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An economic analysis of contemporary oesophagogastric cancer care in a regional UK cancer network and analysis of factors relating to post-operative outcomes

JENNIFER WHEAT

Dedication

To the supervisors and supporters of this thesis

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Glossary of terms

A&E	Accident and Emergency
ABC	Activity-Based Costing
AL	Anastomotic Leak
ASR	Age-Standardised Rate
AUGIS	Association of Upper Gastrointestinal Surgeons
BNF	British National Formulary
BOSS trial	Barrett's Oesophagus Surveillance Study
BSC	Best Supportive Care
CBA	Cost-Benefit Analysis
CCG	Clinical Commissioning Group
CDC	Clavien Dindo Classification
CLASSIC	Adjuvant capecitabine plus oxaliplatin for gastric cancer trial. Post-operative chemotherapy compared with surgery alone
CNS	Clinical Nurse Specialist
CPEX	CardioPulmonary EXercise test
CPR	Complete Pathological Response
CRM	Circumferential Resection Margin
CROSS	ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or Junctional cancer (CROSS) trial
NEO-AEGIS	NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study. Compares perioperative chemotherapy with neoadjuvant chemoradiotherapy
CT	Computerised Tomography
DALY	Disability-Adjusted Life Year
dCRT	definitive ChemoRadioTherapy
Df	Degrees of freedom

DFS	Disease-Free Survival
DNA	DeoxyriboNucleic Acid
ECG	Electrocardiograph
ECOG	Eastern Cooperative Oncology Group
ECX	Chemotherapy regime comprising: Epirubicin, Cisplatin and Capecitabine
EMR	Endoscopic Mucosal Resection
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D	EuroQol -5 Dimensions: a measurement of quality of life devised by the EuroQol research group
ERAS	Enhanced Recovery After Surgery
ERP	Enhanced Recovery Programme
ESD	Endoscopic Submucosal Dissection
EUS	Endoscopic Ultrasound
FACT-G	Functional Assessment of Cancer Therapy - General
FLOT	Chemotherapy regime comprising: Fluorouracil (5FU), Leucovorin, Oxaliplatin and Docetaxel
FOLFOX	Chemotherapy regime of: FOLinic acid (leucovorin), Fluorouracil and OXaliplatin
GIRFT	Getting It Right First Time programme
GORD	Gastro-Oesophageal Reflux Disease
GP	General Practitioner
HDU	High Dependency Unit
HGD	High Grade Dysplasia
HR	Hazard Ratio
hrQOL	health-related Quality Of Life
HSUV	Health State Utility Value
HUI 3	Health Utilities Index 3
ICER	Incremental Cost Effectiveness Ratio
IQR	Inter-Quartile Range
LN	Lymph Node
LOHS	Length of Hospital Stay

MAGIC	MRC (medical research council) Adjuvant Gastric Infusional Chemotherapy trial: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer
MDT	MultiDisciplinary Team
MIO	Minimally Invasive Oesophagectomy
MRI	Magnetic Resonance Imaging
MSS	Clavien Dindo Morbidity Severity Score
NACRT	NeoAdjuvant ChemoRadioTherapy
NACT	NeoAdjuvant ChemoTherapy
NEOSCOPE	A feasibility study of chemoradiotherapy to treat operable oesophageal cancer
ACA	Adenocarcinoma
NHS	National Health Service
NICE	National Institute of health and Care Excellence
NICE HTA	Health Technology Assessment
NOGCA	National OesophagoGastric Cancer Audit
OCCAMS	Oesophageal Cancer Clinical And Molecular Stratification is a network of clinical centres recruiting patients for molecular research
OEO2 trial	MRC (medical research council) oesophageal cancer working group randomised controlled trial into oesophageal resection with or without neoadjuvant chemotherapy
OGD	Oesophago-Gastro-Duodenoscopy
OS	Overall Survival
PACU	Post-Anaesthetic Care Unit
PET-CT	Computerised Tomography performed after administration of ^{18}F-labelled fluoro-2-deoxyglucose Positron Emission Tomography. Metabolically active tissue concentrates uptake of the radiolabelled marker ^{18}F-FDG, which is then imaged using positron emission tomography combined with CT.
PFT	Pulmonary Function Test

PICC	Peripherally Inserted Central Catheter
PSSRU	Personal Social Services Research Unit
QALY	Quality of Life Year
QOL	Quality Of Life
R1	The R classification refers to the absence or presence of residual tumour after treatment. R0 is no residual disease, R1 is microscopic residual disease, R2 is macroscopic residual disease. It can be used in both clinical and pathological assessments but is usually used in the context of pathological assessment of a resection specimen. The classification was adopted by the UICC in 1987.
RFA	RadioFrequency Ablation
ROCS trial	Radiotherapy after Oesophageal Cancer Stenting
SCC	Squamous Cell Carcinoma
SF-36	Short Form (36) health survey: QOL questionnaire
SLM	Surgeon Level Mortality
SPSS	Statistical Package for the Social Sciences: Statistical analysis software owned by IBM (IBM Corporation, Armonk, New York, USA). Versions 20-25 for Mac are used in this thesis.
THO	TransHiatal Oesophagectomy
TNM	Tumour, Nodes, Metastases staging classification. It can have the precursors ‘c’ or ‘p’ to distinguish between clinical and pathological staging, and the prefix ‘yp’ when a specimen is classified after neoadjuvant oncological therapy has been administered.
ToGA	A study of Trastuzumab in combination with chemotherapy compared with chemotherapy alone in patients with HER2-positive advanced gastric cancer
TTO	TransThoracic Oesophagectomy
UGI	Upper GastroIntestinal
UICC	International Union against (Contra) Cancer

UK	United Kingdom
US	United States of America
VAS	Visual Analogue Scale
VTE	Venous ThromboEmbolism
WHO	World Health Organisation
WTE	Whole Time Equivalent

Contents

Summary

This thesis explores the cost-effectiveness of the full spectrum of management options for oesophagogastric cancer, according to stage of disease. There has been a paradigm shift in decision-making regarding oesophagogastric cancer towards greater consideration of quality of life outcomes and a financially-driven interest in the cost-effectiveness of treatment in the NHS.

The triad of cost per treatment option, analysis of stage-for-stage, treatment-by-treatment survival and an in-depth review of health-related quality of life as an outcome of oesophageal and gastric cancer treatment allows cost-utility analysis to be performed. This generates a cost per quality adjusted life year (QALY) according to stage, for contemporaneous oesophagogastric cancer care in a UK setting. These studies provide evidence that treating early stage disease is vastly more cost effective than treating advanced disease, and some treatment pathways for advanced disease exceed the cost per QALY gained 'willingness to pay' thresholds used by the National Institute of Health and Care Excellence (NICE).

The accuracy and value of quality assurance metrics are explored using surgeon-level, department-level, and unit-level mortality data from one UK region. Morbidity rates as a quality assurance tool are explored as an alternative, or adjunctive consideration in the assessment of surgeon performance. The study found that annual quality assurance metrics demonstrate the most variation, and 3-year metrics may be more representative. Quality indicators such as lymph node harvest, circumferential resection margin (CRM) positivity, serious post-operative complications such as anastomotic leak rates add granularity to the assessment of surgeon performance.

Periodically, new technologies revolutionise the investigation or management of disease. The routine use of positron emission

tomography- computerised tomography (PET-CT) in the staging of oesophageal cancer shows independently significant improvements in overall and disease-free survival, and significantly fewer patients develop recurrence, with a particular reduction in distal recurrence.

Published Works

Published abstracts

0657
Wheat J, Karran A, Blake P, Chan D, Lewis W.
Surgeon-level outcome reporting for Upper GI (UGI) cancer operative mortality: a view from over Offa's Dyke
British Journal of Surgery. 2015 September 102 (S7): 9-87

0983
Wheat J, Karran A, Blake P, Anderson P, Lewis W.
Relative cost per life-year gained of treatments with curative intent for T3NxM0 upper gastrointestinal cancer
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Surgeon-level outcome reporting for Upper GI (UGI) cancer operative mortality: a view from over Offa's Dyke
Presented at Association of Surgeons of Great Britain and Ireland, May 2015, Manchester, UK.

Wheat J, Karran A, Blake P, Anderson P, Lewis W.
Relative cost per life-year gained of treatments with curative intent for T3NxM0 upper gastrointestinal cancer
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Chapter 1: Introduction and review of the literature

Management of oesophagogastric cancers has been transformed over the last decade with change driven by evolution of the disease incidence and advances in the diagnostic tests and treatments.

Background of oesophagogastric cancer

Oesophagogastric cancers affect the upper gastrointestinal tract from the lower end of cricopharyngeus muscle to the gastric pylorus. Cancers are treated differently according to cell type and the site of origin. In the Western world, nearly half of all oesophagogastric cancers present at an advanced stage, where only palliative therapies are possible. (1) Treatments with curative intent include surgery, endoscopic resection, and definitive chemoradiotherapy for oesophageal malignancies. Endoscopic resection or surgery are the only potentially curative treatments available for gastric cancer. (3)

Once diagnosed, pre-treatment staging is performed to determine which treatments are suitable. Investigations can identify those patients with metastatic disease for whom curative intent is not possible. Staging accuracy has improved with the widespread use of advanced imaging techniques, such as positron emission tomography- computed tomography (PET-CT), endoscopic ultrasound (EUS), and staging laparoscopy. (3) (4) Risk stratification pre-operatively, by means of cardiopulmonary exercise testing, has improved the prediction of poor outcomes, which can tailor the management of patients peri-operatively (5).

The 5-year survival rate for oesophageal cancer remains one of the lowest in the top 21 types of cancer in the UK, with rates in the order of 10-19%. (6) (7) Approximately 40% of patients have metastatic disease at presentation. (1) (8)

Across countries where oesophagogastric cancer services have been centralised, patient outcomes have improved. (9) (10) The Improving Outcomes Guidance, published in 2001, recommended that each UK regional centre serves a population greater than 1 million, and therefore each surgeon and Multidisciplinary Team (MDT) within the centre operates on a greater number of patients compared to pre-centralisation. (11) The implementation of Enhanced Recovery Programmes (ERPs) has shown improvements in outcomes (12), and advances in definitive chemoradiotherapy (dCRT) have meant that dCRT is now considered an effective alternative to oesophageal surgery for specific disease stages. (13) Emerging data from national trials such as NEOSCOPE shows improved outcomes with neoadjuvant chemoradiotherapy for oesophageal cancer. (14)

Epidemiology

In terms of the global incidence of cancer, gastric cancer is fourth most common, but is the second most common cause of death from cancer. Oesophageal cancer is eighth most common and the sixth most common cause of cancer death. (15) (16) Squamous cell carcinoma (SCC) remains the most common type of oesophageal cancer globally, accounting for approximately 50% of oesophageal cancers. In the Western world, adenocarcinomas (ACA) have rapidly increased in incidence in the last 30 years, (17) (18) now accounting for 67% of oesophageal cancers in the 2017 National Oesophago-Gastric Cancer Audit (NOGCA). (4) Rarer forms of oesophageal cancer include small cell cancer and gastro-intestinal stromal tumours (GISTs). Oesophagogastric junction tumours are subclassified according to the Siewert classification, into types 1 (1-5cm above the cardia), 2 (1cm above to 2cm below the cardia), and 3 (2-5cm below the cardia). (19) Overall, the incidence of gastric cancer has decreased, which sometimes obscures the rapid rise in oesophagogastric junction tumours. (6) (20)

In the US the median age at diagnosis of oesophageal cancer and gastric cancer is 67 and 69 respectively. (21) (22) The age-specific incidence rises sharply beyond 65 years old for both types of cancer (6) (20), thereby most are diagnosed in retirement. The cohort considered for major resectional surgery often have significant (frequently age-related) co-morbidities.

Across the globe, both oesophageal and gastric cancers are more common in men, with twice as many men developing gastric cancer than women, eight men develop oesophageal SCC for every woman, and men are diagnosed three times more frequently than women with oesophageal ACA. (23) (24) Similar differences in incidence between sexes are seen in the UK population. (6) (20)

Estimates from the World Health Organisation show wide variability in the geographic incidence of both gastric and oesophageal cancer. (25) (26) The consequence of this is that incidence and outcome data is not always generalisable across populations with high estimates of incidence to those with low estimates of incidence, and vice versa. Distinct management strategies must be employed in different environments, for example, the incidence of gastric cancer in Japan justifies a screening programme (27), and dysplasia within Barrett's oesophagus can be resected or ablated to reduce risk of progression to cancer (28).

Pathogenesis

Gastric cancer

Two competing theories predominate regarding the pathogenesis of gastric adenocarcinoma. The Correa hypothesis (29) states that gastric cancer is the product of decades of step-wise change from gastric atrophy to intestinal metaplasia to malignant mutational or cell change. Environmental factors such as tobacco smoking, a diet high in nitrosamines, and exposure to *Helicobacter pylori* are considered to be mediators in this process. Indeed, tobacco smoking causes inflammatory

change of the gastric mucosa, and increases the risk of developing gastric cancer with a relative risk of 1.76 compared to non-smokers (30). Diets high in salted or pickled foods, refined carbohydrates and dried fish or meat increase the risk of developing gastric cancer (31). Conversely, a diet rich in antioxidants appears to be protective (32). These dietary changes may account in part for the higher incidence of gastric cancer in low socioeconomic groups. *H. pylori* infection has been designated as a WHO group 1 carcinogen (33) since 1994. A variety of virulence and host factors are hypothesised to create a local cellular environment with oxidative stress, causing susceptibility to malignant transformation. (34)

More recently genomic sequencing has changed the paradigm in gastric cancer pathogenesis to the consideration of subtypes: Epstein-Barr virus, microsatellite unstable, genomically stable, and chromosomally unstable tumours. (35) This may account for the observation that some gastric cancers do not appear to progress through an inflammation-atrophy-metaplasia sequence, and also contribute to understanding which subgroups are most likely to benefit from oncological or immunological therapy. Molecular subgroup analysis appears to correlate with chemoresponsiveness and survival. (36)

Oesophageal squamous cell carcinoma

Smoking or chewing of tobacco, and alcohol consumption are the main risk factors for development of squamous cell carcinoma (SCC) in the western world. The effects are dose-related: higher alcohol intake increases the risk of oesophageal SCC (37), as does greater amounts of smoking (38). Smoking and alcohol together increase the risk of SCC to a greater degree than each factor on their own. (39) The carcinogenic effect affects the entire aerodigestive tract, therefore patients with a head and neck SCC (oropharynx, supraglottis, transglottis and hypopharynx) are at higher risk of developing an oesophageal SCC compared with a baseline population without a head and neck cancer. A study of over 40,000 patients from the USA showed a 14.2% risk of a second

aerodigestive tract cancer in those already diagnosed with SCC at one aerodigestive site. (40)

Dietary factors are implicated in the development of oesophageal SCC. A diet high in fruit and vegetables is shown to be protective (41), whereas diets high in pickled vegetables have been associated with oesophageal SCC development in Chinese populations. Higher rates in oesophageal SCC are also seen in populations with zinc and selenium deficiencies (42). Exposure to high levels of polycyclic aromatic hydrocarbons which cause DNA damage are considered possible explanations of the high incidences of oesophageal SCC in Iran (43) and China. (44) The Iranian study demonstrates a dose-dependent significant association of high levels of polycyclic aromatic hydrocarbons from opium smoking (hazard ratio 1.85), and indoor air pollution (hazard ratio 1.57) with development of oesophageal SCC. Regularly drinking hot drinks (over 60 degrees Celsius), which causes thermal damage to the oesophagus, is also associated with an increased risk of developing oesophageal SCC (hazard ratio 1.6). (43)

It has long been known that caustic injury to the oesophagus increases the risk of oesophageal SCC 1000-fold, usually developing 15-40 years after the injury (45). Moreover, a history of achalasia increases the risk of SCC development, usually more than 10 years after the diagnosis of achalasia is made. It is thought that inflammation of epithelial cells from stagnant fermenting food in the oesophagus predisposes to cancer formation, with up to a 10-fold increased cancer risk (46). Other conditions which result in static food in the oesophagus also predispose to oesophageal SCC, such as the oesophageal webs of Plummer-Vinson syndrome (47). There is an increased risk of SCC where the radiotherapy field includes the oesophagus, with a 5.42 relative risk 10 or more years after breast cancer radiation and 4.3 times greater risk 12 or more years after supradiaphragmatic radiotherapy for Hodgkin lymphoma. (48) (49)

Oesophageal adenocarcinoma

Adenocarcinoma (ACA) constitutes 72% of the 7000 patients a year diagnosed with oesophageal or Siewert types 1 or 2 junctional tumours in the UK. (4) Increasing age is the greatest risk for developing oesophageal ACA, due to cumulative DNA damage (50). In the UK there are four times as many men compared with women who develop distal oesophageal or Siewert type 1 ACA, a pattern which is similar around the world. The male predominance in ACA is not fully understood. It is most defined in developed countries compared with developing countries where the difference is less distinct. (51) The difference cannot be entirely explained by increased exposure to known risk factors for oesophageal ACA: obesity; gastro-oesophageal reflux disease (GORD); and smoking exposure is now similar between men and women in many parts of the developed world. (52,53)

Whilst not as strong a risk factor for ACA compared with SCC, tobacco smoking is a major risk factor for the development of oesophageal ACA because smoking acts as an accelerant for DNA damage and decreases the tone of the lower oesophageal sphincter, allowing more reflux episodes to occur. (53)

The interplay between gastro-oesophageal reflux disease (GORD), obesity and Barrett's metaplasia is complex. A 2013 systematic review showed 10-30% of the US and European population have symptomatic GORD daily, compared with a prevalence under 10% in east Asian studies (54). GORD increases the risk of developing oesophageal ACA 5 to 7 -fold (55) (56), by refluxate causing chemical stress and mucosal injury of the oesophageal squamous epithelium. GORD alone confers a small increase in risk of oesophageal cancer, with a hazard ratio of 1.7 compared to an asymptomatic cohort, whereas oesophagitis has a hazard ratio of 2.2. (57)

Barrett's oesophagus is the process by which the chemical stress and mucosal injury caused by refluxate causes cellular metaplasia in a metaplasia-dysplasia-carcinoma sequence (58). Of those with symptomatic GORD, there is a 5% progression to Barrett's oesophagus, and of the Western population, 2% have Barrett's oesophagus. (59) Figures for the numbers of patients with Barrett's oesophagus who develop oesophageal cancer vary greatly. Large-scale studies have reported a lifetime risk of developing oesophageal ACA of 5% for men and 3% for women (59). The risk of oesophageal ACA has a hazard ratio of 10.6 in a UK cohort study (57), however some other studies suggest the risk imbued by Barrett's oesophagus is over-reported (60). A longer segment of disease (60), being male (59), white (61), obese (62), family history (63), smoking (64), worse severity and increasing frequency of GORD symptoms (55), and dysplasia present at index endoscopy (60) all increase the risk of developing oesophageal ACA. Approximately two thirds of resected oesophageal ACA specimens have Barrett's change. (65)

Obesity, especially visceral obesity, increases the likelihood of developing both GORD (66) and Barrett's oesophagus (62). Over the last few decades there has been a global rise in obesity levels, especially in the Western world (67), and the oesophageal ACA rates follow these trends (17). The pathophysiology is largely due to the increased frequency of GORD and subsequent Barrett's change with obesity. Higher intra-abdominal pressure compared with the intra-thoracic pressure overcomes the lower oesophageal sphincter barrier pressure, which makes reflux more likely. However, obesity is also an independent risk factor for the development of oesophageal ACA. (68) *In vitro* studies have shown adipocyte-derived mediators such as leptin to be independently associated with an increased progression to oesophageal cancer. (68)

Diagnosis

Symptoms

Early gastric or oesophageal cancers rarely cause symptoms (69). NICE guidelines for referral for oesophago-gastro-duodenoscopy (OGD) in the UK are based on GORD symptoms and dyspepsia, in conjunction with other alarm symptoms: dysphagia; or aged over 55 with weight loss and upper abdominal pain, reflux or dyspepsia (70). Three quarters of patients are diagnosed after presenting with symptoms, the most common presentation of oesophageal cancer is progressive dysphagia and weight loss (71). Gastric cancer most frequently presents with iron-deficiency anaemia, overt gastrointestinal bleeding or dyspepsia (71). Those who present with alarm symptoms have a poorer 5-year survival (72). Despite being the lynchpin for accessing relevant investigations, the positive predictive value of alarm symptoms is poor (73). Clinical signs such as jaundice, palpable abdominal mass or palpable lymphadenopathy are infrequent in the majority of patients but when identified, represent advanced disease.

Screening and surveillance

Screening for gastric cancer has been used in Japan since the 1960s, and in Korea since 2000. Barium studies and/or OGD are used to diagnose gastric cancers. The incidence of gastric cancer in Asia means that screening is a cost-effective tool. (74) The incidence of gastric cancer in the UK or other Western countries does not support population screening for the disease as it is not cost-effective and the necessary tests are invasive or involve radiation (75).

There is no national population-based screening programme for oesophageal cancer in the UK for similar reasons to gastric cancer: the incidence is low and the necessary investigations are expensive and invasive. However, patients in the UK with Barrett's metaplasia are surveilled using OGD and multiple biopsies to assess for dysplastic or malignant change (65). The evidence for this is contentious and therefore

The Barrett's Oesophagus Surveillance Study (BOSS trial) has recruited 3400 patients to either two-yearly OGD or OGD at need. It started recruitment in 2009 and is currently in a 10-year follow-up period (76). Nevertheless, the American Society for Gastrointestinal Endoscopy published recommendations in 2019 suggesting that if a screening programme were started for Barrett's oesophagus, it should target an at-risk population such as those with a family history of oesophageal cancer or high-risk Barrett's, or patients with gastro-oesophageal reflux disease and one other risk factor such as being male, white, or having central obesity. (77)

Endoscopy

UK guidelines indicate that OGD is the gold standard first test for a patient in whom gastric or oesophageal cancer is suspected (3). It allows biopsies to be taken for histological confirmation. Radiological diagnosis using computerised tomography (CT) scanning or a contrast swallow or meal is reserved as a first-line test for those patients who are unable to tolerate OGD, as histological confirmation cannot be achieved.

Pre-operative staging

The use of a single classification system allows for comparison between stages, accurate prognostication based on large datasets and targeted evidence-based treatment appropriate to stage. The UICC (Union for International Cancer Control) Tumour, Nodes, Metastases (TNM) classification is used to stage both gastric and oesophageal cancers. (78) Higher stage disease has poorer outcomes. (79) T stage defines the primary tumour depth through the gastrointestinal tract wall. Prognosis worsens with increasing T stage in oesophageal SCC and ACA, and in gastric ACA. (80,81,82) N stage classifies the number of regional lymph nodes with metastases. The prognosis for N0 disease compared with node-positive disease is significantly better (83). Sufficient numbers of lymph nodes are required in surgical specimens to ensure all positive nodes are counted. If fewer than 10-15 lymph nodes are examined there

is a significant chance of stage migration, where the N stage is underestimated in both oesophageal and gastric cancers. (84) (85) The accuracy of assessing involved lymph nodes in oesophageal cancer by different staging modalities is assessed in a paper by Foley et al, where all modalities were found to under-stage nodal disease compared with histopathological assessment (86). M stage refers to the presence or absence of distant metastases. It is scored as M0 for no distant metastases, and M1 for the presence of distant metastases. Current guidelines recommend palliative management of patients with synchronous metastatic disease, (3) largely as the survival is in the region of 6-12 months, which does not allow sufficient time to recover quality of life post-operatively. (87,88) The databases in this document use the 7th Edition (2011) staging. The 8th edition (2016) has not been adopted here.

Tumour, Nodes, Metastases staging 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 or more nodes
T4b	Invades adjacent structures		

Tumour, Nodes, Metastases staging for oesophageal cancer

T stage		N stage	
Tis	Carcinoma *in situ*	N0	No nodes
T1a	Lamina propria or muscularis mucosae	N1	1-2 nodes
T1b	Submucosa	N2	3-6 nodes
T2	Muscularis propria	N3	>6 nodes
T3	Adventitia		
T4a	Invasion into adjacent structures		
	Pleura, pericardium, diaphragm		
	Adjacent peritoneum		

T4b Invasion into other adjacent structures

Aorta, vertebral body, trachea

TNM staging is calculated based on endoscopy, and imaging such as CT, MRI and PET-CT. Gastric and Siewert type 3 junctional cancers are also staged with laparoscopy, and oesophageal cancers are also staged with endoscopic ultrasound. These results generate a pre-treatment clinical grade, cTNM. After resection of a specimen, a pathological grade (pTNM) can be reported, based on histopathology. Where neoadjuvant therapy is administered, the prefix yp is used to differentiate from pTNM. For any given TNM stage, the prognosis is better for a pTNM staged tumour compared with a tumour down-staged to the same ypTNM. (89) The TNM stages are grouped into anatomical stages of disease, which is a coarser classification of groups of TNM stages with similar outcomes. This aids treatment planning and provides an indication of prognosis for patients and clinicians. (90) (81)

Anatomical staging for gastric cancer

Stage 1	T1N0M0, T2N0M0, T1N1M0
Stage 2	T3N0M0, T2N1M0, T1N2M0, T4aN0M0, T3N1M0, T2N2M0, T1N3M0
Stage 3	T4aN1M0, T3N2M0, T2N3M0, T4bN0M0, T4bN1M0, T4aN2M0, T3N3M0, T4aN3M0, T4bN2M0, T4bN3M0
Stage 4	T(any)N(any)M1

Anatomical staging for oesophageal cancer

Stage 1	T1N0M0, T2N0M0
Stage 2	T3N0M0, T1N1M0, T2N1M0
Stage 3	T4aN0M0, T3N1M0, T1N2M0, T2N2M0, T3N2M0, T4aN1M0, T4aN2M0, T4bN(any)M0, T(any)N3M0
Stage 4	T(any)N(any)M1

Method of staging

Staging and management of oesophagogastric malignancies in the UK follows the 2011 guidelines (3). Oesophageal and gastric cancers are usually diagnosed by means of OGD and multiple biopsies. Intravenous contrast-enhanced CT scanning of the thorax, abdomen and pelvis is then performed after administration of a water load to drink and an antispasmodic agent (hyoscine butylbromide). Approximately 40% of patients have metastatic disease identified on staging CT scan (93) and therefore the patient is managed with palliative intent. If staging at this point is assessed as potentially curative, patients with oesophageal cancer proceed to undergo a PET-CT and an EUS. PET-CT identifies CT-occult metastases in up to 10% of patients (94) (95). Potentially curative gastric cancer is investigated further with a staging laparoscopy. Most junctional tumours require both oesophageal and gastric protocol staging. (96)

Management options

Guidelines for the management of oesophageal and gastric cancers describe management with curative or palliative intent. (3) Factors determining treatment options include the site and stage of disease, the Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, and patient preference. Oesophageal tumours sited more than 5cm distal to cricopharyngeus are potentially resectable, whereas advanced tumours with locoregional invasion of adjacent non-resectable organs such as the left main bronchus, the aorta or the pancreas (T4b tumours) and tumours with non-regional lymphadenopathy or distant metastatic disease (M1 disease) are treated with palliative intent. Poor physical status measured by performance status or particular co-morbidities are key determinants of treatment options. Performance status 2-4 are associated with poor outcomes from multimodal oncological therapies and from major surgical resection. (97,98)

Curative options for oesophageal cancer include endoscopic mucosal resection (EMR) for early disease, oesophagectomy with or without neoadjuvant chemotherapy or chemoradiotherapy, or definitive chemoradiotherapy. Gastric cancer can be treated with curative intent either by endoscopic resection (endoscopic submucosal dissection or EMR) of early disease or gastrectomy. Surgery can be alone or multimodal, where perioperative chemotherapy is administered. (3)

Palliative options for oesophageal cancer include palliative chemotherapy or best supportive care. Palliative radiotherapy has been used to alleviate dysphagia symptoms, but it works slower than the self-expanding metal stent insertion. (99) A recent trial of 199 patients examining the combination of radiotherapy and stent insertion has shown adjuvant radiotherapy does not reduce the rate of dysphagia deterioration, nor affect overall survival, nor reduce the requirement for stent re-intervention. It showed a reduction in tumour bleeding. (100) Intraluminal delivery of radiation to an oesophageal tumour is an alternative to external beam radiotherapy. A randomised controlled trial of 209 patients showed that self-expanding metal stents provided quicker relief of dysphagia than brachytherapy, but brachytherapy provided better long-term control of dysphagia. (101) Therefore brachytherapy is advised for those patients with a life expectancy of greater than three months. Provision of brachytherapy services in the UK is variable, due to the practical challenges with service provision compared with oesophageal stenting. (102) Stent insertion, analgesia and nutritional support are some of many tools used within the realm of BSC.

