IIIB, IIIC and IV are as per anatomical stage groups**

Grades: 1 = well differentiated, 2 = moderately differentiated, 3 = poorly differentiated, X = not determined.

Locations are upper, middle or lower third of oesophagus.

**2.4 TNM7 prognostic stage groups for oesophageal adenocarcinoma**

	<b>T</b>	<b>N</b>	<b>M</b>	<b>Grade</b>
Stage IA	T1	N0	M0	1,2,X
Stage IB	T1	N0	M0	3
	T2	N0	M0	1,2,X
Stage IIA	T2	N0	M0	3
Stage IIB	T3	N0	M0	Any
	T1,T2	N1	M0	Any

**Stages IIIA, IIIB, IIIC and IV are as per anatomical stage groups**

Grades: 1 = well differentiated, 2 = moderately differentiated, 3 = poorly differentiated, X = not determined.

## **APPENDIX 3**

### **Documents related to early enteral nutrition trial**

#### **3.1 Patient consent form**

To be issued on Hospital Trust headed paper

#### **A STUDY COMPARING TWO TYPES OF NUTRITION AFTER MAJOR SURGERY**

I (name of patient)

Of (address of patient)

Voluntarily agree to participate in this study.

I confirm that I have been given a full explanation of the purpose of the study by my doctor and/or the lead investigator and have had adequate opportunity to ask questions. I have been made aware of the procedures involved, any potential risk to my health and well-being and what is expected of me during the study.

I understand that I am free to withdraw from this study at any time, without explanation, and that such withdrawal will not affect my future treatment.

I understand that all reasonable steps will be taken to protect my confidentiality and that my name will not be disclosed to any unauthorised person or be referred to in any report concerning this study.

I agree to my doctor informing my GP about my participation in the trial.

SIGNATURE OF PATIENT

Signed \_\_\_\_\_

Date \_\_\_\_\_

Name \_\_\_\_\_

SIGNATURE OF INVESTIGATOR

Signed \_\_\_\_\_ Date \_\_\_\_\_

SIGNATURE OF WITNESS

Signed \_\_\_\_\_

Date \_\_\_\_\_

Name \_\_\_\_\_



AWDURDOD IECHYD  
**BRO TAF**  
HEALTH AUTHORITY

14 October 2002

JJS/JJL

Ms R Barlow,  
Senior Dietitian,  
Department of Surgery,  
University Hospital of Wales  
Heath Park,  
Cardiff.

**COPY**

Dear Ms Barlow,

**02/4714 - A Randomised controlled trial of the effects of early enteral nutritional post-operatively in patients undergoing resection for gastrointestinal malignancy**

Thank you for your letter of the 20<sup>th</sup> September 2002, regarding the above application for ethical approval.

The Acting Chairman of the Bro Taf Local Research Ethics Committee (Panel B), Mr C Weston, has confirmed that your response is satisfactory. Mr Weston has therefore taken 'Chairman's Action' to grant full ethical approval to this application.

*The following documents were received together with your letter:*

*Patient information sheet, Version 2 dated 20/09/02*

*Patient consent form, Version 2, dated 20/09/02*

*GP Letter, Version 2, dated 20/9/02*

I can also confirm that the above study has now been approved by the Risk Assessment Panel as detailed in my letter of the 8<sup>th</sup> October 2002.

I trust this is satisfactory, however, should you require any further information please do not hesitate to contact me.

Yours sincerely,

Mrs Jagjit Sidhu  
Deputy Executive Officer  
Local Research Ethics Committee

☎: 029 20402446/20402309

✉ [JSidhu@bro-taf-ha.wales.nhs.uk](mailto:JSidhu@bro-taf-ha.wales.nhs.uk)

NHS  
CYMRU  
WALES

HEADQUARTERS:  
Churchill House  
17 Churchill Way, Cardiff, CF10 2TW  
PRIF SWYDDFA:  
Tŷ Churchill  
Ffordd Churchill, Caerdydd, CF10 2TW

Temple of Peace and Health  
Cathays Park, Cardiff, CF10 3NW  
Teml Heddwch ac Iechyd:  
Parc Cathays, Caerdydd, CF10 3NW

Tel: 029 20 402401

Fax/Ffôn: 029 20 402401

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