Contemporary outcomes of specialist multidisciplinary treatment

of oesophagogastric cancer in a UK cancer network including an

evaluation of centralisation

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DECLARATION

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For my wife, Sharon and my parents

Galatians 6:9

Let us not grow weary of doing good, for in due season we will reap, if we do not

give up.

1 Corinthians 9:24

Do you not know that in a race all the runners run, but only one receives the

prize? So run that you may obtain it.

CONTENTS

CHAPTER 2 28

Prognostic significance of 18-FDG PET/CT and EUS-defined tumour characteristics in patients with oesophageal cancer

CHAPTER 3 50

Influence of a regional centralised upper gastrointestinal cancer service model on patient safety, quality of care and survival

TABLES AND FIGURES

CHAPTER 1

Tables

CHAPTER 2

Tables

Figures

CHAPTER 3

Tables

CHAPTER 4

CHAPTER 5

CHAPTER 6

Tables

Figures

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SUMMARY

This thesis examines factors influencing contemporary outcomes of patients managed by the South East Wales upper GI cancer network multidisciplinary team. The hypotheses tested were: PET/CT defined tumour characteristics influence outcomes of patients with oesophagogastric cancer; Centralisation of oesophagogastric cancer services improves outcomes significantly; HER2 overexpression is a poor prognostic indicator following oesophagogastric cancer resection; An involved circumferential resection margin (CRM) following oesophagectomy is an independent predictor of survival.

PET/CT N stage was an independent and significant predictor of survival (p=0.022). SUV_{max} correlated positively and significantly with endoluminal ultrasound-defined tumour volume (Spearman's rho=0.339, p=0.001). Centralisation increased the proportion of patients receiving potentially curative treatment by 78% (p<0.0001), reduced serious operative morbidity by 50% (p=0.062), shortened total length of hospital stay from 16 days to 13 days (p=0.024) and improved median and 1-year survival from 8.7 months and 39% to 10.8 months and 46.8% respectively (p=0.032). Centralisation was an independent and significant predictor of survival (p=0.03). HER2 overexpression and gene amplification was a predictor of poor prognosis in patients with curable oesophageal cancer (p=0.03). CRM involvement was also an indicator of poor prognosis in these patients (p<0.001). The College of American Pathologists' criteria differentiate a higher risk group than Royal College of Pathologists' criteria but overlook a patient group with similar poor outcomes (p<0.001).

Chapter 1

Introduction and a review of the literature

1.1 EPIDEMIOLOGY

Gastric and oesophageal cancer are the fourth and eighth most common cancer and second and fourth most common cause of cancer-related death worldwide respectively (Ferlay et al. 2010). Annually, this accounts for 990,00 and 462,000 people diagnosed worldwide with gastric and oesophageal cancer resulting in 740,000 and 386,000 deaths respectively (Ferlay et al. 2010; Jemal et al. 2011). As large geographical variation exists, these two cancer sites represent the thirteenth and eleventh most common cause of cancer and the sixth and fifth most common cause of cancer-related death in the United Kingdom respectively (Cancer Research UK 2012).

Worldwide, the incidence of gastric cancer has been declining for several decades (Parkin 2006). Although the cause is not fully understood, this decline has been attributed to improvements in diet, food preservation and a decrease in prevalence of Helicobacter pylori infection (Cancer Research UK 2012). On the other hand, the incidence of the two main histological types of oesophageal cancer namely squamous cell carcinoma (SCC) and adenocarcinoma (ACA) has changed significantly over the last three decades. SCC accounts for most of the oesophageal cancer in developing countries and the incidence has declined in Western countries (Vizcaino et al. 2002). Conversely, the incidence of ACA has been increasing significantly in most Western countries, with the UK reporting the highest ACA incidence in the world (Bollschweiler et al. 2001).

1.2   AETIOLOGY

1.2.1 Gastric cancer

Gastric cancer is the result of a long multi-step process involving interactions between environmental factors which stimulate changes, H. Pylori infection and host genetic susceptibility. It is a disease of lower socio-economic groups; tobacco smoking is more prevalent in these groups and smokers are at a 1.6 fold risk of developing gastric cancer compared to non-smokers (Lindblad et al. 2005). Certain occupations more common in these groups such as coal mining and pottery have also been found to be associated with an increased risk of developing gastric cancer (Allum 2009). However, lifestyle factors in particular dietary habits are confounding factors in proving a direct causal relationship for these occupations. Diets which consists of a high proportion of salted or pickled foods, dried fish and meat and refined carbohydrates significantly increase the risk of developing gastric cancer (Compare et al. 2010). Conversely, foods rich in antioxidants such as fresh fruit and vegetable have been shown to decrease this risk (Gonzalez et al. 2010).

Besides diet, H. Pylori infection has been implicated in gastric carcinogenesis and since 1994, the International Agency for Research on Cancer designated H. Pylori as a type 1 carcinogen (IARC 1994). It is postulated that H. Pylori infection induces an environment which is susceptible to malignant transformation by reducing gastric juice ascorbic acid thus inducing tissue monocytes to produce reactive oxygen intermediates which are potent carcinogens (Sobala et al. 1993).

1.2.2 Oesophageal cancer - Squamous cell carcinoma

In the West, smoking and alcohol are the main risk factors in the development of oesophageal SCC (Ashktorab et al. 2011). Both these factors are synergistic and exhibit a positive dose-response – heavy smokers and drinkers have up to 2-3 fold greater risk compared to regular users (Szymanska et al. 2011). Additional risk factors such as hookah smoking, nass use, opium consumption and hot tea drinking have been implicated in the East (Mao et al. 2011). Diets which lack important nutrients such as riboflavin, vitamin A and C also predispose to the development of oesophageal SCC (Hu et al. 1994).

Various other factors have also been reported to increase the risk of SCC of the oesophagus. Corrosive injury resulting in oesophageal strictures have been reported to increase the risk of oesophageal SCC by 1000 fold (Ti 1983). Patients with long standing achalasia, a motility disorder of unknown aetiology which results in stasis and fermentation of food residue causing oesophagitis have a 140 fold increased risk of malignant transformation (Leeuwenburgh et al. 2006). However, the treatment of achalasia does not appear to reduce this risk. The combination of dysplasia, iron-deficiency anaemia, koilonychias and oropharyngeal mucosal atrophy otherwise known as Plummer-Vinson syndrome and tylosis which is a rare autosomal dominant disorder are associated with oesophageal SCC (Ribeiro et al. 1996).

1.2.3 **Oesophageal cancer - Adenocarcinoma**

The rising incidence of ACA of the oesophagus in western countries appear to parallel the increase in prevalence of gastro-oesophageal reflux disease (GORD) and the obesity epidemic (Bollschweiler et al. 2001). GORD, which affects up to 10% of adults on a daily basis (Cameron 1997) has been shown to increase the odds of developing oesophageal ACA by 2 to 5 fold in a case-controlled study (Chow et al. 1995). Moreover, the risk of malignancy is related to the severity of GORD. Patients with recurrent and prolonged symptoms have increased odds of developing ACA by up to 8 fold compared with patients who have minimal symptoms (Lagergren et al. 1999). This increased risk is related to the replacement of the normal squamous cell lining of the distal oesophagus with columnar-lined epithelium (Barrett's metaplasia) which is detected in 12% of patients undergoing endoscopy for GORD (Winters et al. 1987). The development of ACA in a Barrett's segment follows a progressive sequence from intestinal metaplasia to low grade dysplasia (LGD), high grade dysplasia (HGD) and finally to cancer (Jankowski et al. 1999). This is thought to be an adaptive response of the oesophageal squamous epithelium to the chronic inflammation caused by prolonged exposure to acid reflux. Although the natural history of Barrett's metaplasia is not fully understood, up to 23% of patients with Barrett's oesophagus develop LGD and the risk of progression from LGD to HGD or cancer is between 10% to 28% (Miros et al. 1991).

Obesity mechanically predisposes to GORD and has been shown to increase the risk of the development of ACA by 3 to 6 fold (Cheng et al. 2000). However,

studies have shown that this increased risk is independent of GORD (Lindblad et al. 2005) and is more pronounced in women (Reeves et al. 2007).

1.3   DIAGNOSIS

1.3.1 Symptoms

The principle symptoms of patients with oesophagogastric cancer are dyspepsia and dysphagia. According to the British Society of Gastroenterology guidelines, alarm symptoms which indicate advanced disease and mandate urgent endoscopy include persistent dyspepsia in patients over the age of 55, dysphagia, anorexia, vomiting, weight loss and anaemia (BSG 2004). However, the presence of alarm symptoms decreases the chance of potentially curative surgery and long-term survival (Stephens et al. 2005). A low threshold for investigation should therefore be adopted to detect early tumours especially in high-risk individuals.

1.3.2 Screening

Screening programmes for oesophagogastric cancer have been implemented in high-prevalence populations with well documented benefits. Oesophageal cancer screening in parts of China with the highest incidence involves collecting oesophageal mucosal cells by withdrawing a swallowed balloon covered with a fine mesh (Shu 1983). Patients with abnormalities are then subjected to endoscopy without the need for radiology.

On the other hand, the screening of gastric cancer in Japan is based on double-contrast radiology followed by endoscopic assessment of any abnormal findings (Hisamichi 1989). The programme which was introduced in the 1960s for men aged over 40 years has led to earlier diagnosis and an improved 5-year survival of up to 30% (Tsubono et al. 2000).

There are currently no screening programmes in the UK where the prevalence of oesophagogastric cancer is lower than the East. Surveillance endoscopy is offered to high-risk groups of patients with gastric ulcers and Barrett's oesophagus (BSG 2004).

1.3.3 Endoscopy

Upper GI endoscopy is the preferred investigation for the diagnosis of oesophagogastric cancer as it allows biopsy for histological confirmation. Radiological diagnosis in the form of a barium swallow is reserved for patients who are unable to tolerate endoscopy as biopsies are not obtainable.

1.4   STAGE CLASSIFICATIONS

1.4.1 Tumour Node Metastases classification

Prior to 1986, numerous staging classification systems were in use. Following agreement between the American Joint Committee on Cancer, Japanese Joint Committee and International Union Against Cancer, a single Tumour Node Metastases (TNM) staging classification was introduced and it is now in its 7th edition (Sobin et al. 2009). This unified classification facilitates planning of

treatment, determining prognosis and allows comparison of outcomes between centres. The TNM system is based on three factors; T stage (depth of invasion of primary tumour), N stage (number of regional lymph node metastases) and M stage (presence or absence of distant metastases).

1.4.2 T Stage

The T stage is based on the depth of tumour invasion and is similar for gastric (Table1.1) and oesophageal cancers (Table 1.2). Early tumours are those which are confined to the mucosa and submucosa and confer a significantly better prognosis compared to more advanced tumours. There is strong evidence that T stage is an important prognostic indicator in oesophagogastric cancer (Ide et al. 1994; Paraf et al. 1995; Lozac'h et al. 1997).

1.4.3 N Stage

The N stage or number of regional lymph node metastases is the most important prognostic factor in both gastric and oesophageal cancer and is used to determine the most appropriate treatment using multi-modal therapy (Mariette et al. 2003; Kunisaki et al. 2005). The accuracy of the N stage is dependent on the number of lymph nodes harvested and a minimum of count of 10 and 15 should be examined to designate the stage as N0 in oesophageal (Twine et al. 2009) and gastric cancer (Bouvier et al. 2002) respectively. This also facilitates the calculation of the lymph node ratio (LNR = number of metastatic nodes divided by the lymph node count) which has been shown to be an important prognostic factor (Dhar et al. 2007; Lagarde et al. 2007).

11

1.4.4 M Stage

The M stage is the assessment of distant metastases. In gastric cancer, the M stage is simply divided into M0 and M1 which represents the absence and presence of distant metastases respectively. This classification has now been adopted in oesophageal cancer and metastases in coeliac lymph nodes is no longer classified as M1a (Sobin et al. 2009).

Table 1.1 TNM 7 for gastric cancer

T stage		N Stage	
T1a	Lamina propria	N0	None
T1b	Submucosa	N1	1-2 nodes
T2	Muscularis propria	N2	3-6 nodes
T3	Subserosa	N3a	7-15 nodes
T4a	Perforates serosa	N3b	≥ 16 nodes
T4b	Adjacent structures		

Table 1.2 TNM 7 for oesophageal cancer

T stage		N Stage	
Tis	Carcinoma in-situ	N0	None
T1a	Lamina propria	N1	1-2 nodes
T1b	Submucosa	N2	3-6 nodes
T2	Muscularis propria	N3	>6 nodes
T3	Adventitia		
T4a	Pleura, pericardium, Diaphragm, peritoneum		
T4b	Aorta, trachea, vertebrae		

1.5   PREOPERATIVE STAGING

Accurate preoperative radiological and endoscopic staging is vital in ensuring the most appropriate stage-directed treatment is offered to patients. As up to 50% of patients present with disseminated disease, the initial investigation is aimed at determining the M stage. In the absence of metastatic disease, further investigations to define the local T and N stages are indicated to tailor management appropriately. The principal imaging modalities are computed tomography (CT), positron emission tomography combined with CT (PET/CT), endoscopic ultrasonography (EUS) and diagnostic laparoscopy.

1.5.1   Computed Tomography

CT of the chest, abdomen and pelvis with intravenous contrast is the initial radiological modality used as it allows the assessment of the primary tumour and more importantly, the detection of distant metastases. Over the last decade, significant improvements in CT with the use of multiple detectors have resulted in improved diagnostic accuracy which is further enhanced by specialist radiologists (Barry et al. 2002).

The accuracy of T stage as defined by CT is dependent on adequate distension by water with the addition of anti-peristaltic agents prior to imaging. Tumours around the oesophagogastric junction are dependent on gravity and can therefore be imaged in the prone or decubitus position for improved accuracy (Allum et al. 2011). The ability to detect invasion of surrounding structures as

determined by the loss of the fat plane around the oesophagus and stomach can be improved further by using multiplanar reformat images (Bhandari et al. 2004).

The sensitivity and specificity of N stage defined by CT are 50% and 83% respectively (van Vliet et al. 2008). Differentiation between lymph node metastases and benign enlargement is difficult on CT and size criteria for malignant involvement is controversial and a combination with positron emission tomography (PET) significantly improves the accuracy (Gillies et al. 2012).

The main strength of CT is the detection of distant metastases with a sensitivity and specificity of 52% and 91% respectively (van Vliet et al. 2008). However, small volume metastatic disease can be missed by CT and investigations such as laparoscopy and PET/CT can improve the accuracy of M stage.

1.5.2 Positron Emission Tomography

Positron emission tomography (PET) is a nuclear medicine technique which relies on the production of gamma rays following introduction of a radionuclide intravenously. 2-[(18F)] fluoro-2-deoxy-d-glucose (FDG) is the most commonly used radionuclide which remains intracellular until radioactive decay occurs. The rate of cellular tracer uptake is proportional to metabolic activity and malignant tumours usually have higher metabolic rates compared with normal tissue (Branstetter et al. 2005).

The first commercial PET scanner was manufactured by Siemens and used in UCLA, Los Angeles in 1976. Since then, integrated PET/CT has been developed which provides both functional and anatomical data (Beyer et al. 2000). This

combination allows co-registration of the PET and CT data as patient position is unchanged therefore minimising movement artefacts. PET/CT is now used in the staging and assessment of treatment response of various cancers such as breast, lung, lymphoma, thyroid and gastrointestinal (Endo et al. 2006).

The main role of PET/CT in oesophagogastric cancer is the detection of distant nodal and metastatic disease. The sensitivity and specificity for the identification of distant metastases by PET/CT is 67% and 97% respectively (Ott et al. 2006). Moreover, the addition of PET/CT in the staging algorithm of oesophageal cancer allows the detection of distant metastases in 10% of patients not detected by CT and altered management in up to 26% (Noble et al. 2009; Gillies et al. 2011). The prognostic role of PET/CT defined tumour characteristics is explored in the following chapter.

Another potential role of PET/CT is in the assessment of response to neoadjuvant chemo/radiotherapy prior to surgery. PET/CT can measure changes in metabolic activity and can therefore identify residual disease. However, recent studies have not been conclusive and further research is needed prior to its routine use in assessment of response (Muijs et al. 2010; Klayton et al. 2012).

1.5.3 Endoscopic Ultrasonography

Endoscopic ultrasonography (EUS) is an established modality in the locoregional staging of oesophageal and junctional tumours and is indicated following exclusion of metastatic disease by CT or PET/CT. The overall accuracy for T stage is 67-78% and EUS is highly effective at discriminating between T1/2 from

T3/4 disease (Kelly et al. 2001). This helps selecting patients for neoadjuvant therapies which are used to downstage tumours prior to surgery. The accuracy of N stage is 65-75% and further information can be obtained by performing FNA of suspicious lymph nodes which can improve N staging accuracy to over 90% (Chang et al. 2003).

The main drawback of EUS is the failure to cross a stricture which occurs in up to 25% of patients (Vickers et al. 1998). However, valuable staging information can still be obtained using blind probes and aid decision-making (Vickers et al. 1998).

In addition to these diagnostic roles, EUS defined tumour characteristics such as tumour length (Twine et al. 2010), total length of disease (Davies et al. 2012) and tumour volume (Twine et al. 2010) provide important prognostic information.

1.5.4 Staging Laparoscopy

Laparoscopy allows the detection of peritoneal disease not detected by CT. Moreover the assessment of serosal involvement and invasion of adjacent tissues can be determined. Laparoscopy is used routinely in patients with distal oesophageal or junctional tumours (Allum et al. 2011) as it prevents unnecessary laparotomy in up to 18% of patients (de Graaf et al. 2007).

1.6   SURGICAL TREATMENT

1.6.1 Gastrectomy

The extent of resection is determined by the position and preoperative stage of the cancer. In patients with early gastric cancer, proximal or distal subtotal resection with limited D1 lymphadenectomy (Allum et al. 2011) is indicated. A

total gastrectomy or oesophagogastrectomy can be performed for tumours around the cardia.

The extent of lymphadenectomy has been a topic of debate among Western surgeons in the last two decades. In D1 lymphadenectomy, only the perigastric nodes closest to the primary tumour are removed en bloc with the stomach. Systematic D2 lymphadenectomy involves the removal of the perigastric nodes and distant nodes along the main arteries supplying the stomach (first 2 tiers of lymph nodes, N1 and N2). In contrast to many Western surgeons, the Japanese have long advocated the more radical D2 approach, reserving D1 surgery for elderly patients with early disease and associated co-morbidities. Initial results from two Western randomised controlled trials have shown little difference between D1 and D2 lymphadenectomy (Cuschieri et al. 1996; Bonenkamp et al. 1999; Cuschieri et al. 1999). However, long-term results in the Dutch trial has shown improved survival following D2 lymphadenectomy (Songun et al. 2010) which is now the recommended standard approach (Allum et al. 2011). At present, there is no role for extended lymphadenectomy beyond the second tier nodes as two multicentre trials in Japan comparing D2 and D4 lymphadenectomy concluded that D4 did not result in improved survival but increased morbidity (Sasako et al. 2008; Yonemura et al. 2008).

Studies have shown that minimally invasive resection for gastric cancer including D2 lymphadenectomy can be performed safely (Huscher et al. 2005; Tanimura et al. 2007). However, most studies include patients with early (T1 and T2) cancers and a meta-analysis of open versus laparoscopic-assisted distal gastrectomy

(LADG) revealed a trend towards faster postoperative recovery at the expense of longer operating times and a reduced nodal yield in LADG (Memon et al. 2008).

1.6.2 Oesophagectomy

The two main operative approaches for oesophagectomies are the transthoracic (Ivor-Lewis) and the transhiatal route which depends on tumour location, extent of lymphadenectomy, patient factors and experience of the surgeon. The transthoracic approach is a two stage procedure involving the resection of the thoracic oesophagus and a complete posterior mediastinal lymphadenectomy via an upper midline laparotomy and a right postero-lateral thoracotomy. The transhiatal procedure is performed via an abdominal roof-top and a left cervical incision. The initial gastric and oesophageal mobilisation is performed under direct vision until the inferior pulmonary vein followed by blunt dissection of the remaining oesophagus. Reconstruction is performed using a gastric conduit with a left cervical anastomosis.

The advantages of the transhiatal approach are the significantly lower postoperative morbidity rates and quicker recovery compared to the transthoracic approach (Hulscher et al. 2002; de Boer et al. 2004). This is at the expense of inadequate mediastinal lymphadenectomy which can be achieved with the transthoracic approach. However, overall survival difference is minimal and the transhiatal route is usually reserved for patients with early stage node negative tumours who may not tolerate a thoracotomy because of comorbidities (Allum et al. 2011).

The development of minimally invasive technique is still in its infancy and early experiences from cohort studies have shown that short-term outcomes are acceptable with adequate lymph node yield (Palanivelu et al. 2006; Berrisford et al. 2008). Data from well-designed randomised controlled trials are needed prior to routine use of these new techniques.

1.7   ENHANCED RECOVERY AFTER SURGERY

Traditional perioperative care of patients undergoing major gastrointestinal resections dictated the need for prolonged periods of fasting and gastrointestinal tract rest until the return of normal function. This has lead to patients routinely staying in hospital for over 15 to 20 days even in the absence of major complications (Karl et al. 2000; Hofstetter et al. 2002). Over the last decade, enhanced recovery after surgery (ERAS) programmes have been implemented routinely in colorectal surgical practice. Originally described by Kehlet in Copenhagen, the ERAS programme is a multidisciplinary package of measures for patients undergoing colorectal surgery which includes preoperative patient education, carbohydrate loading, goal directed anaesthesia, early postoperative enteral nutrition and mobilisation (Basse et al. 2000). This has resulted in improved postoperative morbidity and length of hospital stay (Varadhan et al. 2010). However, ERAS in upper gastrointestinal surgery is less well developed with only the publication of a few small trials and observational studies (Wang et al. 2010; Tang et al. 2013).

1.8 NEOADJUVANT THERAPY

Multimodal therapy has been shown to be beneficial in patients with oesophagogastric cancer. Surgery alone is reserved for the minority of patients who present with early disease due to the high recurrence rates in advanced tumours. Neoadjuvant therapy has the potential advantages of improving resectability and swallowing and treating micrometastases prior to surgery. The two largest randomised controlled trials of preoperative chemotherapy versus surgery alone have reported conflicting results. The American Intergroup Trial (INT 0113) of 440 patients did not report any significant differences in survival in the two arms (Kelsen et al. 1998). However, the largest and most influential trial from the UK of over 800 patients showed a significant survival advantage for patients receiving preoperative chemotherapy (5 year survival of 23% vs. 17%) (MRC Oesophageal Cancer Working Group 2002). This is therefore the standard of care in the UK. The recently completed MRC OEO5 trial comparing OEO2 chemotherapy with four cycles of ECX (epirubicin-cisplatin-capecitabine) may alter practice if this regimen is found to further improve survival (Allum et al. 2009).

Preoperative chemoradiotherapy (CRT) is used in patients with rectal cancer who have a threatened CRM. However, its use in oesophageal cancer is controversial. The only randomised trial comparing preoperative chemotherapy with preoperative CRT of 126 patients showed a non-significant improvement in 3 year survival in the preoperative CRT group (Stahl et al. 2009). Currently, preoperative CRT is only used in the context of a clinical trial in the UK.

1.9 NONSURGICAL TREATMENT

1.9.1 Endoscopic techniques

Endoscopic techniques such as endoscopic mucosal resection (EMR), submucosal dissection (ESD), radiofrequency ablation (RFA), photodynamic therapy (PDT) and argon plasma coagulation (APC) have developed significantly over the last decade. As these techniques do not treat regional lymph nodes, the indications are limited to patients with early cancer (high grade dysplasia and T1a) and to ablate high-risk mucosa. The risk of lymph node metastasis is related to the depth of invasion of the tumour and histological type. There is a suggestion that squamous cell carcinoma is more aggressive than adenocarcinoma (Eguchi et al. 2006). The risk of nodal metastasis in patients with adenocarcinoma and squamous cell carcinoma confined to the mucosa (T1a) is 0% and up to 18% respectively (Eguchi et al. 2006; Griffin et al. 2011). Once the tumour invades the submucosa (T1b), the risk of lymph node metastasis rises significantly up to 60% (Gockel et al. 2011). These patients should therefore undergo oesophagectomy as the most definitive treatment aimed at cure.

After removing high-risk lesions with EMR or ESD, the high-risk mucosa will need to be ablated, most frequently with RFA, but other options include PDT and APC. These techniques have the potential for complete eradication of high grade dysplasia and Barrett's dysplasia in over 90% but recurrence is reported in up to 10% (Ragunath et al. 2005; Ganz et al. 2008). Patients undergoing these therapies usually require repeat treatment and should be performed in specialist centres (Allum et al. 2011).