Almost all patients with oesophagogastric cancer require nutritional support as many develop cancer cachexia (103) and meet the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for severe nutritional risk (104). Early and active nutritional assessment and intervention results in better outcomes from both curative and palliative treatments (105). Nutritional support can be achieved through oral

supplements, enteral feeding via gastrostomy or jejunostomy, oesophageal or pyloric stent insertion, or parenteral nutrition.

Surgical approaches

Operative approaches

Oesophageal cancer can be resected through a two-field or three-field approach: open; laparoscopically or robotically. The site of the tumour defines the operation required in order to achieve adequate longitudinal resection margins and to excise the required lymph node basins *en-bloc* to ensure the draining lymph nodes are removed. The majority of oesophagectomies are performed through a two-field approach, either transthoracic or transhiatal. A two-field lymphadenectomy is suitable for middle and lower oesophageal tumours where abdominal and mediastinal lymph nodes are removed. The transthoracic, or Ivor-Lewis, oesophagectomy involves a midline laparotomy or roof-top incision to perform the abdominal dissection and creation of a gastric tube as a replacement conduit, followed by a right postero-lateral thoracotomy for resection of the oesophagus and complete posterior mediastinal lymphadenopathy. (106) Evidence suggests that Siewert type II ACA tumours spread to intra-abdominal lymph nodes in 56-72% of cases, to para-oesophageal lymph nodes in 15.6% and mediastinal nodes in 2.1% (107). Oesophageal SCC tumours are more likely to involve a wider spread of lymphadenopathy, where a study of 141 three-stage oesophagectomies showed all tumours had coeliac and mediastinal lymphadenopathy, with cervical lymph nodes spared in only the distal oesophageal SCCs (108) The transhiatal approach as described by Orringer (109) is a two-field approach involving a midline laparotomy or roof top incision and a left cervical incision. The initial abdominal dissection and gastric conduit formation is the same as the transthoracic approach, then dissection continues into the posterior mediastinum until the level of the inferior pulmonary vein is reached. Blunt dissection then completes the oesophagectomy and an anastomosis is formed via the left cervical incision. In a trial of 220 patients randomised to either

transthoracic or transhiatal resection for Siewert type I and type II tumours, operative morbidity was significantly lower in the transhiatal group, but in-hospital mortality rates were similar. Transthoracic resection trended towards a survival benefit at five years, but did not reach statistical significance (p=0.06). There was a slight advantage in transthoracic resection for node-positive disease, whereas health-related quality of life (QOL) was improved for the transhiatal group in terms of better activity levels and reduced pain up to one year post-operatively, after which QOL was similar. (110) Based on this evidence, the transhiatal approach is usually reserved for early stage disease, node-negative disease or for those not fit enough to withstand a thoracotomy. (3) Three-field lymphadenectomy, or McKeown oesophagectomy, is suitable for upper oesophageal tumours. The lymphatic drainage of tumours above the tracheal bifurcation travels superiorly to the upper mediastinal and neck lymph node basins, although abdominal and mediastinal lymphadenopathy also occurs. Therefore abdominal, right postero-lateral thoracotomy and left cervical incisions are made to approach all three major lymph node basins (111).

Laparoscopic approaches can be applied to all three types of oesophagectomy described above, with parity of oncological outcomes and survival reported. (112) A hybrid laparoscopic abdominal component with an open right thoracotomy is the most commonly used. The MIRO multicentre randomised trial of 207 patients has reported a 77% reduction in intraoperative and post-operative complications in hybrid Ivor-Lewis oesophagectomy compared with open oesophagectomy. Moreover, pulmonary complications in the hybrid oesophagectomy group were reduced by 50%. (113) A thoracolaparoscopic oesophagectomy usually involves a cervical incision for the anastomosis. The traditional invasive versus minimally invasive oesophagectomy (TIME) trial reported randomisation of 114 patients with similar reductions in pulmonary infections: 34% in the open group versus 12% in the minimally invasive oesophagectomy (MIO) group (p= 0.005). Secondary outcomes reported included shorter length of hospital stay and better short term quality of

life. (114) Whilst pulmonary complications appear to be reduced by a laparoscopic component, other complications such as conduit necrosis and airway injury are reported more frequently. (115)

Gastric cancers can be resected with a total gastrectomy or a subtotal gastrectomy. Clear longitudinal and circumferential margins must be achievable, which means planning an operation to allow five centimetres proximal and distal to the tumour. As with the oesophagus, surgical approach depends on the site of the tumour, and the stomach is separated into thirds. There has been debate for decades over the appropriate management of distal gastric cancers. A meta-analysis of randomised trials including 1364 patients demonstrated that tumours confined to the distal third of the stomach can be managed with a subtotal gastrectomy with equivalent oncological results to a total gastrectomy, with less risk of anastomotic leak. (116) Meta-analysis of trials including 3554 patients also show that many early and locally advanced middle third cancers can be managed with subtotal gastrectomy with equivalent survival outcomes compared with total gastrectomy, as long as a negative proximal resection margin is achieved. (117) In UK practice, proximal gastric tumours are usually managed with a total gastrectomy, or an extended total gastrectomy via an abdomino-transhiatal approach. (118) Proximal gastric tumours may be resected using a proximal gastrectomy with anastomosis of the oesophagus to the distal stomach, though is associated with significant post-operative reflux. Both total and subtotal gastrectomy are then reconstructed using a Roux-en-Y loop to reduce remnant gastritis in subtotal gastrectomy and duodenooesophageal reflux in both approaches (119). There is international agreement that perigastric lymph nodes should be resected *en-bloc*, however, the radicality of lymphadenectomy has been debated amongst western surgeons for decades. The Japanese view is that radical systematic D2 lymphadenectomy has a survival benefit and is therefore the standard of care. A modified D2 lymphadenectomy is advised due to improved outcome compared with D1, without incurring the morbidity associated with distal pancreatectomy and splenectomy

traditionally performed with D2 lymphadenectomy. (120) The Dutch D1D2 trial reported 15 year follow up in 2010. Of 1078 patients randomised to D1 or D2 lymphadenectomy, 25% were alive at 15 years, with overall survival of 21% in the D1 group compared with 29% in the D2 group (p=0.34). The gastric cancer-related mortality was significantly lower in the D2 lymphadenectomy group (D2 37% versus D1 48%) and local recurrence significantly less likely in the D2 lymphadenectomy group (D2 12% versus D1 22%). Laparoscopic gastrectomy was first published in 1994 (121) with meta-analysis demonstrating equivalence of oncological clearance with similar length of hospital stay, mortality rates and complication profiles. (122) Fewer studies examine the long term outcomes after laparoscopic gastrectomy, but the US National Cancer Database has been analysed which shows similar five-year survival rates between laparoscopic and open gastrectomy. (123)

Prehabilitation and Enhanced Recovery After Surgery (ERAS)

Prehabilitation aims to prepare patients for surgery with physical exercise, dietary modifications, treatment of anaemia and psychological preparation. (124) Outcomes are improved in patients undergoing colorectal cancer resection (125) but there are few data on outcomes for oesophagogastric resection.

First described by Kehlet, (126) ERAS programmes include a multi-dimensional package of measures including pre-operative patient education and optimisation of nutrition, intraoperative use of short-acting anaesthetic agents, thoracic epidural analgesia and goal-directed intravenous fluid therapy, and the post-operative use of a goal-directed pathway for post-operative care including early feeding and mobilisation. It includes the avoidance of surgical drains where possible and the routine admission for high-risk patients or those undergoing major or complex major surgeries to a dedicated post-operative high dependency care area.

Neoadjuvant therapy

Long-term survival is improved in both oesophageal and gastric cancer surgery with the use of multimodal therapy: neoadjuvant chemotherapy or chemoradiotherapy, and surgical resection. It is the standard of care for patients fit enough to undergo it.

In gastric cancer surgery the only curative treatment remains surgical or endoscopic resection of the disease. The MAGIC trial published in 2006 showed improved survival for patients undergoing neoadjuvant and adjuvant chemotherapy compared with surgery alone. 503 patients with gastric or Siewert type 3 ACA were randomised into two groups: perioperative chemotherapy with surgery; versus surgery alone. Chemotherapy was 3 cycles of epirubicin, cisplatin and 5-fluoro-uracil (ECF) pre-operatively and 3 further cycles post-operatively. 5-year survival was 36% with perioperative chemotherapy versus 23% without (127). Criticisms of the study include the fact that only 42% of participants completed all 6 cycles of chemotherapy. In 2019 FLOT (fluorouracil, leucovorin, oxaliplatin and docetaxel) regime neoadjuvant chemotherapy was shown to improve outcomes compared with MAGIC-style chemotherapy, where FLOT had a 50 month median overall survival compared with 35 months for MAGIC-style ECF (128).

OEO2 studied 802 patients with oesophageal and junctional SCC and ACA to compare two cycles of 5-fluorouracil and cisplatin (CF) pre-operatively with surgery alone. This showed a 9% survival advantage at 2 years for neoadjuvant chemotherapy (43% versus 34%) and a 6% survival advantage by 5 years (23% versus 17%). There were increased complete (R0) resection rates and reduced nodal involvement in the neoadjuvant chemotherapy group. (129)

The CROSS trial published in 2012 compared preoperative chemoradiotherapy with surgery alone for oesophageal and junctional ACA and SCC in 360 patients. It showed a median survival of 49 months

for chemoradiotherapy compared with 24 months for surgery alone. There were increased rates of complete (R0) resections in the chemoradiotherapy group. The benefit for SCC was clearly demonstrated but less so for ACA. (130)

NEOSCOPE is a randomised phase II study of induction chemotherapy with either oxaliplatin and capecitabine or carboplatin and paclitaxel, followed by radiotherapy. 85 patients with oesophageal ACA with a tumour length of 8cm or shorter, T3N1 or greater were randomised to the two chemotherapy induction regimes. The trial showed high percentages of grade 3 and 4 toxicity (and 3 deaths) 52.4% and 42.1% in the two groups. 29.3% of patients in the carboplatin and paclitaxel group had a complete pathological response. (14)

NEOAEGIS studied chemotherapy versus chemoradiotherapy for oesophageal and type I and II Siewert classification cancers. It has closed to recruitment and it due to report results in 2024.

Complications from chemotherapy and chemoradiotherapy are complications are graded according to the American system devised by the National Cancer Institute where toxicities are graded 1-5 where 1 is mild, 2 is moderate, 3 is severe, and 4 is life-threatening toxicity. Grade 5 is death related to the adverse event (132).

Prognosis

National databases collect survival data from their populations which allows national and international scrutiny of outcomes across national borders. (133) In the UK, the National Oesophago-Gastric Cancer Audit 2017 reports 30-day and 90-day post-operative mortality data, and Cancer Research UK quotes 15% 5-year survival for oesophageal cancer (6) and 19% 5-year survival for gastric cancer (20). A European perspective from a national audit of Dutch, Swedish and Danish data from

the American Cancer Society estimate 18% 5 year survival after oesophageal cancer of all stages between 2006 to 2012. (134)
By far the strongest predictor of prognosis is the stage at diagnosis. With distant metastases, prognosis is poor. In gastric cancer, improved survival is observed in early stage disease compared with advanced stage disease, where overall five-year survival with gastric cancer is reported as 30%, whereas in node-negative, metastases-negative disease, this rises to 67%. (135) For oesophageal cancer survival is independently related to anatomical group stage. (136)

Economics

Health economics

As the national population ages and technology advances, treatment options are increasing with a concomitant financial burden on the health service. As a result, available treatments need to prove efficacy: in a finite budget, there is an opportunity cost to funding a new technology or treatment. Is the new treatment worth it?

Economic analyses take many forms, ranging from a cost-minimisation analysis, where the outcome of the study interventions is the same, the costs of each intervention are compared. Generic compared with proprietary prescribing is an example of this. A cost consequence analysis lists the consequences of each intervention, after calculating the costs. For example, listing the side effect profiles of two medications used to treat the same condition at different costs. (Glyceryl Trinitrate ointment versus diltiazem ointment for anal fissure). A cost benefit analysis (CBA) turns the outcome of the interventions into a monetary value, which allows comparison of spending across different sectors. In health care terms it requires a monetary value to be applied to life years gained or lost, which requires population-based analysis of health-related quality of life, and survival in different disease states. (137) For example, CBA can be used by governments to decide the relative benefit of funding a healthcare intervention compared with a defence project. A cost

effectiveness analysis (CEA) measures life-years gained according to the cost of different interventions. For example, measuring the life-years gained with primary percutaneous coronary intervention compared with coronary artery bypass grafting for acute myocardial infarction. A cost-utility analysis is used uniquely in healthcare intervention comparisons, where the benefits are measured in disability-adjusted life years (DALY) averted or quality-adjusted life-years (QALY) gained. An example of this is comparing the DALYs after ileorectal anastomosis or end ileostomy formation after a subtotal colectomy. (138)

The National Institute for Health and Care Excellence (NICE) was founded in 1999 “to reduce variation in the availability and quality of NHS treatments and care”. (139) This was a response to the public awareness of what the media called a postcode lottery, where some treatments were available from one NHS Trust and not in neighbouring Trusts. NICE aimed to approve the most clinically and cost-effective medications and treatments for use UK-wide, with the intention to improve equity in the NHS. Costs are calculated in terms of costs to the NHS, and Quality-Adjusted Life Years (QALYs) was chosen to measure the benefit of a treatment. A QALY is a health status measurement that combines quality of life and mortality into a single metric and is therefore a useful tool to compare different treatments for the same disease. (140) The threshold for cost effectiveness is defined by NICE, as a cost per QALY. The threshold at which an intervention is deemed cost-effective is controversial. (141) (142) (143) At inception, NICE declined to publish a threshold though it was widely considered to be £30,000 per QALY. More recently, a threshold of £20,000 per QALY is quoted and it is sometimes extended to £50,000 for end-of-life prolonging treatments.

NICE uses cost per QALY to guide national resource allocation, and as such, QALYs are now widely accepted as the currency of cost effectiveness. This metric is intended to reduce the effects of societal values and political influence on health resource allocation, and intended to justify opportunity cost (140). The incremental cost effectiveness ratio

(ICER) is a calculation used to evaluate the QALYs gained by implementing one treatment over another. It is used by NICE to determine if a new intervention is economically preferable to an alternative, usually control or standard treatment. It is:

$$ICER = (C_1 – C_0) / (E_1 – E_0)$$

Where C_1 and E_1 are the cost and effect of the new intervention, and C_0 and E_0 are the cost and effect of the control treatment (144). For ICERs in the UK, cost is measured in pounds sterling (£), effect is measured in QALYs and the output is cost per QALY gained.

However, when adopted in the early 2000s, some criticisms were raised regarding the assumptions upon which QALYs are based. The use of QALYs as a singular unit of measurement allows comparisons across treatments with different outcomes, such as the comparison between a treatment with a mainly QOL benefit and a treatment with a primarily survival benefit. However, it measures only health benefits and neglects other potential dimensions of benefit such as social services input, patient's time or environmental benefit. (140)

Comparisons in economic analysis assumes all QALYs are equal. However, societal values that conflict QALY assessment can lead to alternative conclusions. For example, society or policy makers may elect to apply more value to those with worse problems such as end of life care (a form of vertical equity) (145), or equal treatment for those in equal circumstances (a form of horizontal equity). Sceptics may think policy makers preferentially fund sub-populations that are most likely to vote. In recent years the NHS tariffs potentially act as a tool for these values to be expressed covertly.

Two other factors affect the implementation of QALY-based assessments. The fundamental principle of health economics is that the resource is limited and there is a finite budget. This raises the issue of opportunity cost: that funding one treatment or course of action means another option is not funded (146). Secondly, in some circumstances the

optimal option in QALY-based assessment becomes unaffordable if a disease affects a large proportion of the population (147).

Health-related Quality of Life

Introduction

An assessment of health-related quality of life (QOL) is an integral component of a QALY, and therefore required to perform cost utility analysis for use in the UK. QOL is defined by the WHO as “an individual’s perception of their position in life in the cultural context and in the value system in which they live and in relation to their goals, expectations, standards and concerns.” (148) WHO Evaluation of QOL requires consideration of physiological, psychological and social factors.

The methods used to assess QOL have evolved over time, from clinicians or psychologists recording the QOL of their patients using clinical judgement (149) (150), or tools such as the Spitzer index (151), to questionnaires completed for patients, to patients self-completing QOL questionnaires. These techniques focus on physiological (symptoms) and some psychological metrics, and limited, if any, assessment of social factors. Studies show that opinions of health care professionals and carers of cancer patients vary significantly from the patient’s self-reported QOL. (152) Standards now exist for assessing the quality of QOL data. (153) Key components of good quality QOL data are use of a validated questionnaire, multi-domain assessment (where a selection of QOL factors are assessed rather than pain, vomiting, dysphagia or anxiety singularly), patient self-reporting, explanation of missing data, inclusion of a pre- and post- intervention QOL measurement, and a discussion of the clinical significance of the QOL data. (153) (154) (155).

Multi-domain validated QOL questionnaires result in QOL data for each domain. Often these data are reported in the literature, and differences in each domain can be seen pre- and post- intervention. The conversion of QOL data across domains to a single value, called a health state utility value (HSUV) allows the QOL data to be translated into a QALY. (147)

Examples of multi-domain validated QOL questionnaires include Euro-QOL EQ-5D (156), EORTC QLQ-C30 (157), Health Utility Index 3(HUI 3) (158), FACT-G (159) and the SF-36 (160). Disease-specific instruments are preferred in clinical trials as their questions are more likely to identify clinically important differences. (161)

Methods to determine HSUV using preference-based techniques are described by Torrance such as visual analogue (or rating) scale (VAS); time trade-off (TTO); or standard gamble (SG). These direct techniques apply a utility value to each possible health state that can occur from completing a validated questionnaire. (147) Indirect methods are usually used for efficiency, by using a questionnaire with HSUVs applied to each questionnaire outcome. For example, there are 5 domains in the EQ-5D, with 3 levels of severity. Dead and unconscious are two additional health states within EQ-5D, consequently there are utility values for 243 health states and dead and unconscious in EQ-5D, which are derived from VAS of nationally representative samples (156) (162).

Mapping techniques are employed to calculate an EQ-5D HSUV from the disease-specific questionnaires which do not have validated HSUVs assigned to their results. Examples with published algorithms include conversion from EORTC-QLQ-C30 to EQ-5D (163) (164), and from SF-36 to EQ-5D. (165) The minimally important differences in EQ-5D using UK-based HSUVs is 0.08. (166)

Population-based studies of QOL have shown a steady decline in measured QOL as age increases. (167) (168) Within a cancer population the profile of QOL domains effects vary with age, where financial and social factors were affected to a greater extent in younger cancer patients and older patients had more problems with appetite loss. (169) One might expect the knowledge of a cancer diagnosis to reduce QOL scores, but this seems not to be the case. (170) Presumably within the study population the symptomatic patients are unaffected by knowledge of the diagnosis, any pre-diagnosis anxiety related to uncertainty is matched by

the anxiety caused by knowing the diagnosis. Quality of life during a diagnostic process has been shown to be reduced compared with a general population, which is comparable to a cancer population. (171) This demonstrates the reduction in hrQOL starts from the onset of symptoms, rather than from time of diagnosis. Consequently, QOL studies comparing interventions should be compared to others with the diagnosis rather than to the general population.

Quality of life literature according to treatment option

Gastric cancer

hrQOL has been assessed in patients treated with BSC as the control arm of studies assessing an intervention such as palliative chemotherapy (149) for advanced gastric cancer. Of 61 patients randomised to BSC or palliative chemotherapy, QOL was measured using EORTC-QLQ-C30 at time of randomisation, after 2 months and after 4 months. It showed that patients had worse QOL with BSC compared with palliative chemotherapy, and overall survival was not significantly different. HSUVs are not calculable directly from this study, although it uses a subjective assessment of the patient's QOL made by the treating physician to calculate a quality-adjusted survival for the 2 arms of the study, and for a cost-effectiveness analysis. (150)

hrQOL during palliative chemotherapy has been assessed in a few studies. EQ-5D was completed at baseline and every 3 weeks until disease progression during the ToGA trial (172) of 584 patients randomised to palliative chemotherapy alone or palliative chemotherapy and trastuzumab. (173) The RAINBOW trial (174) comparing the addition of ramucirumab to paclitaxel for previously treated gastric or OGJ cancers used EQ-5D and EORTC QLQ-C30 to assess QOL. (175) It showed no difference between the two arms of the study, but showed the HSUV to be 0.73 and 0.74, which remained static from baseline measurement to the end of the study period (end of treatment or evidence of progression), where it decreased by 0.176-0.206.

To my knowledge there are no specific QOL data available in those undergoing palliative radiotherapy for gastric cancer. Benefits are inferred from the cessation of potentially life-threatening bleeding and the reduced requirement for blood transfusion, (176) and hospital admission, but these are as yet unmeasured.

Surgery for palliation has been compared to endoscopic stenting in a review by Kim et al. (177) Quality of life is central to assessing effectiveness of palliative interventions as improving survival is not the intended benefit. Yet assessing QOL is fraught with difficulty given the short survival times. A study of 77 patients who had a cancer diagnosis (at any site) were sent QOL questionnaires 1 month and 3 months after the decision to treat with palliative intent was made. (178) After 1 month, 25% had died, by 3 months, 40% had died, meaning that the results would have been significantly skewed towards those with relatively positive outcomes. The study showed no significant difference in the FACT-G scores between those undergoing an intervention for palliation with those who had no palliative intervention. The mean score at baseline was 67.3, and 1 month later it was 65.9, where the range of scores possible in FACT-G is 0 to 108.

Patients undergoing interventions with curative intent have been measured in a number of studies. An analysis of 58 patients undergoing either a total or a subtotal gastrectomy completed QLQ-C30 and QLQ-STO22 (the site-specific gastric module) pre-operatively, 6 weeks post-operatively and every 3 months in the first year, followed by 18 months and 24 months post-operatively. (87) 30 patients were still alive at 2 years. The scores from the 2 questionnaires were linearly transformed into a score from 0 to 100. The study period was 2000-2004, before neoadjuvant chemotherapy became standard therapy. All of the 58 patients were treated with surgery alone, then 8 patients had adjuvant chemotherapy, and 2 had palliative radiotherapy. The mean baseline scores of the QLQ-C30 were 68 and 61 for patients who survived 2 years, and those who died within 2 years of surgery respectively. There was a

significant drop (defined in the study as a change of greater than or equal to 10 points) in the 6 week and 3 month scores. By 6 months, the scores had risen to within 10 points of baseline and remained similar for the subsequent timepoints. In the group who died within 2 years there was a non-significant drop in score between 6 and 9 months. This may represent the development of symptoms related to disease progression.

A Korean study of 666 patients undergoing ESD were evaluated at before ESD, 7 days post-procedure, then 3 and 6 months after the procedure. (179) The patients were diagnosed as part of a national cancer screening programme. The EORTC QLQ-C30 and QLQ-STO22 were used, in which the range is 0-100, with 100 being the best QOL in the global health status score. The mean global health status score at baseline was 69.47. After 7 days there was a non-significant reduction in score, but by 3 months the global health score had surpassed the baseline value: it increased up to 72.42 and by 6 months increased further to 73.59. In general, the dimension scores followed a similar pattern, with an initial reduction in functioning followed by a rapid recovery of function, which overtakes the baseline score. However, there was a 34.8% drop-out rate in terms of questionnaire replies by 6 months, which may be a source of bias in the study. The mean age was 62.8 years old (+/-9.2 years), which is younger than the average age at diagnosis in the UK, and a narrower range, which is a result of this being a screening population. Male patients comprised 77% of the study population. Given this is a study of a screening population, with a younger mean age, the results, particularly at baseline, are unlikely to be generalizable to a symptomatic population.

Quality of life whilst undergoing adjuvant chemotherapy has been assessed in 48 patients (164) in a study aiming to map EORTC QLQ-C30 scores to those generated by EQ-5D, SF-6D and 15D scores. The patients had undergone surgery and were undergoing chemotherapy, having completes between 2 and 4 cycles before testing. No patients had evidence of metastatic disease. The mean EQ-5D-derived utility score was 0.550.

Oesophageal cancer

There is a tick-shaped pattern of health-related QOL over time which is constant throughout the QOL literature following curative treatment for disease, including for oesophageal cancer. From a baseline QOL point, the QOL initially reduces during treatment and for a period afterwards. Then there is an increase in QOL which can sometimes remain below baseline, return to baseline or exceed baseline QOL. This pattern occurs in each of the commonly used QOL questionnaires. This is supported by a meta-analysis of 15 articles reporting QOL after oesophagectomy concluding that there was a consistent dip in QOL in the immediate post-operative period with recovery of QOL between 6-12 months. The meta-analysis also demonstrated considerable heterogeneity amongst the QOL domains in the year post-operatively. (88)

In a study aimed to determine the optimum timing of post-operative support, 79 patients were asked to complete the EORTC QLQ-C30 and QLQ-OES18 at 6 time points from baseline and during the first post-operative year. This showed the nadir in QOL to be 2 months post-operatively. (180)

Doherty et al (181) used EQ-5D and FACT-E to question 199 patients across the spectrum of oesophageal cancer patients: all disease stages; pre-treatment; during chemoradiotherapy (definitive or neoadjuvant); within 6 months of curative treatment; more than 6 months after treatment; after diagnosis of progression or recurrent disease; and after onset of palliative chemotherapy. The mean pre-treatment HSUV was 0.78. Those undergoing palliative chemotherapy and those who had recently undergone radical treatment for oesophageal cancer had lower scores but improved in the surveillance interval. The majority of patients studied had stage 2 or 3 disease (62%) and only 10 patients with stage 1 disease were studied. Serial examinations were performed in fewer than half of the patients (42%), the remainder completed one questionnaire

only. The study has limited utility for developing QOL-time profiles because the questionnaires were completed at time points dependent on their treatment rather than pre-determined time intervals (such as baseline, 3, 6, 9 and 12 months).

Studies suggest some specific components of quality of life are worse in more advanced stage of disease. In a study from Glasgow, McKernan et al showed QOL at initial presentation to be worse with more advanced stage of disease. (182) A single-point QOL study of 355 patients in Sweden who had undergone an oesophagectomy completed the EORTC C30 and OES18 questionnaires. Those with more advanced stage disease reported reduced role function, more eating difficulties and worse appetite loss compared with stage 1 disease. (183) Conversely, a study of different methods to generate HSUVs in 50 patients with malignant dysphagia showed no statistical difference in HSUVs according to stage. (184) This perhaps represents the sensitivity of disease-specific questionnaires compared with generic questionnaires.