1.9.2 Definitive chemoradiotherapy

The high proportion of elderly patients diagnosed with oesophageal cancer who have significant comorbidity unfit for major surgery has fuelled the search for non-surgical curative options. High response rates and pathological complete response (pCR) rates after chemoradiotherapy (CRT) has lead to the adoption of this modality as a definitive treatment strategy (Gwynne et al. 2013). Certainly in upper squamous cancers, dCRT can achieve local control in up to 70% of patients and surgery is only reserved as a salvage option (Denham et al. 2003). Despite the lack of randomised trials comparing dCRT versus surgery for adenocarcinoma, numerous studies have reported long-term survival following dCRT comparable to surgical series (Chan et al. 1999; Bedenne et al. 2007; Morgan et al. 2009; Gwynne et al. 2011). At present, dCRT is reserved for patients deemed unsuitable for surgery although its role in patients with operable adenocarcinoma warrants further investigation.

1.10 BIOMARKERS

Cancer biomarkers are biological molecules found in blood or other tissues that can be used not only to identify the presence of a tumour, but also to determine its stage, subtype and ability to respond to therapy (Chhatrala et al. 2014). These assays are useful for cancer detection, diagnosis, patient prognosis and treatment selection. The poor survival rates from oesophagogastric cancer has led to the search for targeted therapies with antagonists of growth factor signaling transduction pathways (Ekman et al. 2007). These growth factors are polypeptide

molecules that regulate various cellular responses including cell proliferation by binding to specific receptors on the cell surface which activates tyrosine kinase pathways (Heldin 1995). If deregulated, these pathways can promote tumorigenesis.

1.10.1 Human Epidermal Growth Factor Receptors

The human epidermal growth factor receptor (HER) family of growth factors comprise of four members: EGFR (HER1, ErbB-1), HER2 (ErbB-2, Neu), HER3 (ErbB-3) and HER4 (ErbB-4) (Bazley et al. 2005). These receptors are tyrosine kinases that are activated by ligand-induced dimerization. However, HER2 does not have a ligand but is used as a heterodimeric partner by the other receptors (Bazley et al. 2005). HER family members are commonly activated in various cancers by mutations or overexpression leading to signals that promote proliferation, survival, migration and angiogenesis (Ekman et al. 2007).

1.10.2 Human Epidermal Growth Factor Receptor 2

Amplification of the HER2 gene and overexpression of HER2 in gastric cancer was first described in 1986 (Yamamoto et al. 1986) and since then, numerous studies have confirmed these findings (Jorgensen et al. 2012). Since 2010 following the ToGA trial, trastuzumab, an anti-HER2 agent in combination with chemotherapy was approved for the treatment of patients with HER2 positive advanced inoperable gastric and junctional cancer (Bang et al. 2010). However, there is still a lack of evidence of its use in oesophageal cancer.

1.10.3 Prognostic significance of HER2

Gastric cancer

A recent systematic review of 49 studies totaling 11337 patients with gastric cancer, most of whom had undergone curative gastrectomy found that HER2 overexpression occurred in 18% (4-53%) and was associated with a poorer survival (Chua et al. 2012).

Table 1.3 Association of HER2 status and survival in patients with gastric cancer (Chua et al. 2012)

	HER2 positive	HER2 negative
3 year disease free survival, %	58	86
5 year overall survival, %	42	52
Median survival (range), months	21 (10 – 57)	33 (13 – 80)

Oesophageal cancer

The frequency of HER2 amplification ranges from 15 to 19% in patients with oesophageal adenocarcinoma (Brien et al. 2000; Reichelt et al. 2007; Hu et al. 2011). There are reports indicating that HER2 expression may change during tumour progression. HER2 expression has been reported to be lost during development of oesophageal adenocarcinoma (Sauter et al. 1993) or a late event (Walch et al. 2004). Moreover, the association between HER2 overexpression and survival in patients with oesophageal cancer is unclear and reports have been conflicting (Hu et al. 2011).

1.11   SERVICE RECONFIGURATION

Centralisation of complex cancer surgery into high-volume centres is a subject of debate in many countries. Improvements in care can be achieved by collating multidisciplinary expertise and experience with specialised equipment in centres of excellence (Brusselaers et al. 2014). However, these benefits will need to be offset against potential disadvantages such as long travel distances, social isolation (Bilimoria et al. 2008) and the negative impact on waiting times for the benign operative workload in specialist units (Forshaw et al. 2006). Nevertheless, the Association of Upper Gastrointestinal Surgeons has recommended that these units should consist of four to six surgeons, each performing a minimum of 15 to 20 resections per year and serving a population of 1 to 2 million (AUGIS 2011). Compliance with this guidance has been achieved in England but received lesser 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, operative mortality was 12%, and 2 year survival was 42% (Pye et al. 2001) following curative surgery compared with 6% and 75% in England (Sue-Ling et al. 1993).

Numerous population based studies have reported improved short-term outcomes (van Lanschot et al. 2001; Wouters et al. 2012) and long-term survival (van de Poll-Franse et al. 2011; Brusselaers et al. 2014) in high-volume units. However, there are only a handful of reports from individual units in England detailing actual improvements following centralisation (Branagan et al. 2004; Forshaw et al. 2006; Boddy et al. 2012). In South East Wales, centralisation of

upper gastrointestinal cancer services at the University Hospital of Wales commenced in August 2010 serving a population of 1.4 million, following a protracted period of negotiation between politicians, managers and clinicians.

1.12 AIMS AND HYPOTHESES

In light of the above, the aims of this thesis are to address the following according to the patient journey from pre-operative staging after diagnosis, surgical treatment in the era of centralisation of specialist services, through to the examination of post-operative histological factors which influence prognosis:

1. To determine the correlation between 18-FDG PET/CT defined SUV_{max} and EDTV in patients with oesophageal cancer and their relative prognostic significance

2. To determine the impact of centralisation on Upper GI cancer survival at one year

3. To determine the influence of HER2 on outcomes in patients with operable oesophageal cancer

4. To determine the prognostic significance of HER2 receptor expression at index biopsy and definitive surgery

5. To determine the influence of CRM involvement in patients with operable oesophageal cancer

The hypotheses are:

1. A significant positive correlation exists between SUV_{max} and EDTV. PET/CT and EUS defined tumour characteristics are important predictors of survival in patients with oesophageal cancer.

2. Centralisation of Upper GI cancer services improves one year survival.

3. HER2 overexpression is associated with poorer outcomes in patients with operable oesophageal cancer.

4. Endoscopic biopsy is accurate at predicting HER2 status.

5. CRM involvement is associated with poorer outcomes following oesophagectomy.

Chapter 2

Prognostic significance of 18-FDG PET/CT and EUS defined tumour

characteristics in patients with oesophageal cancer.

2.1 SUMMARY

The aim of this study was to determine the correlation between 18-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) defined maximum standardised uptake value (SUV_{max}) and endoluminal ultrasound-defined tumour volume (EDTV) in patients with oesophageal cancer (OC) and their relative prognostic significance.

One hundred and eighty-five consecutive patients with OC were staged with CT, EUS and PET/CT. The maximum potential EDTV was calculated ($\pi r^2 L$, where r = tumour thickness and L=total length of disease including proximal and distal lymph node metastases). Primary outcome measure was survival from diagnosis.

Ninety-one percent of patients (168/185) had FDG-avid tumours on PET/CT. SUV_{max} correlated positively and significantly with EDTV (Spearman's rho = 0.339, p=0.001). On univariate analysis, survival was inversely related to the PET/CT lymph node metastasis count (LNMC, p=0.015), EUS N stage (p=0.002), EDTV (<48 cm^3, p=0.001), EUS total length of disease (p=0.001), SUV_{max} (p=0.002), PET/CT N stage (p<0.0001), and EUS LNMC (p<0.0001). On multivariate analysis two factors were significantly and independently associated with survival: EDTV (HR, 3.118; 95% CI, 1.357-7.167; p = 0.007), and PET/CT N stage (HR, 0.496; 95% CI, 0.084-1.577; p=0.022).

EDTV and PET/CT N stage were important predictors of survival and further research is needed to identify critical prognostic values.

2.2   INTRODUCTION

Contemporary radiological staging of patients diagnosed with oesophageal cancer (OC) has recently been upgraded to include 18-fluorodeoxyglucose (FDG) positron emission tomography integrated with computed tomography (PET/CT) (Allum et al. 2011) into the previous algorithm of CT followed by endoscopic ultrasound (EUS). The benefits accrued from this strategy include the detection of distant metastases not detected by CT in about 10% of patients, and altered management in as many as 26% (Noble et al. 2009; Gillies et al. 2011). Moreover, there is growing evidence that the degree of tracer uptake by the tumour measured as the maximum standardised uptake value (SUV_{max}) is an important prognostic factor (Rizk et al. 2006; Pan et al. 2009).

EUS is the principal imaging modality for assessing the depth of tumour invasion, lymph node metastasis count (ELNMC) and the total length of disease including the proximal and distal lymph node metastases (ELoD) (Kelly et al. 2001). ELoD, ELNMC and the maximum endoluminal ultrasound-defined tumour volume (EDTV), derived from the ELoD have been shown to be significant and independent predictors of survival in patients with OC (Twine et al. 2010). However, despite the importance of these factors in defining the optimum

treatment, ELoD ELNMC and the derived EDTV are not routinely reported in standard EUS examinations.

Therefore, the aim of the present study was to determine the correlation between FDG PET/CT defined SUV_{max} and EDTV in patients with OC and their relative prognostic significance.

2.3   METHODS

2.3.1   Patient selection and staging

All patients diagnosed with oesophageal cancer who underwent PET/CT imaging in the South East Wales regional Upper GI cancer network were studied prospectively between January 2009 and June 2011. Patients with Siewert type III oesophagogastric junctional cancer with proximal extension also underwent PET/CT. Patients proceeded to PET/CT imaging only if they were suitable for potentially curative treatment on the grounds of CT stage and performance status, and was arranged concurrent with EUS. Patients' fitness was assessed by means of cardiopulmonary exercise testing (CPX) (Older et al. 2000) and a final management plan was determined at the regional cancer network multidisciplinary team (MDT) meeting. All staging investigations were reported in accordance with the UICC tumour-nodes-metastasis (TNM) 7th Edition (Sobin et al. 2009). The primary outcome measure was survival from diagnosis. Informed consent was obtained from all patients. Ethical approval was sought from the regional ethics committee, but a formal application was deemed unnecessary.

2.3.2 PET/CT protocols

PET/CT examinations on 185 patients were performed at two centres. At the first centre, 87 patients underwent PET/CT examinations performed on a Philips 16 section Gemini GXL dedicated PET/CT system (Philips Medical Systems, Cleveland, OH, USA). The uptake time was 60 minutes. A standard dose of 350 MBq of FDG was injected. Reconstructions were performed using a three-dimensional (3D) acquisition with non-time-of-flight acquisition for 4 minutes per bed position.

Ninety-eight patients were imaged at the second centre on a GE discovery 690 PET/CT system with time-of-flight acquisition (GE Medical Systems, Waukesha, WI, USA). Patients were injected with 3MBq/kg (minimum 200 MBq). Uptake time at the second centre was 90 minutes. Acquisitions were obtained for 3 minutes per bed position. Image analysis was performed on a GE Xeleris workstation. At both centres, all patients were starved for a minimum of 6 hours prior to imaging. The SUV_{max} was determined for all patients by identifying the most avid part of the primary tumour on the maximum intensity projection images and placing a 2 cm diameter spherical region of interest over this, while avoiding activity not arising within the primary tumour. The maximum SUV value within this was recorded as the SUV_{max}. This method was consistent between the two centres.

2.3.3 Details of endosonography

An initial endoscopic examination was performed using a 9 mm diameter Olympus P-10 gastroscope (Key Med, Southend, UK) to assess the degree of the oesophageal luminal stenosis. Patients with an estimated oesophageal luminal diameter less than 15 mm underwent examination using the smaller-diameter MH-908 oesophagoprobe (Key Med). Oesophageal dilation (Savary-Gilliard, Cook Medical, Bloomington, IN) was performed before endosonography for patients with oesophageal lumens less than 9 mm. The type of echoendoscope used was at the discretion of the endoscopist. The primary oesophageal tumour was assessed, together with an evaluation of the paraoesophageal anatomic structures as described previously (Bowrey et al. 1999). The criteria for malignant lymphadenopathy specified a hypoechoic pattern, a spherical contour, the presence of a distinct border, and a short axis diameter of 6 mm or more. Proximal and distal disease lengths were measured in centimetres by reference to the incisor teeth. The maximum tumour thickness was measured in millimetres with electronic callipers using the EUS software (Key Med). All EUS examinations were performed in a single centre by 3 specialist MDT clinicians.

2.3.4 EDTV calculation

The EDTV was calculated as the maximum potential cylinder volume of disease using the formula $\pi r^2 L$ where r = tumour thickness and L = total length of disease including proximal and distal lymph node metastases as described previously (Twine et al. 2010). Although r was measured in millimetres, it was converted to

centimetres for calculation. All the EUS data were recorded in a structured EUS-reporting database.

2.3.5 Treatment

Patients were selected for radical treatment (surgery or definitive chemoradiotherapy) based on perceived radiologic stage, comorbidity and patient choice according to algorithms described previously (Crosby et al. 2004; Stephens et al. 2006; Gwynne et al. 2011)

2.3.6 Follow-up evaluation

Patients were reviewed every 3 months for the first year, then every 6 months thereafter. One hundred and forty-eight patients were followed up for at least 1 year or until death. No patients were lost to follow-up. Death certification was obtained from the Office for National Statistics.

2.3.7 Statistical analysis

Grouped data were expressed as median (range) and non-parametric methods used throughout. Correlation was assessed using Spearman's rho. Cumulative survival was calculated by the life table method of Kaplan and Meier. Cox proportional hazards regression was used to assess the prognostic value of individual variables. Data analysis was carried out with the Statistical Package for Social Sciences (SPSS) version 18 (SPSS, Chicago, IL, USA).

2.4   RESULTS

Between January 2009 and November 2011, 185 patients with potentially curable OC underwent PET/CT and EUS. Thirty-two patients (17.3%) had tumours which were not traversable on endoscopic assessment, but 3 patients underwent successful dilatation prior to EUS. Tumour thickness was not measured if tumours were not traversed. The median SUV_{max} was similar between patients who had traversable and non-traversable tumours (8.7 versus 10.0, p=0.124). Although the median SUV_{max} in the first centre was lower than the second centre, this difference was not statistically significant (8.1 versus 10.1, p=0.056).

All patients were analysed according to an intention-to-treat basis (Table 2.1) of whom 83 underwent surgery (58 neoadjuvant chemotherapy; 25 Ivor Lewis oesophagectomy, 25 transhiatal oesophagectomy, four three-stage oesophagectomy, 13 total gastrectomy and 16 open and close laparotomy), 46 definitive chemoradiotherapy, three endoscopic mucosal resection and 53 received palliative therapy.

Of the 53 patients who received palliative therapy, 25 patients were up-staged by PET/CT detected distant metastases, and 16 patients were found to have inoperable tumours at EUS, five patients had liver or peritoneal metastases on staging laparoscopy that were not picked up on radiological imaging, and seven patients were found to be unfit for curative treatment on CPX. Fifty-five patients

were upstaged by the combination of EUS and PET/CT (Table 2.2). A higher SUV$_{max}$ was associated with more advanced disease (p<0.0001, Table 2.4).

2.4.1 Utility of SUV$_{max}$ and correlation with EDTV

Ninety-one percent of patients (168/185) had FDG-avid tumours on PET/CT. A high SUV$_{max}$ was associated with advanced overall radiological stage but not sex, age or histological subtype (Table 2.4). The median SUV$_{max}$ and EDTV was 8.9 (0-50) and 48.0 (0.28-547.46) cm^3 respectively. A scatter plot of SUV$_{max}$ related to EDTV is illustrated in Figure 2.1. There was a positive and significant correlation between SUV$_{max}$ and EDTV (Spearman's rho=0.339, p=0.001). This correlation was stronger compared to the correlation between SUV$_{max}$ and EUS-defined total length of disease (Spearman's rho=0.112, p=0.08).

2.4.2 Recurrence rates

The median SUV$_{max}$ in patients who developed locoregional, distant or locoregional and distant recurrence was 7.4, 9.3, 14.9 respectively (p=0.424). Overall recurrence rates were higher in patients who had undergone definitive chemoradiotherapy when compared with patients who had undergone surgery (p=0.055, Table 2.3).

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2.4.3 Duration of survival

Univariate analysis

Cumulative survival was significantly better in patients with lower SUV_{max} (2 year survival 55% for SUV_{max} <8.9 versus 34% for SUV_{max} ≥8.9, p=0.002, Fig.2.2) and lower EDTV (2 year survival 79% for EDTV <48.0cm^3 versus 37% for EDTV ≥48cm^3, p=0.001, Fig.2.3). Cumulative survival related to PET/CT N Stage is shown in Figure 2.4 (2 year survival was 58%, 31%, 26% and 0% in N0, N1, N2 and N3 respectively, p<0.0001). All factors associated with survival on univariate analysis are shown in Table 2.5.

In a subgroup analysis of patients who underwent surgical resection, the median SUV_{max} and EDTV was 7.8 (0 – 36) and 39.0 (0.38 – 343.58) cm^3 respectively. The median SUV_{max} was significantly lower in patients who underwent surgery when compared to patients who did not (7.8 vs. 10.9, p=0.007). However, the median EDTV was similar irrespective of treatment types (39.0 versus 58.0 cm^3, p=0.216). Cumulative survival in this subgroup of patients was not associated with SUV_{max} but was associated with EDTV (2 year survival 85% for EDTV <39.0 cm^3 versus 57%, for EDTV ≥39.0 cm^3, p=0.001).

Multivariate analysis

The factors found to be significantly associated with survival on univariate analysis (Table 2.5) were entered into a multivariate analysis using Cox's proportional hazards model, the results of which are shown in Table 2.6.

Table 2.1   Demographic details of 185 patients included in study

Age, years (range)	66 (35-82)
Sex, male:female (%)	131:54 (71:29)
Tumour location (%)	
Middle third oesophagus	38 (20.6)
Distal third oesophagus	81 (43.8)
Oesophagogastric junction	66 (35.7)
Siewert type I	13 (19.7)
Siewert type II	16 (24.2)
Siewert type III	37 (56.1)
Histology (%)	
Adenocarcinoma	139 (75.1)
Squamous cell carcinoma	46 (24.9)
Median SUV_{max} (range)	8.9 (0-50)
EUS tumour length, cm	
Mean (range)	6.88 (1-20)
Median	6.00
Standard deviation	3.88
Median EDTV, cm^3 (range)	48 (0.28-547.46)

Table 2.2   Overall CT and combined radiological stage of all patients

	Overall Radiological Stage (EUS/PET/CT)				
Overall CT Stage	**I**	**II**	**III**	**IV**	**Total**
I	25	5	2	3	35
II	0	44	15	8	67
III	0	0	61	22	83
Total	25	49	78	33	185

Table 2.3   Recurrence rates related to treatment type

	Surgery	**CS**	**dCRT**	**p value**
Total number	25	58	46	
Recurrence rates (%)				0.055
Local	1 (4)	6 (10)	8 (17)	
Distant	0	4 (7)	8 (17)	
Local & distant	0	2 (3)	5 (11)	

CS – Neoadjuvant chemotherapy followed by surgery; dCRT – definitive chemoradiotherapy

Table 2.4   Median SUV_{max} related to sex, age, histological type and overall combined radiological stage of patients with oesophageal cancer

	Median SUV_{max}	p value
Sex		0.183
Male	8.6	
Female	10.3	
Age, years		0.07
<50	8.1	
50-59	8.5	
60-69	11.2	
>70	8.7	
Histology		0.171
Adenocarcinoma	8.5	
Squamous cell carcinoma	10.5	
Overall radiological stage		<0.0001
Stage I	3.8	
Stage II	8.7	
Stage III	9.4	
Stage IV	13.2	

Table 2.5   Univariate analysis of factors associated with survival

Factors	Log Rank	df	p value
PET/CT LNMC	33.684	7	0.015
PET/CT SUV_{max}	9.164	1	0.002
EUS N stage	14.613	3	0.002
ELoD	10.464	1	0.001
EDTV (<48 vs. ≥48cm^3)	11.93	1	0.001
PET/CT N stage	24.285	3	<0.0001
EUS LNMC	133.535	12	<0.0001

Table 2.6   Multivariate analysis of factors associated with survival

Factors	Hazard ratio	95% CI	p value
EDTV (<48 vs. ≥ 48cm^3)	3.118	1.357-7.167	0.007
PET/CT N0	Reference group		0.022
PET/CT N1	0.255	0.084-0.698	0.007
PET/CT N2	0.496	0.159-1.577	0.201

Figure 2.1   Scatter plot of SUV$_{max}$ and EDTV
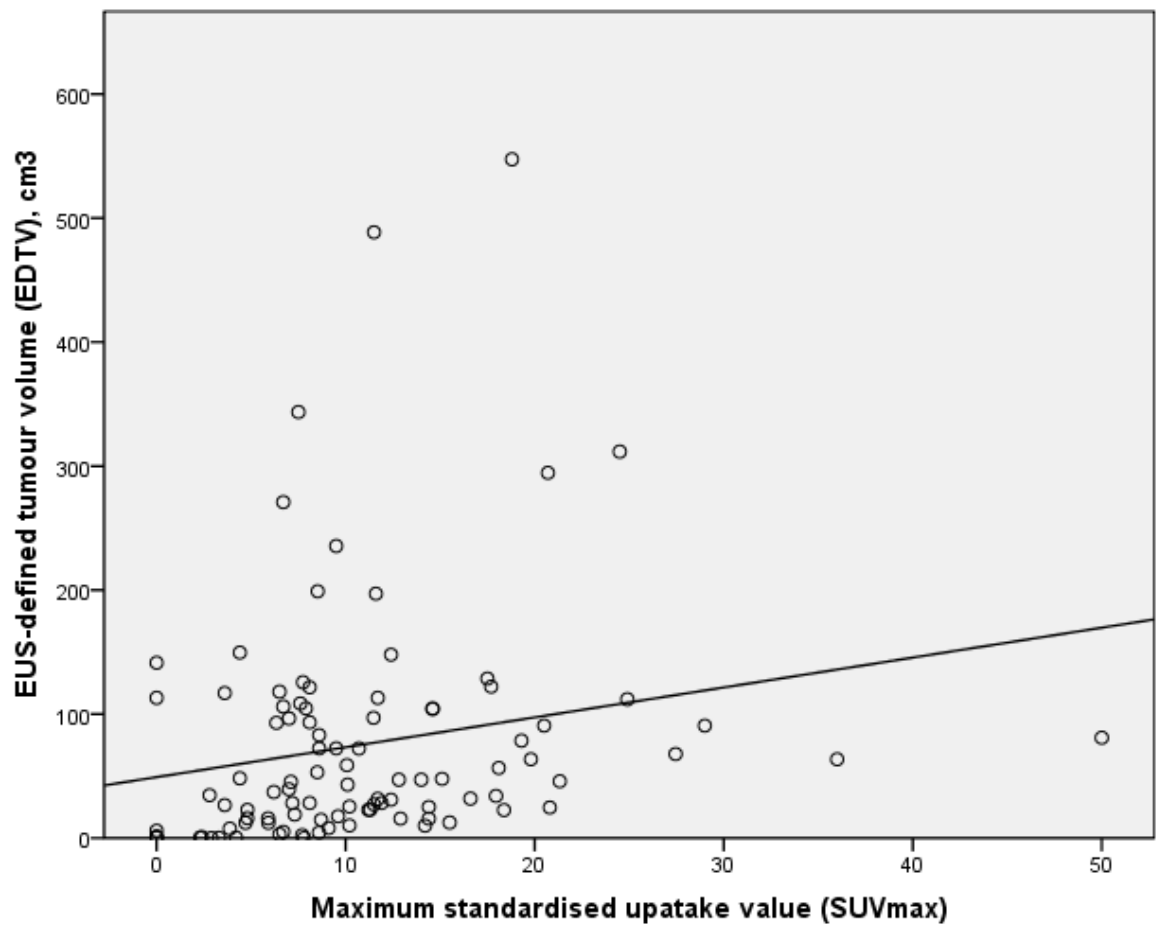
Spearman's rho = 0.339, p = 0.001

Figure 2.2   Kaplan-Meier survival plot related to SUV_{max}
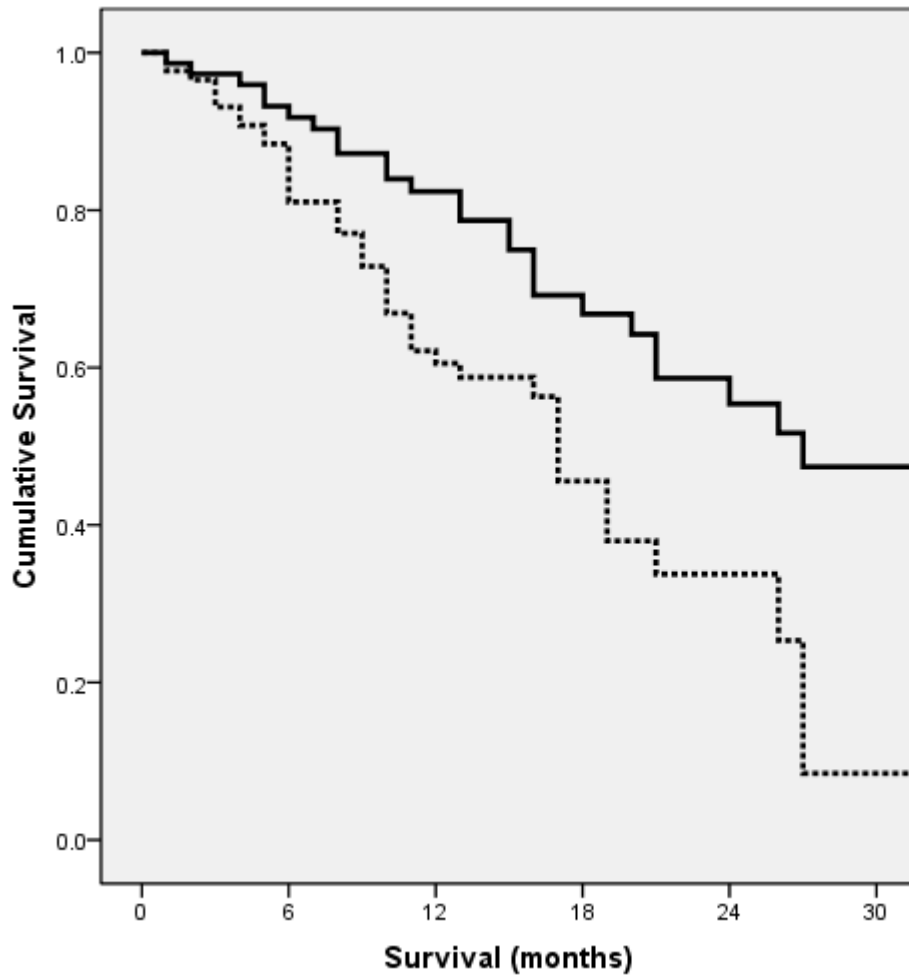
Caption

Numbers at risk

<8.9	74	67	59	49	44	35
≥8.9	87	70	52	39	30	9

———   = <8.9   ----- = ≥8.9

Log rank = 9.164, df. 1, p=0.002

Figure 2.3   Kaplan-Meier survival plot related to EDTV.
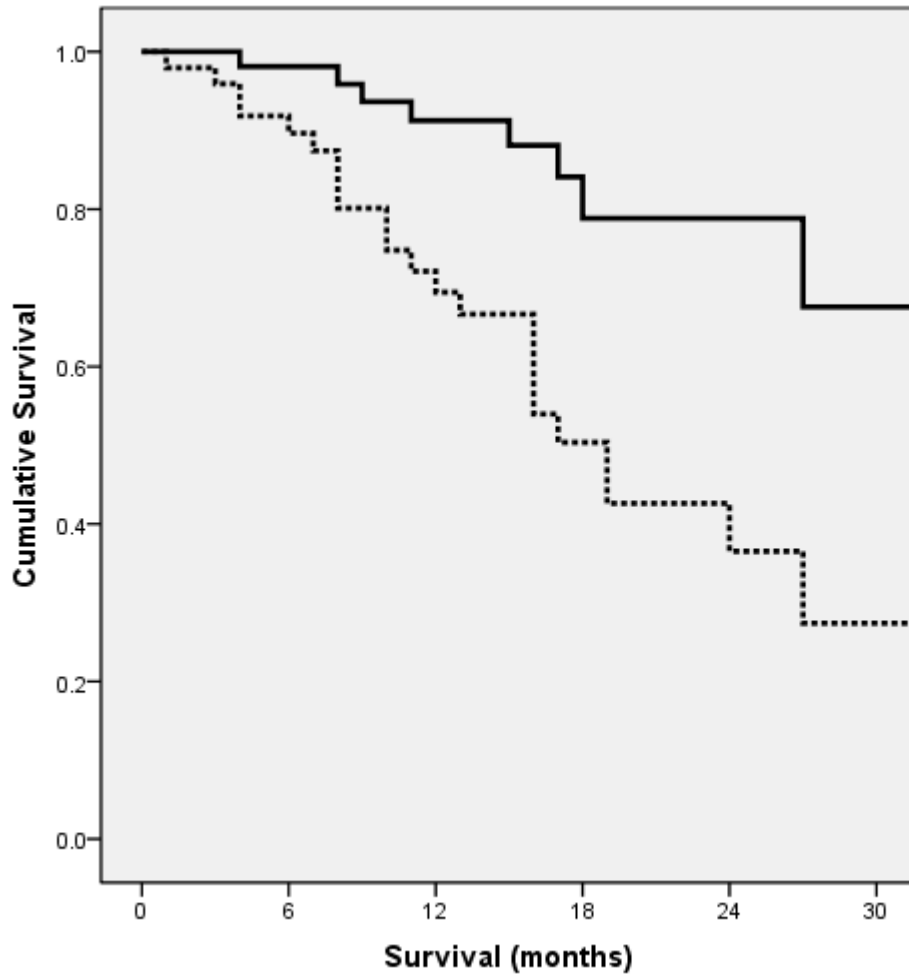
Caption

Numbers at risk

<48cm^3	54	53	49	43	43	37
≥48cm^3	49	45	34	25	18	13

——   = <48cm^3 ----- = ≥48cm^3

Log rank = 11.930, df. 1, p=0.001

Figure 2.4   Kaplan-Meier survival plot related to PET/CT N stage.
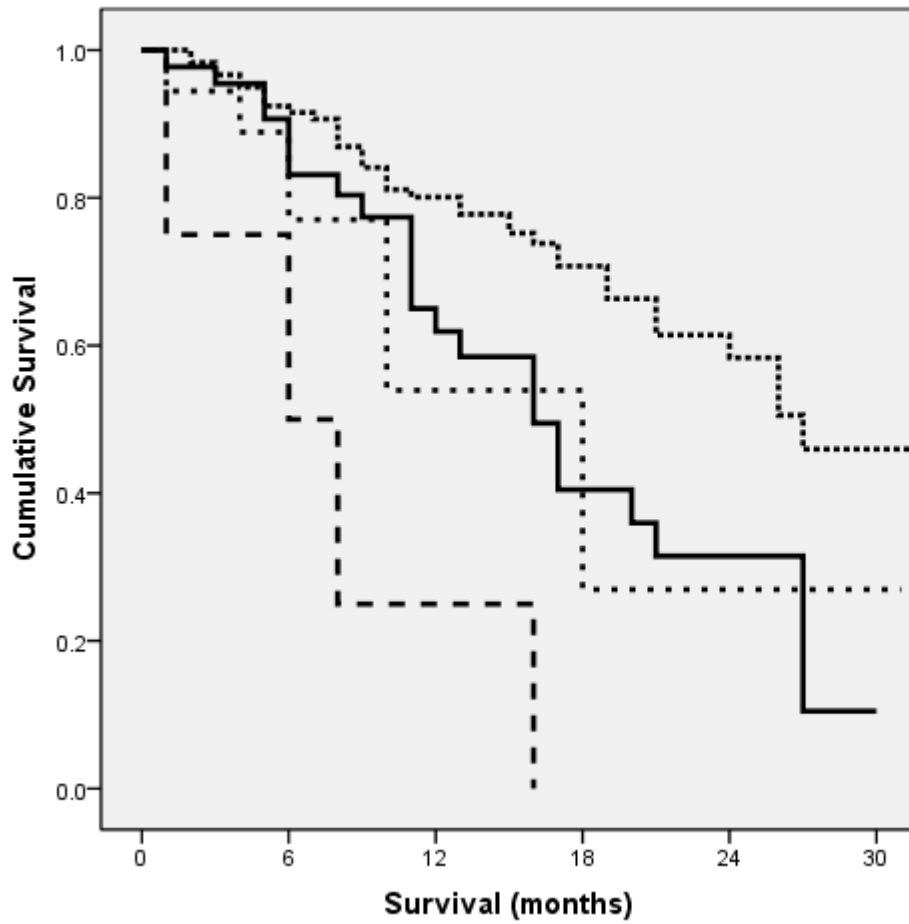
Caption

Numbers at risk

N0	119	105	74	36	19	4
N1	44	35	20	8	2	0
N2	18	14	5	1	1	0
N3	4	2	1	0	0	0

----- = N0   ——— = N1   - - - - = N2   ▬ ▬ ▬ ▬ ▬ = N3

Log rank = 24.285, df. 3, p<0.0001

2.5 DISCUSSION

This is the first study to demonstrate a positive and significant correlation between PET/CT derived SUV_{max} and EDTV, which is an independent predictor of survival in patients with oesophageal cancer. A larger SUV_{max} was associated with more advanced radiological stages of disease and poorer durations of survival on univariate analysis. In keeping with previous reports, 14% of patients (26 / 185) were up-staged after PET/CT (Allum et al. 2011; Gillies et al. 2011).

Reports on the prognostic significance of PET/CT derived SUV_{max} have been equivocal. A meta-analysis of 10 studies which included 542 patients with OC reported that a high pre-treatment SUV was predictive of poor survival (Pan et al. 2009). However, the SUV threshold in the studies ranged from 3 to 15 which were based on the median SUV. This wide range of SUV could be explained by the inclusion of patients of different stages and histological subtypes as the SUV_{max} for adenocarcinomas are significantly lower than those for squamous cell carcinomas, as expected from the inherent biological variation (Gillies et al. 2011). However, this difference in SUV_{max} was not observed in the present study.

A recent report of 121 patients with oesophageal adenocarcinoma who had received neoadjuvant chemotherapy followed by surgery reported that the presence of FDG-avid lymph nodes, but not SUV_{max} was an independent adverse prognostic indicator (Gillies et al. 2012). This could be due to the fact that patients with metastatic disease who had tumours with higher SUV_{max} were

excluded from the analysis. These patients were staged using TNM6 edition (Sobin et al. 2002) whereby the N stage was a dichotomous variable which is not as accurate at predicting prognosis when compared with TNM7 (Reid et al. 2011). Choi et al. reported a cohort study of 69 patients with oesophageal squamous cell carcinoma and demonstrated that the number of PET-positive lymph nodes was an independent predictor of survival (Choi et al. 2004). However, the number of lymph nodes in that study was not analysed as a continuous variable but rather categorised into 0, 1, 2 and ≥3 nodes, and the N stage was analysed as a dichotomous variable. Although the number of PET-positive lymph nodes when analysed as a continuous variable in this study was significant on univariate analysis, only TNM7 PET/CT defined N stage was found to be an independent predictor of survival together with EDTV.

This study had several potential limitations. The tumour volume calculated in this study was arguably an overestimate of the true disease volume as it was assumed that the tumour thickness was the same throughout the length of the tumour. However, this overestimation was potentially negated by the fact that tumour thickness in patients with suspicious lymph nodes lying beyond the maximum tumour thickness was not included in the assessment of tumour radius or diameter. Despite these limitations, EUS-defined total lengths of disease and tumour volume have been reported to be independent and significant predictors of survival (Twine et al. 2010; Davies et al. 2012). Although the EUS-defined tumour thickness was measured to the nearest millimetre, the EUS-defined

length of disease was measured to the nearest centimetre, and was therefore arguably less accurate. Another potential weakness of this study was that the PET/CT examinations were performed at two centres using different machines, protocols and uptake times. Although the SUV_{max} was not standardised between the centres, there was no significant difference in SUV_{max}. Moreover, SUV_{max} and PET/CT N stage were still predictive of survival within the pooled data on univariate analysis suggesting that these are prognostically important variables. Thirty-two patients with Siewert type III oesophagogastric junctional cancer were included because of concern regarding proximal extension of the tumour. The SUV_{max} of these patients was similar to the overall cohort and tumour site was not associated with prognosis.

Conversely, the strengths of the study are that the data was collected prospectively, from a well-defined geographical area served by an established regional upper GI network with a referral base of over 400 upper GI cancer cases per year, generating in excess of 100 potentially curative oesophagogastric resections. The study's survival and prognostic data are especially robust because no patients were lost to follow-up, and causes and exact dates of death were obtained from death certificates provided by the Office for National Statistics. Moreover, all EUS examinations and measurements were performed by three specialist clinicians with published user reliability (Bowrey et al. 1999; Weaver et al. 2004).

The accuracy and prognostic significance of various tumour characteristics determined by PET/CT including tumour length and total length of disease have yet to be determined. Moreover, PET/CT can estimate metabolic disease volume using various methods and is currently being assessed as a tool for planning treatment in oesophageal cancer (Mamede et al. 2007; Guha et al. 2008). Tumour volumes calculated by PET/CT are arguably more accurate when compared with EDTV as it follows the contours of the tumour without assuming a cylindrical volume. A prospective comparison between these two modalities and their relative prognostic significance is therefore warranted.

2.6   CONCLUSION

Despite improvements in technology, EUS remains an important part of the oesophageal cancer staging protocol, and the results of this study reinforce the need for total length of disease to be considered and included in standardised radiological EUS reports. Although SUV_{max} was not an independent predictor of survival on multivariate analysis, EDTV and PET/CT N stage, as defined by TNM7, were important prognostic indicators and further research is needed to identify critical prognostic values. This would facilitate the development of risk stratification groups which would allow targeted optimum treatment strategies.

Chapter 3

Influence of a regional centralised upper gastrointestinal cancer service

model on patient safety, quality of care and survival

3.1 SUMMARY

The aim of this study was to determine outcomes of a reconfigured centralised upper gastrointestinal (UGI) cancer service model, allied to an enhanced recovery programme, when compared with historical controls in a UK cancer network.

Details of 606 consecutive patients diagnosed with UGI cancer were collected prospectively and outcomes before (n=251) and after (n=355) centralisation compared. Primary outcome measures were rates of curative treatment intent, operative morbidity, length of hospital stay, and survival.

The rate of curative treatment intent increased from 21 to 36% after centralisation (p<0.0001). Operative morbidity (mortality) and length of hospital stay before and after centralisation were 40% (2.5%) and 16 days, compared with 45% (2.4%) and 13 days respectively (p=0.024). Median and 1 year survival (all patients) improved from 8.7 months and 39.0%, to 10.8 months and 46.8%, respectively, after centralisation (p=0.032). On multivariate analysis, age (hazard ratio (HR) 1.894, 95% CI 0.743-4.781, p<0.0001), centralisation (HR 0.809, 95%CI 0.668-0.979, p=0.03), and overall radiological TNM stage (HR 3.905, 95% CI 1.413-11.270, p<0.0001) were independently associated with survival. These outcomes confirm the patient safety, quality of care, and survival improvements achievable by compliance with NHS Improving Outcomes Guidance.

3.2   INTRODUCTION

National Health Service reconfiguration driven by Improving Outcomes Guidance has to date resulted in 41 specialist centres providing upper gastrointestinal (UGI) cancer care in England and Wales (Allum et al. 2011), and the Association of Upper Gastrointestinal Surgeons (AUGIS) has recommended that such units should consist of 4 to 6 surgeons, each performing a minimum of 15 to 20 resections per year and serving a population of 1 to 2 million (AUGIS 2011). In 2007, 19 of 31 cancer networks in England were reported to have undergone reconfiguration and centralisation (Palser et al. 2009) yet progress in Wales has received less resources and support. Indeed, the most recent audit of activity related to oesophagogastric management demonstrated that many surgeons' case loads remained small, staging strategies were idiosyncratic, operative mortality was 12%, and 2 year survival was 42% (Pye et al. 2001) after curative surgery compared with 6% and 75% in England (Sue-Ling et al. 1993).

Specialist multidisciplinary team (MDT) expertise has been reported sporadically to improve patient outcomes (Sue-Ling et al. 1993; McCulloch 1994; Stephens et al. 2006), but these hypotheses have not been tested by means of randomised control trials. Moreover, although case volume per surgeon (or unit) has also been reported to be an important factor determining short-term treatment outcomes of several cancers (Matthews et al. 1986; McCulloch 1994; Steele 1996; Swisher et al. 2000; van Lanschot et al. 2001; Bachmann et al. 2002; Birkmeyer et al. 2003; Skipworth et al. 2010; Anderson et al. 2011), data

regarding the factual impact of reconfigured centralised cancer surgery on survival is thin and often conflicting (Al-Sarira et al. 2007; Thompson et al. 2007; van de Poll-Franse et al. 2011; Boddy et al. 2012; Coupland et al. 2013).

The aim of this study was to determine the influence of a new clinical model of care comprising reconfigured centralised surgery, allied to an enhanced recovery programme, when compared with the historical control outcomes of three local hospital trusts over the previous year. The setting was a UK regional cancer network serving a population of 1.4 million.

3.3   METHODS

3.3.1 Patient selection

The South East Wales cancer network serves a population of approximately 1.4 million, and encompasses three NHS Health Boards; Cardiff and Vale University Health Board (C&V UHB, catchment population 450,000), Aneurin Bevan Local Health Board (AB LHB, catchment population 600,000) and Cwm Taf Local Health Board (CT LHB, catchment population 325,000). Together these LHBs are responsible for six acute hospitals; four district general hospitals and two teaching hospitals. Before August 2010, the surgical care of patients with oesophagogastric cancer was delivered by eight surgeons undertaking surgery at four different hospital sites. An agreement was reached in December 2009 to reconfigure and centralise the UGI surgical service on a single site at the University Hospital of Wales, Cardiff, with an agreed start date of 1 August 2010.

The new model was based on five specialist UGI surgeons carrying out all of the resectional surgery; three of the surgeons were based at the surgical centre, whereas the other two were to operate on an in-reach basis, with a facility for joint consultant operating, where necessary. Diagnosis and staging continued to be undertaken locally within each health board, co-ordinated via three local weekly MDT meetings, and all cases deemed suitable for curative treatment were discussed at a weekly regional network South East Wales MDT at Velindre hospital. Specific additional changes at the Royal Gwent Hospital, Newport, included a two-fold increased frequency of local MDT meetings from fortnightly to weekly, and the establishment of a dedicated UGI cancer outpatient clinic, serviced by one of the Cardiff-based surgeons. Integral to the new surgical model was the establishment of an enhanced recovery programme based on the established principles introduced by Kehlet and colleagues in the arena of colorectal surgery (Basse et al. 2000).

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). Pre-centralisation data across the three health boards were collected using a combination of a prospectively maintained database (for two of the three health boards; C&V and CT) in combination with MDT records and retrospective review of hospital records. Measures of outcome included postoperative morbidity and mortality, length of hospital stay and survival, one year from diagnosis. No patients were

lost to follow-up and dates and causes of death were obtained by the Wales Cancer Intelligence and Surveillance unit from the Office for National Statistics. Informed consent was obtained from all patients and ethical approval was sought from the regional ethics committee, but a formal application was deemed unnecessary.

3.3.2 Surgical treatment and neoadjuvant therapy

All patients had management plans individually tailored according to factors relating to both the patient and their disease. Staging was by means of computed tomography, endoscopic ultrasound, computed tomography positron emission tomography and staging laparoscopy as appropriate. The South East Wales MDT treatment algorithms for oesophageal and gastric cancer have been described previously (Lewis et al. 2002; Morgan et al. 2009). Operative morbidity was graded in accordance with the Dindo-Clavien classification (Dindo et al. 2004). Particular emphasis was placed on the incidence of morbidity of Dindo-Clavien grade III or higher, as this represented a complication requiring endoscopic, radiological or surgical intervention, in contrast with morbidity of lower grade requiring only pharmacological treatment. Definitive chemoradiotherapy was offered to patients with localised squamous cell carcinoma, and patients with adenocarcinoma deemed unsuitable for surgery because of disease extent and/or medical co-morbidity (Gwynne et al. 2011; Gwynne et al. 2013)

3.3.3   Data analysis

Grouped data were expressed as median (range) and non-parametric statistical methods were used. Continuous data were compared using the Mann Whitney test and categorical data using the Chi Square test and Fisher's exact test when number of events was low. StataCorp LP was used to analyse the survival information. A nonparametric two-sample test on the equality of medians was carried out. This tested the null hypothesis that pre-centralisation and post-centralisation patients were drawn from populations with the same median. A Log-rank test was performed to determine the equality of the survivor functions. Proportional hazard plots were created and Schoenfeld residuals were calculated to confirm that the proportional hazard assumption was appropriate for overall survival. Differences were deemed to be statistically significant when the p value was less than 0.05.

3.4   RESULTS

The global caseloads of UGI cancer presenting to the regional MDTs were 251 and 355 patients for the years before and after centralisation, respectively. Table 3.1 shows the demographic details and treatment of the patients. There were 153 and 189 deaths at one year before, and after centralisation respectively. All patients were followed-up for at least one year or until death. The median follow-up for all patients and patients who remained alive were 9.8 and 23 months respectively.

3.4.1 Details of the treatment

Treatment intent was potentially curative in 54 (21%) and 127 (36%) patients before and after centralisation respectively (Chi^2=14.91, DF=1, p<0.0001), of whom 40 and 85 patients underwent surgery. Of those patients treated surgically, 19 and 33 underwent oesophagectomy, and 14 and 38 underwent gastrectomy before and after centralisation respectively. The rates of open and close laparotomy were similar at 7 (18%) and 14 (16%) before and after centralisation respectively (Chi^2=0.063, DF=1, p=0.801). The number of patients undergoing palliative chemotherapy increased from 84 (43%) to 135 (59%) (Chi^2=11.62, DF=1, p=0.001)

3.4.2 Operative Morbidity and Mortality

Short term surgical outcomes and duration of hospital stay data are presented in Table 3.2. The cause of the in-hospital death before centralisation was myocardial infarction following total gastrectomy. The causes of the two in-hospital deaths after centralisation were multi-organ failure secondary to conduit necrosis following trans-thoracic oesophagectomy, and intra-abdominal sepsis following subtotal gastrectomy. Morbidity is presented related to Dindo-Clavien classification. There were non-significant 50% reductions in the incidence of serious (Dindo-Clavien ≥ III) morbidity for all the surgical patients. Anastomotic leaks occurred in two (5.0%) and six (7.1%) of patients before and after centralisation, respectively.

3.4.3 Duration of hospital stay

Centralisation was associated with a significant reduction in intensive therapy unit (ITU), (p<0.0001) and critical care (p=0.002) lengths of stay for all patients. The median overall length of hospital stay was shortened by three days (p=0.024). The 30-day hospital re-admission rates were 5.1% (n=2) and 11.8% (n=10) before and after centralisation, respectively (p=0.275). Of the 10 patients who were re-admitted after centralisation (pneumonia = 3; intra-abdominal collection = 2; dysphagia = 1; thoracic incisional hernia = 1; wound infection = 1; chyle leak = 1; pancreatitis = 1), six were from AB LHB, one of whom had to be readmitted to the University Hospital of Wales for conservative management of a chyle leak. The remaining five patients were admitted to their local district general hospitals for medical management.

3.4.4 Duration of overall survival

Centralisation was associated with a significant increase in overall median and one year survival in all patients, 8.7 versus 10.8 months (p=0.011) and 39.0% versus 46.8%, respectively (Figure 3.1). In patients with oesophageal and gastric cancer, the median and one year survival was higher following centralisation although this was not statistically significant [oesophageal cancer: 8.7 versus 10.3 months, 38.9% versus 44.0%, p=0.139; gastric cancer: 7.7 versus 12.5 months, 39.3% versus 51.1%, p=0.065).

3.4.5 Factors influencing overall survival

The univariate analysis of factors influencing overall survival is shown in Table 3.3. All factors found to be significant on univariate analysis were included in the multivariate analysis. Backward elimination stepwise regression was carried out to determine the best model, and as treatment intent was no longer significant it was excluded from the final model (Table 3.4).

3.4.6 Caseload

After centralisation, the proportion of operations performed with a team of two consultants increased from 2.5% (1/40), to 59% (50/85) (Chi^2=28.26, DF=1, p<0.0001). This led to an increase in the median number of operations performed per surgeon from four (2-11) to 23 (16-31) (p<0.0001).