Shenfine et al (185) investigated QOL as part of a cost-effectiveness analysis of palliative interventions in oesophageal cancer. QOL was measured using the QL index, Karnofsky Performance Scale, EQ-5D and EORTC QLQ-C30 and QLQ-OES18. It showed that there was no difference in QOL between those who had oesophageal stents placed and those without a stent (BSC). Questionnaires were completed at baseline, 1 week and 6 weeks. HSUV dropped from an average of 0.56 to 0.45 at 6 weeks.

QOL after endoscopic therapy is rarely published. A paper by Rosmolen et al (186) investigates the QOL after endoscopic therapy for high grade dysplastic lesions and early oesophageal cancers compared with surgery for early or advanced oesophageal cancer. SF-36 and EORTC-QLQ-C30 questionnaires were completed at baseline, 2- and 6 months. Mapping onto the EQ-5D health states from the SF-36 average scores over the first 6 months showed HSUVs of 0.865 for endoscopic therapy, 0.757 for

surgery in early cancer (classified as less than T2N0M0), and 0.781 for surgery in advanced cancer (greater than T1N1M0 disease). A recently published small study by Schwameis et al (187) looked at a mixed group of patients undergoing endoscopic resection for either high grade dysplasia (n=22, where 9 progressed to early oesophageal cancer) or early oesophageal cancer (n=18). The time interval between therapy and QOL measurement was not recorded. Mapping from the SF-36 results to EQ-5D gives a HSUV of 0.742.

Many studies evaluate QOL after oesophagectomy. An early study from the year 2000 observes that patients who remain disease-free for 2 years post-treatment regain their pre-treatment QOL within 9 months, whereas those who develop recurrent disease never regain their QOL. (188) QOL of patients undergoing oesophagectomy alone was compared with those undergoing oesophagectomy with neoadjuvant chemoradiotherapy in a 2006 study by Reynolds et al. (189) Questionnaires completed at 6 timepoints during and after treatment demonstrate that the reduction in QOL lasts for longer during chemoradiotherapy and surgery but reaches the same recovery by one year. The difference in QOL between patients undergoing chemoradiotherapy alone and patients having neoadjuvant chemoradiotherapy followed by surgery was studied by Avery et al. (190) EORTC QLQ-C30 and QLQ-OES18 questionnaires were completed at baseline, 1 month, 3, 6 and 9 months after treatment started. Patients having neoadjuvant chemoradiation had poorer QOL at baseline but the nadir of QOL was not as low as those undergoing chemoradiation alone. Those undergoing surgery had not recovered their QOL by 6 months.

Currently there are no published studies comparing QOL in patients undergoing perioperative chemotherapy compared with either perioperative chemoradiotherapy or surgery alone. QOL is a secondary endpoint in NeoAEGIS, which is presently recruiting. (191)

Definitive chemoradiotherapy has been assessed in secondary analyses of both the PRODIGE 5/ACCORD 17 randomised trial of 2 different CRT

regimes, (192) and the SCOPE 1 trial examining the addition of cetuximab to standard dCRT. (193) In the latter trial EORTC questionnaires showed a deterioration in QOL with a nadir at 13 weeks. This had recovered back to baseline by 1 year. It is not possible to calculate utility values from this data as not all data points are published. However, the PRODIGE 5/ACCORD 17 study published EORTC questionnaire data at baseline and 5 subsequent time points within the first year of treatment. They showed no significant difference in QOL between the two chemoradiotherapy regimes (FOLFOX and Fluorouracil-Cisplatin). Over 1 year, disease-specific components of the questionnaire changed significantly: physical and social functioning scores decreased during treatment but global health score and dysphagia improved during treatment. These factors even out the HSUV over the course of treatment, from 0.9 at baseline to 0.88 at one year. Similar results are reported by Gillham et al, (194) where QOL was measured using EORTC QLQ-C30 and QLQ-OES24 at baseline, 3, 6 and 12 months after treatment.

Palliative radiotherapy has been investigated in a study by Prasad et al. A total of 33 patients were studied before palliative radiotherapy was administered and 6 weeks post-treatment. EORTC QLQ-30 and dysphagia questionnaires were used to measure QOL. An improvement in QOL was found, which the authors attributed to the improvement in dysphagia. (195) EQ-5D questionnaires were used in a paper by Homs et al (196) comparing stent insertion with single dose brachytherapy in patients with inoperable oesophageal cancer. Patients were followed up monthly for 1 year after treatment, and 3 monthly thereafter. Mean EQ-5D scores were 63 at baseline and 42 at 6 months post-treatment. This equates to HSUVs of 0.56 and 0.41 respectively. No studies specifically examine QOL after single fraction radiotherapy for bleeding.

QOL after palliative chemotherapy has been shown to be better than BSC alone, in terms of QOL and cost-effectiveness. (197) The reported HSUVs were similar at baseline but diverged by 1 year to 0.27 for the

chemotherapy group and 0.20 for the BSC group, with QOL preserved for a greater proportion of the year in the palliative chemotherapy group.

Conclusion

Overall, studies have shown that undergoing a major operation reduces QOL initially and it returns close to baseline between 3-9 months post-operatively. Factors such as surgical complications (198) (199) and prolonged hospital stay have been shown to lengthen the time taken to recover QOL in colorectal patients. It is probable that the same factors affect oesophagogastric surgery patients. Overall, there is a range of QOL data published but the methods are variable and the metrics used differ. This makes comparison across studies is difficult due to the different patient populations: screening versus non-screening; all cancer sites versus gastrointestinal versus site-specific; and generic versus site-specific questionnaires. The qualitative data gained from disease-specific questionnaires are more detailed that that gained from the generic QOL questionnaires, and results in 100,000s of health states. This means that health state utility values are not available for the disease-specific questionnaires. There are no published studies investigating QOL according to stage of disease and treatment pathway, yet QOL is an equal consideration for patients alongside survival, as they discuss consent for treatment with clinicians. (200)

Service reconfiguration

The Department of Health's Improving Outcomes Guidance (11) led to changes in the delivery of OG cancer services. It drew upon the field of evidence at the time showing that patient outcomes improved where treatment was in a high volume centre and by surgeons performing resectional surgery frequently.

The guidance proposed that centralisation of OG cancer services would lead to:

- A greater proportion treated with curative intent
- Minimised diagnostic delay
- Reduction in duplication of investigations
- Reduction in operative mortality
- Reduction in operative morbidity
- Reduction in open/close rate
- Better patient selection
- Increased overall survival
- Improved access to palliative care (oncology and stenting)

It concluded that “Surgery by specialists, combined with improved selection of patients, would reduce the proportion whose survival time is short and who suffer deterioration in quality of life after surgery”.

Materials and Methods

Patient database

A cohort of more than 2500 consecutive patients managed a UK regional MDT between 2008 and 2015 are analysed in these chapters. Staging at diagnosis, management decisions, and treatment outcomes will be recorded in a prospectively maintained database. Approximately 800 patients underwent radical treatment with curative intent. The results of pre-operative diagnostic, staging and fitness investigations (Endoscopy, CT, EUS, PET-CT, and Cardiopulmonary exercise testing) are recorded. Disease staging is logged according to the UICC TNM classification of malignant tumours (202). Treatment outcomes are recorded including post-operative morbidity, disease progression or recurrence, and mortality data is collected from the Office of National Statistics (ONS). Informed consent for treatment was obtained from all patients, and ethical approval was sought from the regional ethics committee, but a formal application was deemed unnecessary for anonymised secondary outcomes reporting.

Statistical methods

Data analysis reports the median values as the data is non-parametric. Tests appropriate for non-parametric data are used. Cumulative survival is calculated according to the method of Kaplan and Meier. Database recording and analysis is performed in SPSS® 20 for Mac (IBM® SPSS® Statistics v20, IBM Corporation, Armonk, New York, USA). Statistical methods relevant to each chapter are discussed in the methods sections in each chapter. A p value of 0.05 is considered statistically significant throughout this thesis.

Economic analysis

Costs

The standard pathway for each treatment option is itemised and costed, including costs of investigations, appointments, surgical oncological or palliative treatment, and length of hospital stay. Costs are derived from local data and procurement data where available, and activity-based costing and regional healthcare tariffs where no other data is available. The costs are calculated from diagnosis for one year of treatment. Sensitivity analyses are examined to assess those factors that have the greatest effect on cost.

Survival analysis

The benefits of each treatment option are measured as median survival advantage, compared to best supportive care (BSC), adjusted for quality of life.

Quality of Life assessment

Disease-specific quality of life data is reviewed from the literature to determine health state utility values (HSUVs), which is then used to quality-adjust the median overall survival.

Surgeon-level quality metrics data

The outcomes for each operating surgeon (as recorded in the prospectively maintained database) in the UK regional network are analysed and compared with the nationally published data for other regions of the UK.

Chapter 2: Aims of study

The aims of this study are to determine the cost utility of treating oesophageal and gastric cancer in a UK regional network, relating to stage of disease. An assessment of the health-related quality of life (QOL) during and after different treatment modalities will be assessed. The accuracy and utility of surgeon-level and unit-level mortality rates will be explored, and alternative compound metrics investigated. The effect of the introduction of PET-CT into the standard staging algorithm of oesophageal cancer will be investigated, in terms of overall survival, disease-free survival and patterns of recurrence.

Chapter 3: Hypotheses

1. The cost utility (cost effectiveness per QALY) of contemporary centralised oesophagogastric cancer treatment in a regional UK centre meets the National Institute for Health and Care Excellence (NICE) thresholds for clinical effectiveness.
2. Quality of life measured one year post-surgery is equivalent to that after definitive chemoradiotherapy (dCRT) and quality of life during palliative therapies is poor.
3. Unit-based compound level quality assurance analysis over a timeframe of multiple years provides a more useful metric of surgeon level performance than surgeon-level mortality rates.
4. State of the art radiological imaging (PET-CT) improves overall and disease-free survival after oesophagectomy and reduces early disease recurrence rate.

Chapter 4: Cost Utility Analysis of Gastric Cancer Care related to stage

Abstract

Background

The treatment of patients with gastric cancer imposes a substantial financial burden on the NHS. Treatment is with curative or palliative intent and is multimodal: endoscopic resection; surgical resection; chemotherapy; and palliative interventions are all offered. Prognosis worsens with increasing stage of disease, and survival with best supportive care is poor. Cost utility analysis uses quality of life (QOL) adjustment of the survival benefit, using QALYs. The aim of this study is to determine the cost utility of gastric cancer treatment related to stage of disease, compared with best supportive care (BSC).

Methods

Costs to the NHS for one year of treatment from referral were calculated according to locally agreed diagnostic, staging and treatment pathways for patients being treated for gastric cancer. Costs were calculated from national reference costs, published staff and medication costs, and activity-based costing.

Median overall survival from diagnosis was derived from a prospectively maintained database of all patients treated via a centralised regional MDT over 8 years. Patients were categorised according to clinical, pre-treatment stage of disease (TNM anatomical group stages 1 to 4), and treatment pathway undertaken, according to intention to treat (Endoscopic resection, total gastrectomy with perioperative chemotherapy, subtotal gastrectomy with perioperative chemotherapy, total gastrectomy, subtotal gastrectomy, palliative chemotherapy, single fraction palliative chemotherapy, BSC).

QOL was derived from the published literature and applied to the survival benefit of each treatment arm compared to best supportive care. Primary outcome was cumulative quality-adjusted overall survival from diagnosis.

Results

Of 727 patients studied, overall median survival was 8 months (62 months stage 1, 22 months stage 2, 14 months stage 3, 3 months stage 4). Survival was better with endoscopic resection and surgical management compared with palliative pathways. QOL was 0.905 for endoscopic resection, 0.866 for surgery, reducing to 0.550 during adjuvant chemotherapy, 0.750 in palliative chemotherapy and 0.576 in BSC. The most expensive treatment pathway was total gastrectomy with perioperative chemotherapy (£23270.63), BSC cost the least (£4586.90). The cost per QALY of stage 1 is £7526.76, stage 2 is £11572.14, stage 3 is £16248.55, stage 4 is £51554.66.

Conclusion

Surgical and endoscopic resection and primary oncological therapies improve overall survival and quality of life compared with best supportive care. A detailed cost analysis shows that the cost per QALY of stage 1 and 2 treatments are cost-effective at a £20,000/QALY threshold. Stage 3 and 4 interventions are not cost effective at this threshold, according to cost per QALY analysis. It costs at least 68 times more to treat stage 4 disease compared with stage 1, per QALY.

Introduction

Cost effective healthcare has come into sharper focus over the last 2 decades, not least because of widespread media coverage of a perceived postcode lottery and the founding of NICE (now the National Institute for Health and Care Excellence) in 1999. Since the global and UK-wide economic downturn in 2008, further scrutiny has been applied to healthcare funding. NHS budget deficits and forecasts of an £8 billion annual shortfall until 2020, (203) are a result of the rising costs of healthcare, because of a rising and ageing population, expensive new medications and technologies, and growing patient expectation. The NHS five-year forward view (2015) challenges the sector to increase productivity and achieve a £22 billion saving by 2020/21, and a key component of any successful strategy in this regard, is a drive to minimise low value treatments (204) (205) which requires an evaluation of the baseline costs of all potential treatments for comparison purposes. In the context of gastric cancer care, the drive to centralise services in the UK (11) has drawn attention to the cost of service provision, and as centres reach out for work, caseloads increase, the costs multiply, and potential inefficiencies emerge.

The TNM staging of gastric cancer is translated into 4 stages, 1 being the earliest stage, 4 being the most advanced stage. Stage 1 disease is often referred to as early, stage 3 and 4 disease as late. Palliative management is used initially in 49% of gastric cancers diagnosed in the UK. (1) Prognosis worsens with increasing stage, and by analysing cost related to stage, it is possible to generate a cost utility analysis of the relative benefit of treating early versus advanced stage of disease. Assuming that disease progress is iterative, then economic analysis will determine whether it is cost effective to invest in novel, potentially expensive technical diagnostics and treatment of early disease.

Gastric cancer is treated with curative intent with endoscopic submucosal dissection (ESD) for early stage lesions or gastrectomy for more

advanced tumours. Treatments with palliative intent are gastrojejunal bypass, endoscopic stenting, or palliative chemotherapy or radiotherapy. Best Supportive Care (BSC) is offered to those patients who choose not to have other treatments and those who are considered unfit to undergo other treatments. (3) This is no active treatment beyond the immediate relief of symptoms. (206)

NICE uses patient QALYs to measure the clinical effectiveness of a course of treatment. (138) This requires calculation of the cost of treatment, the quality of life associated with the treatment and the survival benefit of the treatment. Costs are calculated as costs to the NHS, rather than costs to the patient, their family, employer, or to the wider society. (207) Quality of life is measured through patient surveys, using questionnaires such as EuroQol 5-Dimensions (EQ-5D), SF-36, SF-60, FACT-G or EORTC QLQ-C30 and relevant modules. Questionnaire results generate health states, which then transform into a proportion of full quality of life, called utility values (HSUV). EQ-5D is the only questionnaire with validated utility values and is therefore the standard questionnaire for use in economic analysis. The cost per QALY then determines whether NICE recommends a treatment. Over the last 20 years, NICE has become increasingly explicit about the thresholds at which treatments are supported. Under £20,000 per QALY, a treatment will be recommended, at £20,000 to £30,000 per QALY a treatment is likely to be recommended, but the threshold can be increased up to £50,000 per QALY for end of life treatments. (141) (208) (137)

The aim of this study was to calculate the cost utility of treatments related to stage of disease, compared with BSC. The authors hypothesise that the effect of reduced QALY in stage 4 disease exceeds the cost of treating early stage disease. Primary health care outcomes were quality-adjusted life-years (QALYs) gained with each treatment, and the economic outcome was the incremental cost-effectiveness ratio (ICER).

Methods

The economic evaluation methods comply with the checklist for Consolidated Health Economic Evaluation Reporting Standards (CHEERS) to maximise validity and aid comparison with other studies. (209)

A prospectively maintained database was used to collect consecutive cases diagnosed with gastric adenocarcinoma within a regional cancer network. Gastric and type 3 junctional tumours were included. Diagnosis was by oesophagogastroduodenoscopy (OGD) and biopsy, or by computed tomography (CT) alone in those patients undergoing CT first and considered not suitable for further treatment, either due to advanced incurable stage of disease or unfitness for further investigation or treatment, such as Performance Status (210) greater than 3. Staging was performed using CT, staging laparoscopy, and endoscopic ultrasound (EUS) according to staging protocols published previously (3) (211). Computed tomography positron emission tomography (CT-PET) is used in junctional cancers. Staging was recorded according to UICC TNM 7 for gastric adenocarcinoma. (202) All analysis was performed based on intended treatment plan.

All available management options were analysed and compared with BSC: Single modality surgery; surgery and perioperative chemotherapy; endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR); palliative chemotherapy; and palliative radiotherapy. (3) The patient pathways used within the regional network for these options were itemised according to the principle of operational efficiency, using the minimum necessary resources to deliver a particular activity. The management of comorbidities were not included in the cost calculations. Costs to the NHS were calculated, personal and societal costs were not included. Costs are calculated and reported in Pounds Sterling (£), and given in 2016 prices. A variety of sources were used to derive the cost of

investigations and treatments. Sources are recorded in Appendix 1. Activity-based costings were used preferentially to maximise regional accuracy. Cardiopulmonary exercise testing (CPEX), EUS, and out of region service provision of CT-PET were calculated using activity-based costing. English NHS reference costs 2015-6 were used for some other investigations, outpatient appointment costs and critical care stay costs, where bottom-up costing approaches were not possible. (212) Reference costs use a top-down costing approach and have been adopted for use in Scotland and to a lesser extent in Wales. They are increasingly used for economic analysis in the UK. (213) Staff costs were taken from the Personal Social Services Research Unit (PSSRU), (214) using the cost per hour which includes the capital training costs divided over the total whole time equivalent (WTE) hours of service. Length of time per patient interaction was obtained from personal communications with the staff involved: clinical nurse specialists; dieticians; physiotherapists and consultants. Medication costs were taken from the British National Formulary (BNF), Chemotherapy regimes were costed according to local chemo protocols, which are based on contemporary trial data. (127) Procurement costs for disposables in theatre, and operating theatre running costs, per minute, from Information Services Division (ISD) Scotland. (215) Chemotherapy doses were calculated according to an average male height and weight of 5'9" and 70kg, giving a body surface area of 1.85m^2, according to the Du Bois formula. (216)
Costs were calculated from referral for a year of treatment and follow-up within that year.

Overall survival was calculated from the date of diagnosis recorded in the regional database and the date of death as recorded from the Office of National Statistics feed into Cancer Network Information System Cymru (CaNISC). Non-parametric statistical methods were used and median values were used for grouped data. IBM SPSS Statistics version 20 for Mac was used to record and analyse the data. Median overall survival per stage and per treatment was calculated using Kaplan-Meier charts (217), where the survival curve crosses the 50% survival line, and the median

recorded length of survival where it does not. A non-parametric test of independent samples was performed to identify statistically significant differences in median survival, at a probability level (p-value) of less than 0.05.

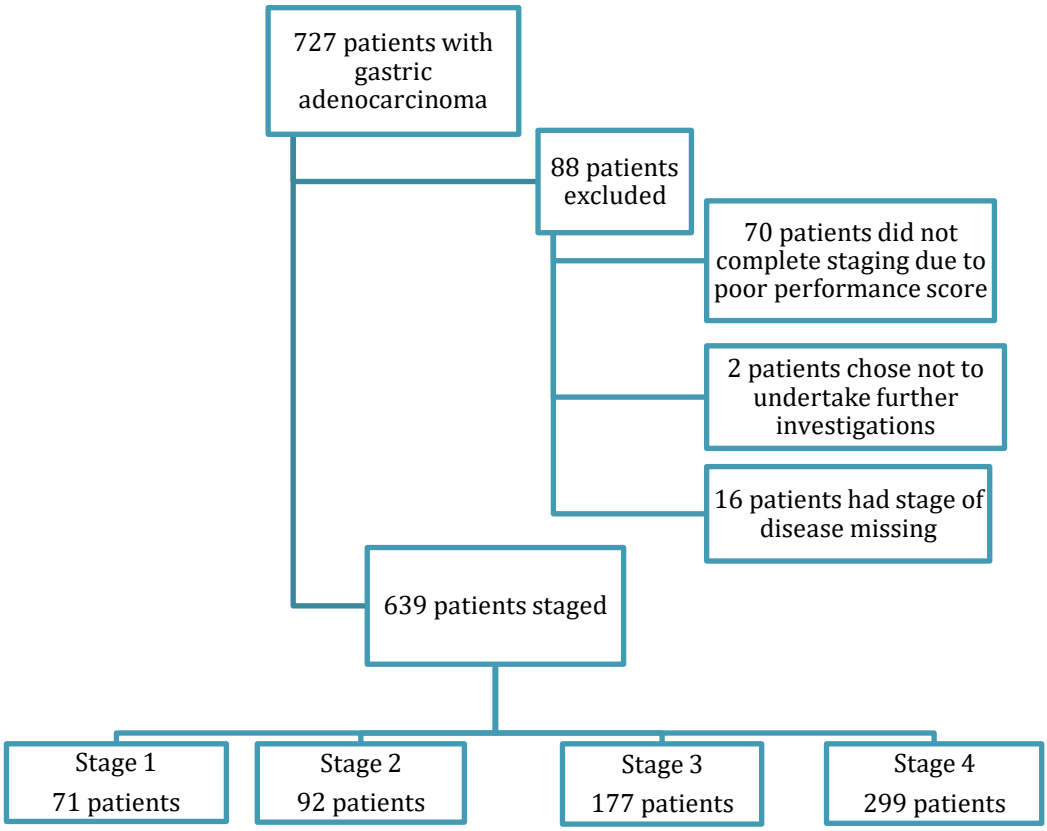
Quality of life data was derived from the published literature as discussed in the introduction. The HSUVs are on a 0 to 1 scale where 0 represents death and 1 represents full health. Mapping techniques have been used to convert questionnaire outcomes without HSUVs to scores from which HSUVs can be generated. Quality-adjusted life years were calculated by multiplying the time spent in each HSUV (measured in years) by the utility score. The QALYs accrued are calculated assuming the change in HSUV between QOL measurement points is a straight line. Incremental cost effectiveness ratios (ICERs) are then calculated within each stage for each treatment compared to BSC. The slope of the ray on the ICER chart represents the relative benefit compared with the relative increase in cost.

A sensitivity analysis is included to consider the effect of increased costs and decreased QALY. The costs of all treatments were initial outlay costs, and no delayed costs were, therefore no discount rate was applicable to costs. A discount rate will be examined in the sensitivity analysis for survival benefits, in those treatment/stage groups where median overall survival exceeds one year. A rate of 3.5% is standard for UK-based health economic analyses (218), based on social time preference: the value that society applies to present benefits compared with future benefits.

Results

A total of 727 consecutive patients diagnosed with gastric adenocarcinoma between 2006 and 2014 were analysed. Figure (a) shows inclusion and numbers of patients in each stage.

Figure (a): Flow diagram of inclusion of patients and stage of disease.



Costs

Table 1:

Treatment pathway	Cost for 1 year of treatment (£)
EMR or ESD	5058.45
Total gastrectomy and perioperative chemotherapy	23270.63
Subtotal gastrectomy and perioperative chemotherapy	21972.81
Total gastrectomy	18193.07
Subtotal gastrectomy	16895.25
Palliative chemotherapy	7395.54
Palliative radiotherapy (single fraction)	5200.50
Best supportive care (BSC)	4586.90

Appendix 1 shows the itemised costs per stage of disease and sources thereof.

Survival

Overall median survival was 8 months. Median survival related to stage of disease was: 62 months for stage 1 disease; 22 months for stage 2; 14 months for stage 3; and 3 months for stage 4 disease. Cumulative survival (Kaplan-Meier) related to stage is shown in figures (b)-(e)

Table 2 shows the median survival, in months, for each treatment arm per stage. Endoscopic techniques are only suitable for stage 1 gastric cancers with features suggestive of low risk of lymphatic involvement (219), therefore only patients with stage 1 disease underwent ESD/EMR. All 3 patients who underwent endoscopic therapy were alive at the end of the study period therefore 14 months represents the median follow-up in the study rather than median survival. This is likely to underestimate of the survival of these patients. Similarly, stage 1 and 2 cancer patients undergoing surgery alone and stage 1 patients undergoing surgery with perioperative chemotherapy also had survival rates where the survival curve did not decrease to 50% on the Kaplan-Meier plots (figures (b) and (c)). Again, this is likely to represent median follow-up in the study rather than median survival, and likely causes an underestimation of the survival advantage.

Patients treated with surgery for stage 4 disease represent patients undergoing palliative bypass procedures. Surgery and perioperative chemotherapy in the stage 4 group relates to those patients who underwent neoadjuvant chemotherapy and then had irresectable or metastatic disease at time of operation, therefore their disease was upgraded to stage 4. The increased median survival for stage 2 and 3 disease treated with surgery alone compared with surgery and perioperative chemotherapy is contrary to the published trial data available showing improved survival with perioperative chemotherapy (127) (220), however, the difference in this study does not reach statistical significance (stage 2 p=0.52, stage 3 p=0.887)

There is an increased survival in those undergoing palliative chemotherapy compared with BSC in all stages of gastric cancer, with a decreasing median survival benefit as the stage increases. However, the median survival in those undergoing palliative radiotherapy for stage 1 and stage 2 disease is the same (stage 1) or reduced (stage 2) compared with BSC. This is likely to represent a symptomatic subset who have gastrointestinal bleeding, who are likely to present as an emergency. This group are known to have a poorer survival. (221) (222) Some patients undergoing palliative radiotherapy may proceed to have palliative chemotherapy, which may explain the increased survival of stage 3 cancers recorded as having been treated with radiotherapy. The median survival decreases as the stage of disease increases.

Table 2: Median survival (in months) for each treatment arm per stage.

	Stage 1	Stage 2	Stage 3	Stage 4
ESD/EMR	14[a]	-	-	-
Surgery	44[a]	51[a]	24	10
Surgery and perioperative chemotherapy	27[a]	26	20	34
Palliative chemotherapy	26	17	8	5
Palliative radiotherapy	15	1	17	5
BSC	15	6	6	2

[a] derived from median survival as recorded in the database rather than via Kaplan-Meier method.

Health-related quality of life

Quality of life per treatment arm is derived from the literature. There is no significant difference in QOL according to stage of disease (223) (224), and no QOL data that assesses the whole range of gastric cancer patients, across stage and treatment. Most studies use disease specific QOL questionnaires for which there is no validated set of HSUVs. Mapping techniques have been applied to translate EORTC QLQ-C30

scores into EQ-5D HSUVs. The evidence for this approach is discussed in the introduction. Where there is sufficient data in the literature, a QOL-time profile has been generated from the available data points per treatment (figure f). Table 3 shows the QOL data used. Studies were analysed for QOL data if there was more than one QOL measurement using a validated multi-domain QOL questionnaire. Using figure (f), the area under the line (similar to an area under the curve, AUC) has been calculated to produce a quality of life adjustment, which is then multiplied by survival in months, to give a quality-adjusted survival time. There is no separate QOL data in the literature for patients undergoing surgery and perioperative chemotherapy compared with those undergoing surgery alone. The data used to generate the HSUV includes 75% who had surgery alone, and 25% who received perioperative chemotherapy, therefore this HSUV has been applied to both groups. As there is no QOL data for patients undergoing palliative radiotherapy, the HSUV from BSC has been applied. Table 4 shows the overall survival and the quality-adjusted survival (in bold).