3.4.7 Access to the designated surgical centre

Patient satisfaction was assessed and feedback obtained from 85 patients who had surgery after centralisation via a postal questionnaire three months after surgery. The response rate was 68% (58/85, 18 from C&V, 23 from AB and 17 from CT). Overall patient satisfaction was assessed using a Likert scale from 0 (least satisfied) to 10 (most satisfied), and the median satisfaction score was 9.6 (5-10). Forty-six patients (79.3%) were content to travel for treatment at the designated treatment centre at the University Hospital of Wales, Cardiff. Of the 12 patients who cited access difficulties, six (50%) were from CT, five (41.7%) from AB, and one (8.3%) from C&V.

Table 3.1 Demographic details and treatment of the patients pre- and post-centralisation

	Pre-centralisation	Post-centralisation	p-value
Total	251	355	
Median age (range), yrs	74 (32-97)	71 (33-95)	0.007
Male:Female	166:85 (66:34)	231:124 (65:35)	0.813
Oesophageal:Gastric	139:112 (56:44)	216:139 (61:39)	0.197
Radiological Stage I	26 (10)	34 (10)	0.973
II	40 (16)	53 (15)	
III	78 (31)	107 (30)	
IV	97 (39)	144 (40)	
Not staged	10 (4)	17 (5)	
Curative:Palliative treatment			
Total	54:197 (21:79)	127:228 (36:64)	<0.0001
Oesophageal	33:106 (24:76)	76:140 (35:65)	0.023
Gastric	21:91 (18:82)	51:88 (37:63)	0.002
dCRT	12 (5)	32 (9)	0.056
Neochemo	17 (43)	48 (56)	0.351
Surgery	40 (16)	85 (24)	0.005
Palliative chemotherapy	84 (43)	135 (59)	0.001

Figures are numbers (%). Neochemo – neoadjuvant chemotherapy, dCRT – Definitive chemoradiotherapy

Table 3.2 Short-term surgical outcomes

	Pre-centralisation	Post-centralisation	p value
Number	40	85	
Morbidity and mortality			
All morbidity	16 (40)	38 (45)	0.681
Morbidity of Dindo-Clavien Grade≥III	10 (25)	10 (12)	0.0062
30 day mortality	1 (2.5)	1 (1.2)	
In-hospital mortality	1 (2.5)	2 (2.4)	
Length of stay			
ITU stay	0 (0-70)	0 (0-12)	<0.0001
HDU stay	1 (0-11)	1 (0-9)	0.043
Critical care stay	2 (0-70)	1 (0-20)	0.002
Total hospital stay	16 (2-72)	13 (3-49)	0.024

Figures are numbers (%). Lengths of stay are median in days (range)

Table 3.3 Univariate analysis of factors associated with overall survival

Factor	Hazard Ratio	95% CI	p value
Age ≤50			
Age 51-60	1.1867	0.7094-1.9852	0.514
Age 61-70	1.4361	0.9024-2.2854	0.127
Age 71-80	1.503	0.9498-2.3787	0.082
Age >80	2.5113	1.5834-4.0053	<0.0001
Pre-centralisation	1.0000		
Post-centralisation	0.7851	0.6506-0.9474	0.012
CT Stage 1	1.0000		
CT Stage 2	2.4182	1.4015-4.1722	0.002
CT Stage 3	3.7373	2.2532-6.1989	<0.0001
CT Stage 4	7.9656	4.8451-13.0958	<0.0001
Non curative	1.0000		
Curative	0.1821	0.1396-0.2376	<0.0001

Table 3.4 Multivariate analysis of factors associated with overall survival

Factor	Hazard Ratio	95% CI	p-value
Age ≤50	1.0000		
Age 51-60	1.2488	0.743-2.100	0.402
Age 61-70	1.4816	0.929-2.363	0.099
Age 71-80	1.8944	1.193-3.009	0.007
Age >80	2.9749	1.851-4.781	<0.0001
Pre-centralisation	1.0000		
Post-centralisation	0.8090	0.668-0.979	0.030
rTNM Stage I	1.0000		
rTNM Stage II	2.4384	1.413-4.207	0.001
rTNM Stage III	3.9051	2.353-6.480	<0.0001
rTNM Stage IV	8.8962	5.403-14.647	<0.0001

rTNM – Radiological overall TNM Stage

Figure 3.1 Kaplan-Meier survival plot related to centralisation
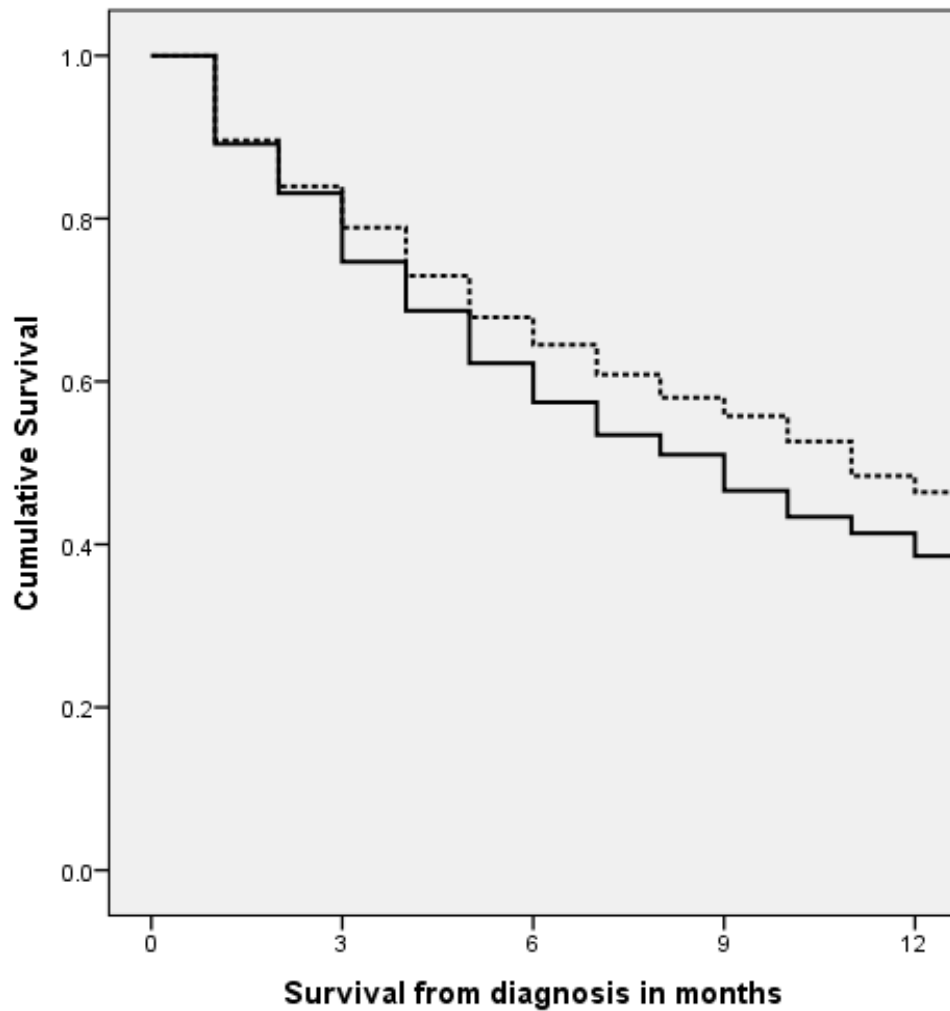
Numbers at risk

Time (months)

	0	3	6	9	12
Pre	251	199	151	120	98
Post	355	289	235	200	166

Log-rank test for equality of survivor functions:

$Chi^2 = 6.41$ p value = 0.0113

_____   Pre-centralisation   - - - - - -   Post-centralisation

3.5   DISCUSSION

UGI cancer service development and configuration in the UK remains controversial and opinion polarised. The principal findings of this study were that centralisation was feasible and safe. The curative to palliative treatment ratio increased by 71%, operative morbidity fell 50%, lengths of hospital stay reduced on average by three days, median survival improved by 20%, and overall one year survival improved by nearly 20%.

The strengths of this study are that it represents, by some margin, the largest of very few UK reports regarding UGI cancer service centralisation, relating to 606 consecutive patients presenting to a single UK regional cancer network. Data were collected prospectively at all local and regional MDT meetings over a period of two years; data on readmission to hospital was complete, survival data is particularly robust because no patients were lost to follow up, and death certification was obtained from the Office of National Statistics. At the time of writing, only three other UK centres have reported their experience of centralising oesophagogastric cancer surgery. Branagan and Davies reported outcomes from the Wessex region in 2004. Although the number of patients treated was relatively modest, operative mortality decreased significantly from 15.2% to zero (5 of 33 versus 0 of 40, p=0.022), pathology reports improved, and mean lymph node harvest increased from 19 to 30.5 after centralisation (Branagan et al. 2004). Forshaw *et. al.* reported a larger experience of oesophagogastric resection from a high volume unit in London (Forshaw et al. 2006). Thirty day

mortality was 0.5% and one year survival was 78%, without detrimental effect on the benign elective workload. The findings of this study are in keeping with the above in terms of cancer management, although with 65% of theatre capacity used wholly or in part for cancer surgery, there will arguably have been an associated impact on the benign UGI work stream. More recently, Boddy *et. al.* reported an improved median survival after centralisation in Gloucestershire in 2006 (Boddy et al. 2012). However, this improvement was only observed after oesophagectomy, and the study was retrospective in nature without detailed follow-up data.

In contrast, the study has a number of potential limitations. The data related to surgical outcomes in historical control patients was collected retrospectively from one hospital site (40%, 16/40), and arguably may be less robust than that collected prospectively the following year, as the value of retrospective case note review depends on accurate contemporaneous documentation at presentation. However, this is mitigated by two factors; first, data were collected prospectively on all patients undergoing surgery before centralisation from two of the three health boards (60%, 24/40); second computerised digital records at the remaining health board recorded all radiological and pathological test results, operation notes, and discharge documentation. It is therefore unlikely that major errors existed related to outcomes and in particular hospital length of stay. The rise in the number of patients following centralisation may arguably be due to more accurate prospective data capture, allied to a detailed reconfigured service

evaluation that included a dedicated research fellow in attendance at all local and regional MDT meetings. Before centralisation, it is possible that some equivocal palliative cases may have bypassed MDT discussion, as MDT meetings in one LHB were held less frequently (fortnightly). Definition of the case subjects and of the controls is critical in determining outcomes and subsequent conclusions, and in this study centralisation inception after on August 1st 2010 was chosen. In 2009 and 2010, the same five surgeons were in surgical practice on two hospital sites, but without guaranteed consultant colleague support in theatre to facilitate team operating. Two surgeons from AB LHB chose not to take part in the reconfigured model and relinquished MDT participation. Moreover, the improved outcomes cannot be explained by poorer than average results in our historical control group, as outcomes in the year prior to centralisation were comparable with those reported in the national (NOGCA 2011).

The exact explicit reason for the improved outcomes witnessed remains uncertain. The probable answer lies in a combination of small incremental improvements in service, such as the increased frequency of local MDT meetings, increased caseload, single centre surgery by teams of surgeons, allied to the benefits associated with an enhanced recovery programme, and akin to those described in lower gastrointestinal surgical models. Certainly, there is a wealth of evidence in support of case volume outcome interactions from international population based studies (Matthews et al. 1986; Swisher et al. 2000; van Lanschot et al. 2001; Bachmann et al. 2002; Birkmeyer et al. 2003;

Birkmeyer et al. 2007; Skipworth et al. 2010; Anderson et al. 2011; van de Poll-Franse et al. 2011), and more recently data from the Netherlands has reported that the type of hospital in which oesophagogastric resectional surgery is carried out influences outcomes (Dikken et al. 2012). These benefits must be weighed against potential disadvantages, such as downgrading district general hospital surgical assets (Dickson et al. 2001), and little evidence of survival benefit associated with individual surgeon caseload (Gillison et al. 2002; Thompson et al. 2007), or surgical centralisation (Birkmeyer et al. 2007). The findings of this study have shown that serving a population of 1.4 million generated an annual caseload of 85 potentially curative resections for five surgeons. The median number of operations performed by the individual surgeons over the year concerned increased five-fold from four to 23, with 56% performed by consultant teams of two.

Patient access to services is crucial, and frequently the focus of the most intense political pressure during any health service reconfiguration. In South East Wales the new service resulted in longer distances of travel to hospital for a proportion of patients, specifically 17 patients from CT LHB, and 23 patients from AB LHB. Of these, 11 (27.5%) cited access difficulties (five from AB, and six from CT). However, before centralisation, patients often travelled to a specified surgical centre within their LHB for surgery, and therefore in most cases the additional distance were relatively small, and diagnosis and radiological staging continued locally for all. Allied to this issue is the rate of hospital re-admissions which

occurred in 10 patients after centralisation, six of whom resided in the catchment areas of the outreach hospitals (AB LHB). However, only one patient of the six required readmission to the cancer centre and did not report access difficulties. Nevertheless, the hospital readmission rate doubled following centralisation, and although not statistically significant, will necessitate continued future audit. Arguably this finding may be due to the intense scrutiny, and enhanced follow-up protocols to which the reconfigured service was subject, allied to prospective data collection by a dedicated research fellow.

3.6   CONCLUSION

Although not a randomised control trial, the results of this study clearly demonstrate unequivocally what can be achieved by contemporary specialist care in a UK regional cancer network, and highlights the impact of an enhanced reconfigured and centralised service model on UGI cancer outcomes. A hybrid centralised clinical model of care allied to an enhanced recovery after surgery programme were introduced safely and effectively. This model increased the proportion of patients receiving potentially curative treatment, reduced serious operative morbidity, shortened total length of hospital stay, and improved survival, all by significant margins. Further long-term follow-up for five years is desirable and necessary to appreciate the full spectrum and magnitude of the patient safety, quality, and survival improvements achievable by reconfiguring regional UGI cancer services.

Chapter 4

Systematic review and meta-analysis of the influence of human epidermal growth factor receptor-2 (HER2) in patients with operable oesophageal cancer

4.1 Summary

The prognostic significance of human epidermal growth factor 2 (HER2) overexpression in patients diagnosed with oesophageal cancer is controversial. A systematic review and meta-analysis was performed to determine the influence of HER2 overexpression and amplification on outcomes in operable oesophageal cancer .

MEDLINE and Embase (January 1990 to November 2011) was searched for translational studies that correlated HER2 expression with survival in operable oesophageal cancer. Fourteen studies involving 1464 patients who had undergone potentially curative oesophagectomy for oesophageal cancer [322 (22%) HER2 positive] were included. Five year mortality was significantly higher in HER2 positive patients [odds ratio (OR) 1.43, 95% confidence interval (CI) 1.01-1.95, p=0.03]. Analysis related to histological cell type demonstrated significantly higher 5 year mortality in HER2 positive squamous cell carcinoma [OR 2.88, 95% CI 1.34-6.17, p=0.006] and adenocarcinoma [OR 1.91, 95% CI 1.15-3.17, p=0.01] on sensitivity analysis of higher quality studies. HER2 overexpression and gene amplification in operable oesophageal cancer was an indicator of poor prognosis.

4.2 INTRODUCTION

Each year, 462,000 people are diagnosed worldwide with oesophageal cancer resulting in 386,000 deaths (Parkin et al. 2005). The optimal contemporary treatment is controversial and opinion divided. In the UK, following the publication of the MRC OEO2 trial, neoadjuvant chemotherapy followed by surgery is the standard of care for patients with operable oesophageal cancer (MRC Oesophageal Cancer Working Group 2002), whereas neoadjuvant chemoradiotherapy followed by surgery is the preferred modality in Europe and the United States (Ilson 2008). However, overall survival reports remain poor and no established global standard for treatment exists. New therapies which target specific genetic alterations arguably offer the best chance for improving patient survival.

The human epidermal growth factor receptor 2 (HER2) gene is a proto-oncogene which is located on chromosome 17q11.2-12 and encodes a transmembrane tyrosine kinase receptor which is responsible for cell growth, differentiation, migration and apoptosis (Normanno et al. 2005). HER2 is involved in the development of numerous types of cancer such as breast, ovarian, pancreatic and is overexpressed in up to 20% of gastric cancer patients, conferring a poor prognosis (Slamon et al. 1987). However, reports on the influence of HER2 overexpression in patients with oesophageal cancer have been equivocal. The aim of this study therefore was to perform a systematic review and meta-analysis

of the influence of HER2 overexpression on outcomes in patients diagnosed with oesophageal cancer.

4.3   METHODS

4.3.1 Literature search strategy

A systematic review of published work was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009). A computerised search of MEDLINE was performed via PubMed and Embase from January 1990 to November 2011 using the MeSH subject headings: oesophageal neoplasm and human epidermal growth factor receptor 2 or HER2 or Neu or HER-2 or c-erbB-2 or c-erbB2 or erbB2 or CD340 or p185 to identify studies investigating the influence of HER2 protein overexpression or gene amplification on survival in patients with oesophageal cancer. The searches were limited to human articles published in the English language. Further articles were identified by hand searching reference lists of all articles retrieved to identify potentially relevant studies. Searches were cross-referenced on PubMed using the related articles function. The last search date was 1 November 2011.

4.3.2 Data extraction

Data were extracted independently using a standard protocol. The following information was extracted from each study: first author, year of publication, study design, number of subjects in each group (HER2+ and HER2-), histological

subtype (adenocarcinoma or squamous cell carcinoma), use of neoadjuvant chemotherapy and or chemoradiotherapy, method of identifying HER2 expression or gene amplification, quality of study (see below) and outcome measures (all-cause mortality).

4.3.3 Inclusion and exclusion criteria

Translational studies comparing overall survival outcomes in patients with operable oesophageal cancer with and without HER2 overexpression or gene amplification were included. When there were multiple articles by the same authors analysing data from the same or similar patient group, the most recent publication was included. Review articles, case reports, experimental studies and studies that did not report outcomes were excluded. Unpublished data from conference abstracts were excluded.

4.3.4 Statistical analysis

The meta-analysis was performed in line with the recommendations from the Cochrane Collaboration and PRISMA guidelines (Moher et al. 2009) using Review Manager 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Statistical analysis of dichotomous variables were carried out using odds ratio (OR) as the summary statistic. Random-effects models were used and were reported with 95% confidence intervals (CI). ORs represent the odds of death during the study interval in a patient who was HER2 positive compared with a patient who was HER2 negative. An OR of less than 1

favoured patients who were HER2 negative and the point estimate of the OR was considered significant at the p<0.05 level if the 95% CI did not include the value 1.

4.3.5 Heterogeneity

The quality of non-randomised studies was assessed using the Newcastle-Ottawa scale (Higgins JPT 2009) which examines patient selection methods, comparability of study groups and assessment of outcome. A score of at least 7 stars from a maximum of 9 were considered to be of higher quality. Heterogeneity was assessed by sensitivity analysis, which was undertaken using the subgroup studies of higher quality and those reporting outcomes on more than 100 patients. The I^2 value was reported for each analysis.

4.3.6 Publication bias

Funnel plots were used to assess bias (Egger et al. 1998). Funnel plot asymmetry implied that results were subject to reporting or publication bias, whereas symmetry implied a lack of bias.

4.4 RESULTS

The full text of 37 papers were obtained of which 14 were cohort studies which fulfilled the criteria for review (Figure 4.1). Analysis was carried out on 1464 patients (1149 males, 315 females) who had undergone potentially curative oesophagectomy for oesophageal (1221, 83%) and oesophagogastric junctional

cancer (243, 17%). Three hundred and twenty-two patients (22%) were HER2 positive and 1142 were HER2 negative.

Figure 4.1   Identification process for eligible studies

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┌─────────────────────────────┐  ┌─────────────────────────────┐
│ Records identified through  │  │ Records identified through  │
│    database searching       │  │        other sources        │
│         (n=93)              │  │ (n=44: all from references) │
└─────────────────────────────┘  └─────────────────────────────┘
              │                               │
              ▼                               ▼
        ┌───────────────────────────────────────────┐
        │    Records after duplicates removed        │
        │                (n=88)                      │
        └───────────────────────────────────────────┘
                            │
                            ▼
        ┌───────────────────────────────────────────┐
        │       Records screened by abstract         │
        │                (n=88)                      │
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                            │────────────────▶│   Records excluded      │
                            │                 │        (n=51)           │
                            ▼                 └─────────────────────────┘
        ┌───────────────────────────────────────────┐
        │      Full text assessed for eligibility    │
        │                (n=37)                      │
        └───────────────────────────────────────────┘
                            │            ┌──────────────────────────────┐
                            │            │ Records excluded (n=23)      │
                            │───────────▶│ 7 reviews                    │
                            │            │ 16 not meeting inclusion     │
                            │            │ criteria                     │
                            ▼            └──────────────────────────────┘
        ┌───────────────────────────────────────────┐
        │      Studies included in meta-analysis     │
        │                (n=14)                      │
        └───────────────────────────────────────────┘
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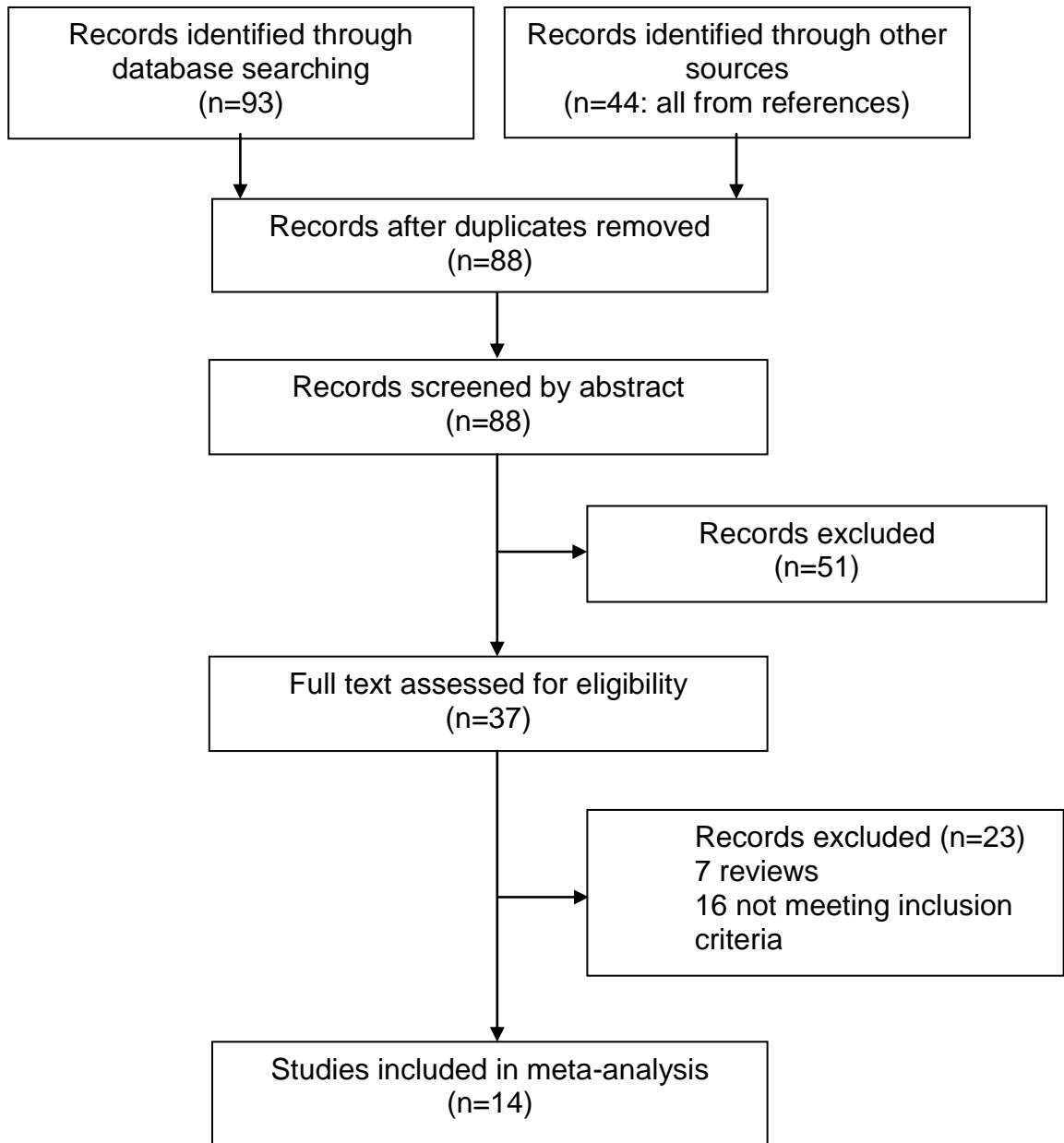
4.4.1 Characteristics of included studies

All studies included were retrospective cohort studies except for one which was a prospective cohort study (Stoecklein et al. 2008). Table 4.1 summarizes the study characteristics. Seven studies were of high quality (Nakamura et al. 1994; Polkowski et al. 1999; Brien et al. 2000; Stoecklein et al. 2008; Hu et al. 2011; Langer et al. 2011; Thompson et al. 2011). Two studies investigated patients with oesophageal squamous cell carcinoma only (Mimura et al. 2005; Sato-Kuwabara et al. 2009) and eight studies with oesophageal adenocarcinoma (Flejou et al. 1994; Nakamura et al. 1994; Duhaylongsod et al. 1995; Polkowski et al. 1999; Brien et al. 2000; Hu et al. 2011; Langer et al. 2011; Thompson et al. 2011). Four studies included both histological types (Hardwick et al. 1997; Friess et al. 1999; Reichelt et al. 2007; Stoecklein et al. 2008) of which three (Hardwick et al. 1997; Friess et al. 1999; Stoecklein et al. 2008) did not have separate outcomes for adenocarcinoma and squamous cell carcinoma. Ten studies included only oesophageal tumours and four studies also included oesophagogastric junctional tumours (Duhaylongsod et al. 1995; Hardwick et al. 1997; Polkowski et al. 1999; Thompson et al. 2011). Survival data for individual tumour sites were not available in those studies. Only one study included patients who had undergone neoadjuvant chemoradiotherapy (Duhaylongsod et al. 1995). Details of stage of disease in HER2 positive and negative patients were described in all but four studies (Duhaylongsod et al. 1995; Hardwick et al. 1997; Polkowski et al. 1999; Hu et al. 2011). The stage of disease was similar in both groups of patients in all studies except for Nakamura et al (Nakamura et al. 1994). HER2 positive patients

77

in that study had a significantly higher proportion of stage IV disease compared with HER2 negative patients. However, a correction was applied in the multivariate analysis, and HER2 overexpression was an independent predictor of poor survival (Nakamura et al. 1994).

4.4.2 Method of evaluation HER2 status

Immunohistochemistry (IHC) and in-situ hybridisation (ISH) were used to determine HER2 overexpression and gene amplification in six (Flejou et al. 1994; Nakamura et al. 1994; Duhaylongsod et al. 1995; Hardwick et al. 1997; Friess et al. 1999; Polkowski et al. 1999) and five (Brien et al. 2000; Reichelt et al. 2007; Stoecklein et al. 2008; Hu et al. 2011; Thompson et al. 2011) studies, respectively. Three studies (Mimura et al. 2005; Sato-Kuwabara et al. 2009; Langer et al. 2011) used both methods for determining HER2 status. HER2 positive status was defined using various cut-offs (Table 4.1). HER2 overexpression was defined according to the intensity of membrane staining [≥+2 (Nakamura et al. 1994; Friess et al. 1999) and +3 (Sato-Kuwabara et al. 2009; Langer et al. 2011)]. HER2 gene amplification was defined as a HER2/chromosome 17 ratio of greater than 2 (Sato-Kuwabara et al. 2009; Langer et al. 2011), 2.2 (Thompson et al. 2011) and 3 (Reichelt et al. 2007). Two studies had a lower threshold for defining HER2 positivity. Flejou (1994) included all patients with any level membrane staining and Polkowski (1999) included patients who had membrane staining in at least 5% of tumor cells. HER2 positivity ranged from 9 to 64%.

4.4.3 Short- and long-term survival related to HER2 status

Seven studies reported a significantly poorer survival in patients who were HER2 positive (Flejou et al. 1994; Nakamura et al. 1994; Polkowski et al. 1999; Brien et al. 2000; Mimura et al. 2005; Sato-Kuwabara et al. 2009; Langer et al. 2011). Six studies reported no difference in survival of patients who were HER2 positive or negative (Hardwick et al. 1997; Friess et al. 1999; Reichelt et al. 2007; Stoecklein et al. 2008; Hu et al. 2011; Thompson et al. 2011). One study reported a higher survival in patients who were HER2 positive (Duhaylongsod et al. 1995). One, two and five-year survival rates were available in all studies except for two studies which did not report five-year survival (Friess et al. 1999; Polkowski et al. 1999).

4.4.4 Survival in all patients

In the meta-analysis of all studies, there was a significantly higher 5 year mortality rate in patients who were HER2 positive compared with patients who were HER2 negative whereas 1 and 2 year mortality rates were not significantly different. Sensitivity analysis of higher quality studies and studies with over 100 patients were similar to the overall analysis. Heterogeneity between studies of all patients was significant at 1, 2 and 5 years (Table 4.2 and Figure 4.2).

4.4.5 Survival in patients with adenocarcinoma

In the analysis of all studies, there was no significant difference in survival in patients diagnosed with HER2 positive adenocarcinoma compared to those who were HER2 negative. However, sensitivity analysis of higher quality studies and

studies with over 100 patients with adenocarcinoma confirmed the poorer survival rate in HER2 positive patients (Table 4.3 and Figure 4.3). Heterogeneity between studies of all patients with adenocarcinoma at 5 years was significant (I^2 = 73%, p=0.0005). The influence of HER2 overexpression and amplification was greater when studies which only included oesophageal tumours (excluding junctional tumours) were analysed [OR 2.37, 95% CI (1.59-3.54), p<0.0001]. Heterogeneity of these studies was not significant (I^2 = 41%, p=0.009).

4.4.6 Survival in patients with squamous cell carcinoma

The influence of HER2 positivity was greater in patients with squamous cell carcinoma (Table 4.4 and Figure 4.4) compared to patients with adenocarcinoma. Sensitivity analysis of studies involving patients with squamous cell carcinoma was not performed due to the small number of studies. There was no heterogeneity between studies of patients at 5 years (I^2 = 0%, p=0.52).

4.4.7 Publication bias

The funnel plots for 5 year mortality rate lacked symmetry for all studies, which was reflected in the observed heterogeneity (p=0.0002), and may represent publication bias. However, the number of studies included (>100 patients) was less than 10, making the funnel plot difficult to interpret (Parmar et al. 1998). The funnel plots for 5 year mortality rate was asymmetrical for studies of patients with adenocarcinoma (heterogeneity p=0.0005) although it was symmetrical for studies of patients with squamous cell carcinoma (heterogeneity p=0.52).

Table 4.1 Characteristics of studies included in the meta-analysis

First author (year)	Test	Classification of HER2+ status	Total number	HER2+ (%)	Survival related to HER2+	Study quality score
Brien (2000)	ISH	Average number of HER2 signals	63	12 (19)	Worse	7
Duhaylongsod (1995)	IHC	N/A	42	18 (43)	Better	6
Flejou (1994)	IHC	'Membrane staining'	66	7 (11)	Worse	5
Friess (1999)	IHC	≥ +2	39	25 (64)	No difference	6
Hardwick (1997)	IHC	≥ 10 % of cells	205	49 (24)	No difference	6
Hu (2011)	ISH	>10 % of cells	116	21 (18)	No difference	7
Langer (2011)	Both	+3 and Ratio ≥ 2	142	41 (29)	Worse	8
Mimura (2005)	Both	≥ +2	66	9 (14)	Worse	6
Nakamura (1994)	IHC	≥ +2	62	8 (13)	Worse	7
Polkowski (1999)	IHC	≥ 5 % of cells	33	9 (27)	Worse	7
Reichlt (2007)	ISH	Ratio > 3	255	23 (9)	No difference	6
Sato-Kuwabara (2009)	Both	+3 and Ratio > 2	185	68 (37)	Worse	6
Stoecklein (2008)	ISH	≥ 1 tumour cell with 'HER2 gain'	101	18 (18)	No difference	8
Thompson (2011)	ISH	Ratio > 2.2	89	14 (16)	No difference	7

Table 4.2 Meta-analysis of the influence of HER2 overexpression/amplification on mortality in patients with oeosphageal carcinoma

Outcome	No. of studies	HER2 +	HER2 -	OR (95% CI)	Overall effect Z	p value	HG I^2 (%)	HG p value
All studies								
1 year all cause mortality	14	322	1142	0.98 (0.72-1.32)	0.16	0.88	61	0.001
2 year all cause mortality	14	322	1142	1.01 (0.78-1.31)	0.09	0.92	68	0.0001
5 year all cause mortality	12	288	1104	1.43 (1.04-1.95)	2.23	0.03	69	0.0002
High quality studies								
1 year all cause mortality	7	123	483	1.06 (0.68-1.67)	0.27	0.79	62	0.02
2 year all cause mortality	7	123	483	1.41 (0.94-2.11)	1.64	0.100	68	0.004
5 year all cause mortality	6	114	459	1.90 (1.18-3.05)	2.65	0.008	72	0.003
Studies with >100 patients								
1 year all cause mortality	6	220	784	0.95 (0.64-1.39)	0.28	0.78	50	0.08
2 year all cause mortality	6	220	784	0.90 (0.66-1.22)	0.69	0.49	44	0.11
5 year all cause mortality	6	220	784	1.52 (1.05-2.20)	2.20	0.03	65	0.01

Table 4.3 Meta-analysis of the influence of HER2 overexpression/amplification on mortality in patients with oesophageal adenocarcinoma

Outcome	No. of studies	HER2 +	HER2 -	OR (95% CI)	Overall effect Z	p value	HG I^2 (%)	HG p value
All studies								
1 year all cause mortality	9	146	573	1.03 (0.69-1.54)	0.15	0.88	65	0.004
2 year all cause mortality	9	146	573	1.21 (0.84-1.75)	1.01	0.31	75	<0.0001
5 year all cause mortality	8	137	549	1.33 (0.89-2.00)	1.38	0.17	73	0.0005
High quality studies								
1 year all cause mortality	6	105	400	1.17 (0.72-1.88)	0.63	0.53	64	0.02
2 year all cause mortality	6	105	400	1.64 (1.05-2.57)	2.17	0.003	70	0.005
5 year all cause mortality	5	96	376	1.91 (1.15-3.17)	2.50	0.01	78	0.001
Studies with >100 patients								
1 year all cause mortality	3	78	286	0.85 (0.47-1.53)	0.55	0.58	70	0.03
2 year all cause mortality	3	78	286	1.26 (0.75-2.12)	0.89	0.38	52	0.12
5 year all cause mortality	3	78	286	1.73 (1.01-2.97)	1.98	0.05	73	0.02

Table 4.4 Meta-analysis of the influence of HER2 overexpression/amplification

on mortality in patients with oesophageal squamous cell carcinoma

Outcome	No. of studies	HER2 +	HER2 -	OR (95% CI)	Overall effect Z	p value	HG I^2 (%)	HG p value
All studies								
1 year all cause mortality	3	84	312	2.43 (0.93-6.37)	1.80	0.07	6	0.34
2 year all cause mortality	3	84	312	0.76 (0.45-1.27)	1.06	0.29	62	0.07
5 year all cause mortality	3	84	312	2.88 (1.34-6.17)	2.72	0.006	0	0.52

Figure 4.2 Influence of HER2 overexpression or amplification on 5 year mortality in

all patients with oesophageal carcinoma. Weights are from random-effects analysis.

Squares indicate the point estimates of the effect of disease (odds ratio) and

diamonds the summary estimate from the pooled studies; 95% confidence intervals

are indicated by horizontal bars and shown in parentheses

Study or Subgroup	HER2+ Events	HER2+ Total	HER2- Events	HER2- Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.3.1 All studies						
Brien 2000	12	12	32	51	0.7%	15.00 [0.84, 267.73]
Duhaylongsod 1995	8	18	20	24	13.7%	0.16 [0.04, 0.66]
Flejou 1994	7	7	38	59	0.8%	8.38 [0.46, 153.91]
Hardwick 1997	37	49	129	156	21.8%	0.65 [0.30, 1.40]
Hu 2011	14	21	68	95	11.8%	0.79 [0.29, 2.18]
Langer 2011	34	41	48	101	6.8%	5.36 [2.18, 13.22]
Mimura 2005	7	9	21	57	1.8%	6.00 [1.14, 31.59]
Nakamura 1994	8	8	47	54	1.1%	2.68 [0.14, 51.51]
Reichelt 2007	17	23	164	232	11.1%	1.17 [0.44, 3.11]
Sato-Kuwabara 2009	60	68	94	117	11.7%	1.84 [0.77, 4.37]
Stoecklein 2008	15	18	61	83	5.2%	1.80 [0.48, 6.83]
Thompson 2011	6	14	51	75	13.2%	0.35 [0.11, 1.13]
Subtotal (95% CI)		288		1104	100.0%	1.43 [1.04, 1.95]
Total events	225		773			

Heterogeneity: Chi² = 35.89, df = 11 (P = 0.0002); I² = 69%
Test for overall effect: Z = 2.23 (P = 0.03)

Study or Subgroup	HER2+ Events	HER2+ Total	HER2- Events	HER2- Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.3.2 High-quality studies						
Brien 2000	12	12	32	51	1.9%	15.00 [0.84, 267.73]
Hu 2011	14	21	68	95	30.4%	0.79 [0.29, 2.18]
Langer 2011	34	41	48	101	17.5%	5.36 [2.18, 13.22]
Nakamura 1994	8	8	47	54	2.8%	2.68 [0.14, 51.51]
Stoecklein 2008	15	18	61	83	13.4%	1.80 [0.48, 6.83]
Thompson 2011	6	14	51	75	34.0%	0.35 [0.11, 1.13]
Subtotal (95% CI)		114		459	100.0%	1.90 [1.18, 3.05]
Total events	89		307			

Heterogeneity: Chi² = 17.99, df = 5 (P = 0.003); I² = 72%
Test for overall effect: Z = 2.65 (P = 0.008)

Study or Subgroup	HER2+ Events	HER2+ Total	HER2- Events	HER2- Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.3.3 Studies with >100 patients						
Hardwick 1997	37	49	129	156	31.8%	0.65 [0.30, 1.40]
Hu 2011	14	21	68	95	17.3%	0.79 [0.29, 2.18]
Langer 2011	34	41	48	101	10.0%	5.36 [2.18, 13.22]
Reichelt 2007	17	23	164	232	16.2%	1.17 [0.44, 3.11]
Sato-Kuwabara 2009	60	68	94	117	17.1%	1.84 [0.77, 4.37]
Stoecklein 2008	15	18	61	83	7.6%	1.80 [0.48, 6.83]
Subtotal (95% CI)		220		784	100.0%	1.52 [1.05, 2.20]
Total events	177		564			

Heterogeneity: Chi² = 14.33, df = 5 (P = 0.01); I² = 65%
Test for overall effect: Z = 2.20 (P = 0.03)

Test for subgroup differences: Chi² = 0.98, df = 2 (P = 0.61), I² = 0%

Figure 4.3 Influence of HER2 overexpression or amplification on 5 year mortality in

patients with oesophageal *adenocarcinoma*

Study or Subgroup	HER2+ Events	Total	HER2- Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.3.1 All studies						
Brien 2000	12	12	32	51	1.2%	15.00 [0.84, 267.73]
Duhaylongsod 1995	8	18	20	24	23.0%	0.16 [0.04, 0.66]
Flejou 1994	7	7	38	59	1.4%	8.38 [0.46, 153.91]
Hu 2011	14	21	68	95	19.8%	0.79 [0.29, 2.18]
Langer 2011	32	41	48	101	14.7%	3.93 [1.70, 9.06]
Nakamura 1994	8	8	47	54	1.8%	2.68 [0.14, 51.51]
Reichelt 2007	10	16	59	90	16.1%	0.88 [0.29, 2.63]
Thompson 2011	6	14	51	75	22.1%	0.35 [0.11, 1.13]
Subtotal (95% CI)		137		549	100.0%	1.33 [0.89, 2.00]
Total events	97		363			

Heterogeneity: Chi² = 25.99, df = 7 (P = 0.0005); I² = 73%
Test for overall effect: Z = 1.38 (P = 0.17)

Study or Subgroup	HER2+ Events	Total	HER2- Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.3.2 High-quality studies						
Brien 2000	12	12	32	51	2.1%	15.00 [0.84, 267.73]
Hu 2011	14	21	68	95	35.1%	0.79 [0.29, 2.18]
Langer 2011	34	41	48	101	20.3%	5.36 [2.18, 13.22]
Nakamura 1994	8	8	47	54	3.2%	2.68 [0.14, 51.51]
Thompson 2011	6	14	51	75	39.3%	0.35 [0.11, 1.13]
Subtotal (95% CI)		96		376	100.0%	1.91 [1.15, 3.17]
Total events	74		246			

Heterogeneity: Chi² = 18.02, df = 4 (P = 0.001); I² = 78%
Test for overall effect: Z = 2.50 (P = 0.01)

Study or Subgroup	HER2+ Events	Total	HER2- Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.3.3 Studies >100 patients						
Hu 2011	14	21	68	95	39.1%	0.79 [0.29, 2.18]
Langer 2011	32	41	48	101	29.0%	3.93 [1.70, 9.06]
Reichelt 2007	10	16	59	90	31.9%	0.88 [0.29, 2.63]
Subtotal (95% CI)		78		286	100.0%	1.73 [1.01, 2.97]
Total events	56		175			

Heterogeneity: Chi² = 7.43, df = 2 (P = 0.02); I² = 73%
Test for overall effect: Z = 1.98 (P = 0.05)

Test for subgroup differences: Chi² = 1.32, df = 2 (P = 0.52), I² = 0%

Figure 4.4 Influence of HER2 overexpression or amplification on 5 year mortality in

patients with oesophageal *squamous cell carcinoma*

Study or Subgroup	HER2 + Events	HER2 + Total	HER2 - Events	HER2 - Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Mimura 2005	7	9	21	57	14.0%	6.00 [1.14, 31.59]	
Reichelt 2007	7	7	105	138	7.9%	4.76 [0.26, 85.62]	
Sato-Kuwabara 2009	61	68	94	117	78.1%	2.13 [0.86, 5.27]	
Total (95% CI)		84		312	100.0%	2.88 [1.34, 6.17]	
Total events	75		220				

Heterogeneity: Chi² = 1.29, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 2.72 (P = 0.006)

0.01 0.1 1 10 100
Favours HER2+ Favours HER2-

4.5   DISCUSSION

This study represents the largest and only specific meta-analysis of the prognostic significance of HER2 overexpression and gene amplification in patients with oesophageal carcinoma, all of whom had undergone potentially curative oesophagectomy. The main findings from the 14 studies identified were that 5 year mortality in patients diagnosed with HER2 positive oesophageal cancer were significantly higher compared with patients diagnosed with HER2 negative cancer. This difference was greater in patients with oesophageal squamous cell carcinoma when compared to adenocarcinoma and when oesophagogastric junctional cancers were excluded.

The authors searched extensively for relevant studies but most were small and inadequately powered on an individual basis to show a significant difference in outcomes between patients with HER2 positive and negative oesophageal cancer. Only published studies were included as unpublished data from conference abstracts lack rigorous peer review. Five of the fourteen studies were

ostensibly about other prognostic variables such as p53 (Duhaylongsod et al. 1995; Hardwick et al. 1997), epidermal growth factor receptor (Friess et al. 1999), DNA ploidy (Nakamura et al. 1994) and the Lauren classification (Polkowski et al. 1999). Two studies investigated the correlation between HER2 status at the primary tumour site and metastatic deposits (Reichelt et al. 2007; Stoecklein et al. 2008). Including such studies reduced concern about publication bias as the decision to publish was unrelated to HER2 status and outcome.

Meta-analysis of retrospective cohort studies is regrettably sensitive to confounding. In cancer studies, multiple factors influence prognosis following surgery such as age, stage of disease, surgical technique and use of neoadjuvant chemotherapy or chemoradiotherapy. To try and account for this, only three studies adjusted for two or more of these variables during analysis (Nakamura et al. 1994; Polkowski et al. 1999; Langer et al. 2011). This may lead to bias which was difficult to assess thoroughly as funnel plots including less than ten studies are difficult to interpret. Meta-regression was not performed for the same reason (Higgins JPT 2009), but study quality was high in seven of the included studies (Nakamura et al. 1994; Polkowski et al. 1999; Brien et al. 2000; Stoecklein et al. 2008; Hu et al. 2011; Langer et al. 2011; Thompson et al. 2011). Six studies included in this analysis involved more than 100 patients (Hardwick et al. 1997; Reichelt et al. 2007; Stoecklein et al. 2008; Sato-Kuwabara et al. 2009; Hu et al. 2011; Langer et al. 2011), and use of these latter studies for sensitivity

analyses decreased heterogeneity and reinforced significant analyses, making the results valid and informative.

The study period spanned 17 years, and hence various laboratory assays were used to determine HER2 protein expression and gene amplification. Different criteria were also used to define HER2 positivity. Before 2000, all studies used IHC to measure the protein overexpressed by the HER2 gene. ISH techniques are used to measure gene amplification that rely on either fluorescence (FISH) or in more recent studies, chromogenic (Hu et al. 2011) and silver (Thompson et al. 2011) in-situ hybridization (CISH and SISH). These differences in methodology can be seen from the wide range of HER2 positivity in this study (9 to 64%). Standardization of IHC and ISH testing is therefore essential. A HER2 scoring system for gastric cancer used in the ToGA trial was validated and a concordance of 93.5% between FISH and IHC was demonstrated (Hofmann et al. 2008). However, such a system does not exist for oesophageal cancer and whether a separate score should be implemented remains uncertain. Nevertheless, most of the studies in this review did not use this validated scoring system but various subjective scoring without standardization. Despite these differences, results from subgroup analysis related to specific methodology (IHC or ISH) were similar to the overall analysis (results not shown).

Subgroup analysis according to histological type showed that HER2 overexpression and amplification had a greater influence on prognosis in patients

with squamous cell carcinoma when compared with adenocarcinoma. It has been suggested that this poorer survival in HER2 positive patients with squamous cell carcinoma could be due to increased resistance to radiation therapy (Dreilich et al. 2006) and cisplatinum-based chemotherapy (Akamatsu et al. 2003). Moreover, the addition of trastuzumab in head and neck squamous cell carcinoma cell lines seemed to enhance the effect of irradiation (Uno et al. 2001). However, as only three studies were included in the analysis of patients with squamous cell carcinoma (Hardwick et al. 1997; Friess et al. 1999; Stoecklein et al. 2008), these data must be interpreted with caution.

Trastuzumab in combination with standard chemotherapy has been shown to improve survival in patients with advanced gastric cancer (Bang et al. 2010) but the benefit of neoadjuvant trastuzumab prior to surgery in patients with operable oesophageal cancer remains unknown. A randomised controlled trial to address this potentially beneficial therapeutic option is warranted. However, recruiting sufficient numbers of patients for this trial would be challenging. According to the results of this study, approximately 500 patients would be needed to detect this survival difference. Assuming that 22% of patients are HER2 positive, 2300 patients with operable oesophageal cancer would therefore have to be screened for eligibility. Despite this, a multinational and multicentre trial could overcome these recruitment challenges.

4.7   CONCLUSION

In conclusion, these results confirm that HER2 overexpression and gene amplification was an indicator of poor prognosis in patients with operable oesophageal cancer.

Chapter 5

Relative prognostic value of HER2 expression in

operable oesophagogastric cancer

5.1   SUMMARY

The aim of this study was to determine the prognostic significance of HER2 receptor expression in operable oesophagogastric adenocarcinoma. Eighty-five consecutive patients diagnosed with oesophagogastric adenocarcinoma [18 oesophageal (OC), 32 junctional (JC) and 35 gastric (GC)] undergoing potentially curative resection were studied retrospectively. Immunohistochemistry was used to determine HER2 status at endoscopic biopsy and resection specimen. The primary outcome measure was survival.

Twenty (24%) patients had HER2 positive tumours which was commoner in JC (14/32, 44% versus 2/18, 11% in OC and 4/35, 11% in GC, p=0.003). The sensitivity, specificity, positive and negative predictive values of HER2 status at endoscopic biopsy were 56%, 93%, 63%, 91% respectively (weighted Kappa=0.504, p<0.0001). Five year survival in OC HER2 positive vs. HER2 negative was 100% and 36% (p=0.167) compared with 14% and 44% (p=0.0726) in JC and 50% and 46% (p=0.942) in GC respectively.

Endoscopic biopsy had a high specificity and negative predictive value in determining HER2 status. Patients with JC had a significantly higher rate of HER2 overexpression and this was associated with a nonsignificant poorer survival trend. A larger study is needed to confirm these findings because of the implications for neoadjuvant and adjuvant chemotherapy regimens.