Table 4: Overall survival and quality-adjusted survival

	Stage 1	Stage 2	Stage 3	Stage 4
ESD/EMR	14[a]	-	-	-
	12.67			
Surgery	44[a]	51[a]	24	10
	38.104	**44.166**	**20.784**	**7.22**
Surgery and perioperative chemotherapy	27[a]	26	20	34
	23.382	**22.516**	**17.32**	**29.444**
Palliative chemotherapy	26	17	8	5
	25.44	**16.825**	**3.896**	**1.52**
Palliative radiotherapy	15	1	17	5
	8.64	**0.576**	**9.792**	**2.88**
BSC	15	6	6	2
	8.64	**3.456**	**3.456**	**1.152**

[a] derived from median survival as recorded in the database rather than via Kaplan-Meier method.

Decision tree analyses were mapped showing probabilities of undergoing each course of treatment according to stage, costs, and QALYs associated with each outcome. (Figure g) The results were then averaged out per stage and rolled back to calculate the cost per QALY gained per stage.

This study shows that compared with best supportive care, oncological and operative managements of gastric cancer increased survival and quality of life. The cost per QALY is £7526.76 for stage 1, £11572.14 for stage 2, £16248.55 for stage 3, and £51554.66 for stage 4 disease. There is nearly a 7-fold increase in the cost per QALY gained in treating gastric cancer at stage 1 compared with stage 4.

Figure (h) shows the cost per QALY represented on ICER charts. ICERs have been calculated comparing treatments per stage to BSC per stage in table 5. These results give a cost per QALY compared with BSC.

Table 5: Incremental cost-effectiveness ratio (ICER) per stage and treatment arm, compared with BSC (£/QALY).

	Stage 1	Stage 2	Stage 3	Stage 4
ESD/EMR	1404.12	-	-	-
Surgery	5541.48	4010.66	9422.56	26907.39
Surgery and perioperative chemotherapy	15208.57	11763.10	16171.72	7924.67
Palliative chemotherapy	2010.96	2521.03	76599.29	91586.11
Palliative radiotherapy	Dominated	Dominated	1162.12	4261.11

This shows that all treatments for stage 1 and 2 disease are cost-effective at an ICER threshold of £20,000 per QALY. Surgery for stage 4 disease is below the £30,000 per QALY, meaning it is likely to be considered cost-effective. Conversely, palliative chemotherapy in stage 3

and 4 disease is well above the £30,000/QALY threshold, and interestingly, they are both above the £50,000/QALY threshold considered for life-extending treatments at the end of life. Palliative radiotherapy is dominated by BSC for stage 1 and 2 disease, i.e. palliative radiotherapy is more expensive and is associated with a QALY reduction. When evaluated related to stage, stage 1 and 2 are cost-effective (at a threshold of £20,000/QALY) with ICERs of £264.25/QALY and £16814.19/QALY respectively. Treatment of stage 3 and stage 4 are dominated by BSC, with ICERs of -£1982.00/QALY and -£17,836.11/QALY, meaning that all other interventions cost more per QALY than with BSC.

Sensitivity analysis

The greatest sources of increased costs are operating theatre time and durations of inpatient hospital stay. Additional admissions to hospital, procedures such as stent insertions, repeat endoscopies or unplanned return to theatre post-operatively all add to the cost of treatment. The use of advanced bipolar or ultrasound energy devices in theatre adds approximately £600 to the cost per operation, though arguably reduces the duration of the operation.

Discussion

This is the first study that analyses the cost utility of treating the whole spectrum of gastric cancer presentation in the UK. The principle findings of this study of over 700 patients shows the use of surgery and primary oncological therapies for the treatment of gastric cancer improves overall survival and quality of life compared with BSC. It costs 68 times more to treat stage 4 compared to stage 1. A detailed cost analysis shows that the cost per QALY of stage 1 and 2 contemporary gastric cancer treatments are cost effective at a £20,000/QALY threshold. Stage 3 and 4 interventions are not cost-effective according to cost/QALY analysis.

Many trials integrate cost utility analysis in their design. However, usually these compare one treatment regime or novel technology to the standard practice for a particular stage of disease. (127) (225) (226) These trials necessitate a relatively homogenous population to assess the primary outcome measures, which is the clinical efficacy of the study characteristic rather than the cost utility. QOL is not assessed in the study by Cunningham et al (127) of perioperative chemotherapy compared with surgery alone. Given perioperative chemotherapy has been widely adopted as the management of choice (3) for operable gastric cancers, the absence of QOL evaluation in the literature is notable. The increasing eminence of QOL and economic analysis over time is probably a contributing factor to the incorporation of QOL assessment in the design of the subsequent ToGA and CLASSIC trials in 2010 and 2012 respectively.

Multiple economic analyses have been published regarding screening for gastric cancer where the screening intervention is assessed in population settings with high and intermediate age-standardised rate (ASR) per 100,000 population (gastric cancer risk). ASRs of 29.9/100,000 (Japan), 8.2/100,000 (Singapore), 13.1/100,000 (Portugal), and 3.9/100,000 (USA) are compared for cost-effectiveness. (227) Here, the comparator is no screening, and shows that screening with 5 yearly OGD between the age of 50 and 75 years old demonstrates cost utility in high gastric cancer risk populations only. A cost-utility analysis comparing serum pepsinogen testing and OGD as a screening tool with no screening was performed in a high gastric cancer risk population in northeastern China. (228) Despite not being randomised, this study of nearly 30,000 participants showed that screening and detection of early stage disease was cost-effective, although the threshold at which the cost per QALY is considered cost-effective is not reported.

Beyond the field of gastric cancer, Hall et al (213) analysed 223 breast cancer, 145 colorectal and 104 prostate cancer patients over 15 months from diagnosis. Costs were obtained from pilots of Patient Level

Information and Costing Systems (PLICS), and QOL was assessed using EQ-5D at 6, 12 and 15 months after diagnosis. Patients who died within the 15 month study period were excluded. Mean hospital costs for 15 months were £12,595 for breast cancer, £12,643 for colorectal cancer, and £3722 for prostate cancer. These costs are similar to those calculated in this study, where a patient treated with gastrectomy alone costs £18193, with a longer inpatient hospital stay than generally required for breast or colorectal operations and including costs to the NHS in the community. The reduced mean cost for prostate cancer probably illustrates the reduced inpatient stay and smaller role of surgery in the management of prostate cancer. On the whole, QOL was well-preserved, with a HSUV range of 0.755 to 0.868. This may represent the exclusion of patients who died within the study period or the better prognosis of the included cancers compared with gastric cancer. It showed that baseline stage of disease was a strong predictor of hospital costs, with costs increasing with increasing stage, in keeping with our findings.

A cost-effectiveness analysis was added to a study of second line chemotherapy in patients with metastatic colorectal cancer who have failed first line treatment (229). EQ-5D QOL data from another study (230) was applied to the life-years gained to generate QALYs. A mean utility value of 0.746 was applied to both the chemotherapy and BSC groups. This utility value is similar in the current study for those undergoing palliative chemotherapy for gastric cancer, where values ranging from 0.73 to 0.75 were identified in the literature. (149) (174)

BSC is an appropriate comparator for ICER calculations in this study, as it is the minimum treatment required for gastric cancer. This study follows the CHEERS guidelines which maximises comparability for future economic analyses. (209)

As with all economic analyses, this study relies on a number of methodological assumptions. The costs of the base cases for each treatment option are calculated by operational efficiency, therefore may

not represent the authentic costs in clinical practice. Additional costs of managing comorbidities and complications such as insertion of inferior vena cava filters, administration of anticoagulants, return to theatre, or admission to hospital during oncological therapy or BSC are not assessed. Deviation from the base case pathways such as repeated MDT discussions, repeat CT staging, non-completion of perioperative chemotherapy or receiving adjuvant chemotherapy are not assessed. The impact of additional costs can be huge: in the UK national schedule of reference costs increases of 37-78% can be added for comorbidities or complications (231).

The cost of BSC is very variable as the treatment varies according to the needs of the patient. This BSC pathway assumes care continues in the home environment and there are no admissions to hospital or NHS-funded hospice. Hospital admissions or interventions such as pyloric stent insertion or venting gastrostomy insertion increase the costs of treating this group. Best supportive care for stage 1 disease is sometimes chosen as the disease is early and unlikely to affect an elderly person's quality or quantity of life. In this subgroup, survival is relatively long and symptom free.

The use of trastuzumab as an adjunct to palliative chemotherapy has not been assessed in this study, although the study period includes the inception of trastuzumab being used in the palliative chemotherapy setting. The clinical efficacy and quality of life has been published in the ToGA trial. (226) (232) The deployment of pyloric stents as a palliative treatment of gastric outlet obstruction has not been analysed in this study.

Resource demands are greatest in the first six months after diagnosis (213). As an intention to treat analysis, if patients change treatment, often the costs are incurred but the survival and QOL is affected differently. For example, developing disease progression whilst undergoing neoadjuvant chemotherapy thereby precluding surgery, or undergoing palliative

radiotherapy for bleeding and then going on to undergo palliative chemotherapy, or having irresectable disease at the time of surgery.

This study is likely to underestimate survival with early stage disease. Median survival has been calculated as the median recorded survival time where Kaplan-Meier estimates of survival do not reach the 50% survival line during the follow-up period. Literature from the Far East suggests 88% to 97% 5-year survival rates after ESD, and greater than 90% after gastrectomy for early gastric cancer, (233) although caution is needed when comparing outcomes from the Far East with those from the West. (27) Intra-stage variability may account for some survival differences observed this study, as those in stage 2 and 3 with more extensive lymph node involvement are more likely to be treated with perioperative chemotherapy, but are also more likely to have a poorer outcome. (234) Conversely, those considered to be frail or who had poor ECOG performance scores may have been suitable only for single modality therapy, Historically, TNM stage was not always fully recorded in patients who had died before MDT discussion nor in those with extensive metastatic disease. The cases excluded from this study due to incomplete staging tended to be from the earlier years.

The QOL adjustment to generate QALYs is based on a heterogenous data set, with various population samples including the QOL of a screening population from Korea undergoing ESD, and different metrics and methods for QOL evaluation. It is likely that the QOL reduction in those undergoing perioperative chemotherapy is longer than in those undergoing surgery alone. This is not represented in the values used in this study due to lack of published literature on the subject. The RAINBOW study (174) shows that QOL reduces by 0.176-0.206 with progression of disease. This feature is likely to exist across the range of treatments, which would cause a rounding off on the QOL-time profiles and reduce the AUC. To analyse this accurately, the progression-free survival would need to be recorded, which would allow the point at which

QOL starts reducing to be determined. There is a potential bias from non-responders in QOL trials, as this favours those with positive outcomes.

Cost utility analysis is useful to demonstrate the opportunity cost of treating one condition over another by making trade-offs explicit. It guides healthcare policy but it should be applied with care. Economic evaluation may miss other relevant factors for health system decision-making, such as societal and individual benefits other than health-related QOL. By using a healthcare costs perspective, the costs to the individual and to society are disregarded. A report by the University of Bristol commissioned by MacMillan cancer support and part-funded by RBS in 2013 described individual costs associated with a cancer diagnosis of nearly £7000 per year: for transport; parking; lost earnings despite sick pay (pay rise and overtime loss); increased home energy bills; different food; and different sized clothes. (235) Societal costs are also significant, given the rapid rise of oesophagogastric cancer diagnosis from approximately 60 years old onwards. (236)

Caution must be applied to generalisation of this study to populations outside the UK because the treatment pathways, cost structures, survival data and the utility values in EQ-5D are specific to the UK. HSUVs can be different in other countries as the values attributed to particular health states vary according to national social norms. Further research is required into patient-reported outcomes such as QOL to strengthen the profiling of QOL over time.

In conclusion, this study demonstrates the cost utility benefits of treating earlier stage disease and quantifies the benefit in terms of cost per QALY. Whilst this study should not necessarily change practice, developing an awareness of trade-offs and opportunity cost is an important consideration for policy makers and clinical decision-makers alike. The large increase in cost-effectiveness of surgical and oncological therapies in early stage disease strongly supports earlier diagnosis as a cost-effectiveness measure, and indeed, suggests investment in

diagnosing gastric cancers earlier may be cost-beneficial in itself. With such financial pressures on the NHS this financially validates the clinical and political quest to encourage earlier diagnosis and treatment of gastric cancer.

Chapter 5: Cost-Utility Analysis of Oesophageal Cancer Care related to stage.

Abstract

Background

Despite advances in oncology and surgery, oesophagectomy for cancer remains one of the most mortal elective operations performed in the UK, and 2- and 5- year survival remains poor. Surgery, neoadjuvant oncology and definitive chemoradiotherapy (dCRT) are used with intention to cure oesophageal cancer. Palliative treatments include chemotherapy is used to extend survival, and radiotherapy is used with palliative intent to treat bleeding tumours. Organ-sparing endoscopic resections can treat early cancers. Appropriate treatment depends on patient fitness and TNM stage of disease. The National Institute for Health and Care Excellence (NICE) use cost per Quality of life years (QALYs) gained to approve treatments based on cost utility analysis. The aim of this study is to determine the cost utility of treating oesophageal cancer related to stage of disease, compared with best supportive care (BSC).

Methods

Costs to the NHS of one year of treatment from time of referral were calculated from activity-based costing, published staff and medication costs, and national reference costs. Treatment components were determined according to locally agreed diagnostic, staging and treatment pathways based on national guidance for the management of oesophageal cancer.

Median overall survival (OS) from diagnosis was calculated from a prospectively maintained database of all patients treated via a centralised regional MDT over 8 years. OS was analysed according to disease stage (TNM anatomical group stages 1 to 4) and treatment pathway undertaken, according to intention to treat (Endoscopic resection, oesophagectomy with neoadjuvant chemotherapy, oesophagectomy with neoadjuvant chemoradiotherapy, single modality oesophagectomy,

definitive chemoradiotherapy (dCRT), palliative chemotherapy, palliative radiotherapy, BSC).
QALYs were calculated using quality of life (QOL) data from the literature, and applied to the median OS of each treatment arm. The cost per QALYs gained compared with BSC was calculated and represented as incremental cost effectiveness ratios (ICERs).

Results

Over a period of 8 years, 1043 patients had an overall median survival of 12 months. (26.5 months stage 1, 19 months stage 2, 13 months stage 3, 5 months stage 4). Survival was better with curative intent than with palliative intent. Utility values for QOL over 1 year were 0.865 for endoscopic resection, 0.853 for oesophagectomy and chemotherapy, 0.853 for oesophagectomy and chemoradiotherapy, 0.834 for oesophagectomy, 0.89 for dCRT, 0.59 for palliative chemotherapy, 0.41 for palliative radiotherapy, and 0.45 for BSC. The most expensive treatment arm was oesophagectomy with perioperative chemoradiotherapy (£26731.05) and BSC was the least expensive (£4586.90). The cost per QALY (£/QALY) of stage 1 is £6474, stage 2 is £11246.75, stage 3 is £15474.88, and stage 4 £34233.51. ICERs show oesophagectomy for stages 1 to 3, with or without neoadjuvant oncology are under the £20,000/QALY gained threshold. dCRT, and palliative oncology options for all stages are also under this threshold. Endoscopic resection is the most cost-effective option with an ICER of 1517.82 £/QALY gained.

Conclusions

Most treatments per stage are more cost effective than BSC. This study supports all active treatments of stage 1 to stage 3 disease, according to the NICE cost effectiveness willingness to pay threshold of £20,000/QALY. Treating stage 4 disease is more than double the cost of stage 3 disease. The cost is iterative, proving beyond doubt the multidimensional benefits of identifying and treating disease at an early

stage. The cost per QALY (£/QALY) of treating stage 4 disease with oesophagectomy and oesophagectomy with chemotherapy are not supported at the NICE threshold.

Background

Over 9000 people were diagnosed with oesophageal cancer in the UK in 2015. (1) Globally, oesophageal cancer is the eighth most common cancer and the sixth most common cause of cancer-related death. (15) The incidence is increasing in both the Western world and moderate to high incidence rates persist in other parts of the globe. Despite improvements in outcomes from oesophageal cancer treatment over recent years, the mortality (1) and quality of life outcomes remain poor (237).

Treatment of oesophageal cancer depends on the stage of disease, as calculated by translating the UICC TNM stage into 4 anatomical stage groups, with stage 1 being early disease and stage 4 being advanced disease. Patient fitness is paramount in the suitability of treatment for patients: oesophagectomy involves significant cardiorespiratory physiological stress and carries 90-day or in-hospital post-operative mortality rates of 3.3%; and morbidity rates of 36.4%. (4) In the context of substantial risk, patient choice plays a large part in the decision-making process. Treatments with curative intent for oesophageal cancer include oesophagectomy, definitive chemoradiotherapy, and endoscopic mucosal resection (EMR) for early stage lesions. Palliative intent therapies include chemotherapy, radiotherapy and oesophageal stenting.
Definitive chemotherapy (dCRT) originally developed as an alternative to chemotherapy alone for those deemed unfit for surgery. (238) Studies show equivalence in outcomes between dCRT, surgery and chemotherapy, and surgery alone (239) (240), and two-year recurrence rates are similar between dCRT and surgery. (241)

As is standard practice, Siewert type 1 and 2 junctional tumours are analysed as oesophageal tumours as the treatment pathways are more closely aligned to oesophageal tumours (3); operations and oncological options are similar therefore costs and QOL should be similar; and the

prognosis correlates closer with oesophageal cancer rather than gastric cancer (4).

Upon diagnosis with oesophageal cancer, an individual's priority is survival, and quality of life. However, from an institutional perspective, value-for-money is also paramount. (242) The influence of cost effectiveness assessment has grown vastly since the National Institute for Health and Care Excellence (NICE) was founded in 1999 to evaluate the clinical efficacy of healthcare technologies, with the explicit aim of reducing geographical variability of healthcare availability. More recently, the Carter report into productivity in NHS hospitals (243) and the Getting It Right First Time (GIRFT) programme (244) have emerged over the last few years as government-led and clinician-led drives to reduce unwarranted variability in NHS care, citing cost-effectiveness as a key outcome. News from NHS England in June 2018 advises English Clinical Commissioning Groups (CCGs) to stop or reduce routine commissioning of 17 procedures deemed 'ineffective or risky', (245) again, using clinical effectiveness and cost efficiency as drivers for change in healthcare. The National Oesophagogastric Cancer Audit (NOGCA) publishes an annual report of outcomes and key performance indicators for all oesophageal cancer cases in the UK. Cost effectiveness of new technology usually uses standard care as the comparator.
The aim of this study is to compare the cost utility of treating oesophageal cancer related to stage compared with BSC.

Methods

This economic evaluation follows the NICE HTA and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines which outline methods for economic analysis to ensure comparability between studies, which will allow for comparison with other studies (209).

A prospectively maintained database was used to collect consecutive cases diagnosed with oesophageal cancer within a UK regional cancer

network. Oesophageal and Siewert type 1 and 2 junctional tumours (19) were included. Diagnosis was by oesophagogastroduodenoscopy (OGD) and biopsy, or by computed tomography (CT) alone in those patients undergoing CT first and considered not suitable for further treatment, either due to advanced incurable stage of disease or unfitness for further investigation or treatment, such as Performance Status (210) greater than 3. Clinical, pre-treatment staging was performed using CT, computed tomography positron emission tomography (PET-CT), and endoscopic ultrasound (EUS) according to staging protocols published previously (3) (211). The clinical stage as agreed by the multidisciplinary team was recorded according to UICC TNM 7 for oesophageal cancer. (202) All analysis was performed based on intention to treat.

All available management options were analysed and compared with BSC: Single modality surgery; surgery and perioperative chemotherapy; surgery and neoadjuvant chemoradiotherapy; endoscopic mucosal resection (EMR); definitive chemoradiotherapy (dCRT); palliative chemotherapy; and palliative radiotherapy. (3) The patient pathways used within the regional network for these options were itemised according to the principle of operational efficiency: using the minimum necessary resources to deliver a particular activity. The management of comorbidities were not included in the cost calculations.
Costs to the NHS were calculated, personal and societal costs were not included. Costs are calculated and reported in Pounds Sterling (£), and given in 2016 prices. A variety of sources were used to derive the cost of investigations and treatments. Sources are recorded in Appendix 2. Activity-based costings were used preferentially to maximise regional accuracy. Cardiopulmonary exercise testing (CPEX), EUS, and out of region service provision of CT-PET were calculated using activity-based costing. English NHS reference costs 2015-6 were used for some other investigations, outpatient appointment costs and critical care stay costs, where bottom-up costing approaches were not possible. (212) Reference costs use a top-down costing approach and have been adopted for use in Scotland and to a lesser extent in Wales. They are increasingly used for

economic analysis in the UK. (213) Staff costs were taken from the Personal Social Services Research Unit (PSSRU), (214) using the cost per hour which includes the capital training costs divided over the total WTE hours of service. Length of time per patient interaction was obtained from personal communications with the staff involved: clinical nurse specialists; dieticians; physiotherapists and consultants. Medication costs were taken from the British National Formulary (BNF), Chemotherapy and radiotherapy regimes were costed according to local oncology protocols, which are based on contemporary trial data. (127) Procurement costs for disposables in theatre, and operating theatre running costs, per minute, from Information Services Division (ISD) Scotland. (215) Chemotherapy doses were calculated according to an average male height and weight of 5'9" and 70kg, giving a body surface area of 1.85m^2, according to the Du Bois formula. (216)
Costs were calculated from referral for a year of treatment and follow-up within that year.

Overall survival was calculated from the date of diagnosis recorded in the regional database and the date of death as recorded from the Office of National Statistics feed into Cancer Network Information System Cymru (CaNISC). Non-parametric statistical methods were used and median values were used for grouped data. IBM SPSS Statistics version 20 for Mac was used to record and analyse the data. Median overall survival per stage and per treatment was calculated using Kaplan-Meier charts (217), where the survival curve crosses the 50% survival line, and the median recorded length of survival where it does not. A non-parametric test of independent samples was performed to identify statistically significant differences in median survival, at a probability level (p-value) of less than 0.05.

Quality of life data was derived from the published literature as discussed in the introduction. The HSUVs are on a 0 to 1 scale where 0 represents death and 1 represents full health. Mapping techniques have been used to convert questionnaire outcomes without HSUVs to scores from which

HSUVs can be generated. Quality-adjusted life years were calculated by multiplying the time spent in each HSUV (measured in years) by the utility score. The QALYs accrued are calculated assuming the change in HSUV between QOL measurement points is a straight line. Incremental cost effectiveness ratios (ICERs) are then calculated within each stage for each treatment compared to BSC. The slope of the ray on the ICER chart represents the relative benefit compared with the relative increase in cost.

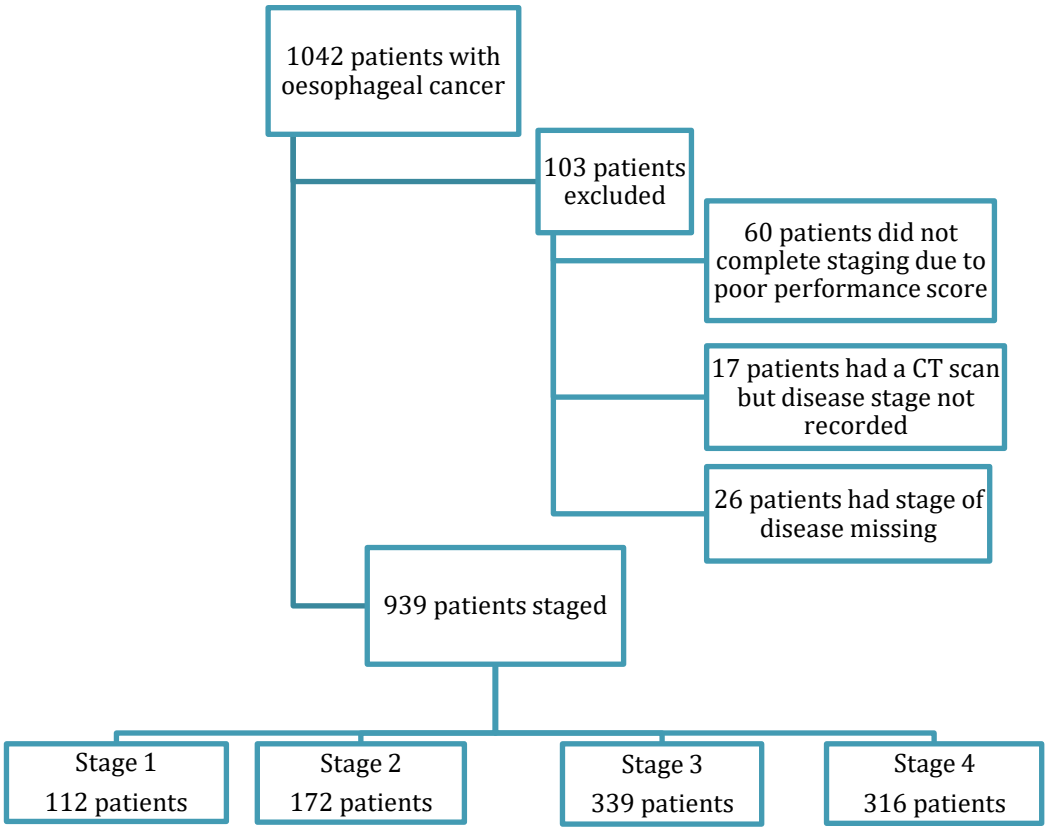
A sensitivity analysis is included to consider which factors have the greatest effect on the results, including factors which change costs, survival and QOL.

The costs of all treatments were initial outlay costs, and no delayed costs were involved, therefore no discount rate was applicable to costs. A discount rate will be examined in the sensitivity analysis for survival benefits, in those treatment/stage groups where median overall survival exceeds one year. A rate of 3.5% is standard for UK-based health economic analyses (218), based on social time preference: the value that society applies to present benefits compared with future benefits.

Results

1042 consecutive cases diagnosed with oesophageal cancer between January 2006 and July 2014 were analysed. A flow diagram showing the included and excluded cases is shown in Figure (i). 729 (70%) were adenocarcinoma, 295 (28%) were squamous cell carcinoma, 10 cases (1%) were undifferentiated, and 9 cases were small cell carcinoma (1%).

Figure (i): Flow diagram showing inclusion of patients and stage of disease.



Costs

Costs for a year of treatment are shown in table 6, based on a standard regional pathway which follows the 2011 guidelines for the management of oesophageal and gastric cancer (3). The itemised costs per treatment arm, with sources thereof, are shown in Appendix 2 (a-h).

Table 6:

Treatment pathway	Cost for 1 year of treatment (£)
EMR	5964.95
Oesophagectomy and perioperative chemotherapy	22926.05
Oesophagectomy and perioperative chemoradiotherapy	26731.05
Oesophagectomy	17798.49
Definitive chemoradiotherapy	10472.77
Palliative chemotherapy	7249.84

Palliative radiotherapy (single fraction)	5200.50
Best supportive care (BSC)	4586.90

Costs are not discounted as the study period is one year. The majority of the cost is incurred in the first 6 months after diagnosis. This also means inflation is not relevant. A discount rate of 3.5% per annum could be applied to the median survival but this would be a negligible reduction as the survival rates are largely in the order of 1-2 years.

Survival

Median overall survival in the cohort was 12 months. Survival related to stage was 26.5 months for stage 1 disease, 19 months for stage 2, 13 months for stage 3, and 5 months for stage 4. An independent samples Kruskal-Wallis test showed no significant survival difference between adenocarcinoma and squamous cell carcinoma ($p>0.097$). Figures j – m shows the cumulative survival (Kaplan-Meier method) related to stage.