5.2   INTRODUCTION

The worldwide burden of oesophagogastric cancer is growing. Each year 482,300 and 989,600 people are diagnosed with oesophageal and gastric cancer resulting in 406,000 and 738,00 deaths respectively (Jemal et al. 2011). The optimal contemporary treatment is controversial and opinion divided. In oesophageal cancer, following the publication of the MRC OEO2 trial, neoadjuvant chemotherapy followed by surgery is the standard of care for patients with operable oesophageal cancer (MRC Oesophageal Cancer Working Group 2002) in the United Kingdom, whereas neoadjuvant chemoradiotherapy followed by surgery is the preferred modality in Europe and the United States (Ilson 2008). Moreover, the optimum treatment for patients diagnosed with gastric cancer in the UK remains controversial, both in terms of neoadjuvant chemotherapy (Cunningham et al. 2006) and the extent of the lymphadenectomy. However, overall survival reports remain poor and no established global standard for treatment exists. New therapies which target specific genetic alterations arguably offer the best chance for improving patient survival.

The human epidermal growth factor receptor 2 (HER2) gene is a proto-oncogene which is located on chromosome 17q11.2-12 and encodes a transmembrane tyrosine kinase receptor which is responsible for cell growth, differentiation, migration and apoptosis (Normanno et al. 2005). HER2 is involved in the development of numerous types of cancer and is overexpressed in up to 25% of breast cancer patients, conferring a poor prognosis (Slamon et al. 1987). In

oesophagogastric cancer, HER2 overexpression has been reported at frequencies similar to those observed in breast cancer, ranging from 16% to 27% (Polkowski et al. 1999; Tanner et al. 2005; Park et al. 2006; Thompson et al. 2011).

A combination of the monoclonal antibody against HER2 (trastuzumab) with standard chemotherapy improved survival significantly in patients with HER2 positive advanced gastric cancer in the Trastuzumab for Gastric Cancer (ToGA) trial (Bang et al. 2010). All patients in this trial had inoperable junctional or gastric adenocarcinoma and there is currently no evidence for the use of trastuzumab in operable HER2 positive oesophagogastric cancer in the neoadjuvant setting prior to surgery.

The relationship between HER2 overexpression and prognosis in operable oesopahgogastric cancer is controversial (Brien et al. 2000; Reichelt et al. 2007). Some studies have suggested that HER2 overexpression is associated with poor survival in oesophageal (Flejou et al. 1994; Langer et al. 2011) and gastric cancer (Tanner et al. 2005; Park et al. 2006) whereas others have shown no association with prognosis (Hardwick et al. 1997; Barros-Silva et al. 2009; Grabsch et al. 2010; Hu et al. 2011; Thompson et al. 2011).

The primary aim of this study was therefore to determine the prognostic significance of HER2 overexpression in patients with operable oesophagogastric

adenocarcinoma. The secondary aim was to determine the accuracy of the endoscopic index biopsy in assessing HER2 overexpression when compared with the final operative resection specimen.

5.3   METHODS

Eighty-five consecutive patients diagnosed with oesophagogastric adenocarcinoma [18 oesophageal (OC), 32 junctional (JC) and 35 gastric (GC] undergoing R0 resection between 1 February 2001 and 30 June 2006 were studied retrospectively. All tumours were staged in accordance with the International Union against Cancer tumour node metastasis (TNM) classification of malignant tumours TNM6 (Sobin et al. 2003). The primary outcome measure was survival from diagnosis. Ethical approval was obtained from the local ethics committee.

5.3.1 Neoadjuvant chemotherapy

The selective use of neoadjuvant chemotherapy was adopted in the latter part of the study period and was given to 25 patients with minimal comorbidities who were deemed to have relatively advanced disease and would benefit from down-staging of the tumour prior to surgery. Chemotherapy was administered for three or four cycles preoperatively and postoperatively. Each cycle consisted of epirubicin (50mg/ m^2) by intravenous bolus, cisplatin (60mg/ m^2) as a four-hour infusion on day one and 5-fluorouracil (200mg/ m^2/day) daily by a continuous intravenous infusion.

5.3.2 Surgical treatment

Patients with oesophageal cancer were selected for radical treatment based on perceived radiologic stage, comorbidity and patient choice according to algorithms described previously (Crosby et al. 2004; Stephens et al. 2006; Gwynne et al. 2011). The type of surgery for gastric cancer was determined by the anatomical location of the tumour; subtotal gastrectomy was performed in patients with antral tumours and total gastrectomy was performed in tumours of the cardia (Siewert type III), body and linitis plastica. A modified D2 lymphadenectomy preserving the spleen and pancreas was performed (Edwards et al. 2004).

5.3.3 Immunohistochemistry

Immunohistochemistry (IHC) was used to determine patients' HER2 status at the endoscopic index biopsy and the final operative resection specimen. Sections (4μm) of tissue were cut, mounted on coated slides, labeled and then placed on the Ventana Benchmark XT (Roche Diagnostics) for detection of the HER2 oncoprotein. The sections were dewaxed then subjected to pretreatment with CC1 for 30 minutes. Sections were then washed with reaction buffer followed by incubation with the rabbit monoclonal primary antibody HER2/neu (Clone 4B5, PATHWAY) for 16 minutes. On board detection using ultraView Universal DAB kit (Roche Diagnostics), used in accordance with the manufacturer's recommendations, was used to detect the location of the primary antibody HER2

followed by counterstain with haematoxylin II for four minutes (Roche Diagnostics).

All sections were reviewed independently by two consultant histopathologists who were blinded to all clinical and pathological information. Discordant cases were reviewed together and a final consensus was reached. Evaluation and scoring of HER2 protein overexpression was performed according to the Dako HercepTest scoring system for breast cancer. Only membranous staining was considered. This scoring system has been validated for use in gastric cancer with minimal modifications: 0/negative = staining or membranous reactivity in <10% of cells; 1+/negative = faint membranous reactivity in >10% of cells or cells with reactivity only in part of their membrane; 2+/equivocal = weak/moderate complete or basolateral membranous staining in >10% of tumour cells; and 3+/positive = strong complete or basolateral membranous staining in >10% of tumour cells (Hofmann et al. 2008; Walker et al. 2008).

5.3.4 Follow-up evaluation

Patients were reviewed every three months for the first year, then every six months thereafter. The median follow-up period was 71 months. A total of 79 patients (93%) were followed up for at least five years or until death. Death certification was obtained from the Office for National Statistics.

5.3.5 Statistical analysis

Statistical analysis appropriate for non-parametric data was used. Grouped data were expressed as median (range). Groups were compared with the Mann-Whitney U test for unpaired data. The agreement between HER2 status at index biopsy and the postoperative histopathological resection specimen was determined using the weighted Kappa statistic (Kw) (Landis et al. 1977). The value of Kappa has a maximum of 1.00 when agreement is perfect, a value of zero indicates no agreement better than chance and negative values show worse than chance agreement. The strength of agreement was assessed according to the guidelines of Landis and Koch (Landis et al. 1977). The sensitivity and specificity, positive predictive value and negative predictive value were also estimated. Cumulative survival was calculated by the life table method of Kaplan and Meier (Kaplan et al. 1958). Differences in survival times between groups of patients were analysed by the log rank method (Altman 1991). Multivariate Cox regression was used to assess the prognostic value of individual variables. Data analysis was carried out with the Statistical Package for Social Sciences (SPSS) version 18 (SPSS, Chicago, Illinois, USA).

5.4   RESULTS

Twenty (24%) patients had HER2 positive tumours, and positive HER2 status was commoner in JC (14/32, 44% versus 2/18, 11% in OC and 4/35, 11% in GC; Chi^2 = 11.66, p=0.003), Table 5.1.

5.4.1 Accuracy of biopsy in determining HER2 status

Comparison of HER2 expression status between the index biopsy and final operative resection specimen revealed sensitivity, specificity, positive and negative predictive values were 56%, 93%, 63%, 91% respectively. There was strong agreement between the index biopsy and final operative resection specimen [weighted Kappa statistic was 0.504; 95% CI 0.128 - 0.856; p<0.0001)]. Only three patients had a false positive biopsy result, all of whom had undergone gastrectomy without neoadjuvant chemotherapy.

5.4.2 Outcomes related to HER2 expression

Short-term outcomes were similar in patients with HER2 positive and negative tumours (Table 5.2). Cumulative five year survival related to HER2 status was 30% for the HER2 positive cohort compared with 43% for the HER2 negative cohort (p=0.221), (Figure 5.1). With regard to tumour site, five year survival in OC HER2 positive versus negative cohorts was 100% and 36% (p=0.167) compared with 14% and 44% (p=0.0726) in JC (Figure 5.2) and 50% and 46% (p=0.942) in GC respectively. Univariate analysis of factors associated with duration of survival is shown in Table 5.3.

Table 5.1   Details of patients

		OC	JC	GC	p value
Number		18	32	35	
Median age (years)		60	66	72	0.012
Gender M:F (%)		18:0 (100:0)	27:5 (84:16)	19:16 (54:46)	<0.0001
Surgery (%)	TTO	7 (39)	9 (28)	-	
	THO	11 (61)	13 (41)	-	
	TG	-	10 (31)	9 (26)	
	STG	-	-	26 (74)	
HER2+ (%)		2 (11)	14 (44)	4 (11)	0.003
pTNM (%)	I&II	10 (56)	12 (37)	20 (57)	0.062
	III&IV	8 (44)	20 (63)	15 (43)	

OC: Oesophageal adenocarcinoma; JC: Junctional adenocarcinoma; GC: Gastric adenocarcinoma; TTO: Transthoracic oesophagectomy; THO: Transhiatal oesophagectomy; TG: Total gastrectomy; STG: Subtotal gastrectomy

Table 5.2   Outcome related to HER2 overexpression

	HER2 -	HER2 +	p value
Number (%)	65 (76)	20 (24)	
Median age (years)	66	69	0.705
Gender M:F (%)	48:17 (74:26)	16:4 (80:20)	0.577
pTNM (%) I & II	(52)	(40)	0.089
III & IV	(48)	(60)	
Morbidity (%)	23 (35)	7 (35)	0.975
Mortality (%)	2 (3)	1 (5)	0.47
Median survival (months)	43	27	0.221
1 year survival (%)	89	80	
2 year survival (%)	61	55	
5 year survival (%)	43	30	

Table 5.3   Univariate analysis of factors associated with duration of survival

Factor	Chi^2	df	p value
HER2 overexpression	1.497	1	0.221
pT stage	17.346	3	0.001
Age	68.826	4	0.001
pN stage	34.272	3	<0.0001
pTNM stage	30.786	3	<0.0001
Lymph node ratio	183.926	3	<0.0001

Figure 5.1   Survival related to HER2 overexpression in *all patients*
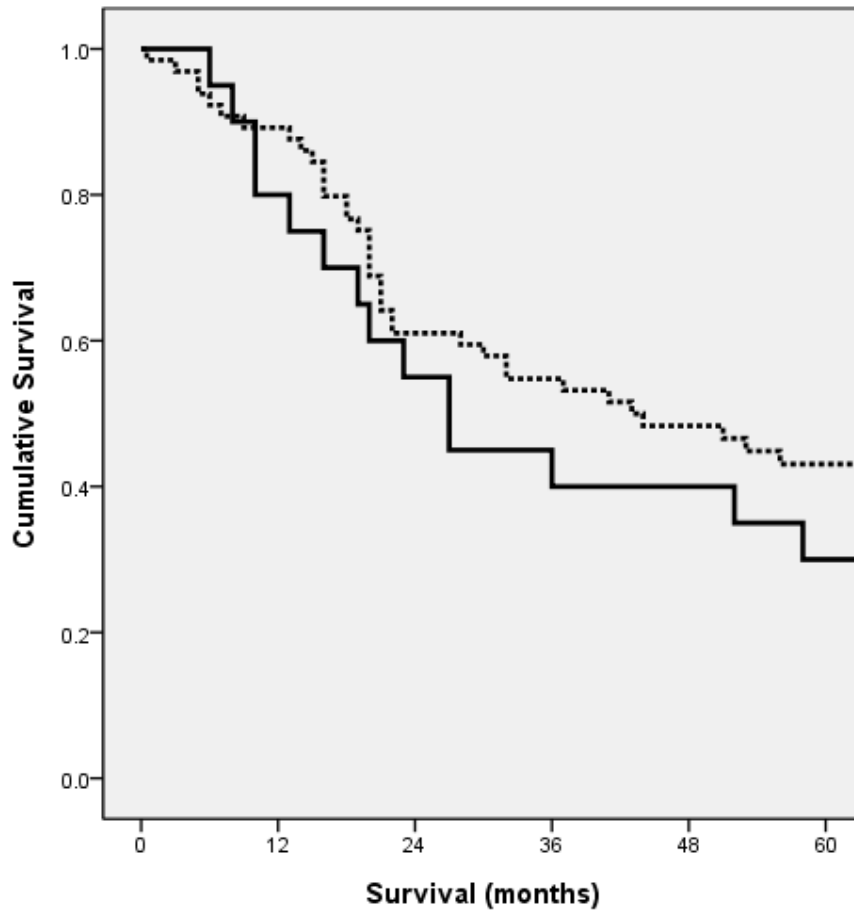
Caption

Numbers at risk

HER2 -	65	56	39	35	29	21
HER2 +	20	16	11	8	7	5

─── = HER2 +   ----- = HER2 -

Log rank = 1.497, df. 1 (p=0.221)

Figure 6.2 Survival related to HER2 overexpression in patients with *junctional*

adenocarcinoma
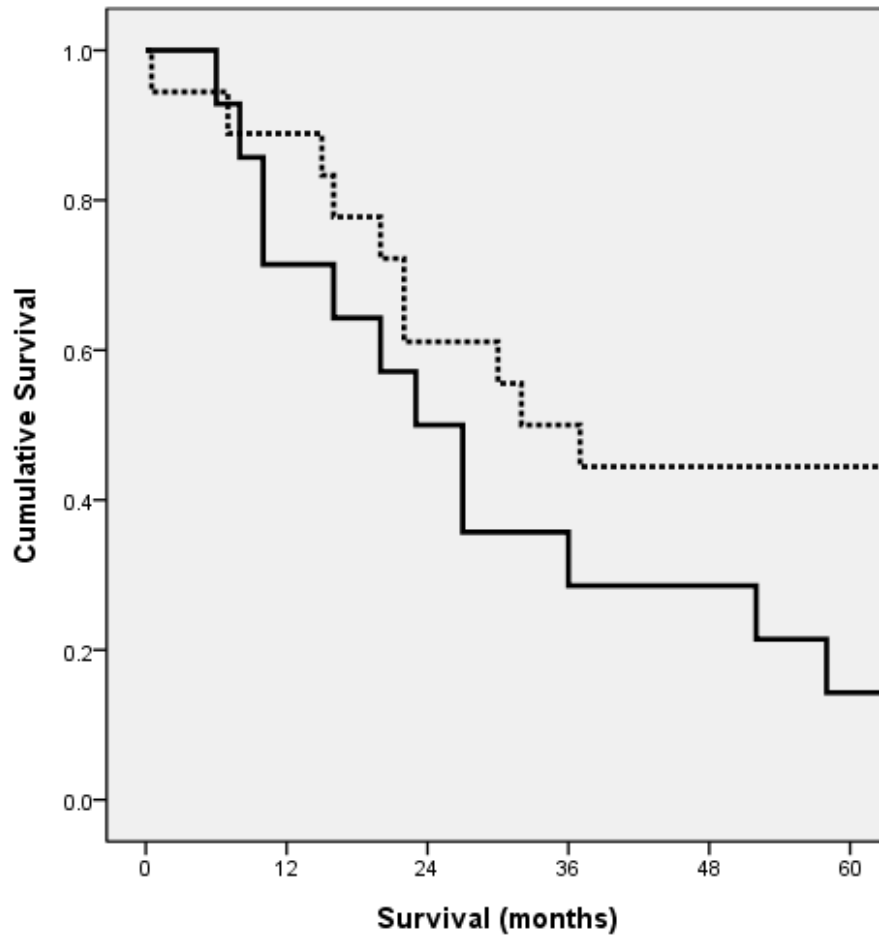
Caption

Numbers at risk

HER2 -	18	16	11	9	8	4
HER2 +	14	10	7	4	4	2

    ——— = HER2 +   ----- = HER2 -

Log rank = 3.233, df. 1, p=0.072

5.5 DISCUSSION

HER2 overexpression was found in 24% of patients in this cohort, the majority of whom had tumours situated around the oesophagogastric junction. This is in keeping with recent studies reporting a prevalence rate of 15 to 30% (Bang et al. 2010; Langer et al. 2011; Thompson et al. 2011). The previously quoted range of 11 to 73% largely originates from studies conducted in the 1990s which adopted various cutoffs for the classification of HER2 status preventing valid comparisons to be made (Flejou et al. 1994; Nakamura et al. 1994; Duhaylongsod et al. 1995; Friess et al. 1999). There was a trend towards poorer long-term survival in patients diagnosed with HER2 positive operable oesophagogastric cancer compared to patients with HER2 negative tumours. However, this difference was not statistically significant and this finding echoes more recent reports which have also shown that HER2 overexpression was not associated with duration of survival (Reichelt et al. 2007; Stoecklein et al. 2008; Hu et al. 2011; Thompson et al. 2011).

The accuracy of endoscopic biopsy in determining HER2 status in oesophagogastric cancer has not been documented previously. We report a high specificity and negative predictive value of endoscopic biopsy in determining HER2 status in oesophagogastric cancer. However, the sensitivity and positive predictive value was lower when compared with breast core-needle biopsies (Arnould et al. 2012). The pattern of HER2 staining in breast cancer tends to be homogenous whereas HER2 staining in gastric cancer is heterogeneous

(Hofmann et al. 2008). A modified scoring system which only takes into account the pattern of reactivity irrespective of the number of reactive cells in biopsy specimens has therefore been introduced (Hofmann et al. 2008).

This study has several potential limitations. This was a retrospective observational study and is therefore open to selection bias. The relatively small sample size could have resulted in a type II error. HER2 status was determined using IHC on tissue samples which have been stored for a few years prior to analysis. Deterioration in antigenicity can occur once sections from paraffin blocks have been put onto slides (Jacobs et al. 1996) and could arguably underestimate the prevalence of HER2 overexpression in our cohort. However, this appears to be a limitation of most studies published on this subject (Hardwick et al. 1997; Akamatsu et al. 2003; Thompson et al. 2011). Although the assessment of HER2 gene amplification with in-situ hybridisation (ISH) techniques has been recommended to determine the final HER2 status in equivocal IHC 2+ (Hofmann et al. 2008), we did not perform ISH on the five patients in our cohort who had IHC 2+ as the concordance between IHC and ISH have been shown to be high (Dowsett et al. 2003; Hofmann et al. 2008).

Conversely, the strengths of the study are that the demographic data and outcomes were collected prospectively, from a well-defined geographical area served by an established regional upper GI network. The study's survival and prognostic data are especially robust because no patients were lost to follow-up,

and causes and exact dates of death were obtained from death certificates provided by the Office for National Statistics. HER2 status was determined by two specialist consultant histopathologists, one of whom was part of the steering group recommending guidelines for HER2 testing in the UK (Ellis et al. 2004; Walker et al. 2008; Bartlett et al. 2011).

A larger prospective study using validated and reproducible methods in IHC and ISH is needed to clarify the prognostic role of HER2 in patients with operable oesophagogastric cancer. The accuracy of the index biopsy at determining HER2 status is important as the addition of anti-HER2 therapy to the standard neoadjuvant chemotherapy regime may be beneficial in HER2 positive patients. Future studies into targeted molecular therapies should also take into account characteristics of both the primary tumour and disseminated tumour cells (Thompson et al. 2011).

5.5   CONCLUSION

Endoscopic biopsy had a high specificity and negative predictive value in determining HER2 status. Patients with JC had a significantly higher rate of HER2 overexpression and this was associated with a nonsignificant poorer survival trend. A larger study is needed to confirm these findings because of the implications for neoadjuvant and adjuvant chemotherapy regimens.

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Chapter 6

Systematic review and meta-analysis of the influence of

circumferential resection margin involvement on survival in patients with

operable oesophageal cancer

6.1 SUMMARY

The prognostic role and definition of circumferential resection margin (CRM) involvement in operable oesophageal cancer remains controversial. The College of American Pathologists (CAP) and Royal College of Pathologists (RCP) define CRM involvement as tumour found at the cut resection margin and within 1 mm of the cut resection margin respectively. This systematic review and meta-analysis was performed to determine the influence of CRM involvement on outcomes in operable oesophageal cancer.

PubMed, MEDLINE and the Cochrane Library (January 1990 to June 2012) were searched for studies correlating CRM involvement with five year mortality. Statistical analysis of dichotomous variables was performed using odds ratio (OR) as the summary statistic.

Fourteen studies involving 2433 patients with oesophageal cancer who had undergone potentially curative oesophagectomy were analysed. Rates of CRM involvement were 15.3% (173/1133) and 36.5% (889/2433) according to the CAP and RCP criteria respectively. Overall five year mortality rates were significantly higher in patients with CRM involvement compared with CRM-negative patients according to the CAP [OR 4.02, 95% confidence interval (CI) 2.25-7.20, p<0.00001] and RCP (OR 2.52, 95% CI 1.96-3.25, p<0.0001) criteria. CRM involvement between 0.1 to 1 mm was associated with significantly higher five

year mortality than CRM negative status (involvement more than 1 mm from CRM) [OR 2.05, 95% CI 1.41-2.99, p<0.00001].

CRM involvement is an important predictor of poor prognosis. CAP criteria differentiate a higher risk group than RCP criteria, but overlook a patient group with similar poor outcomes.

6.2   INTRODUCTION

Although prognosis after oesophageal cancer resection has improved over the last decade, long-term survival remains poor (Khan et al. 2010; Cancer Research UK 2012). Traditionally, the depth of tumour invasion and the number of lymph node metastases have been the most important prognostic indicators following curative oesophagectomy (Shahbaz Sarwar et al. 2010) but more recently increasing interest has developed in the prognostic value of circumferential resection margin (CRM) involvement.

Although CRM involvement is a well established independent prognostic indicator in patients with rectal cancer (Adam et al. 1994; Birbeck et al. 2002), reports on its role in oesophageal cancer have been conflicting (Dexter et al. 2001; Khan et al. 2003; Deeter et al. 2009; Harvin et al. 2012). The two largest series of over 300 patients have each reported that CRM involvement was not an independent predictor of prognosis (Khan et al. 2003; Mirnezami et al. 2010), in contrast to smaller studies (Dexter et al. 2001; Griffiths et al. 2006; Deeter et al. 2009).

On the basis of evidence available at the time suggesting that CRM involvement resulted in higher rates of local recurrence and poorer survival (Sagar et al. 1993), the UK Royal College of Pathologists (RCP) included CRM status as a required data item in the 1998 minimum dataset for oesophageal cancer (Mapstone 1998; Mapstone 2006). The RCP defined CRM involvement as tumour involvement within 1 mm of the cut margin, whereas the College of

American Pathologists (CAP) considered CRM involvement as tumour found at the cut margin of resection (Pathologists 2005). The optimum definition for CRM involvement in predicting outcome remains uncertain and several studies have supported either the RCP (Scheepers et al. 2009; Pultrum et al. 2010; Salih et al. 2013) or CAP (Deeter et al. 2009; Verhage et al. 2011) classification.

The aim of this study was to perform a systematic review and meta-analysis of the influence of CRM involvement on overall survival in patients with operable oesophageal cancer. Secondary aims included determining the optimum definition of CRM involvement and the prognostic significance of CRM involvement in patients with T3 tumours with and without nodal involvement and those undergoing neoadjuvant therapy before surgery.

6.3 METHODS

6.3.1 Literature Search Strategy

A systematic review of published work was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009). A systematic search of PubMed, MEDLINE and the Cochrane Library databases was performed from January 1990 to June 2012 using the following terms to identify studies investigating the influence of CRM involvement on survival in patients with operable oesophageal cancer: oesophageal neoplasm, oesophagectomy, surgery, circumferential resection margin, outcomes and survival. The searches were limited to human articles

published in the English language. Further articles were identified by hand searching reference lists of all articles retrieved to identify potentially relevant studies. Searches were cross-referenced on PubMed using the related articles function. The last search date was 30 June 2012.

6.3.2 Data extraction

Data were extracted independently by three authors using a standard protocol. Any discrepancies were dealt with by discussion among all authors and a consensus was reached. The following information was extracted from each study: first author, year of publication, study design, country of origin, definition of CRM involvment used, number of subjects with CRM involvement, histological subtype (adenocarcinoma or squamous cell carcinoma), use of neoadjuvant chemotherapy and or chemoradiotherapy, mean follow-up, quality of study and outcome measures (all-cause mortality). Sub-group analysis was performed according to classification of CRM involvement, T3 tumours and use of neoadjuvant chemotheray or chemoradiotherapy.

6.3.3 Inclusion and exclusion criteria

Studies comparing overall survival outcomes in patients with operable oesophageal cancer with and without CRM involvement were included. Where there were multiple articles by the same authors analysing data from the same or a similar patient group, the most recent publication was included if the study periods overlapped. Review articles, case reports, experimental studies and

studies that did not report outcomes were excluded. Unpublished data from conference abstracts were excluded. Only high-quality studies with more than 100 patients were included.

6.3.4 Statistical analysis

The meta-analysis was performed in line with the recommendations from the Cochrane Collaboration and PRISMA guidelines (Moher et al. 2009) using Review Manager 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Statistical analysis of dichotomous variables were carried out using odds ratio (OR) as the summary statistic. The decision to use a fixed-effects model was made in advance as minimal heterogeneity was expected. The pooled ORs were reported with 95% confidence intervals (CI). ORs represent the odds of death during the study interval in a patient who was CRM-positive compared with a patient who was CRM-negative. An OR of greater than 1 indicated a higher mortality rate in patients who had CRM involvement, and the point estimate of the OR was considered significant at the $p<0.050$ level if the 95% CI did not include 1.

The quality of non-randomised studies was assessed using the Newcastle-Ottawa scale (Higgins JPT 2009) which examines patient selection methods, comparability of study groups and assessment of outcome. A score of at least seven stars from a maximum of nine were considered to be of higher quality. Heterogeneity was assessed using the I^2 value which was reported for each

analysis. Funnel plots were used to assess publication bias (Egger et al. 1998). Funnel plot asymmetry implied that results were subject to reporting or publication bias.

6.4   RESULTS

The full text of 30 papers were obtained, of which 14 cohort studies fulfilled the criteria for review (Figure 6.1). Analysis was carried out on 2433 patients (1884 male; median age 64 years) with oesophageal carcinoma (adenocarcinoma, 1789; squamous cell carcinoma, 623; other histology, 21), all of whom had undergone attempted curative oesophagectomy (transthoracic, 1929; transhiatal, 277; three-stage, 124; laparoscopically assisted, 103).

6.4.1 Characteristics of included studies (Table 6.1)

All studies analysed were observational cohort, of which two had a prospective design (Dexter et al. 2001; Deeter et al. 2009). Of the 14 studies, 13 (Dexter et al. 2001; Khan et al. 2003; Griffiths et al. 2006; Sujendran et al. 2008; Deeter et al. 2009; Saha et al. 2009; Scheepers et al. 2009; Pultrum et al. 2010; Chao et al. 2011; Verhage et al. 2011; Harvin et al. 2012; Rao et al. 2012; Salih et al. 2013) reported three year and ten (Khan et al. 2003; Griffiths et al. 2006; Thompson et al. 2008; Deeter et al. 2009; Scheepers et al. 2009; Pultrum et al. 2010; Chao et al. 2011; Verhage et al. 2011; Harvin et al. 2012; Rao et al. 2012) reported five year mortality outcomes. Only two studies reported local recurrence rates (Chao et al. 2011; Harvin et al. 2012). The RCP classification was used in all studies to

116

define CRM involvement. Eight studies used both the RCP and CAP classifications (Deeter et al. 2009; Scheepers et al. 2009; Pultrum et al. 2010; Chao et al. 2011; Verhage et al. 2011; Harvin et al. 2012; Rao et al. 2012; Salih et al. 2013). Nine studies reported CRM involvement to be a significant predictor of poor prognosis in univariable (Chao et al. 2011) and multivariable analysis (Dexter et al. 2001; Griffiths et al. 2006; Sujendran et al. 2008; Deeter et al. 2009; Saha et al. 2009; Scheepers et al. 2009; Pultrum et al. 2010; Verhage et al. 2011). In six studies, the significance of CRM involvement was negated by other factors such as the number of lymph node metastases (Khan et al. 2003; Thompson et al. 2008; Harvin et al. 2012; Rao et al. 2012; Salih et al. 2013), T stage (Khan et al. 2003), lymphovascular invasion (Mirnezami et al. 2010) and tumour grade (Thompson et al. 2008; Mirnezami et al. 2010).

6.4.2 Characteristics of excluded studies

Four studies were excluded from analysis (Sagar et al. 1993; Roh et al. 2004; Barbour et al. 2007; Sillah et al. 2009). Two studies had small sample sizes (less than 100) with short durations of follow-up and Newcastle-Ottawa scores of less than 7 (Sagar et al. 1993; Roh et al. 2004). Although CRM involvement was reported in these two studies as a predictor of poor prognosis, other factors were not corrected for in multivariable analysis. Two other studies examined the influence of other factors such as the degree of involvement of oesophageal circumference (Sillah et al. 2009) and longitudinal resection margins (Barbour et al. 2007).

117

6.4.3 Method of examining CRM involvement

In 11 studies (Dexter et al. 2001; Khan et al. 2003; Griffiths et al. 2006; Sujendran et al. 2008; Deeter et al. 2009; Saha et al. 2009; Scheepers et al. 2009; Pultrum et al. 2010; Chao et al. 2011; Verhage et al. 2011; Salih et al. 2013), the specimen was delivered fresh and unopened to the pathology department with no dissection of lymph nodes. Specimens were then painted with Indian ink to allow better microscopic assessment followed by fixation in formalin for 24 to 48 hours. Specimens were then cut to between 3 and 5 mm in thickness and assessed by one to three consultant histopathologists for CRM involvement according to the RCP and CAP criteria. Three studies did not detail the method of specimen preparation prior to assessment of CRM involvement (Thompson et al. 2008; Harvin et al. 2012; Rao et al. 2012). In 12 studies, the specimens were reviewed by either a single specialist pathologist (Thompson et al. 2008; Deeter et al. 2009; Saha et al. 2009; Chao et al. 2011; Verhage et al. 2011; Harvin et al. 2012) or a team of up to three pathologists (Khan et al. 2003; Griffiths et al. 2006; Sujendran et al. 2008; Scheepers et al. 2009; Rao et al. 2012; Salih et al. 2013).

6.4.4 CRM involvement in all patients

The rates of CRM involvement were 15.3% (173/1133) and 36.5% (889/2433) according to the CAP and RCP criteria respectively. Overall three year mortality was significantly higher in patients with CRM involvement compared with CRM-negative patients according to the CAP (OR 3.13, 95% CI 2.12-4.63, p<0.00001) and RCP (OR 2.49, 95% CI 2.02-3.06, p<0.0001) criteria (Table 6.2). Overall five

year mortality rates were also significantly higher in patients with CRM involvement compared with CRM-negative patients according to the CAP [OR 4.02, 95% CI 2.25-7.20, p<0.00001] and RCP (OR 2.52, 95% CI. 1.96-3.25, p<0.0001) criteria (Table 6.3, Figures 6.2 and 6.3). The CAP criteria resulted in larger ORs than the RCP criteria.

6.4.5 CRM involvement in patients with T3 tumours

Overall, ten studies reported separate outcomes for patients with T3 tumours (Khan et al. 2003; Griffiths et al. 2006; Sujendran et al. 2008; Deeter et al. 2009; Saha et al. 2009; Scheepers et al. 2009; Chao et al. 2011; Verhage et al. 2011; Rao et al. 2012). The rate of CRM involvement was 14.6% (110/754) and 42.5% (597/1405) according to the CAP and RCP criteria respectively.

Of the ten studies, three (Griffiths et al. 2006; Sujendran et al. 2008; Scheepers et al. 2009) reported separate outcomes according to node status using the RCP criteria. Positive node status negated the importance of CRM involvement in the three year mortality analysis but not the five year mortality analysis (Tables 6.2 and 6.3).

6.4.6 CRM involvement in patients undergoing surgery alone

Five studies reported separate outcomes for patients who had undergone surgery alone (Dexter et al. 2001; Khan et al. 2003; Thompson et al. 2008; Pultrum et al.

2010; Verhage et al. 2011). The rate of CRM involvement was 22.2% (51/230) and 40.1% (325/810) according to the CAP and RCP criteria respectively.

6.4.7 CRM involvement in patients undergoing neoadjuvant chemotherapy

Six studies (Griffiths et al. 2006; Sujendran et al. 2008; Saha et al. 2009; Scheepers et al. 2009; Rao et al. 2012; Salih et al. 2013) included patients who had undergone neoadjuvant CT prior to surgery according to the MRC OEO2 regimen (Medical Research Council Oesophageal Cancer Working Group 2002). The rate of CRM involvement was 15.8% (72/457) and 34.3% (361/1053) according to the CAP and RCP criteria respectively.

6.4.8 CRM involvement in patients undergoing neoadjuvant chemo-radiotherapy

Five studies included patients who had undergone neoadjuvant chemoradiotherapy prior to surgery (Sujendran et al. 2008; Thompson et al. 2008; Deeter et al. 2009; Chao et al. 2011; Harvin et al. 2012), one of which did not report combined outcomes (Thompson et al. 2008). One study only included nine patients who had undergone neoadjuvant CRT and was therefore excluded from the analysis (Sujendran et al. 2008). The rate of CRM involvement was 11.2% (50/446) and 31.9% (259/812) according to the CAP and RCP criteria respectively.

6.4.9 Local recurrence related to CRM involvement

Two studies reported local recurrence outcome (Chao et al. 2011; Harvin et al. 2012) and both only included patients with T3 tumours who had undergone neoadjuvant CRT. The local recurrence rate was 35.3% (12/34) in patients with CRM involvement and 16.2% (45/277) in patients without CRM involvement according to the CAP criteria (OR 1.90 95% CI 0.84-4.28, p=0.12, I^2=0%). According to the RCP criteria, the local recurrence rate was 28.6% (34/119) in patients with CRM involvement and 12.0% (23/192) in patients without CRM involvement (OR 2.15 95% CI 1.15-4.01, p=0.02, I^2=0%).

6.4.10 Outcome in patients with CRM involvement of 0.1 to 1mm

Meta-analysis of the eight studies which used both definitions was performed to determine the outcome in patients differentiated by the RCP but not the CAP criteria (Table 6.4, Figures 6.4 and 6.5). Three and five year mortality was significantly higher in this group of patients compared with rates in those with no involvement within 1mm of the cut margin (OR 2.15 95% CI 1.59-2.91, p<0.001 and OR 2.05 95% CI 1.41-2.99, p<0.001 respectively). However, this difference in outcome was not significant in patients who had undergone neoadjuvant chemoradiotherapy.

6.4.11 Heterogeneity and publication bias

Statistical heterogeneity was identified in only three analyses using the RCP criteria: three and five year mortality in patients who had undergone surgery

alone, and five year mortality in all patients. There was no heterogeneity among analyses using the CAP criteria. The funnel plots for three and five year mortality rates for all patients were symmetrical, indicative of the absence of publication bias.

Table 6.1   Characteristics of studies included in the meta-analysis

First author, year	Country	CRM definition	Total No.	CRM at margin (per cent)	CRM ≤1mm (per cent)	No. ≥T3 (per cent)	Neo-adjuvant therapy	Survival related to CRM+ on MA	Mean follow-up (months)	NO
Chao 2011	Taiwan	CAP*& RCP	151	26 (17.2)	51 (33.8)	151 (100.0)	CRT	No	50.0	7
Deeter 2009	USA	CAP*& RCP	135	16 (11.9)	83 (61.5)	135 (100.0)	CRT	Yes	37.2	8
Dexter 2001	UK	RCP	135	N/A	64 (47.4)	95 (70.4)	None	Yes	19.0	8
Griffiths 2006	UK	RCP	249	N/A	79 (31.7)	145 (58.2)	CT	Yes	70.0	9
Harvin 2012	USA	CAP*& RCP	160	8 (5.0)	42 (26.3)	160 (100.0)	CRT	No	N/A	7
Khan 2003	UK	RCP	329	N/A	67 (20.4)	267 (81.2)	None	No	60.0	9
Pultrum 2010	Netherlands	CAP& RCP*	98	25 (25.5)	47 (48.0)	58 (59.2)	None	Yes	37.0	9
Rao 2012	UK	CAP& RCP*	115	17 (14.8)	57 (49.6)	80 (69.6)	CT	No	38.0	8
Saha 2009	UK	RCP	105	N/A	38 (36.2)	70 (66.7)	CT	Yes	26.0	8
Salih 2013	UK	CAP& RCP*	232	38 (16.4)	89 (38.4)	171 (73.7)	CT	No	18.0	8
Scheepers 2009	Netherlands	CAP& RCP*	110	17 (15.5)	42 (38.2)	86 (78.2)	CT	Yes	N/A	8
Sujendran 2007	UK	RCP	242	N/A	56 (23.1)	151 (62.4)	CT & CRT	Yes	N/A	8
Thompson 2008	Australia	RCP	240	N/A	85 (35.4)	127 (52.9)	CRT	No	N/A	8
Verhage 2011	Netherlands	CAP*& RCP	132	26 (19.7)	89 (67.4)	132 (100.0)	None	Yes	28.4	8

N/A: Not available, CAP: College of American Pathologist (CRM at margin), RCP: Royal College of Pathologist (CRM≤1mm), UA – univariable analysis, MA – multivariable analysis, NO – Newcastle-Ottawa Study Quality Score, CT – Neoadjuvant chemotherapy, CRT – neoadjuvant chemoradiotherapy. In studies which used both definitions of CRM involvement, * indicates the definition which is more prognostically significant.

Table 6.2   Three year mortality related to CRM involvement according to
a) RCP and b) CAP criteria.

a. **RCP criteria**

	No. of studies	CRM +		CRM -		OR (95% CI)	p	Heteroge-neity	
		Events	Total	Events	Total			I^2 %	p
All	13	607	861	652	1178	2.49 (2.02-3.06)	<0.001	38	0.08
Surgery	4	191	267	247	427	2.11 (1.47-3.03)	<0.001	68	0.02
NCT	6	267	392	257	507	2.88 (2.11-3.92)	<0.001	0	0.59
NCRT	3	149	202	148	244	2.34 (1.51-3.61)	0.001	54	0.12
T3	9	430	556	364	582	2.35 (1.79-3.10)	<0.001	0	0.70
T3N0	3	55	73	43	82	2.88 (1.43-5.77)	0.003	0	0.55
T3N1	3	86	97	99	121	1.92 (0.87-4.26)	0.110	0	0.83

b. **CAP criteria**

	No. of studies	CRM +		CRM -		OR (95% CI)	p	Heteroge-neity	
		Events	Total	Events	Total			I^2 %	p
All	8	128	173	515	960	3.13 (2.12-4.63)	<0.001	13	0.33
Surgery	2	39	51	101	179	3.69 (1.65-8.29)	0.002	0	0.85
NCT	3	45	72	163	385	2.40 (1.41-4.08)	0.001	60	0.08
NCRT	3	44	50	251	396	4.51 (1.91-10.7)	0.0006	0	0.84
T3	6	94	110	420	669	3.83 (2.20-6.69)	<0.001	0	0.35
T3N0	0					N/A			
T3N1	0					N/A			

RCP – Royal College of Pathologists; CAP – College of American Pathologists; N

– number of studies included; OR – Odds ratio; NCT – Neoadjuvant

chemotherapy; NCRT – Neoadjuvant chemoradiotherapy.

Table 6.3   Five year mortality related to CRM involvement according to
a) RCP and b) CAP criteria.

a. **RCP criteria**

	No. of studies	CRM +		CRM -		OR (95% CI)	p	Heterogen-eity	
		Events	Total	Events	Total			I^2 %	p
All	10	541	661	689	1034	2.52 (1.96-3.25)	<0.001	50	0.03
Surgery	4	219	261	263	414	3.08 (2.04-4.66)	<0.001	74	0.009
NCT	3	149	171	183	279	4.06 (2.39-6.89)	<0.001	44	0.17
NCRT	4	185	229	241	341	2.08 (1.34-3.22)	0.001	2	0.38
T3	8	438	529	492	659	1.94 (1.43-2.63)	<0.001	36	0.14
T3N0	2	50	58	42	60	2.65 (1.03-6.83)	0.040	0	0.49
T3N1	2	55	56	45	54	7.63 (1.33-40.6)	0.020	60	0.11

b. **CAP criteria**

	No. of studies	CRM +		CRM -		OR (95% CI)	P	Heterogen-eity	
		Events	Total	Events	Total			I^2 %	p
All	7	121	135	560	766	4.02 (2.25-7.20)	<0.001	21	0.27
Surgery	2	44	51	123	179	4.25 (1.66-10.9)	0.003	0	0.82
NCT	2	29	34	130	191	2.50 (0.96-6.53)	0.060	73	0.05
NCRT	3	48	50	307	396	6.34 (1.92-20.9)	0.002	0	0.50
T3	6	102	110	515	669	3.78 (1.88-7.57)	0.0002	30	0.21
T3N0	0					N/A			
T3N1	0					N/A			

RCP – Royal College of Pathologists; CAP – College of American Pathologists; N

– number of studies included; OR – Odds ratio; NCT – Neoadjuvant

chemotherapy; NCRT – Neoadjuvant chemoradiotherapy.

Table 6.4 Overall mortality in patients with CRM involvement between 0.1 and 1mm

a. **Three year mortality**

	No. of studies	CRM 0.1-1mm		CRM >1mm		OR (95% CI)	p	Heteroge-neity	
		Events	Total	Events	Total			I^2%	p
All	8	211	327	265	569	2.15 (1.59-2.91)	<0.001	31	0.18
Surgery	2	62	85	39	94	2.66 (1.36-5.20)	0.004	76	0.04
NCT	3	66	116	78	231	2.70 (1.68-4.33)	<0.001	0	0.66
NCRT	3	83	126	148	244	1.53 (0.94-2.49)	0.090	0	0.39
T3	5	159	229	202	345	1.75 (1.19-2.56)	0.004	0	0.44
T3N0	0					N/A			
T3N1	0					N/A			

b. **Five year mortality**

	No. of studies	CRM 0.1-1mm		CRM >1mm		OR (95% CI)	p	Heterogen-eity	
		Events	Total	Events	Total			I^2%	p
All	7	220	276	308	464	2.05 (1.41-2.99)	0.0002	52	0.05
Surgery	2	73	85	50	94	3.81 (1.72-8.45)	0.001	0	0.42
NCT	2	54	65	69	126	3.89 (1.85-8.18)	0.0003	0	0.50
NCRT	3	93	126	189	244	1.03 (0.59-1.79)	0.910	0	0.88
T3	5	184	229	259	345	1.50 (0.97-2.33)	0.070	22	0.28
T3N0	0					N/A			
T3N1	0					N/A			