Table 7: Median survival (in months) for each treatment arm per stage.

	Stage 1	Stage 2	Stage 3	Stage 4
EMR	23[a]	-	-	-
Oesophagectomy	37[a]	64	25	12[c]
Oesophagectomy and perioperative chemotherapy	47.5[a]	26	22	8[b]
Oesophagectomy and perioperative chemoradiotherapy	10	34	49	66[c]
Definitive chemoradiotherapy	21[a]	35	17	15[b]
Palliative chemotherapy	27	11	11	7[b]
Palliative radiotherapy	15	6	8	5[b]
BSC	20	8	5	2[b]

[a] derived from median survival as recorded in the database rather than via Kaplan-Meier method because median not reached in follow-up period.

[b] derived from median survival as recorded in the database rather than via Kaplan-Meier method because almost all cases censored during follow-up period so medians not calculated by K-M method.

[c]Actual survival, rather than median, as there was only 1 patient in each of these groups.

Table 7 shows the median survival, in months, for each treatment arm per stage. Endoscopic techniques are suitable only for early stage 1 cancers and therefore there are no cases in stages 2-4. Indications for EMR in oesophageal cancer include superficial SCCs without submucosal involvement, or intramucosal ACA within Barrett's. Lesions less than 1cm diameter, with no or minimal risk of lymphovascular invasion are suitable. (219) For some lesions, ESD is preferred to resect the submucosa to ascertain complete resection. The median survival recorded is the median follow up time in the study as the Kaplan-Meier survival curve did not cross the median (50% survival) line. This means the recorded survival is likely to be an underestimate of the true median survival.

For patients treated for stage 1 disease with surgery alone, surgery and perioperative chemotherapy and dCRT, the median follow-up time is recorded as the median follow-up in the study period because the median survival was not reached in the study period using the Kaplan-Meier method.

Treatments usually reserved for the treatment with curative intent were performed on 8 patients with stage 4 disease. This either represents adjustment of the stage once treatment had commenced, or historical management before the national guidelines were explicit. The long survival of one patient undergoing neoadjuvant chemoradiotherapy and surgery for stage 4 disease may represent a case lost to follow up, or a complete pathological response.

Health-related Quality of Life

Quality of life data is derived from the literature. QOL data was used if validated multi-domain questionnaires were used in a longitudinal study including baseline and post-treatment QOL data. Most studies use disease-specific questionnaires rather than the generic EQ5D questionnaire, and therefore mapping techniques have been used to generate HSUVs where disease-specific data is available.

There is no published literature on QOL after neoadjuvant chemotherapy, therefore the HSUVs for neoadjuvant chemoradiotherapy are used to create a QOL-time profile in order to quality-adjust the survival following oesophagectomy with neoadjuvant chemotherapy.

The HSUVs used in this analysis are drawn from the QOL data detailed in Table 8. Where multiple studies generated HSUVs, data was used from UK-based studies and those closest matching the database population. QOL-time profiles were generated and are shown in figure (n). The area under the curve is calculated to produce a QOL adjustment over 1 year. This is then multiplied by the survival in months to give the quality-adjusted survival time, as shown in table 9.

Table 9: Overall survival and quality-adjusted survival **(in bold)**

	Stage 1	Stage 2	Stage 3	Stage 4
EMR	23[a]	-	-	-
	19.895			
Oesophagectomy	37[a]	64[a]	25	12[c]
	30.858	**53.376**	**20.85**	**10**
Oesophagectomy and perioperative chemotherapy	47.5[a]	26	22	8[b]
	40.518	**22.178**	**18.766**	**6.824**
Oesophagectomy and perioperative chemoradiotherapy	10	34	49	66[c]
	8.53	**29**	**41.797**	**56.298**

Definitive	21[a]	35	17	15[b]
chemoradiotherapy	**18.69**	**31.15**	**15.13**	**13.35**
Palliative	27	11	11	7[b]
chemotherapy	**15.93**	**6.49**	**6.49**	**4.13**
Palliative	15	6	8	5[b]
radiotherapy	**6.15**	**2.46**	**3.28**	**2.05**
BSC	20	8	5	2[b]
	9	**3.6**	**2.25**	**0.9**

[a] derived from median survival as recorded in the database rather than via Kaplan-Meier method because median not reached in follow-up period.

[b] derived from median survival as recorded in the database rather than via Kaplan-Meier method because almost all cases censored during follow-up period so medians not calculated by K-M method.

[c]Actual survival, rather than median, as there was only 1 patient in each of these groups.

Decision tree analysis was performed showing the probability of undergoing each treatment pathway according to stage, and the cost per QALY associated with each pathway (figure o).

Curative treatment pathways for stages 1 to 3 had better median overall survival and quality-adjusted survival compared with stage 4 disease and palliative therapies. The cost per QALY is £6474.00 for stage 1, £11246.75 for stage 2, £15474.88 for stage 3, and £34233.51 for stage 4 disease. It costs more than twice as much per QALY to treat stage 4 disease as stage 3, and more than 5 times as much per QALY to treat stage 4 disease compared with stage 1.

For each stage, the costs per QALY for all treatments excluding BSC were calculated proportionately and costs per QALY of BSC subtracted to calculate the cost per QALY gained, compared with BSC. Incremental cost-effectiveness ratios (ICERs) were then calculated for each treatment pathway, according to stage, shown in figure (p).

Table 10: ICERs per stage and treatment pathway, compared with BSC (£/QALY gained).

	Stage 1	Stage 2	Stage 3	Stage 4
EMR	1517.82	-	-	-
Oesophagectomy	10068.16	4421.20	11831.71	24183.49
Oesophagectomy and perioperative chemotherapy	8431.05	14303.47	16089.23	44856.48
Oesophagectomy and perioperative chemoradiotherapy	Dominated (-337317.19)	6241.70	4008.88	2861.82
Definitive chemoradiotherapy	7289.00	2563.72	5483.73	5673.13
Palliative chemotherapy	4611.15	11057.19	7536.62	9893.28
Palliative radiotherapy (single fraction)	Dominated	Dominated	7148.74	6402.78

The ICERs in table 10 demonstrate that all treatment pathways for all stages are more cost-effective than BSC, with the exception of palliative radiotherapy for stage 1 and stage 2 disease, and oesophagectomy and perioperative chemoradiotherapy for stage 1, which are dominated by BSC. All treatment pathways at all stages of disease are cost-effective at an ICER threshold of £20,000 per QALY except oesophagectomy and oesophagectomy with perioperative chemotherapy for stage 4 disease.

An earlier iteration of this database in 2009 (240) published better survivals for oesophagectomy and dCRT in stage 1 disease, and oesophagectomy with perioperative chemotherapy for stage 2 disease. One might also expect a better survival for endoscopic therapies, and this is likely to represent the method used to gain this survival value. The 10 month median survival for stage 1 oesophagectomy with perioperative chemoradiotherapy is based on 1 patient, as is the 66 month median

survival for stage 4 in the same treatment pathway. Threshold analysis shows that oesophagectomy with perioperative chemoradiotherapy for stage 1 becomes cost-effective when the QALY exceeds 9 months. Other published literature such as the CROSS trial (130) shows that the median survival with stage 1, 2, or 3 disease was 49.4 months (of whom, 81% were stage 3 disease). However, this comparison should be made cautiously as the CROSS trial excluded patients with T4, N2, or N3 disease, and excluded a tumour length greater than 8cm. The data used in this analysis is of consecutive, unselected cases.

Sensitivity analysis

Deterministic one-way sensitivity analysis would be most markedly affected by operating theatre time, duration of inpatient hospital stay and use of radiotherapy, as these incur the greatest costs. The quality-adjustment of survival is another sensitive factor in the analysis as a change of 0.1 HSUV makes a 10% change in QALY.
Scenario analysis would be sensitive to adjustments in the pathways such as recurrent endoscopic treatments, unplanned hospital admissions, or the cost of managing complications such as chemotherapy-induced thromboembolism or post-operative anastomotic leak.

Discussion

This is the first time the economics of oesophageal cancer care have been studied as a cohort. In the era of national databases of incidence, management, and outcomes of oesophageal cancer treatments, this study fulfils the economic analysis perspective in the scientific knowledge. It provides a baseline cost-effectiveness by which novel treatments can be assessed. It shows that curative treatment pathways for stages 1 to 3 had better median overall survival and quality-adjusted survival compared with stage 4 disease and palliative therapies. This study indicates that treatments for stage 1 disease are more than five times more cost-effective than those for stage 4 disease. Indeed, it is more than twice as cost-effective to treat stage 3 disease compared with stage 4. This

augments the argument for targeting oesophageal cancer detection and treatment at an early stage of disease, as it is more cost-effective.

Quality of life adjustment of survival (QALYs) provides cost-effectiveness figures that can be compared to other healthcare treatments, and is the modern universal currency of health economics. The HSUVs are significantly poorer for palliative pathways compared with curative pathways. By following methods for economic analysis outlined in the CHEERS guidelines (209), the results of this study are maximally valuable as a comparator for the economic analysis of new treatments of oesophageal cancer.

Key drivers of cost identified in this study are length of hospital stay, operation duration, and the use of radiotherapy. Consequently, situations that increase the use of any of these factors would significantly affect the cost-effectiveness of a treatment strategy, such as return to theatre for a post-operative complication or inpatient management during oncological therapy. Conversely, identification of the effect of these factors allows strategies to be employed to minimise these costs.

Economic analyses are often considered not generalisable to other populations due the variation in costs. Oesophageal cancer treatment pathways have many variations in costs. For example, some patients undergo not only neoadjuvant chemotherapy but adjuvant chemotherapy also. Drug costs can vary due to comorbidities or dose-reductions due to chemotoxicity. Surgical costs vary depending on length of hospital stay and surgical complications. Palliative costs vary significantly as the required care is determined according to patient need. Inpatient hospital stays for palliation and the insertion of oesophageal stents increase costs compared with the treatment pathway. Some of these costs are borne by carers and the voluntary sector such as hospices.

The greatest weakness in this study is the use of small groups for calculating median overall survival. Some groups there are fewer than 10

patients, which can skew the median survivals used in this analysis. This could be overcome by using national datasets for this analysis, such as the NOGCA data. QOL adjustment is highly sensitive to variation, so measuring median survival in days would maintain better accuracy through QOL adjustment. QOL data collected from our cohort of patients would have increased the validity and allowed an evaluation according to stage of disease. Although mapping techniques to generate HSUVs from qualitative QOL questionnaires is considered valid (246) any inaccuracies caused by using mapping within this study is unknown. This analysis evaluates junctional type 1 and 2 tumours alongside other oesophageal tumour sites, yet arguably they have a different treatment pathway, often including EUS, CT-PET and staging laparoscopy. Perhaps junctional tumours should be analysed as a separate cohort. All resections in this cohort were open rather than laparoscopic, so the costs, HSUVs and HSUVs may change.

As an observational cohort study there may be changes in treatments over the duration of the eight year study period. In particular, the use of CT-PET from 2010 occurred during this time, which upstages disease in 10% of patients (247) , which could result in pre-2010 patients in stages 1 to 3 having poorer survival than post-CT-PET inception. More patients may have undergone neoadjuvant chemoradiotherapy since the CROSS trial was published in 2012. The cost of chemotherapy regimes will have changed over this period, as 3 cycles of epirubicin, cisplatin and capecitabine (ECX) has replaced the OEO2 regime of cisplatin and 5-FU.

This study compliments previously published literature. Cost-utility analysis has been performed in a Chinese setting investigating the cost utility of treating oesophageal squamous cell carcinoma with neoadjuvant chemoradiotherapy compared with surgery alone (248). Markov modelling is used to determine that the ICER of chemoradiotherapy is below the Chinese ‘willingness to pay’ threshold. This is in direct contrast to our study where the ICERs for surgery alone and those for neoadjuvant chemoradiotherapy were similar. This is likely to represent

the increased efficacy of radiotherapy in SCC (overall survival of 100.1 months in their neoadjuvant chemoradiotherapy group, 66.5 months for their surgery alone group) compared with our mixed SCC and adenocarcinoma cohort. As in our study, QALYs were used from the literature but they were used from a Dutch population of post-operative patients. Interestingly this paper claims to calculate costs from a societal perspective by including a cost per day for 'absenteeism', as the patient would not be at work.

The national Dutch Upper GI Cancer Audit has been used to analyse the cost of complications after oesophagectomy for cancer (249). This uses activity-based costing and nationally recorded outcome data. It reports significantly increased costs after minor or severe complications compared with uncomplicated surgery. This is a cost comparative study which doesn't attempt to investigate survival or QOL after complications. A smaller Dutch study of 47 patients showed no difference in QOL at 6 months between those who had uncomplicated versus complicated surgery, although the costs for the latter group were 33% greater (250).

Both a US and a Canadian publication separate treatment into three phases: initial; continuing; and end of life (251) (252). This reflects the insurance-based models used in both countries, and both aim to predict the cost of treating oesophageal cancer across a nation. The costs are calculated from a top-down approach where healthcare interactions are billed to the insurer. No QOL adjustment was applied in either study. Similar to the current study, these two papers report radiotherapy, chemotherapy and surgery to be the greatest drivers of cost.

Recommendations for future studies include the use population-based datasets such as NOGCA to perform cost utility analysis per stage of disease and ensure that patient-reporting outcome tools have a function to calculate HSUVs to allow future QOL research.

Chapter 6: Surgeon level outcome reporting for oesophagogastric cancer operative mortality

Abstract

Background

Surgeon level operative mortality (SLM) is the UK designated quality assurance measure. This study aimed to perform a compound level outcome analysis of a UK regional Upper GI (UGI) cancer network.

Methods

Consecutive 525 patients [median age 66 yr. 77.3% male, 56.2% neoadjuvant therapy, 8 year period] underwent surgery by a multidisciplinary team (MDT, 7 specialist surgeons); primary outcome measure was death within 30 days of surgery; secondary measures were anastomotic leak (AL), Clavien-Dindo morbidity severity score (MSS), (LN) harvest, circumferential margin (CRM) status, disease-free (DFS) and overall survival (OS).

Results

Median surgeon annual resection number was 10 (5-25, p=0.855), but joint consultant teams performed 14 (5-25). Median annual SLM was 0% (0-9.1) and overall network annual operative mortality 1.8% (0-3.7, p=0.389). Joint consultant team procedures were associated with fewer operative deaths (0.5 vs. 3.4%, p=0.027). Median (range) surgeon AL was 12% (9-20, p=0.625), overall morbidity 46.7% (31-60, p=0.066), LN harvest 16 (9-29, p<0.001), CRM positive 32% (16-46, p=0.003), overall 5 yr. DFS 44.8% (28.6-60.0, p=0.257) and OS 46.5% (35.0-52.5, p=0.573). No designated metrics were independently associated with DFS or OS on multivariable analysis.

Conclusions

Annual SLMs demonstrated the greatest variation (9-fold) risking inappropriate target thresholds. Surgeon level performance metrics were not associated with survival suggesting that compound level quality assurance provides better overall performance appraisal.

Introduction

Never before have surgeon level clinical outcomes been under such scrutiny. 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 (3) and the Association of Upper Gastrointestinal Surgeons (AUGIS) has recommended that such units should consist of four to six surgeons, each carrying out a minimum of 15 to 20 resections per year and serving a population of 1-2 million (253). In 2018, 19 of 31 cancer networks in England were reported to have undergone reconfiguration and centralisation (4), yet progress in Wales has received less resource and support. Specialist multidisciplinary team (MDT) expertise has been reported sporadically to improve patient outcomes (254) (255) (256) (257) (258), 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 (255) (257) (258) (259) (260) (261) (262) (263) (264), data regarding the factual impact of reconfigured centralised cancer surgery on survival is thin and often conflicting. (265) (266) (267) (268) (269)

Quality assurance metrics used in surgical arenas have by tradition focused on operative mortality within 30 days of surgery, which are frequently utilised to construct performance league tables. More recently the National Oesophago Gastric Cancer Audit (NOGCA) has reported other variables related to surgical quality including, lymph node harvest, circumferential margin involvement and duration of hospital stay, but not disease-free or overall survival. The early outcomes of the SE Wales UGI cancer network reconfiguration have been encouraging and reported previously. The curative to palliative treatment ratio increased by 71%,

operative morbidity fell 50%, lengths of hospital stay reduced on average by 3 days, median survival improved by 20%, and overall 1-year survival improved by nearly 20%. (8)

The aim of this study was to prospectively evaluate all of the compound metrics of surgical quality assurance at surgeon and unit level, and by time frames of 1- and 3-years. The hypothesis was that no significant overall inter-surgeon variation would be observed related to operative mortality and long term survival but that outcomes related to time frame would demonstrate variance.

Methods

The South East Wales cancer network serves a population of about 1.75 million and encompasses four National Health Service Health Boards; Cardiff and Vale University Health Board (C&V UHB, catchment population 450,000), Aneurin Bevan University Health Board (AB UHB, catchment population 600,000), Cwm Taf University Health Board (CT UHB, catchment population 325,000), and Hywel Dda University Health Board (H Dda UHB, catchment population 373,000). Together these UHBs are responsible for ten acute hospitals, eight district general hospitals, and two teaching hospitals. Before August 2010, eight surgeons undertaking surgery at four different hospital sites delivered the surgical care of patients with oesophagogastric cancer. Agreement was reached in December 2009 to reconfigure and centralize the UGI surgical service on a single site at the University Hospital of Wales, Cardiff, with a start date of 1 August 2010. The new model was based on six specialist UGI surgeons carrying out all of the cancer resectional surgery; three of the surgeons were based at the surgical centre, whereas the other three were to operate on an in-reach basis, with a facility for joint consultant operating, when considered appropriate. A seventh surgeon joined the MDT in 2017.

Diagnosis and staging was undertaken locally within each UHB, coordinated 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. Integral to the new surgical model was the establishment of an enhanced recovery programme (12) based on the established principles introduced by Basse and colleagues (270) in the arena of colorectal surgery.

Data regarding the oesophageal and gastric cancer caseload referred to the MDTs 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. Pathological variables were recorded from histopathology reports issued at the time of surgery. Circumferential resection margin status was defined using the Royal College of Pathologists guidelines. (271) (272) Measures of outcome included postoperative morbidity and mortality, length of hospital stay and survival, 1 year from diagnosis. No patients were lost to follow-up and dates and causes of death were obtained from the Wales Cancer Intelligence 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 because the study was in keeping with service evaluation.

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. (240) (273) Sixteen patients underwent laparoscopic assisted surgery during the study period. Operative morbidity was graded in accordance with the

Clavien-Dindo Classification (CDC). (274) Particular emphasis was placed on the incidence of morbidity of Clavien-Dindo 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 localized squamous cell carcinoma and patients with adenocarcinoma deemed unsuitable for surgery because of disease extent and/or medical co-morbidity. (275) (276)

Data Analysis

Grouped data were expressed as the median (range) and non-parametric statistical methods were used. Continuous data were compared using the Mann-Whitney test and categorical data using the chi-squared test and Fisher's exact test when the number of events was low. Data analysis was performed with SPSS® (IBM® SPSS® Statistics v25.0.0.0, IBM Corporation, Armonk, New York, USA). A non-parametric two-sample test on the equality of medians was carried out. A Log-rank test was carried out 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.

Results

In total, 525 patients were identified who underwent surgery for oesophagogastric cancer (oesophageal n=311, gastric n=214) by seven surgeons with 206 procedures (39.2%, oesophageal cancer n=120, 58.3%; gastric cancer n=86, 41.7%) performed with dual team consultant operating. Median surgeon annual resection number was 10 (5-25, p=0.855), but joint consultant teams performed 14 (5-25). Across the study time frame the number of surgical procedures for each surgeon was S1 n=63, S2 n=92, S3 n=112, S4 n=90, S5 n=67, S6 n=48, and S7 n=75. The median age for patients undergoing resection was 66 years

(inter-quartile range (IQR) 59-72) with the majority (43.7%) aged below 65 years. Most patients were male (77.3%), and had oesophageal cancer (59.2%). Neoadjuvant therapy was prescribed to 296 (56.4%) patients (chemotherapy 45.3% and chemoradiotherapy 11.0%). There were 244 (46.5%) patients who developed post-operative complications, of which 56 (12.4%) were due to anastomotic leak. There were 12 (2.3%) post-operative deaths within 30 days of surgery. The median in-hospital length of stay (LOS) for patients who underwent resection was 14 days (11-20). During follow-up, 122 patients (23.2%) developed cancer recurrence and 213 patients (40.6%) died.

Unit versus. individual surgeon surgical parameters

The majority of patients were younger than 65 years (42.3%) (surgeon range min. 33.3%, max. 50.9%) followed by 65-75 years (41.3%) (min. 32.8%, max. 55.3%) and >75 years (16.4%) (min. 10.5%, max. 31.3%). The majority of patients were male (77.3%) (min. 71.4%, max. 83.3%) and had oesophageal cancer (59.2%) (min. 48.9%, max. 68.4%). The majority of patients underwent neoadjuvant chemotherapy n=200 (44.4%) (min. 33.8%, max. 62.2%), with n=53 (11.8%) undergoing chemoradiotherapy (min. 9.1%, max. 18.9%) and n=197 (43.8%) undergoing surgery alone (min. 18.9%, max. 57.1%). A trans-hiatal oesophagectomy was the commonest procedure n=140 (31.1%) (min. 5.4% max. 45.5%), followed by Ivor-Lewis oesophagectomy n=126 (28.0%) (min. 11.4% max. 54.1%), total gastrectomy n=96 (21.3%) (min. 16.5%, max. 27.3%) and subtotal gastrectomy n=88 (19.6%) (min.10.1%, max. 24.7%). Open and close laparotomy was performed in 75 patients (14.3%, min 2.6%, max 31.3%).

The combined circumferential margin status was deemed positive in 128 patients (30.8%, min. 15.6%, max. 45.7%) and median lymph node yield was 16 (IQR 11-23) (min. 11 (IQR 9-20), max. 24 (IQR 17-29)). Post-operative morbidity occurred in 244 patients (46.5%, min. 31.3%, max. 60.0%). Anastomotic leak occurred in 56 patients (12.4%, min. 9.1%,

max. 15.9%). Major post-operative morbidity (CDC > 2) was observed in 98 patients (18.7%, min. 9.3%, max. 26.0%), and median length of hospital stay was 14 (IQR 11-20) days, and similar for all surgeons. Operative mortality within 30-days of surgery occurred in 12 patients (2.3%, min. 0.0%, max. 7.9%).

The 1-, 3- and 5-year overall survival for all patients was 92.1% (min. 87.8%, max 97.7%), 62.2% (min 58.2%, max. 70.0%) and 46.5% (min. 35.0%, max. 52.5%) respectively. The 1-, 3- and 5- year disease-free survival was 83.0% (min. 76.9%, max. 92.0%), 55.0% (min. 30.0%, max. 66.7%) and 44.8% (min. 28.6%, max. 60.0%) respectively. With regard to oesophageal cancer, the 1-, 3- and 5-year overall survival was 93.7% (min. 86.4%, max. 100.0%), 62.5% (min. 53.8%, max. 71.4%) and 44.6% (min. 36.4%, max. 52.2%) respectively with a 1-, 3- and 5- year disease-free survival of 79.3% (min. 68.8%, max. 90.5%), 50.0% (min. 20.0%, max. 58.8%) and 37.2% (min. 25.0%, max. 55.6%) respectively. For gastric cancer, the 1-, 3- and 5-year overall survival was 89.6% (min. 73.3%, max. 100.0%), 61.8 (min. 41.7%, max. 100.0%) and 48.7% (min. 33.3%, max. 56.5%) respectively with a 1-, 3- and 5- year disease-free survival of 88.4% (min. 85.2%, max. 100.0%), 62.8% (min. 40.0%, max. 80.0%) and 57.4% (min. 33.3%, max. 71.4%) respectively.

Consultant team approach outcome parameters

The baseline characteristics for patients grouped into individual consultant and dual team consultant operating can be found in table 13. Dual consultant operating was performed in 206 procedures (39.2%). Patients were younger (<65 years) in the individual consultant led operator cohort when compared with patients in the dual team operator cohort (p=0.029). Proportions were similar related to gender (p=0.986), neoadjuvant therapy (p=0.394), tumour location (p=0.712), and operation type (p=0.505). Open and close operations, were more commonly performed by dual consultant teams (p=0.053), with lower lymph node harvest (p=0.012), and lower operative mortality within 30/7 of surgery

(0.5 vs. 3.4%, p=0.027). CRM status (p=0.205), post-operative morbidity (p=0.807), anastomotic leak (p=0.993), and CDC (p=0.467) were similar irrespective of operative team.

Collective, annual and 3-year measures of surgical quality assurance

Complete characteristics related to quality assurance and outcome measures are shown in table 11.

Comparing annual metrics between 2011 and 2018 revealed that more patients received chemoradiotherapy (1.4% 2011 vs. 14.5% 2018), more patients underwent an Ivor-Lewis oesophagectomy (24.1% 2011 vs. 40.8% 2018) and fewer patients underwent open and close procedures (17.1% 2011 vs. 8.4% 2018) in the latter period. Other notable variances were observed in the rates of open and close procedures (21.0% 2014 vs. 8.4% 2018), lymph node yield (11 (IQR 8-17) 2014 vs. 20 (IQR 15-27) 2018), post-operative morbidity (26.3% 2013 vs. 53.8% 2016), operative mortality (0.0% 2012 & 2014 vs. 6.4% 2016), and 5-year overall survival (55.2% 2014 vs. 35.3% 2013) (table 11).

In contrast, when 3-year time frames were examined, other than the prescription of neoadjuvant chemoradiotherapy (0.8% 2010-2012 vs. 16.9% 2012-2015) and the number of patients receiving Ivor-Lewis oesophagectomy (18.1% 2012-2015 vs. 39.7% 2015-2018), all other performance metrics were similar (table 11).

Survival analysis

Univariable and multivariable survival analyses related to all cases, oesophageal cancer, and gastric cancer were performed and can be found in table 12.

There was no difference between overall or disease-free survival and operating surgeon (figures q, r).

Discussion

The age of measured accountability has arrived, of reward for measured performance, and belief in the virtues of publicising those metrics ensuring transparency. It is frequently claimed and confidently asserted at scientific meetings that collecting metrics of measured performance and then making them public is a way to improve the functioning of our institutions. Nowhere have the virtues of accountability, performance metrics, and transparency been more touted than in the arena of medicine; and understandably so, because seldom are the stakes higher, for lives are on the line. This is the first study to prospectively collate an UGI cancer network's compound level clinical outcome metrics, and the principal findings were that surgeon level annual operative mortality varied 9-fold, anastomotic leak and overall morbidity 2-fold, lymph-node harvest 3-fold, CRM status 3-fold, overall 5 year cumulative survival varied by 50%, and 5 year disease free survival varied by a 32% margin. However, only the variance in lymph node harvest and CRM status exhibited statistical significance, and surgeon level performance metrics were not associated with overall or disease-free survival. A consultant team focused operative approach on patients with high risk-profiles, was six-fold safer in terms of operative mortality within 30 days. From a three-year metric perspective, operative mortality varied by 1.5%, anastomotic leak 2.2%, overall morbidity 13.9%, lymph-node harvest 29.4%, CRM status 7.5%, overall 5 year cumulative survival varied by a 3.4% margin. The hypothesis that no significant inter-surgeon variation existed related to operative mortality was supported, and also that three-year time frames provide a more balanced and uniform measure of performance than annual snap-shots.

Governance by targets implies the ability to set targets relating to some domain (small or large) of total performance which is to be given priority. To date in the arena of UGI cancer surgery metrics, operative mortality has been the domain measured. But the publication of mortality data as an indicator of quality of clinical care may itself produce reactive gaming

responses. There is anecdotal evidence that such publication results in reluctance by surgeons to operate on high-risk cases, those who stand to gain most from surgery. (277) Because mortality rates are extremely low (about 2 per cent), one extra death has a dramatic impact on a surgeon's performance in a year, and risk-adjustment methods cannot resolve such problems. The data presented here suggests that 3-yearly measures of operative (margin status and lymph node yield), post-operative (CDC >2 and post-operative death) and 5-year survival (overall and disease-free) are required to report on surgical performance.

At the time of writing, only three other UK centres have reported their experience of centralising oesophagogastric cancer surgery. (266) (278) (279) In terms of compound level metrics, the reported rates for anastomotic leak are 7.3% (278) to 10.0% (279), margin involvement was 46.0% (278), LOS was 14 days (278), and post-operative mortality was 0% to 3.6% (266) (279) (278). These figures are similar to those reported here and support the notion that higher case volumes result in improved outcomes. (261) The centralisation effect is not restricted to the fluidity of the operating surgeon with the technical aspect of the surgery, but also improves the performance of all members of the MDT which will include perioperative care, the recognition and management of complications, and longer-term nutritional support following discharge.

The annual UK NOGCA reports that between 2015 and 2017, 30-day and 90-day mortality for patients undergoing oesophagectomy was 2.4% and 3.9% respectively, with gastrectomy mortality lower at 1.3% and 3.3%, respectively. The median LOS after oesophagectomy was 9 days (11-17) compared with 7 days (9-13) after gastrectomy. These figures clearly demonstrate the positive impact of improvising the quality of perioperative care seen with the introduction of ERAS and more research in prehabilitation; arguably boosted by concentrating patients in fewer centralized units. Of the 41 centres providing data to NOGCA, 75% of units achieved adequate lymph node yield on 76.2 to 100.0% of occasions and demonstrated involved margin rates on 3.9 to 31.3% of

occasions. Despite the observed variance in quality indicator metrics, 5-year survival rates (50%) remain similar over the last decade. Whilst chemotherapy response rates remain modest at 14.8%, (280) pursuing this quality metric alone may only boost 5-year survival to a certain level, given the current cadre of chemotherapeutic agents. Improvements in perioperative care and more widespread implementation of a precision medicine approach are also desirable to optimise survival.

This study has a number of inherent potential limitations. The data is derived from one UK regional cancer network and the data must therefore be interpreted with caution because it is unclear to what extent the conclusions may apply elsewhere. Relatively few patients underwent a minimally invasive approach to either oesophagectomy (5.5%) or gastrectomy (1.1%), which was introduced in 2017. In contrast, the strengths of this study are that it represents, by some margin, the largest of very few UK reports regarding UGI cancer service centralization, relating to 525 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 over eight years; survival data are particularly robust because no patients were lost to follow-up and death certification was obtained from the Office of National Statistics.

In conclusion, rapid improvement in any arena demands measuring results, a familiar management principle. Teams advance and shine by tracing progress over time and relating their performance to that of rivals both inside and outside their group. Debatably, rigorous value measurement (outcomes and costs) is the single most vital step in refining healthcare. In the arena of UGI cancer, operative mortality alone does not appear to predict robust long-term survival. A similar robust national data analysis should be performed to identify objective agreed designated metrics.

Chapter 7: Prognostic significance of 18-FDG PET-CT use in staging patients undergoing surgery for oesophageal cancer

Abstract

Background

PET-CT is now integral to the staging pathway for potentially curable oesophageal cancer, primarily to identify occult distant metastases unseen by conventional radiological modalities. The aim of this study was to analyse the effect of PET-CT introduction on survival and assess patterns of recurrence after oesophagectomy.

Methods

A cohort of 496 patients undergoing oesophagectomy for cancer [median age 63 (31-80) yr., 395 male, 425 ACA, 71 SCC, 325 underwent neoadjuvant therapy] was available for study. Two hundred and twenty-three patients underwent PET-CT enhanced staging protocols and the primary outcome measure was overall survival (OS) based on intention to treat.

Results

Three-year OS pre-PET-CT was 42.5% compared with 57.8% post-PET-CT (Chi^2 6.571, df 1, p=0.004). On multivariable analysis, pT stage (HR 1.496 [95% CI 1.28 - 1.75] p<0.0001), pN stage (HR 1.114 [95% CI 1.04 - 1.19] p=0.001) and PET-CT (HR 0.688 [95% CI 0.53 - 0.89] p=0.004) were independently associated with OS. Recurrent cancer was observed in 125 patients (51.4%) pre-PET-CT, compared with 74 patients post-PET-CT (37.8%, p=0.004), and was less likely to be distal in location after PET-CT introduction (39.5 vs. 27.0%, p=0.006).

Conclusion

PET-CT enhanced staging is an important and independent factor associated with improved survival in patients undergoing oesophagectomy for cancer.

Introduction

Computed tomography enhanced with ^{18}F-FDG (^{18}F-labelled fluoro-2-deoxyglucose) positron emission tomography (PET-CT) is now an established and evidence-based part of the modern radiological staging algorithm of oesophageal cancer (3) (94). It works by imaging a radiolabelled marker (^{18}F-FDG) which is concentrated in metabolically active tissue. Reported benefits include the detection of distant metastases not detected by CT in 10% of patients, qualified treatment in as many as 25%, (94) (95) and modified MDT prescribed treatment in up to 38% of patients. (247) Yet PET-CT is not without limitations: endoluminal ultrasound (EUS) has been reported to be superior in staging both the primary tumour and local lymph nodes (281); and no evidence has yet emerged that use of PET-CT has been associated with improved overall survival. (282) Moreover, important reconfiguration of UK oesophagogastric cancer services has occurred over the last decade, which has been accompanied by better clinical outcomes. The early reports from the National Oesophago-Gastric Cancer Audit (NOGCA) have emphasised that better patient selection by improved radiological and physiological staging accuracy is among many significant factors that have improved survival after potentially curative oesophagectomy, alongside increased use of neo-adjuvant chemotherapy, reduced post-operative morbidity and mortality, and centralisation of oesophago-gastric cancer services. (283) Determining the specific effect of PET-CT on outcome after potentially curative oesophageal cancer surgery is consequently challenging.

The aim of this study was to analyse the influence of 18-FDG PET-CT introduction on overall survival (OS) after oesophagectomy for cancer, compared with historical controls. The hypothesis was that PET-CT introduction into the routine staging algorithm of patients diagnosed with oesophageal cancer was associated with improved OS after potentially curative surgery. The setting was a UK oesophago-gastric cancer network serving a population of 1.8 million.

Methods

All patients diagnosed with oesophageal cancer of any cell type who underwent oesophageal surgery and had PET-CT imaging during the preoperative staging period in the South East Wales regional UGI cancer network were studied prospectively between January 1, 2009 and August 31, 2016. These patients were compared with a historical cohort of consecutive patients undergoing oesophageal cancer surgery between January 1, 1998 and January 1, 2009, staged with the network's historical staging algorithm without PET-CT. Exclusion criteria included patients undergoing PET-CT for Siewert type III oesophagogastric junctional cancer with proximal oesophageal extension, and patients undergoing salvage oesophagectomy following initial definitive chemoradiotherapy (dCRT).

Patients proceeded to PET-CT imaging only if they were suitable for potentially curative treatment on the grounds of CT stage and performance status. PET-CT was concurrently arranged with Endoscopic Ultrasound (EUS) examination. PET-CT was used for initial staging only and was not used for restaging after neoadjuvant therapy. All PET studies were integrated PET-CT and no patients received PET imaging alone. Detail of the networks' EUS staging protocol has been described previously. (13) Patients' fitness was assessed by means of cardiopulmonary exercise testing (CPEX), (12) and the 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. (202) The primary outcome measure was OS from diagnosis. Secondary outcome measures were proven recurrence patterns and disease-free survival (DFS). Ethical approval, sought from the regional ethics committee, was considered unnecessary because the study was deemed to represent service evaluation. A number of developments in the management of oesophageal cancer occurred during the study period, including changes in practice based upon the publication of randomised clinical trials, the introduction of an enhanced recovery program in 2008,

(12) and finally, centralisation of the upper gastrointestinal cancer regional network service in Cardiff from August 1, 2010. (8)

PET-CT protocol

PET-CT examinations were performed at two centres. At the first centre, 87 patients had PET-CT examinations performed using a Philips 16 slice Gemini GXL dedicated PET-CT scanner (Philips Medical Systems, Cleveland, Ohio, USA). The uptake time was 60 minutes. A standard administered activity of 350 MBq of FDG was given. Reconstructions were performed using a 3D acquisition with non-time of flight acquisition for 4 minutes per bed position.

At the second centre, 485 patients were imaged using a GE discovery 690 PET-CT scanner (GE Healthcare, Pollards Wood, Buckinghamshire, UK). Serum glucose levels were routinely checked and confirmed to be less than 7.0 mmol/L prior to imaging. Patients received an activity of 4 MBq of ^{18}F-FDG per kilogram of body weight. Uptake time was 90 minutes. PET images were acquired at 3 minutes per field of view. The length of the axial field of view was 15.7 cm. Images were reconstructed with the ordered subset expectation maximisation algorithm, with 24 subsets and 2 iterations. Matrix size was 256 x 256 pixels, using the VUE Point™ time of flight algorithm. CT images were acquired in a helical acquisition with a pitch of 0.98 and a tube rotation speed of 0.5 seconds. Tube output was 120 kVp with output modulation between 20 and 200 mA. Matrix size for the CT acquisition was 512 x 512 pixels with a 50cm field of view. At both centres, all patients were starved for a minimum of 6 hours prior to imaging and no oral or intravenous contrast was administered.

Lymph nodes were classed as involved on PET-CT if identified on the CT component and showed FDG-uptake appreciably higher than background values. No specific standardised uptake value was used for the inclusion of regional nodes. Lymph nodes considered physiological or related to an alternative aetiology were excluded from the N-stage.

Treatment

Patients were selected for radical treatment [surgery or definitive chemoradiotherapy (dCRT)] based on perceived radiologic stage, comorbidity and patient choice according to algorithms described previously. (284) (256) (275) The standard surgical approach was subtotal trans-thoracic oesophagectomy (TTO) as described by Lewis and Tanner. (285) (286) Trans-hiatal oesophagectomy (THO), as described by Orringer (287) was used selectively in patients with adenocarcinoma of the lower third of the oesophagus with significant cardiorespiratory risk-profiles, or T1/2 N0 disease. All procedures used an open approach, and oesophageal resection was defined as potentially curative if all visible tumour was removed, and both proximal and distal resection margins were free of tumour on histological examination. R1 resection was defined as positive longitudinal and circumferential margin status on histological examination. (288)

Follow-up evaluation

Patients were reviewed every 3 months for the first year, and 6 monthly thereafter until 5 years or death. Disease recurrence was suspected clinically and confirmed by computed tomography or endoscopy. Patterns of recurrence were defined as loco-regional, distal (metastatic), or both loco-regional and distal, when both were diagnosed concurrently. The time of recurrence was taken as the date of the confirmatory investigation. The patient cohort was analysed in January 2017. The median follow-up was 26 months (range 6 to 220), with 476 patients (96.1%) followed up for 1 year or until death, 447 (90.0%) for 2 years, 418 (84.3%) for 3 years, and 375 (81.4%) for 5 years. No patients were lost to follow-up and death certification was obtained from the Office for National Statistics via Cancer Network Information System Cymru (CaNISC).

Statistical methods

Grouped data were expressed as median (range) and non-parametric methods used throughout. All relevant independent variables thought to

be potential confounding factors and those which affect outcome were evaluated in a multivariate analysis. These were considered by the MDT and comprised age group, sex, tumour histology, pathological T and N stage, operation type and location of PET-CT staging scan. The dependent variable was whether or not the patient underwent PET-CT staging. Disease free survival (DFS) was calculated by measuring the interval from a landmark time of 6 months after diagnosis to the date of recurrence; an approach mirroring previous randomised trials (289) (129) and allowing for variance in time to definitive surgery. Events resulting in a failure to complete curative treatment, such as palliative surgery, operative mortality, and disease progression during neoadjuvant therapy, were assumed to occur at this landmark time, to facilitate intention-to-treat analysis. Overall survival was measured from the date of diagnosis, and cumulative survival calculated according to the method of Kaplan and Meier; differences between groups were analysed with the log rank test. Univariable analyses examining factors influencing survival were examined initially by the life table method of Kaplan and Meier, and variables significant at the $p<0{\cdot}010$ level were entered into a forward conditional Cox proportional hazards model. All statistical analysis was performed with SPSS® (IBM® SPSS® Statistics v23.0.0.0, IBM Corporation, Armonk, New York, USA).

Results

Overall, 496 consecutive patients were eligible for inclusion, 273 pre-dating PET-CT, and 223 patients where PET-CT staging protocols were used. Twenty-two (9.9%) patients had non-avid tumours on PET-CT but were included in the cohort on an intention to treat analysis basis. Following PET-CT inception, 572 patients underwent PET-CT staging for potentially curative oesophageal and junctional cancers; 223 (40.0%) patients underwent oesophageal cancer resection. Of the 349 (61.0%) patients that did not progress to surgical resection, 239 (68.4%) received dCRT or palliative therapy due to age, comorbidity, patient choice, inoperable disease, or disease progression; 78 (22.3%) were upstaged

by PET-CT, 16 (4.6%) had predominantly gastric cancer extending above the oesophagogastric junction (an exclusion criterion in this study), and 16 (4.6%) underwent endoscopic mucosal resection (EMR). Details of the patients related to staging protocol are shown in Table 13.

The operative approach was trans-thoracic in 233 (47.0%), trans-hiatal in 200 (40.3%), and a three-stage approach was used in 6 (1.2%) patients. Open and close laparotomy was performed in 57 (11.5%) patients either due to unresectable tumour or metastatic disease. Pathological examination revealed the resection specimens to be palliative R1 (microscopic involvement of the resected margins) status in 166 (33.5%) patients. Operative mortality occurred in 17 (3.4%) patients within 30 days of surgery. More trans-hiatal oesophagectomies and 3-stage oesophagogastrectomies were performed in the post-PET-CT cohort than the pre-PET-CT cohort, which contained more trans-thoracic oesophagectomies ($p<0.0001$). The post-PET-CT cohort also underwent marginally more open and close laparotomies (n=27, 12.1%) compared with the pre-PET-CT cohort (n=30, 11%, p=0.698).

Duration of survival

Disease Free Survival

For patients with all pathological stages of disease, median DFS was 16 months in the pre-PET-CT cohort, compared with 35 months in the post-PET-CT cohort (p=0.049; figure (s)). One-, 2- and 3-year cumulative DFS in the pre-PET-CT cohort was 56.5%, 41.4% and 34.4% respectively, compared with 61.9%, 52.6% and 49.3%, in the post-PET-CT cohort. Following PET-CT introduction, median-, 1-, 2- and 3-year DFS increased by 19 months, 5.4, 11.2 and 14.9%, respectively. All factors associated with DFS on univariable analysis are shown in Table 14.

Overall Survival

For patients with all pathological stages of disease, median OS was 28 months in the pre-PET-CT cohort, compared with 50 months in the post-PET-CT cohort (p=0.004; figure (t)). One-, 2- and 3-year cumulative overall survival in the pre-PET-CT cohort was 79.1%, 55.7% and 42.5%

respectively, compared with 86.2%, 68.8% and 57.8% in the post-PET-CT cohort. Following PET-CT introduction median-, 1-, 2- and 3-year OS increased by 22 months, 7.1, 13.1 and 15.3%, respectively. All factors associated with OS on univariable analysis are shown in Table 15.

Multivariable analysis

The factors found to be significantly associated with DFS and OS on univariable analysis were entered into a multivariable analysis using Cox's proportional hazards model, the results of which are shown in Tables 16 and 17. The number of events per variable was 38.14.

Recurrence rates

Table 18 illustrates the recurrence patterns within the 2 cohorts. The overall number of patients diagnosed with cancer recurrence was 199 (45.3%).

Recurrent cancer was observed in 125 patients (51.4%) in the pre-PET-CT cohort, compared with 74 patients in the post-PET-CT cohort (37.8%, Chi^2 8.199; df 1, p=0.004). The site of recurrent cancer was less likely to be distal in location after PET-CT introduction (39.5 vs. 27.0%, p=0.006).

Discussion

This is the first study to demonstrate a positive significant correlation between the introduction of PET-CT into an oesophageal cancer staging algorithm and a reduction in cancer recurrence, with a commensurate increase in durations of survival, irrespective of stage, in patients undergoing potentially curative surgery. In keeping with previous reports (94) (95) (247), PET-CT upstaged 78 patients (13.2%), changing their treatment modality and precluding surgery. Median-, 1-, and 3-year OS increased significantly by 22 months, 13.1% and 15.3%, respectively after introduction of PET-CT. Cancer recurrence was 13.6% less common after PET-CT introduction, with fewer loco-regional and distal recurrence events when compared with historical controls. Consequently the hypothesis of this study is upheld: namely that introduction of PET-CT into the routine oesophageal cancer-staging algorithm was associated with improved OS after potentially curative surgery.

Reports regarding the influence of PET-CT within oesophageal cancer staging algorithms on patient long-term outcomes related to recurrence and durations of survival are few. Torrance et al (282), from Cheltenham, England, reported in a retrospective review of 200 OC patients undergoing PET-CT, 128 of whom underwent oesophageal resection. Although PET-CT altered treatment intent in 19 patients (9.5%), no significant difference was noted in post-operative mortality, or early recurrence where PET-CT was performed when adjusted for age, gender, stage or neoadjuvant chemotherapy (OR 1.136, p=0.761). Moreover, PET-CT had no significant effect on survival (Chi^2 0.710, p=0.400). The difference in survival pre- and post-PET-CT was approximately 2%, 6% and 7% at 1, 2 and 3 years, compared with 7.1%, 13.1% and 15.3% in this study. Torrance et al concluded that PET-CT improved the accuracy of oesophageal cancer staging, avoiding potentially unnecessary surgery, and contended that missed occult metastases did not appear to be the primary cause of early oesophageal cancer recurrence.

The current study has a number of potential inherent limitations. The PET-CT examinations were performed at two centres, using different scanners, protocols, and uptake times, with patients in the early part of the study referred to an out of region centre (Philips 16 slice Gemini GXL), prior to the installation of a local PET scanner in 2010. The main differences between the two centres were firstly; a 60-minute uptake time on the first scanner, and a 90-minute uptake time at the second centre. Longer uptake times lead to higher tumour to background tracer uptake and may therefore increase conspicuity of nodal and distant metastases. (290) Secondly; the second scanner had time of flight correction whereas the first scanner did not. Time of flight reconstructions improve signal to noise ratio and improve lesion conspicuity. (291) Thirdly; at the first centre, images were acquired for 4 minutes per bed position, whereas at the second centre the acquisition was 3 minutes per bed position. This would be expected to lead to some improvement of image quality at the first centre, provided that the patient was able to remain motionless throughout the longer acquisition, which might mitigate the other factors. The potential heterogeneity introduced within the PET-CT imaged group

was a reason why the location of the PET-CT scan was a covariate within the multivariate analysis, as it was a potential cofounder and adds strength to this study.

The study included patients treated over a 17-year period with a variety of treatment strategies. Evolution in oesophagogastric cancer practice would have naturally occurred during the time frame of this study, including neoadjuvant therapy regimen modifications, more detailed patient risk profile assessment related to patients' fitness for surgery including objective assessment of physical fitness with cardiopulmonary exercise testing, centralisation of surgical services, and the introduction of an enhanced recovery program, all of which might represent potential confounding factors.

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 cancer network and multidisciplinary team. This team included 6 experienced specialist surgeons, with a referring population base of 1.8 million, accepting over 500 cases per year, generating in excess of 100 potentially curative oesophagogastric resections, whose outcome data is well audited and of public record. (292) (240) The survival and prognostic data are especially robust because no patients were lost to follow-up, and causes and dates of death were obtained from death certificates provided by the Office for National Statistics. Moreover, the improvement in survival cannot be explained by poor outcomes in the historical control cohort, which compare favourably with the clinical outcomes data published in the most recent NOGCA report. (293) NOGCA cumulative survival at 1-, 2- and 3-years was approximately 70%, 50%, and 40% compared with 79.1%, 55.7% and 42.5% in historical controls. Furthermore, NOGCA reported 30-day mortality of 4.5%, between 2007 and 2009, comparable with the 4% observed in the historical cohort of this study.

In conclusion, this analysis supports the use of PET-CT in oesophageal cancer staging pathways. Risk profile assessment represents an important development in the selection algorithm for patients diagnosed

with invasive oesophageal cancer. While this is often assumed to relate to patients' physical fitness, clearly avoiding hopeless radical, and unnecessary surgery, in patients with undetected occult metastases is an important allied strategy, if oesophageal cancer treatment outcomes are to be optimised. The findings of this study have shown that the introduction of PET-CT into the global patient assessment process changed the risk profile of over 1 in 10 patients, reduced global recurrence by one quarter, and improved median survival by a full year. On account of the improved overall and disease-free survival, a cost-utility health economic analysis of PET-CT may add another dimension of justification for its continued employ.

Chapter 8: General discussion and prospect

The outcomes of oesophagogastric cancer in the UK remain poor: where five-year survival for oesophageal cancer is 15%, and for gastric cancer is 30%. This is largely a consequence of late presentation with advanced incurable disease, although surgical and oncological treatment options also contribute to the morbidity and mortality inflicted upon patients. Modern UK oesophagogastric cancer care is going through a period of refinement: the revolutions of centralisation of the early 2000s and the paradigm shift towards the use of neoadjuvant therapy in multimodal cancer treatments have become established practice and the healthcare community is refining how we measure outcomes.

This thesis assesses the whole of oesophagogastric cancer care in an economic context. NICE set the framework in which clinical effectiveness is discussed and require assessments to be based on QALY survival advantage. Economic analyses of gastric and oesophageal cancer care (Chapters 4 and 5) provide strong evidence supporting financial investment to diagnose earlier disease in order to save money in the long term. It also provides data about the reality of poor survival and QOL outcomes from palliative therapies. The novel data in this thesis establishes a baseline against which new technologies and management options can be evaluated. Potential advances include the increased scope of endoscopic resections, increasing utility of radiofrequency ablation in Barrett's oesophagus, advances in radiotherapy such as three-dimensional conformal radiotherapy or proton beam radiotherapy, and the use of systemic anti-cancer treatments such as monoclonal antibodies.

As the database matures over the coming years, the effects of more modern surgical approaches will be available for evaluation. Hybrid laparoscopic oesophagectomy and laparoscopic gastrectomy and the left thoracoabdominal approach for proximal margin threatened gastrectomy are all increasingly employed for post-operative recovery and oncological benefit. It will be possible to analysis the relative economic benefit of

reduced length of hospital stay and improved QOL within one year post-operatively after laparoscopic resections compared with the increased operative time and equipment expenses.

Markov modelling can be performed to show a mortality rate at which oesophagogastric resections become not cost-effective, or how the cost and incidence of complications affects the cost-effectiveness. Using a standardised classification of complications of surgery such as those proposed by Low et al, (294) would allow further studies to investigate the cost of complications. The shifts in cost-effectiveness accounting for post-operative complications would provide interesting information, particularly in the knowledge that post-op complications are common: approximately 40% of patients have a post-operative complication (295), and 39.3% and 60.2% have a grade 3 or 4 toxicity respectively from chemotherapy or radiotherapy. (239) Such events are associated with shorter survival and poorer QOL, and also increased costs. This could shift the balance of cost effectiveness away from surgery or oncology as the costs might outweigh the benefits. Further statistical modelling could be applied to the economic analyses to account for uncertainty: there is an inherent uncertainty in economic model estimates, which can be explored using Monte-Carlo simulation which uses statistical distributions rather than point estimates to calculate a range of results with 95% confidence intervals. (296)

QOL assessment has been performed in oesophagogastric cancer care from the late 1990s and shaped modern standard of practice by demonstrating that it took a year to regain QOL after a major oesophagogastric resection. QOL is re-emerging to the forefront again, in the guise of patient-reported outcomes (PROs). These PROs face the same challenges of the QOL assessments: whether assessment should be disease-specific or multidomain, and whether qualitative or quantitative data is more valuable. More accurate QOL data would strengthen the QOL and patient-centred decision-making in treatment pathway planning, as well as strengthening the economic case.

Introduction of PROs may set the precedent for routine patient questionnaire feedback. Although not examined in this thesis, the role of QOL assessment in the uptake and commissioning of MIO is an emerging interest, where QOL is reportedly better 3-6 months post-operatively but returns to same as open surgery by one year post-operatively. (114) Given that pain is a disproportionate factor in Western society QOL assessments, this element could be directly targeted to improve QOL outcomes of surgery.

Clinical medicine is in a state of flux regarding whether treatment pathways should be 'one-size-fits-all' standardised by programmes such as ERAS and GIRFT, or individualised, such as HER2 testing for trastuzumab therapy, or tailoring chemotherapy to the molecular subtype of gastric cancer. Recent findings by the OCCAMS consortium demonstrates that only 14.8% of oesophageal tumours show a significant effect of chemotherapy on tumour specimens, suggesting that chemotherapy should be reserved for those who are most likely to be chemotherapy responders (280). Perhaps increased molecular understanding of histological subtypes of cancers, as indicated by Chia and Tan for gastric cancer (297), will allow specific targets for treatments in different molecular environments.

Ultimately, economic analysis is a social science, which is strongly influenced by the societal values of the era and culture. From an individual patient perspective, the concept of 'doing something', is very powerful in our culture, and therefore the QOL associated with palliative therapies and BSC is adversely affected. This value is also reflected in the NICE threshold variability for end of life therapies, where the £20,000-£30,000/ QALY is raised to £50,000/QALY. Being pain-free and being at home are also highly valued in our society, and also therefore affect QOL. It is critical that economic analyses are interpreted bearing these values in mind.

How quality of treatment is measured is being refined. Initial reports of single-surgeon annual mortality outcomes have given way to risk-adjusted mortality rates, but in Chapter 6 through a detailed investigation of quality assurance metrics, I argue that quality of surgery is not only measured by the crude 30- or 90- day mortality rates, but must include other quality indicators such as morbidity and be analysed across units over multiple years to create meaningful quality assurance. Risk-adjusted mortality rates are designed to mitigate for particular risks, which must be explicit. They mask the truth of raw data in a veil of pragmatism. There is concern that management decisions can be adjusted to avoid operations or curative therapies in high risk patients. This is an expression of Goodhart's law, paraphrased by Strathern:

> "when a measure becomes a target, it ceases to be a good measure" (298)

Future work will need to look at the outcomes of the denominator, not only the outcomes of those deemed suitable for curative treatment but also the outcomes of the large proportion of patients defined as palliative at diagnosis or become palliative during their staging and treatment pathways. The analysis is based on minimum operative cases guidance (253), which doesn't account for varying volumes of operative experience between surgeons throughout their careers. In the future, a quality improvement approach using run-charts may be useful to record quality over time. The question remains, how much morbidity or mortality is tolerable per surgeon or per unit?

Staging of oesophagogastric cancers is an expensive, convoluted multi-step pathway, therefore it is critical to know that all components in the pathway improve the accuracy of stage and ultimately, improve survival. Chapter 7 provides a sound exploration of the value of CT-PET in improving survival of oesophagectomy patients and reducing the recurrence rates.