Figure 6.1   Identification process for eligible studies

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┌─────────────────────────────┐   ┌─────────────────────────────┐
│ Records identified through  │   │ Records identified through  │
│    database searching       │   │       other sources         │
│         (n=709)             │   │          (n= 18)            │
└─────────────────────────────┘   └─────────────────────────────┘
              │                                  │
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        ┌───────────────────────────────────────────┐
        │     Records after duplicates removed        │
        │                (n=709)                      │
        └───────────────────────────────────────────┘
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                            ▼
        ┌───────────────────────────────────────────┐
        │       Records screened by abstract          │
        │                (n=709)                      │
        └───────────────────────────────────────────┘
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                            │──────────▶│      Records excluded       │
                            │           │          (n=691)            │
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        ┌───────────────────────────────────────────┐
        │      Full text assessed for eligibility     │
        │                 (n=30)                      │
        └───────────────────────────────────────────┘
                            │           ┌─────────────────────────────┐
                            │           │      Records excluded       │
                            │──────────▶│          (n=16)             │
                            │           │ 16 not meeting inclusion    │
                            │           │         criteria            │
                            │           └─────────────────────────────┘
                            ▼
        ┌───────────────────────────────────────────┐
        │     Studies included in meta-analysis       │
        │                 (n=14)                      │
        └───────────────────────────────────────────┘
```
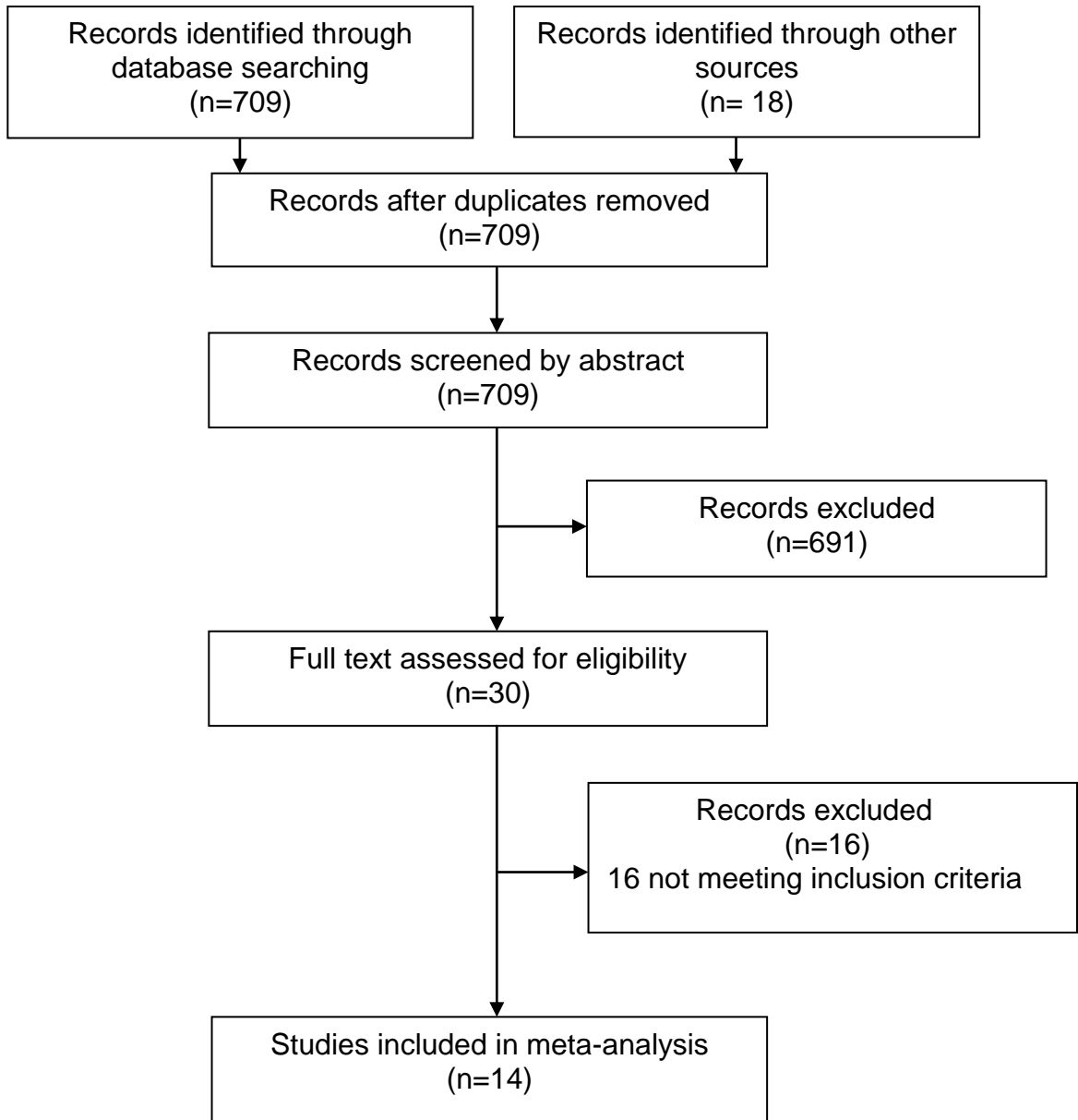
Figure 6.2 Influence of CRM involvement on 5 year mortality in all patients with oesophageal carcinoma according to the *RCP* criteria. Weights are from fixed effects analysis. Squares indicate the point estimates of the effect of disease (odds ratio) and diamonds the summary estimate from the pooled studies; 95% confidence intervals are indicated by horizontal bars and shown in parentheses.

Study or Subgroup	CRM + Events	CRM + Total	CRM - Events	CRM - Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chao 2011	63	77	44	74	10.1%	3.07 [1.46, 6.44]
Deeter 2009	63	83	35	52	12.8%	1.53 [0.71, 3.30]
Griffiths 2006	66	72	114	153	7.5%	3.76 [1.51, 9.36]
Harvin 2012	39	42	110	118	5.1%	0.95 [0.24, 3.74]
Khan 2003	52	67	186	262	21.0%	1.42 [0.75, 2.67]
Pultrum 2010	34	47	15	51	4.9%	6.28 [2.61, 15.11]
Rao 2012	45	57	35	58	9.0%	2.46 [1.08, 5.63]
Scheepers 2009	38	42	34	68	3.1%	9.50 [3.05, 29.55]
Sujendran 2007	0	0	0	0		Not estimable
Thompson 2008	58	85	81	155	22.5%	1.96 [1.13, 3.42]
Verhage 2011	83	89	35	43	3.9%	3.16 [1.02, 9.79]
Total (95% CI)		661		1034	100.0%	2.52 [1.96, 3.25]
Total events	541		689			

Heterogeneity: Chi² = 18.11, df = 9 (P = 0.03); I² = 50%
Test for overall effect: Z = 7.20 (P < 0.00001)

Odds Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100
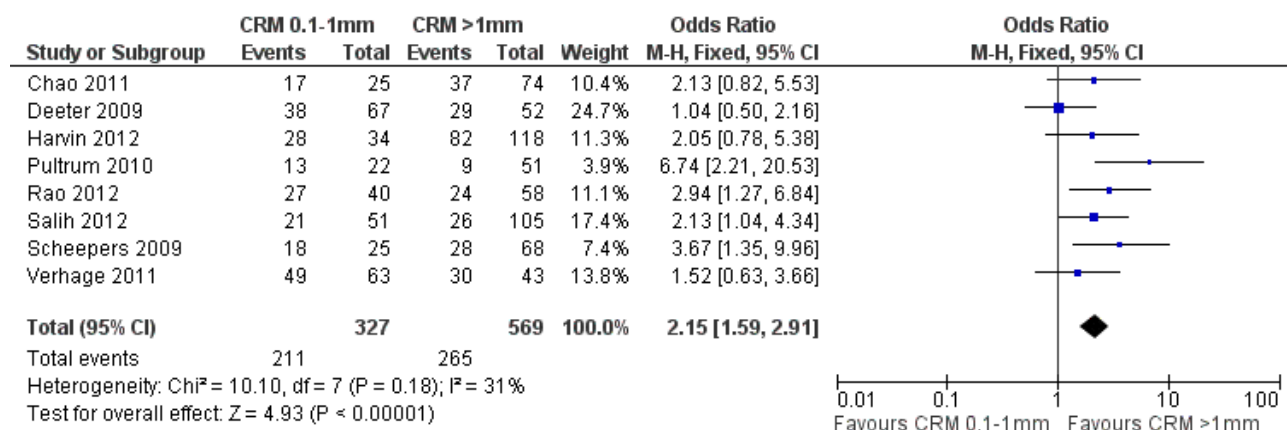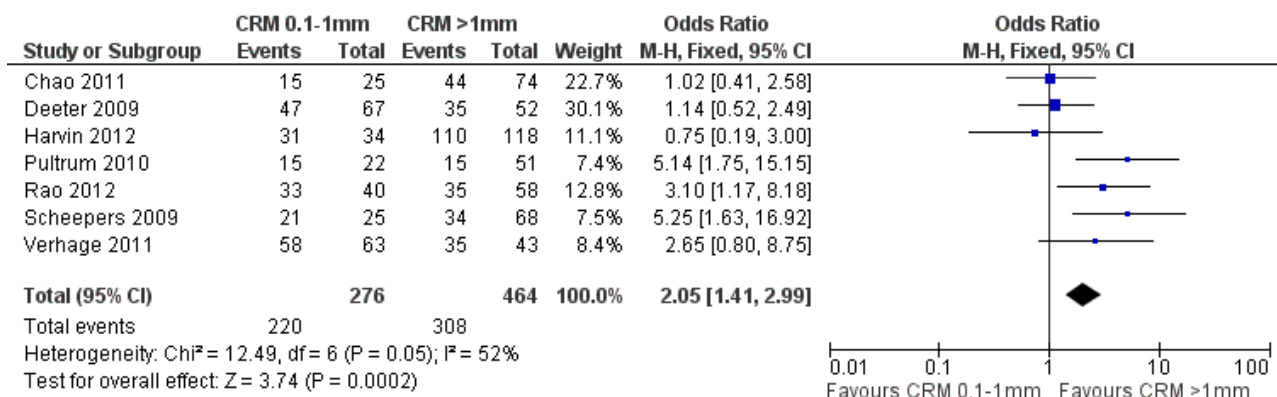Favours CRM +   Favours CRM -

Figure 6.3 Influence of CRM involvement on 5 year mortality in all patients

with oesophageal carcinoma according to the *CAP* criteria.

Study or Subgroup	CRM + Events	Total	CRM - Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chao 2011	24	26	83	125	14.5%	6.07 [1.37, 26.93]
Deeter 2009	16	16	83	119	4.0%	14.43 [0.84, 246.96]
Harvin 2012	8	8	141	152	5.8%	1.38 [0.07, 25.48]
Pultrum 2010	19	25	30	73	24.2%	4.54 [1.62, 12.71]
Rao 2012	12	17	67	98	38.4%	1.11 [0.36, 3.43]
Scheepers 2009	17	17	63	93	3.7%	16.81 [0.98, 288.91]
Verhage 2011	25	26	93	106	9.3%	3.49 [0.44, 28.01]
Total (95% CI)		135		766	100.0%	4.02 [2.25, 7.20]
Total events	121		560			

Heterogeneity: Chi² = 7.64, df = 6 (P = 0.27); I² = 21%
Test for overall effect: Z = 4.69 (P < 0.00001)

Odds Ratio M-H, Fixed, 95% CI — Favours CRM + Favours CRM -

Figure 6.4 Influence of CRM involvement between 0.1 and 1mm on three

year mortality in all patients with oesophageal carcinoma.

Study or Subgroup	CRM 0.1-1mm Events	Total	CRM >1mm Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chao 2011	17	25	37	74	10.4%	2.13 [0.82, 5.53]
Deeter 2009	38	67	29	52	24.7%	1.04 [0.50, 2.16]
Harvin 2012	28	34	82	118	11.3%	2.05 [0.78, 5.38]
Pultrum 2010	13	22	9	51	3.9%	6.74 [2.21, 20.53]
Rao 2012	27	40	24	58	11.1%	2.94 [1.27, 6.84]
Salih 2012	21	51	26	105	17.4%	2.13 [1.04, 4.34]
Scheepers 2009	18	25	28	68	7.4%	3.67 [1.35, 9.96]
Verhage 2011	49	63	30	43	13.8%	1.52 [0.63, 3.66]
Total (95% CI)		327		569	100.0%	2.15 [1.59, 2.91]
Total events	211		265			

Heterogeneity: Chi² = 10.10, df = 7 (P = 0.18); I² = 31%
Test for overall effect: Z = 4.93 (P < 0.00001)

Odds Ratio M-H, Fixed, 95% CI — Favours CRM 0.1-1mm Favours CRM >1mm

Figure 6.5 Influence of CRM involvement between 0.1 and 1 mm on five year mortality in all patients with oesophageal carcinoma.

Study or Subgroup	CRM 0.1-1mm Events	Total	CRM >1mm Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chao 2011	15	25	44	74	22.7%	1.02 [0.41, 2.58]
Deeter 2009	47	67	35	52	30.1%	1.14 [0.52, 2.49]
Harvin 2012	31	34	110	118	11.1%	0.75 [0.19, 3.00]
Pultrum 2010	15	22	15	51	7.4%	5.14 [1.75, 15.15]
Rao 2012	33	40	35	58	12.8%	3.10 [1.17, 8.18]
Scheepers 2009	21	25	34	68	7.5%	5.25 [1.63, 16.92]
Verhage 2011	58	63	35	43	8.4%	2.65 [0.80, 8.75]
Total (95% CI)		276		464	100.0%	2.05 [1.41, 2.99]
Total events	220		308			

Heterogeneity: Chi² = 12.49, df = 6 (P = 0.05); I² = 52%
Test for overall effect: Z = 3.74 (P = 0.0002)

Odds Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours CRM 0.1-1mm   Favours CRM >1mm

6.5   DISCUSSION

The main findings from the 14 studies identified were that three and five year mortality in patients with CRM involvement according to both CAP and RCP criteria were significantly higher compared with patients without CRM involvement. CRM involvement as defined by the CAP criteria differentiated a higher-risk group of patients than the RCP criteria as evidenced by the larger OR values in the three and five year mortality analysis of all patients. However, the group of patients overlooked by the CAP criteria did have a significantly poorer outcome compared to patients without CRM involvement. The RCP criteria therefore give important additional information compared with the CAP criteria. CRM involvement remained an important prognostic indicator despite being lower in patients who had undergone neoadjuvant chemoradiotherapy.

Fewer studies utilised the CAP criteria but analysis of studies utilising the RCP criteria resulted in heterogeneity limiting interpretation. The evidence for the RCP criteria was derived from reports regarding the surgical treatment of rectal cancer in which circumferential margins of less than 1mm were found to be important predictors of local recurrence and survival (Adam et al. 1994; Wibe et al. 2002). Arguably, application of these findings to the surgical treatment of oesophageal cancer is limited, as the oesophagus has no comparable anatomic boundaries such as the mesorectum, and is in close proximity to vital organs such as the heart, aorta and trachea. Oesophageal tumours therefore encounter a relatively small barrier to local invasion (Verhage et al. 2011). CRM involvement in oesophageal cancer is likely to reflect the presence of advanced disease rather than the performance of poor surgery and inadequate resection margin and CRM involvement according to the RCP criteria will consequently be higher (36.5 vs. 15.3%).

The presence of lymph node metastases appeared to negate the importance of CRM involvement with the odds ratio for three year mortality in patients with lymph node metastases straddling 1, indicating that CRM involvement was not associated with poorer outcomes. Conversely, the ORs for five year mortality were greater than 1, indicating that CRM involvement remained important. However, these outcomes should be interpreted with caution as only three studies which used the RCP criteria stratified for the presence of lymph node metastases (Griffiths et al. 2006; Sujendran et al. 2008; Scheepers et al. 2009).

The strengths of this study are the large sample size analysed, allowing the controversies surrounding the definition and prognostic significance of CRM involvement to be addressed. Only published studies were included as unpublished data from conference abstracts lack rigorous peer review. Two of the 14 studies were ostensibly about other prognostic variables such as histological grade of tumour and the number of lymph node metastases (Thompson et al. 2008; Mirnezami et al. 2010). The inclusion of such studies reduced concern about publication bias as the decision to publish was unrelated to CRM involvement and outcome. Moreover, in most analyses, heterogeneity was low, and there was no publication bias. Only high quality studies as assessed by the Newcastle-Ottawa score and studies with more than 100 patients were included in this analysis, thereby strengthening the conclusions. Most studies used similar histopathological specimen preparation and analysis, thus allowing comparison of CRM measurements.

This study has limitations. Meta-analysis of retrospective cohort studies is regrettably sensitive to confounding. Many factors influence prognosis following surgery such as age, stage of disease, surgical technique and use of neoadjuvant chemotherapy or chemoradiotherapy. In attempts to reduce confounding, 12 studies adjusted for two or more of these variables during analysis. Subgroup analysis was limited, as not all studies reported separate outcomes according to stage of disease and treatment, and not all studies reported five year mortality. Three year mortality rates were therefore analysed,

as this allowed inclusion of four additional studies (Dexter et al. 2001; Sujendran et al. 2008; Saha et al. 2009; Salih et al. 2013).

6.6   CONCLUSION

CRM involvement is an important and significant predictor of poor prognosis. The issue of a threatened CRM forms an integral part of the wider argument relating to the most appropriate neoadjuvant therapy regimes for patients with operable yet locally advanced oesophageal cancer. Although CRM involvement as defined by the CAP criteria differentiates a higher-risk group of patients than the RCP criteria, this system overlooks the group of patients with poorer outcomes identified by the RCP system where there is tumour within 1 mm of the margin. Consensus regarding the most accurate and prognostically important definition of CRM involvement would be welcome; in the interim, arguably the exact nearest distance of the oesophageal tumour from the CRM should form part of routine pathology reporting in oesophageal cancer.

Chapter 7

General discussion and prospect

GENERAL DISCUSSION AND PROSPECT

The management of patients diagnosed with oesophagogastric cancer has evolved significantly over the past few decades. Despite contemporary multidisciplinary approach with improvements in staging and patient selection, outcomes remain poor when compared with other malignancies. This is largely the result of late presentation with advanced incurable disease, however radical surgery and toxic chemo-radiotherapy regimes are associated with significant morbidity.

Further improvements can be achieved by increasing our understanding of the prognostic factors which may be gained from various staging modalities and the assessment of tumour histology which are used to guide management. This thesis examines key uncertainties and controversies in the staging and treatment of patients with oesophagogastric cancer. It follows the patient journey from pre-operative staging after diagnosis, surgical treatment in the era of centralisation of specialist services, through to the examination of post-operative histological factors which influence prognosis. Specifically, this thesis addresses the combined role of PET/CT and EUS-defined tumour characteristics, the impact of centralisation on survival, the prognostic significance of HER2 expression and CRM involvement in patients with operable oesophageal cancer.

7.1 PET/CT AND EUS

PET/CT has been integrated into contemporary radiological staging algorithms for patients diagnosed with oesophageal cancer with the confirmed benefit of upstaging and altering management in up to 25% of patients (Gillies et al. 2011; You et al. 2013). EUS is the principal modality for assessing local tumour characteristics including total length of disease and tumour volume which have been shown to be significant predictors of survival (Twine et al. 2010; Davies et al. 2012).

Additional information such as the degree of tracer uptake by the tumour (SUV_{max}) and N stage can be obtained from PET/CT imaging. Although a high SUV_{max} was associated with poor survival only on univariate analysis, SUV_{max} correlated significantly and positively with EUS-defined tumour volume (Chapter 2). This suggests that SUV_{max} may be used as a surrogate marker of tumour burden and could refine the prognostication of these patients. Moreover, along with EUS-defined tumour volume, PET/CT defined N stage was shown to be an independent predictor of poor prognosis.

Future research would be directed towards assessing the relative accuracy of PET/CT in assessing peritumoural and distant lymph node metastasis when compared with histolopathological N stage. A comparison between PET/CT and EUS-defined length of tumour and tumour volume must be investigated to determine the most accurate modality as this additional information would guide surgical and neoadjuvant treatment.

7.2   CENTRALISATION OF UPPER GI CANCER SERVICES

There has been a wealth of evidence supporting concentration and centralisation of oesophagogastric cancer surgery in large centres resulting in significant improvements in both short-term surgical outcomes and long-term survival (Anderson et al. 2011; Brusselaers et al. 2014). Despite the recommendations from the NHS Improving Outcomes Guidance which advocate centralisation of upper gastrointestinal services in units performing a minimum of 15 resections per year, progress has been slow and sporadic. Of the centres which have centralised, only a few have reported short-term outcomes after reconfiguration of services. The only report from Wales has shown that centralisation resulted in lower morbidity, mortality and length of hospital stay in patients undergoing surgery (Chapter 3). Moreover, one year survival increased in all patients diagnosed with oesophagogastric cancer. These positive results will lend support to reconfiguration of services in other areas and specialties.

The reasons for the witnessed improvements are multi-factorial; more frequent MDT meetings, improved staging and patient selection, increased use of palliative chemotherapy and improved peri-operative care. The South-East Wales Upper GI Cancer Network serves a population of 1.4 million, most of whom reside in areas of significant socio-economic deprivation resulting in diagnostic delays which may negatively influence outcomes. Further research investigating the effects of deprivation and diagnostic delays on outcomes will guide health policy makers to prioritise funding into preventing these delays.

In tandem with centralisation, the enhanced recovery after surgery programme was established after unequivocal evidence supporting its benefits in colorectal surgery. Future research must be directed towards establishing its safety in oesophagogastric surgery and identifying the significance of individual components of the programme. This includes preoperative optimisation of patients' nutritional status as malnutrition is associated with poor outcomes. Patients with oesophagogastric cancer are especially likely to suffer from substantial weight loss. Objective assessments of sarcopaenia with CT-measured psoas muscle density and body composition with bioelectrical impedance analysis would further contribute to the understanding of how these physiological factors can be optimised to improve outcomes.

An important aspect of centralisation of cancer services that has been neglected is its economic impact (Ke et al. 2012). It is still not known if centralisation increases or decreases the overall costs to the NHS and if it is cost-effective in terms of quality-adjusted life years. Centralisation also leads to increased costs of accessing healthcare by patients and their carers and the overall impact on them will need to be quantified. There has been a trend towards centralisation of cancer services despite the lack of evidence that it will lead to cost-effective care. Therefore, there is a strong need for good quality studies aimed at determining which aspects of centralisation which would lead to efficient health care, thus informing policy decision makers in the reorganisation of cancer services.

7.3 HER2 OVEREXPRESSION AND AMPLIFICATION

Over the last decade, drugs targeting different growth factors and their receptors have been championed in the treatment of various cancers. The role and prognostic significance of these various growth factors in oesophagogastric cancer remain uncertain. Targeted therapy towards the HER2 receptor (trastuzumab) is currently used with palliative intent in patients with advanced gastric cancer with evidence of HER2 overexpression or amplification. The relationship between HER2 overexpression in oesophageal cancer is controversial. Reports vary in the method of identifying HER2 overexpression and the heterogeneity observed in oesophagogastric tissue samples add to the uncertainties. The findings reported in the meta-analysis of 14 studies confirm that HER2 overexpression and gene amplification was a significant predictor of poor prognosis in patients with operable oesophageal cancer (Chapter 4). Although these findings were not reproduced in our unit due to the small sample size, the results from Chapter 5 showed that endoscopic biopsy had a high specificity and negative predictive value in determining HER2 status.

Future research must be directed towards the role of anti-HER2 therapy in the neoadjuvant setting prior to oesophagectomy and in the palliative setting in patients with advanced oesophageal cancer. Although recruiting sufficient number of patients for these trials would be difficult in individual units, a well-designed, multi-national collaborative could overcome these recruitment challenges.

7.4   CRM INVOLVEMENT

The prognostic role and definition of CRM involvement in oesophageal cancer are widely debated issues and currently, no formal consensus exists. The findings reported in Chapter 6 are arguably the most significant of this thesis. The meta-analysis of 14 studies of over 2400 patients with operable oesophageal cancer confirms the significance of CRM involvement as a predictor of poor prognosis. Moreover, the definition of CRM involvement according to the CAP criteria differentiates a higher-risk group than the RCP criteria, but overlooks a patient group with similar poor outcomes. The RCP criteria therefore give important additional information when compared with the CAP criteria. Whilst a consensus is being reached, the exact nearest distance of the tumour from the CRM should be reported in oesophageal cancer.

The issue of an involved CRM forms an integral part of the much wider argument regarding the optimum neoadjuvant therapy regimes for patients with operable yet locally advanced oesophageal cancer. The rates of CRM involvement were lower in patients who had undergone neoadjuvant chemoradiotherapy. Future research should therefore be targeted towards identifying the role of neoadjuvant chemoradiotherapy in patients with T3 tumours who have a high risk of CRM involvement. The results of the NeoSCOPE trial, a multi-centred trial based in Cardiff of two pre-operative chemoradiotherapy regimes are greatly anticipated (Gwynne et al. 2013).

Definitive chemoradiotherapy has been shown to be an effective alternative to surgery in patients with oesophageal cancer in various case series. However, no

randomised controlled trial (RCT) has been conducted to compare these treatment modalities. Propensity score analysis is an alternative to RCTs in situations when interventions cannot be allocated randomly as it adjusts for potential confounders such as baseline demographics or interventions in observational data (Austin 2011). Such analyses can be used to determine the outcomes of dCRT in patients with oesophageal cancer from large observational studies.

7.5   CONCLUSION

The diagnosis of oesophagogastric cancer is still considered to be a sentence of death by many clinicians. However, significant improvements in staging, perioperative care, surgical and oncological treatment have been achieved and continue to challenge this view. Further research should strive to increase earlier diagnosis and accurate stage directed multidisciplinary treatment will remain to be the foundation of the management of these patients. The hypothesis and results generated in this thesis should be built upon to further improve treatment algorithms and outcome for patients with oesophagogastric cancer.

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J Thorac Oncol **8**(12): 1563-1569.

APPENDIX 1

Publications, communications and prizes derived from work in this thesis

1.1 Published articles

<u>**Chapter 2**</u>   **Chan DSY**, Fielding P, Roberts SA, Reid TD, Ellis-Owen R, Lewis WG. Prognostic significance of 18-FDG PET/CT and EUS defined tumour characteristics in patients with oesophageal cancer.
Clin Rad 2013; **68**(4):352-357.

<u>**Chapter 3**</u>   **Chan DSY,** Reid TD, White C, Willicombe A, Blackshaw G, Clark GW, Havard TJ, Escofet X, Crosby TD, Roberts SA, Lewis WG.
Influence of a regional centralised upper gastrointestinal cancer service model on patient safety, quality of care and survival.
Clin Oncol 2013; **25**(12):719-25.

<u>**Chapter 4**</u>   **Chan DSY**, Twine CP, Lewis WG.
Systematic review and meta-analysis of the influence of HER2 expression and amplification in operable oesophageal cancer.
J Gastrointest Surg 2012; **16**(10):1821-1829.

<u>**Chapter 5**</u>   **Chan DSY**, Campbell F, Edwards P, Jasani B, Williams GT, Lewis WG. Relative prognostic value of Human Epidermal Growth Factor 2 (HER2) receptor expression in operable oesophagogastric cancer*.*
ISRN Surgery 2012; **2012**:804891.

<u>**Chapter 6**</u>   **Chan DSY**, Reid TD, Howell I, Lewis WG.
Systematic review and meta-analysis of the influence of circumferential margin involvement on outcomes in patients with operable oesophageal cancer.
Br J Surg 2013; **100**(4):456-464.

1.2 Published abstracts

Chan DSY, Campbell F, Reid TD, Edwards P, Jasani B, Williams GT, Lewis WG.
Prognostic significance of HER2 expression in operable oesophageal and gastric cancer.
Gastroenterol 2012; **142 (S1)**: 528.

Chan D, Reid T, Havard T, Clark G, Lewis W.
Upper gastrointestinal cancer service multidisciplinary team centralisation allied to enhanced recovery after surgery improve outcomes significantly; a prospective observational cohort study.
Br J Surg 2012; **99 (S6)**:28.

Chan DSY, Reid TD, Campbell F, Edwards P, Jasani B, Williams GT, Lewis WG.
Prognostic significance of HER2 expression in operable gastric cancer.
Proceedings of the Welsh Surgical Society 2011; **57**.

1.3 Oral presentations to learned societies

Chan DSY, Reid TD, Crosby TD, Clark G, Lewis W.
Multidisciplinary Upper Gastrointestinal Cancer Team Service Centralization and Enhanced Recovery improve patient safety, outcome quality and survival significantly.

Association of Surgeons of Great Britain and Ireland, Liverpool, 2012.
Welsh Association of Gastroenterologists and Endoscopists, Llandrindod Wells, 2011.
Dr WT Edwards Medal Research Presentation – Prize Winner, Cardiff, 2012.

Chan DSY, Reid TD Campbell F, Edwards P, Jasani B, Williams GT, Lewis WG. Relative prognostic value of HER2 expression in operable oesophageal and gastric cancer.

Prize Session, European Society of Esophagology, Newcastle-upon-Tyne, 2011.

1.4 Poster presentations to learned societies

Chan DSY, Twine C and Lewis WG.
Systematic review and meta-analysis of HER2 overexpression in patients with operable oesophageal cancer.

Digestive Disease Federation, Liverpool, 2012.

Chan DSY, Reid TD, Crosby TD, Clark G, Lewis W.
Multidisciplinary Upper Gastrointestinal Cancer Team Service Centralization and Enhanced Recovery improve patient safety, outcome quality and survival significantly.

Digestive Disease Week May, San Diego, 2012.

Chan DSY, Reid TD Campbell F, Edwards P, Jasani B, Williams GT, Lewis WG. Relative prognostic value of HER2 expression in operable oesophageal and gastric cancer.

Digestive Disease Week, San Diego, 2012.
Welsh Surgical Society, Llantrisant, 2011.

1.5 Prizes awarded

1. Chapter 2:   Editor's Medal for Best Paper in *Clinical Radiology* in 2013
2. Chapter 2:   Robert and Elma Kemp Harper Prize for Best Paper in gastrointestinal radiology in *Clinical Radiology* in 2013
3. Chapter 3:   Best Research Registrar Prize – *Cardiff Medical Society*

1.6 Citation indices

Number of citations according to *Google Scholar* (01/06/15)

Chapter 2	7
Chapter 3	1
Chapter 4	21
Chapter 5	2
Chapter 6	17