Conclusions

Key points for this thesis are that oesophagogastric cancers represent relatively common cancers with poor prognoses that haven't changed much over time. The UK incidence is not high enough to justify screening with currently available modalities. The absence of significant symptoms or signs until disease is advanced means that patients present to healthcare services late. By investing in diagnosis at an early stage of disease, cost-effectiveness could be dramatically improved. Prognosis varies according to stage, but overall it remains poor. Novel advances in investigation and treatment can make significant differences to survival. It is essential to define appropriate options, which are often multimodal, including oncology, surgery, or palliative care. It is a specialty that demands multidisciplinary team working, and published quality assurance metrics should reflect this. Decisions regarding management options should consider outcomes in terms of overall survival, disease-free survival and quality of life.

Tables and Figures

Table 3: QOL in Gastric Cancer

	Studies used	QOL metric used	Conversion to HSUV	Quality-adjustment over 1 year	Comments
ESD/EMR	Kim, S 2017	QLQ-C30, QLQ-STO22		0.905[1]	Screening population
Surgery	Zieren 1998	QLQ-C36	No mapping algorithm	-	
	Rausei 2013	QLQ-C30	No time points reported	-	
	Avery 2010	QLQ-C30 and STO22	Doesn't report raw scores for symptom scales	-	
	Kim AR 2012	QLQ-C30		0.866[1]	Mainly Stage 1 disease, 25% had chemotherapy

Surgery and perioperative chemotherapy	Kontodimopoulos		0.550		During adjuvant chemotherapy
	Karanicolas 2014	QLQ-C30, STO22	only comparative scores reported	-	Comparing total, distal and proximal gastrectomies
Palliative chemotherapy	Glimelius 1997	QLQ-C30	-	0.75	Comparing BSC with palliative chemotherapy
	Bang (ToGA)				
	Wilke (Rainbow)	EQ-5D and QLQ-C30	0.73-0.74 (reducing by 0.176-0.206 with progression)		
Palliative radiotherapy	N/A	-	-	-	-
BSC	Glimelius 1997	QLQ-C30	-	0.576*	
	Poole 2014	EQ5D	0.751	0.751	GISTs

[1]Calculated by mapping

*Calculated using clinician assessment of QOL

Table 8: QOL in Oesophageal Cancer

	Studies used	QOL metric used	Conversion to HSUV	Quality-adjustment over 1 year	Comments
EMR	Schwameis 2018	SF36	Single measurement point at up to 10 years later	0.741[1]	No baseline measurements, single surgeon, single centre results, USA
	Rosmolen 2017	SF36	Reports average QOL over 6 months	0.865[1]	Comparison of endoscopic or surgical treatment, Netherlands
Oesophagectomy and perioperative chemotherapy	N/A	-	-	-	-
Oesophagectomy and perioperative chemoradiotherapy	Reynolds 2006	QLQ-C30	-	0.853[1]	6 timepoint QOL measurement, UK
Oesophagectomy	Reynolds 2006	QLQ-C30	-	0.834[1]	6 timepoint QOL measurement
	Rosmolen 2017	SF36	-	0.757[1]	Over first 6 months, disease less than T2N0

				0.781[1]	Over first 6 months, disease greater than T1N1
dCRT	Rees 2015	QLQ-C30	Not all domains reported	-	-
	Bascoul-Mollevi 2017	QLQ-C30	Baseline, week 15 and 1 year reported.	0.89[1]	
	Gillham 2008	QLQ-C30	Baseline, 3, 6, 12 months.	0.89[1]	
Palliative chemotherapy	Meads 2016	EQ5D	Baseline 0.69, and 0.59 at 24 weeks	0.59	
Palliative radiotherapy	Homs 2004	EQ5D	0.56 reducing to 0.41 at 6 months	0.41	
BSC	Shenfine 2005	EQ5D	Baseline 0.56 (+/-0.3), 1 week 0.46, 6 week 0.45	0.45	No significant difference between stent and no stent after 6 weeks
	Meads 2016	EQ5D	0.7 to 0.53 at 42 weeks	0.615	

[1]Calculated by mapping

Table 10: Collective and individual surgeon level post-operative outcome

	Collective	S1	S2	S3	S4	S5	S6	S7
Age								
<65 years	222 (42.3)	23 (35.9)	40 (43.5)	57 (50.9)	30 (33.3)	26 (48.1)	13 (34.2)	33 (44.0)
65-75 years	217 (41.3)	21 (32.8)	36 (39.1)	41 (36.6)	42 (46.7)	23 (42.6)	21 (55.3)	33 (44.0)
>75 years	86 (16.4)	20 (31.3)	16 (17.4)	14 (12.5)	18 (20.0)	18 (20.0)	4 (10.5)	9 (12.0)
Gender								
Female	119 (22.7)	18 (28.1)	24 (26.1)	32 (28.6)	17 (18.9)	9 (16.7)	6 (15.8)	13 (17.3)
Male	406 (77.3)	46 (71.9)	68 (73.9)	80 (71.4)	73 (81.1)	45 (83.3)	32 (84.2)	62 (82.7)
Neoadjuvant therapy								
None	197 (43.8)	23 (52.3)	33 (40.7)	49 (50.5)	44 (57.1)	20 (44.4)	7 (18.9)	21 (30.4)
Chemotherapy	200 (44.4)	16 (36.4)	39 (48.1)	38 (39.2)	26 (33.8)	18 (40.0)	23 (62.2)	40 (58.0)
Chemoradiotherapy	53 (11.8)	5 (11.4)	9 (11.1)	10 (10.3)	7 (9.1)	7 (15.6)	7 (18.9)	8 (11.6)
Tumour location								
Oesophagus	311 (59.2)	33 (51.6)	55 (59.8)	69 (61.6)	44 (48.9)	34 (63.0)	26 (68.4)	50 (66.7)
Stomach	214 (40.8)	31 (48.4)	37 (40.2)	43 (38.4)	46 (51.1)	20 (37.0)	12 (31.6)	25 (33.3)
Operation Type*								
Transhiatal	140 (31.1)	20 (45.5)	23 (28.4)	44 (45.5)	23 (29.9)	15 (33.3)	2 (5.4)	13 (18.8)
Ivor-Lewis	126 (28.0)	5 (11.4)	27 (33.3)	15 (15.5)	14 (18.2)	12 (26.7)	20 (54.1)	33 (47.8)
Total Gastrectomy	96 (21.3)	17 (21.0)	17 (21.0)	16 (16.5)	21 (27.3)	10 (22.2)	10 (27.0)	16 (23.2)
Subtotal Gastrectomy	88 (19.6)	14 (17.3)	14 (17.3)	22 (22.7)	19 (24.7)	8 (17.8)	5 (13.5)	7 (10.1)
Open and close								
No	450 (85.7)	44 (68.8)	81 (88.0)	97 (86.6)	77 (85.6)	45 (83.3)	37 (97.4)	69 (92.0)
Yes	75 (14.3)	20 (31.3)	11 (12.0)	15 (13.4)	13 (14.4)	9 (16.7)	1 (2.6)	6 (8.0)
Margin status*								
Negative	288 (69.2)	34 (77.3)	44 (54.3)	66 (68.0)	65 (84.4)	33 (73.3)	21 (56.8)	43 (62.3)
Positive	128 (30.8)	10 (22.7)	37 (45.7)	31 (32.0)	12 (15.6)	12 (26.7)	16 (43.2)	26 (37.7)
Lymph node yield	16 (11-23)	15 (9-21)	17 (13-24)	14 (10-18)	14 (10-20)	11 (9-20)	13 (11-20)	24 (17-29)

Morbidity								
No	281 (53.5)	44 (68.8)	49 (53.3)	62 (55.4)	49 (54.4)	27 (50.0)	20 (52.6)	30 (40.0)
Yes	244 (46.5)	20 (31.3)	43 (46.7)	50 (44.6)	41 (45.6)	27 (50.0)	18 (47.4)	45 (60.0)
Anastomotic leak*								
No	393 (87.3)	40 (90.9)	71 (87.7)	87 (89.7)	69 (89.6)	36 (80.0)	33 (89.2)	58 (84.1)
Yes	56 (12.4)	4 (9.1)	10 (12.3)	10 (10.3)	8 (10.4)	9 (20.0)	4 (10.8)	11 (15.9)
Clavien Dindo								
0	255 (48.6)	42 (65.5)	42 (45.7)	57 (50.9)	43 (47.8)	24 (44.4)	19 (50.0)	28 (37.3)
1	25 (4.8)	2 (3.1)	7 (7.6)	4 (3.6)	6 (6.7)	3 (5.6)	1 (2.6)	2 (2.7)
2	147 (28.0)	14 (21.9)	24 (26.1)	29 (25.9)	25 (27.8)	13 (24.1)	9 (23.7)	33 (44.0)
3	61 (11.6)	4 (6.2)	13 (14.1)	13 (11.6)	9 (10.0)	9 (16.7)	3 (7.9)	10 (13.3)
4	25 (4.8)	2 (3.1)	4 (4.4)	7 (6.3)	5 (5.5)	3 (5.6)	3 (7.9)	1 (1.3)
5	12 (2.3)	0 (0.0)	2 (2.2)	2 (1.8)	2 (2.2)	2 (3.7)	3 (7.9)	1 (1.3)
30 day mortality								
No	513 (97.7)	64 (100.0)	90 (97.8)	110 (98.2)	88 (97.8)	52 (96.3)	35 (92.1)	74 (98.7)
Yes	12 (2.3)	0 (0.0)	2 (2.2)	2 (1.8)	2 (2.2)	2 (3.7)	3 (7.9)	1 (1.3)
Length of hospital stay (days)	14 (11-20)	13 (11-15)	15 (12-21)	15 (12-21)	14 (12-23)	13 (11-18)	14 (11-18)	14 (12-18)
Survival								
1 year	92.1	97.7	92.4	90.4	90.8	87.8	90.6	96.2
2 year	72.9	80.0	74.3	71.4	71.4	68.6	75.0	72.4
3 year	62.2	63.6	62.5	63.2	58.2	60.6	70.0	61.1
5 year	46.5	47.8	52.5	51.0	38.9	35.0	N/A	N/A

Table 11: Departmental and individual surgeon level post-operative outcome, over 1, 2, 3 and 5 years.

	Department	S1	S2	S3	S4	S5	S6	S7
Combined survival								
Overall survival								
1 year	92.1	97.7	92.4	90.4	90.8	87.8	90.6	96.2
2 year	72.9	80.0	74.3	71.4	71.4	68.6	75.0	72.4
3 year	62.2	63.6	62.5	63.2	58.2	60.6	70.0	61.1
5 year	46.5	47.8	52.5	51.0	38.9	35.0	N/A	N/A
Disease free survival								
1 year	83.0	90.9	83.3	78.2	83.8	82.4	92.0	76.9
2 year	67.0	71.4	66.7	63.1	70.4	65.6	84.6	53.3
3 year	55.0	66.7	55.1	58.6	52.5	50.0	50.0	30.0
5 year	44.8	47.1	60.0	44.4	35.7	28.6	N/A	N/A
Oesophageal resection								
Overall survival								
1 year	93.7	100.0	92.0	94.9	88.9	96.2	86.4	97.2
2 year	73.3	84.2	73.3	71.2	72.7	77.3	63.2	75.0
3 year	62.5	61.1	66.7	60.0	60.7	71.4	53.8	55.6
5 year	44.6	41.7	52.2	46.4	38.9	36.4	N/A	N/A
Disease free survival								
1 year	79.3	83.3	79.5	74.5	78.1	90.5	87.5	68.8
2 year	62.3	58.8	64.1	52.4	70.4	70.0	77.8	50.0
3 year	50.0	58.8	53.1	47.2	50.0	53.3	40.0	20.0
5 year	37.2	30.0	55.6	36.0	29.4	25.0	N/A	N/A
Gastric resection								
Overall survival								
1 year	89.6	94.4	93.1	82.9	92.5	73.3	100.0	94.1

2 year	72.4	75.0	76.0	71.9	70.3	53.8	100.0	69.2
3 year	61.8	66.7	54.5	67.7	55.6	41.7	100.0	66.7
5 year	48.7	54.5	52.9	56.5	38.9	33.3	N/A	N/A
Disease free survival								
1 year	88.4	100.0	89.3	85.2	88.9	69.2	100.0	90.0
2 year	74.3	90.9	71.4	82.6	70.4	58.3	100.0	57.1
3 year	62.8	80.0	58.8	77.3	55.6	44.4	60.0	40.0
5 year	57.4	71.4	66.7	63.6	45.5	33.3	N/A	N/A

Table 12: Collective and individual surgeon level quality indicators

	Team operating	Individual operating	p-value
Age			
<65 years	98 (47.6)	124 (38.9)	
65-75 years	81 (39.3)	136 (42.6)	
>75 years	27 (13.1)	59 (18.5)	0.029
Gender			
Female	47 (22.8)	72 (22.6)	
Male	159 (77.4)	247 (77.4)	0.986
Neoadjuvant therapy			
None	93 (45.1)	136 (42.6)	
Chemotherapy	95 (46.1)	143 (44.8)	
Chemoradiotherapy	18 (8.7)	40 (12.5)	0.394
Cancer location			
Oesophagus	120 (58.3)	191 (59.9)	
Stomach	86 (41.7)	128 (40.1)	0.712
Operation Type			
Transhiatal	63 (37.3)	77 (27.5)	
Ivor-Lewis	36 (21.3)	90 (32.0)	
Total Gastrectomy	35 (20.7)	61 (21.7)	
Subtotal Gastrectomy	35 (20.7)	53 (18.9)	0.505
Open and close			
No	169 (82.0)	281 (88.1)	
Yes	37 (18.0)	38 (11.9)	0.053
Margin status			
Negative	121 (71.6)	185 (65.8)	
Positive	48 (28.4)	96 (34.2)	0.205
Lymph node yield	14 (10-21)	16 (11-24)	0.012
Morbidity			
No	82 (48.5)	133 (47.3)	
Yes	87 (51.5)	148 (52.7)	0.807
Anastomotic leak			
No	148 (87.6)	246 (87.5)	
Yes	21 (12.4)	35 (12.5)	0.993
Clavien Dindo			
0	73 (43.2)	120 (42.7)	
1	9 (5.3)	13 (4.6)	
2	54 (32.0)	85 (30.2)	
3	23 (13.6)	37 (13.2)	
4	9 (5.3)	15 (5.3)	
5	1 (0.6)	11 (3.9)	0.467
30 day mortality			
No	205 (99.0)	308 (96.6)	
Yes	1 (0.5)	11 (3.4)	0.027
Length of hospital stay	14 (12-20)	14 (11-20)	0.966
Overall survival			
1 year	94.0	90.8	
2 year	74.7	71.6	
3 year	61.1	63.0	
5 year	41.5	51.1	

Table 13. Details of the patients before and after PET-CT inception.

	Pre PET-CT	Post PET-CT	p-value
Number (%)	273 (55)	223 (45)	
Median age, in years (range)	61 (31-80)	64 (36-77)	0.036§
<50	38	23	
50-59	80	51	
60-69	100	97	
>70	55	52	
Sex			0.323†
Male	213	182	
Female	60	41	
Tumour type			0.011†
ACA	224	201	
SCC	49	22	
Oncological therapy			
Neoadjuvant – all types	176	149	0.584†
Neoadjuvant chemotherapy	125	109	0.493†
Neoadjuvant chemoradiotherapy	50	40	0.914†
Surgery alone	97	74	0.584†
Operation type			<0.0001†
TTO (%)	150 (54.9)	83 (37.2)	
THO (%)	93 (34.1)	107 (50.0)	
3-stage (%)	0 (0)	6 (2.7)	
Open and Close (%)	30 (11.0)	27 (12.1)	
Pathological T stage			0.012†
HGD/CPR	16	17	
T1	33	48	
T2	31	24	

T3	141	101	
T4	22	6	
Pathological N stage			0.381†
N0	112	103	
N1	67	48	
N2	38	33	
N3	26	12	
Pathological Stage (TNM 7)			0.069†
CPR (%)	15 (5.0)	13 (5.8)	
Stage 1 (%)	48 (17.6)	56 (25.1)	
Stage 2 (%)	60 (22.0)	48 (19.7)	
Stage 3 (%)	20 (44.0)	75 (33.6)	
Stage 4 (%)	0 (0)	2 (0.8)	
R1 (%)	83 (30.4)	83 (37.2)	0.198†
Operative	11 (4.0)	6 (2.7)	0.415†
Mortality (%)			

ACA, Adenocarcinoma; SCC, Squamous cell carcinoma; Neoadjuvant therapy –all types, chemotherapy/chemo radiotherapy; Neoadjuvant Chemoradiotherapy, neoadjuvant chemotherapy; Neoadjuvant chemoradiotherapy, neoadjuvant chemo radiotherapy; THO, trans hiatal oesophagectomy; TTO, transthoracic oesophagectomy; 3 stage, 3 stage oesophagectomy; HGD/CPR, high grade dysplasia/ complete pathological response; R1, positive resection margin; § Mann Whitney U Test; † Chi Squared test.

Table 14: Univariable analysis of factors associated with disease free survival.

	Chi^2	DF	p-value
Sex	0.446	1	0.504
Age	3.427	3	0.330
Tumour histology	0.164	1	0.686
PET-CT	3.964	1	**0.046**
PET-CT scanner/location	0.244	1	0.621
Neoadjuvant therapy (all types)	10.837	1	**0.001**
Neoadjuvant chemotherapy	19.474	1	**<0.0001**
Neoadjuvant chemoradiotherapy	0.684	1	0.408
Surgery type	2.620	2	0.270
pT stage	390.092	5	**<0.0001**
pN stage	418.258	4	**<0.0001**
R1 resection	365.946	2	**<0.0001**

DF, Degrees of freedom; Age, <50, 50-59, 60-79, >70; PET/CT Scanner/location, Centre 1 or 2; Neoadjuvant therapy –all types, chemotherapy/chemo radiotherapy; Neoadjuvant Chemotherapy, neoadjuvant chemotherapy; Neoadjuvant Chemoradiotherapy, neoadjuvant chemo radiotherapy; Surgery type, Trans hiatal oesophagectomy / Trans thoracic oesophagectomy / 3 stage oesophagectomy; pT, pathological T stage; pN, pathological N stage; R1, positive resection margin.

Table 15: Univariable analysis of factors associated with overall survival.

	Chi^2	**DF**	**p-value**
Sex	0.246	1	0.620
Age	4.609	3	0.203
Tumour histology	0.032	1	0.859
PET-CT	8.388	1	**0.004**
PET-CT scanner/location	0.306	2	0.580
Neoadjuvant therapy (all types)	10.837	1	**0.001**
Neoadjuvant chemotherapy	17.388	1	**<0.0001**
Neoadjuvant chemoradiotherapy	1.028	1	0.311
Surgery type	4.356	2	0.113
pT stage	160.877	5	**<0.0001**
pN stage	177.154	4	**<0.0001**
R1 resection	136.000	2	**<0.0001**

DF, Degrees of freedom; Age, <50, 50-59, 60-79, >70; PET/CT Scanner/location, Centre 1 or 2; Neoadjuvant therapy –all types, chemotherapy/chemo radiotherapy; Neoadjuvant Chemotherapy, neoadjuvant chemotherapy; Neoadjuvant Chemoradiotherapy, neoadjuvant chemo radiotherapy; Surgery type, Trans hiatal oesophagectomy / Trans thoracic oesophagectomy / 3 stage oesophagectomy; pT, pathological T stage; pN, pathological N stage; R1, positive resection margin.

Table 16: Multivariable analysis of factors associated with disease free survival.

Variable	HR	95% Confidence Interval	p-value
pT stage	1.526	1.31 – 1.78	<0.0001
pN stage	1.371	1.26 – 1.49	<0.0001

pT, pathological T stage; pN, pathological N stage

Table 17: Multivariable analysis of factors associated with overall survival.

Variable	HR	95% Confidence Interval	p-value
PET-CT	0.688	0.53-0.89	0.004
pT stage	1.496	1.28 – 1.75	<0.0001
pN stage	1.114	1.04 – 1.19	0.001

pT, pathological T stage; pN, pathological N stage

Table 18: Recurrence rates related to cohort for patients who received curative surgery.

	Pre PET-CT	**Post PET-CT**	**Total**	**p-value**
Number of patients	243	196	439	
Recurrence (%)	125 (51.4)	74 (37.8)	199	**0.004**
Site of recurrence				
Locoregional (%)	55 (22.6)	34 (17.3)		0.171
Distant (%)	96 (39.5)	53 (27.0)		**0.006**
Time to recurrence, in months				
Overall (range)	15 (2-85)	10 (2-93)		0.308
Locoregional (range)	15 (2-85)	14.5 (4-93)		0.392
Distal (range)	14 (2-72)	10 (2-69)		0.707
Non-curative surgery	30	27		

Figures are numbers of patients with percentages in parentheses; Site of recurrence, inclusive of patients diagnoses with both locoregional and distant disease at time of diagnosis; Non-curative, open and close procedures and positive longitudinal resection margin.

Figure (b): Kaplan-Meier plot for survival in months, stage 1 gastric cancer

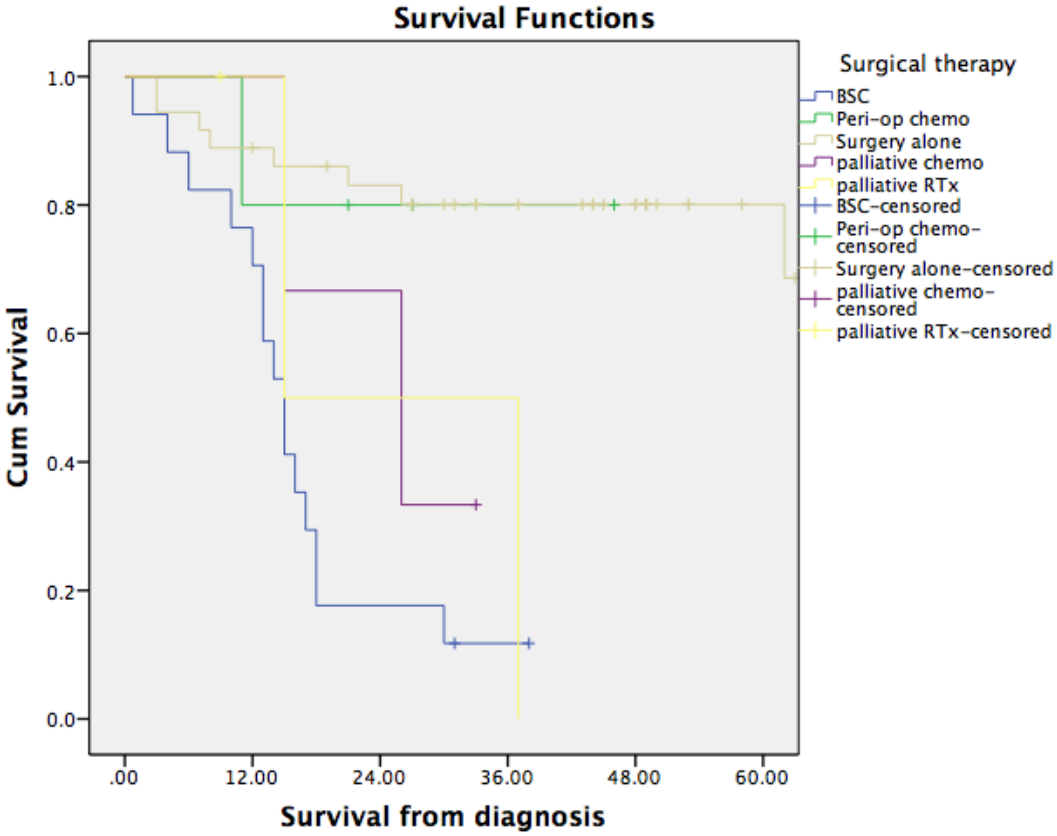


Figure (c): Kaplan-Meier plot for survival in months, stage 2 gastric cancer

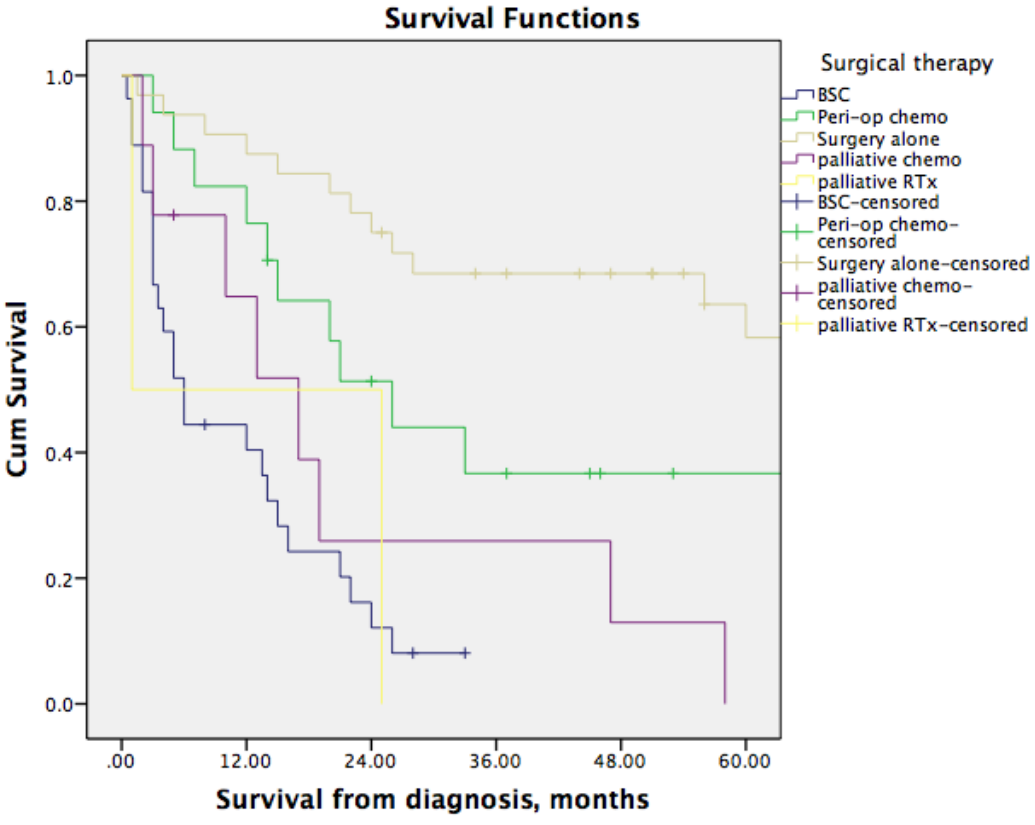


Figure (d): Kaplan-Meier plot for survival in months, stage 3 gastric cancer

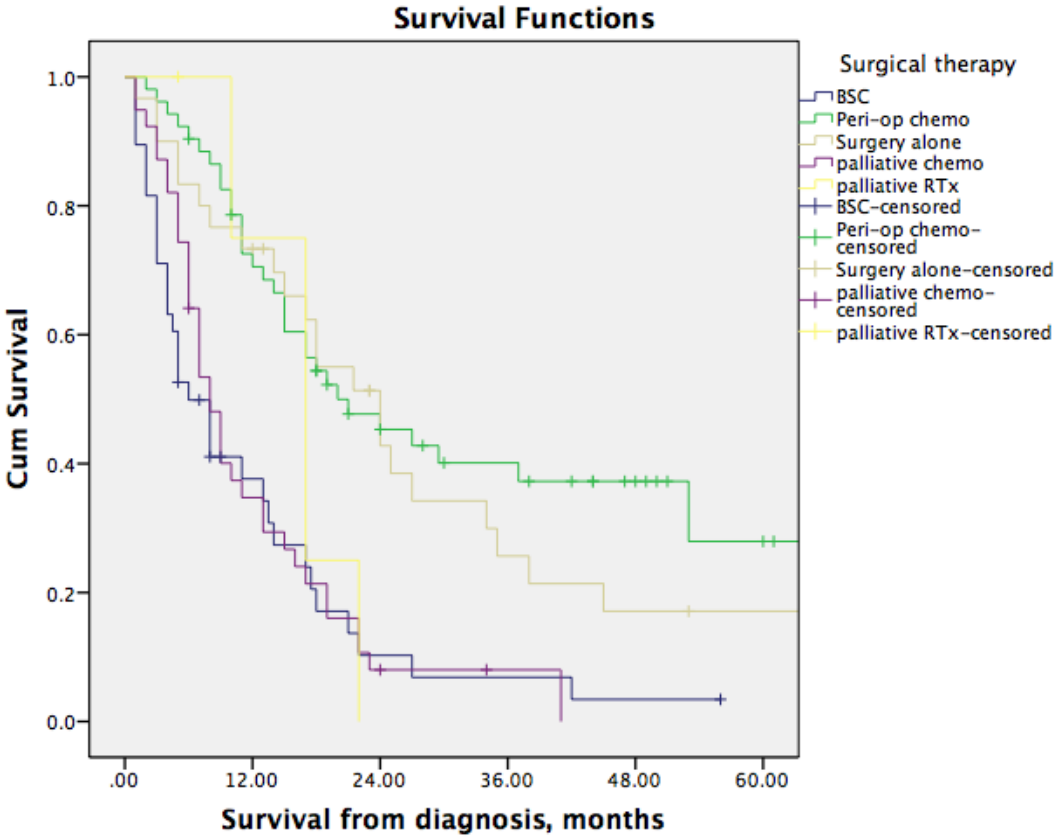


Figure (e): Kaplan-Meier plot for survival in months, stage 4 gastric cancer

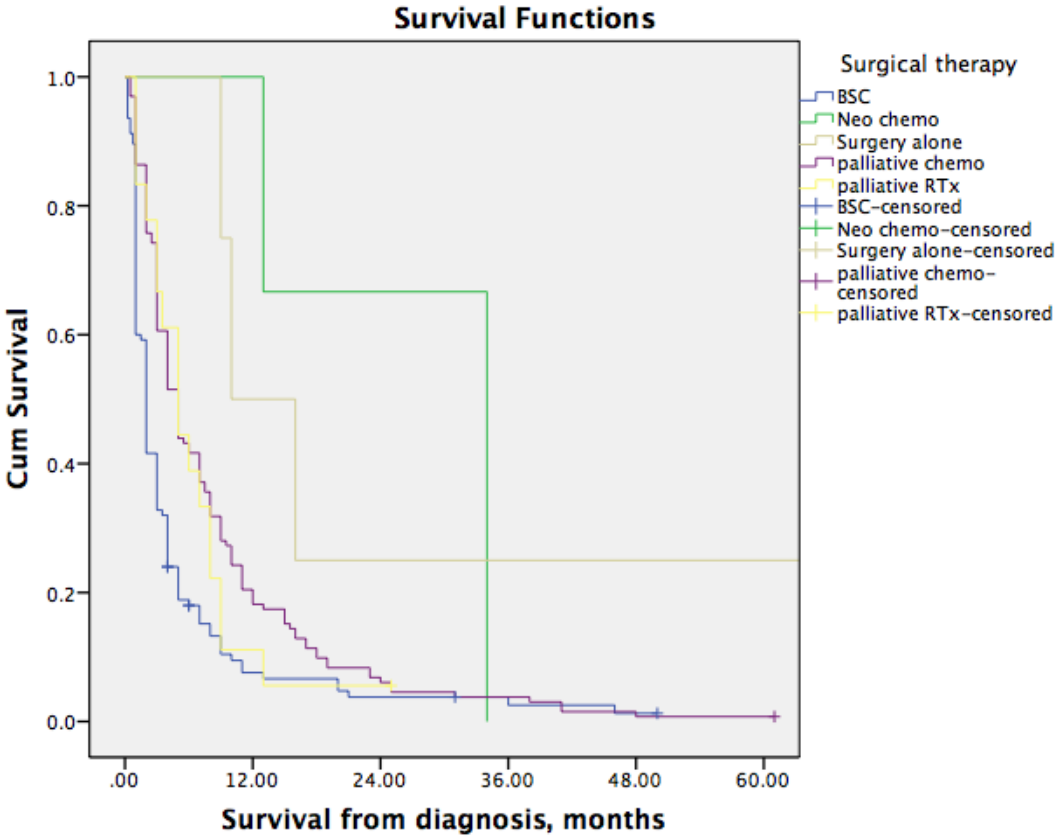
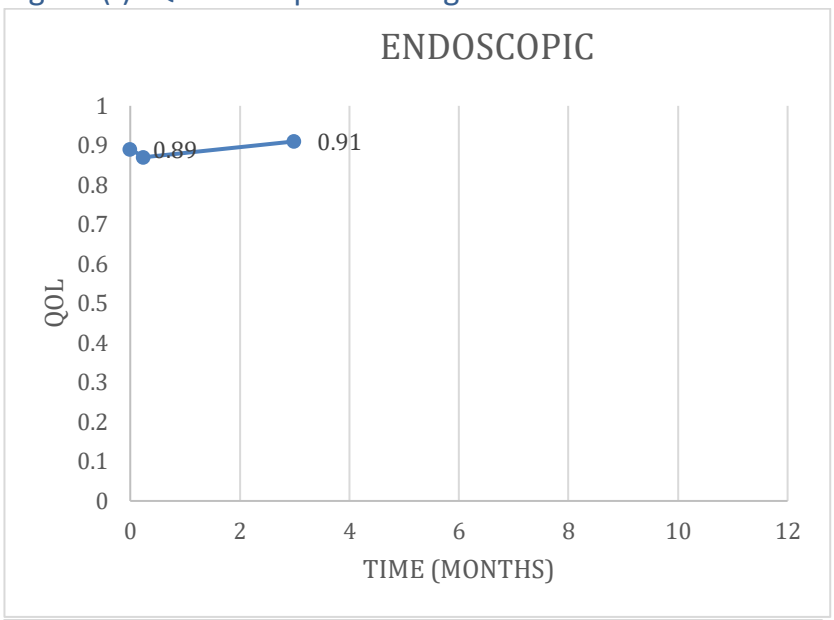
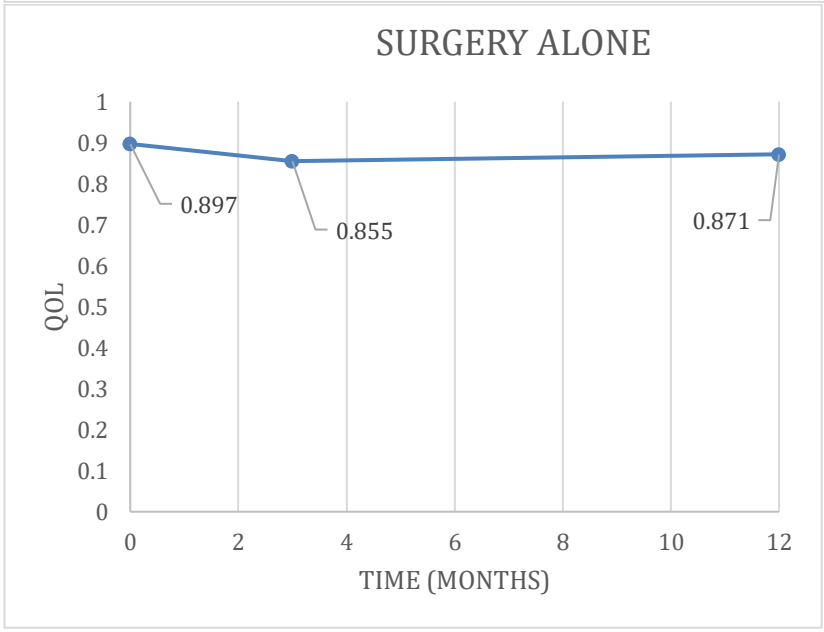
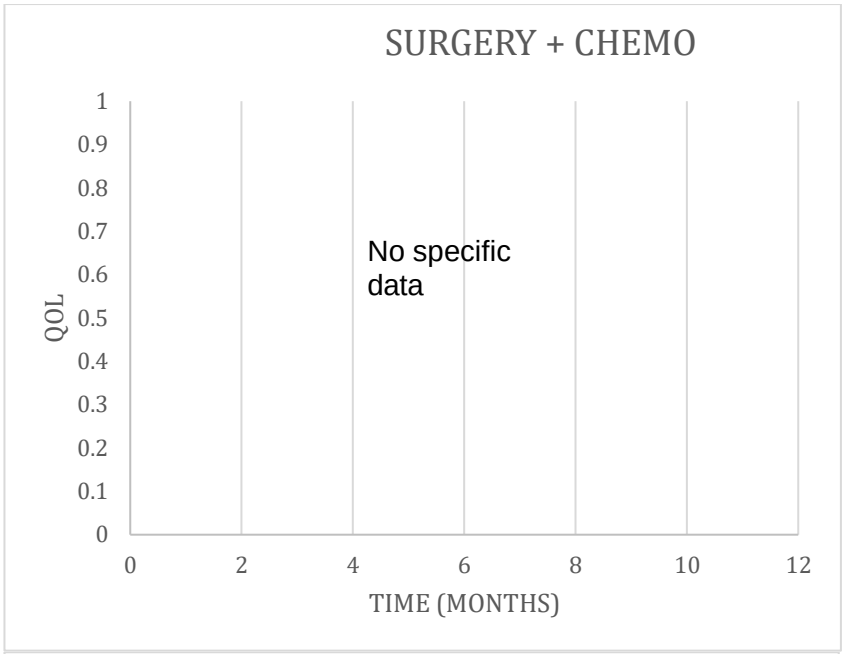
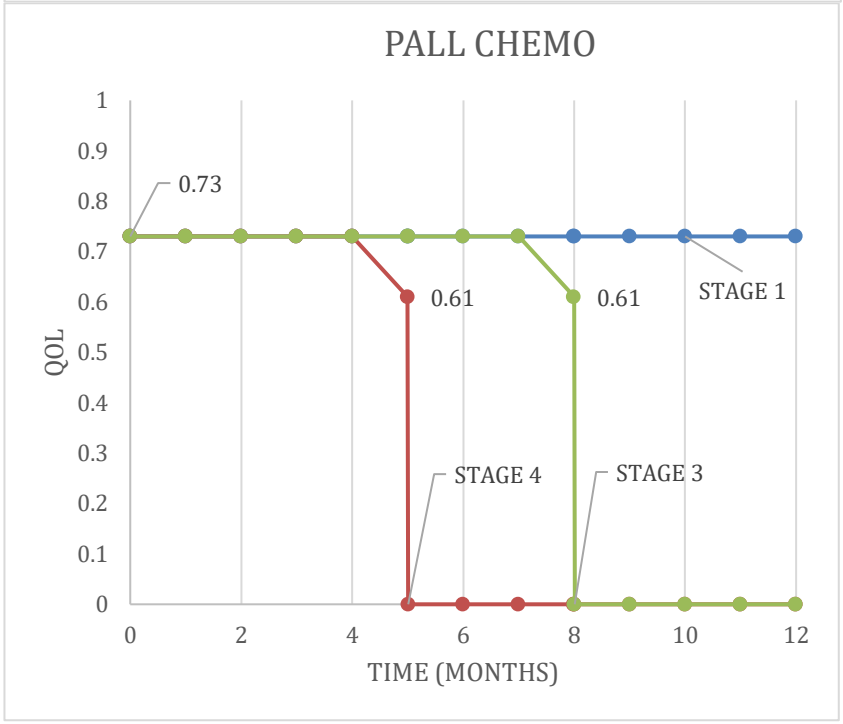


Figure (f): QOL-time profiles of gastric cancer treatments






SURGERY + CHEMO
No specific data
QOL
TIME (MONTHS)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12


PALL CHEMO
0.73
0.61
0.61
STAGE 1
STAGE 4
STAGE 3
QOL
TIME (MONTHS)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12

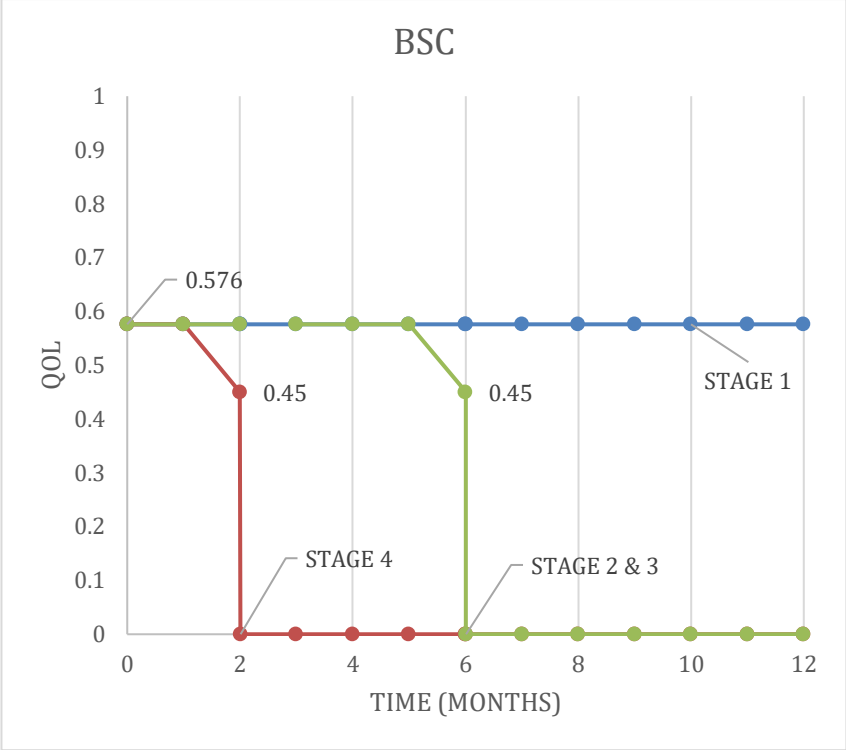
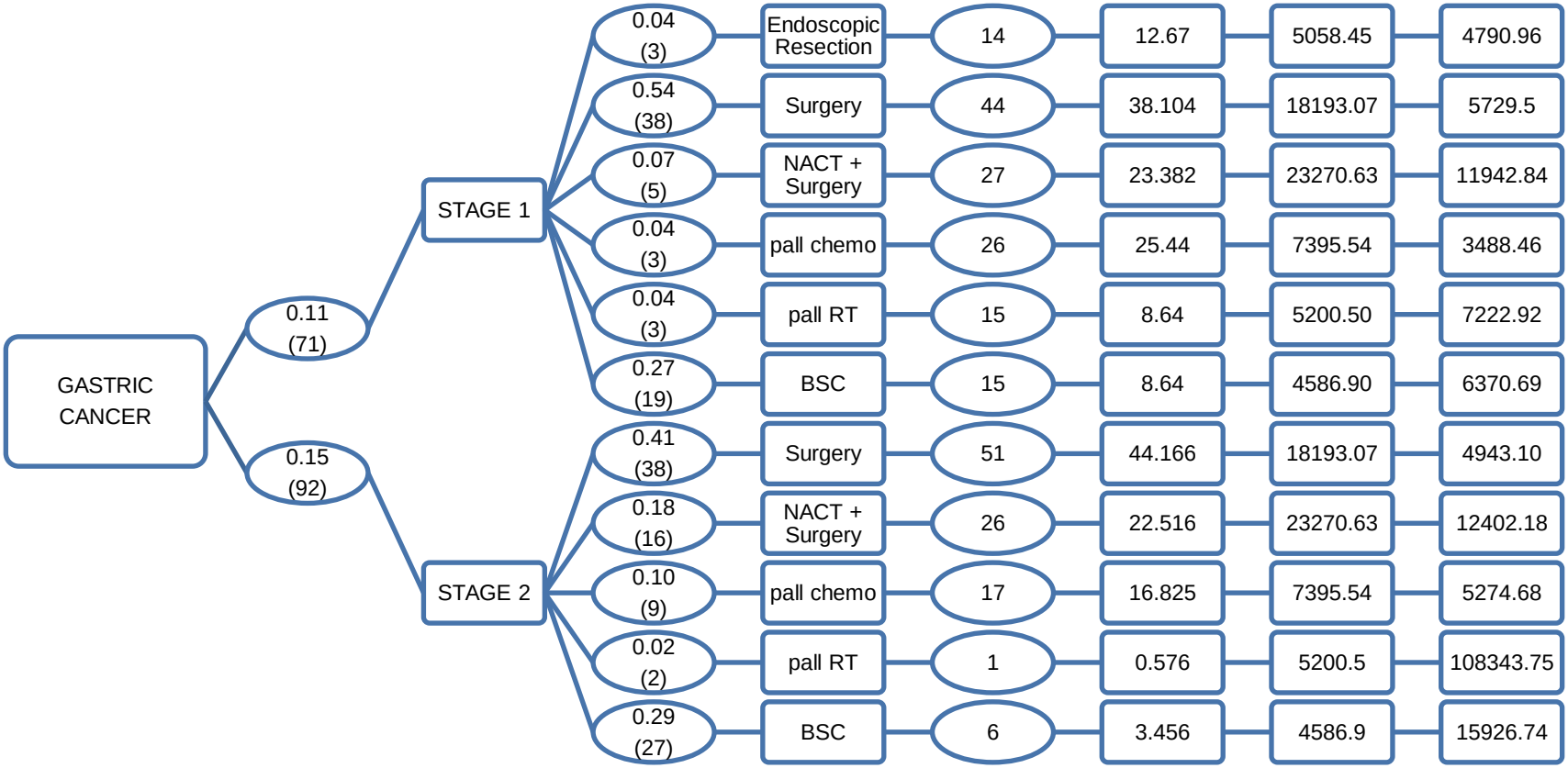
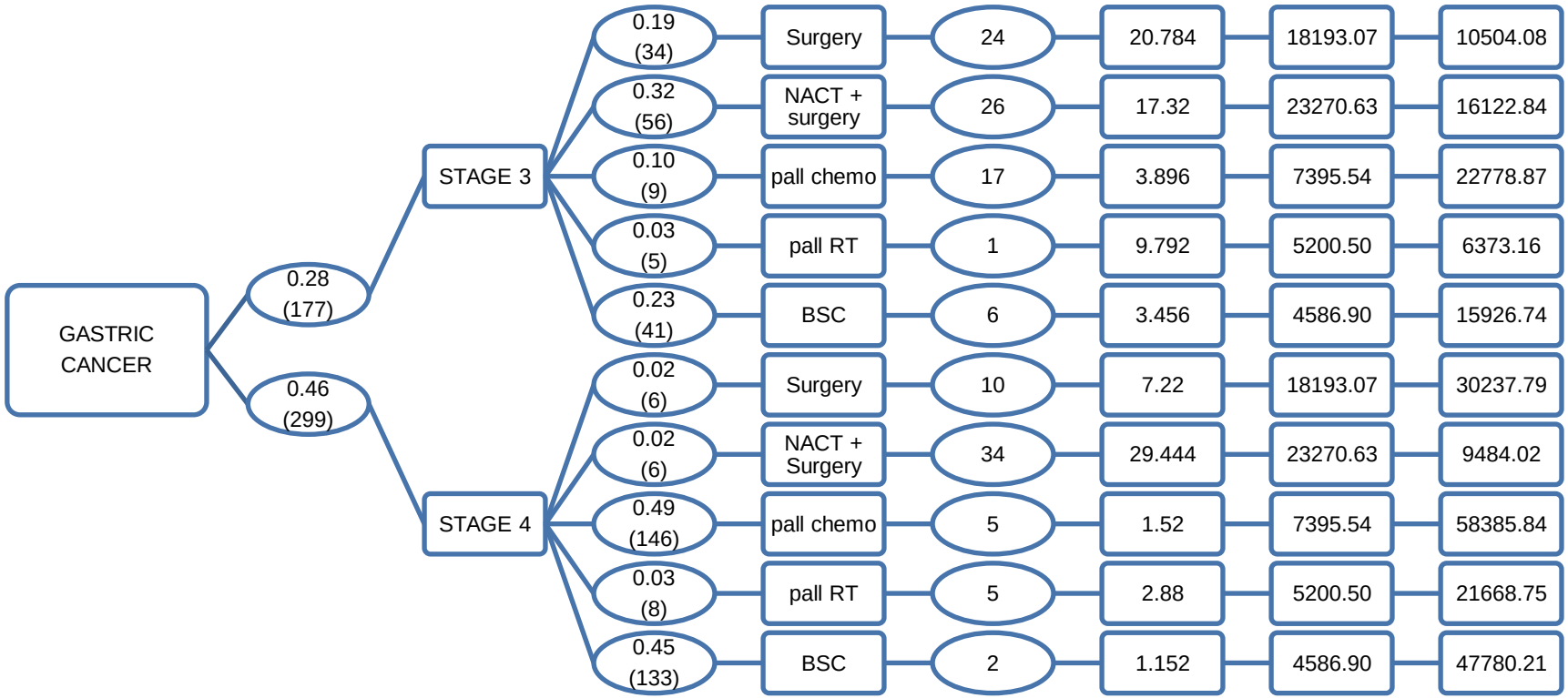

BSC
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
TOO
0.576
0.45
0.45
STAGE 1
STAGE 4
STAGE 2 & 3
0
2
4
6
8
10
12
TIME (MONTHS)

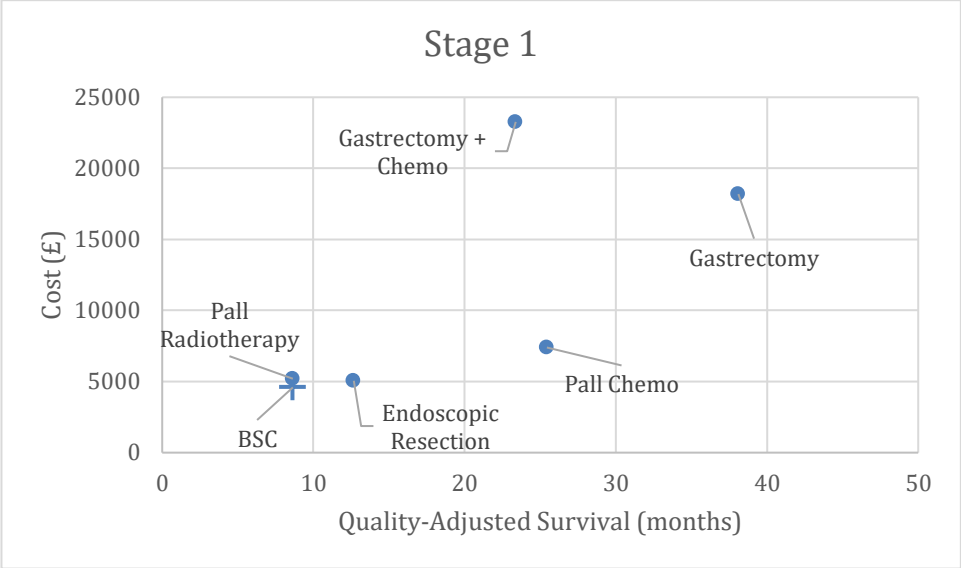
Figure (g): Decision tree analysis of gastric cancer care

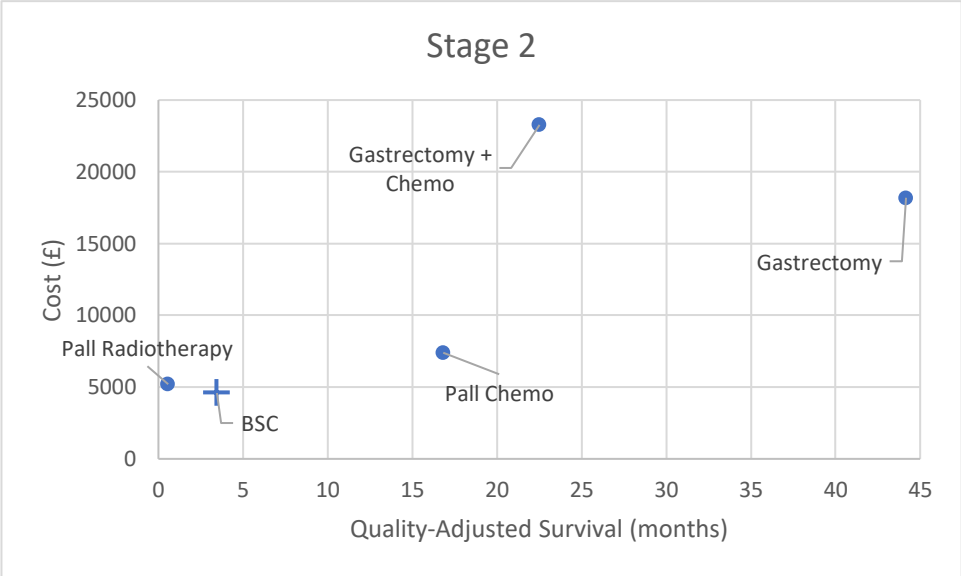


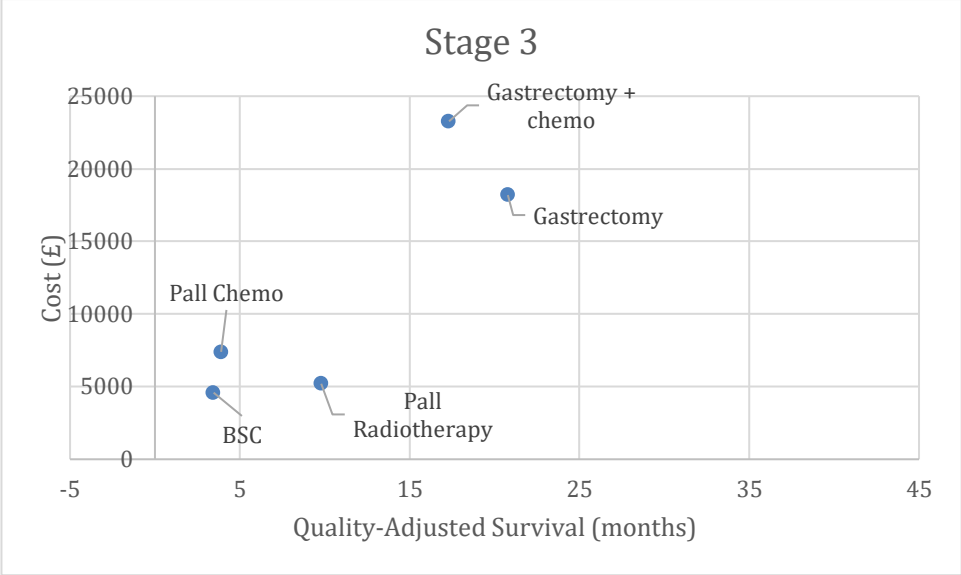


	Proportion (total no.)	Proportion (total no.)	Treatment pathway	Survival (months)	Quality-adjusted survival (months)	Cost (£)	Cost /QALY

Figure (h): The cost per QALY of gastric cancer treatments, according to stage, represented on ICER charts






Stage 3
25000
20000
15000
10000
5000
0
Cost (£)
Gastrectomy + chemo
Gastrectomy
Pall Chemo
BSC
Pall Radiotherapy
-5
5
15
25
35
45
Quality-Adjusted Survival (months)

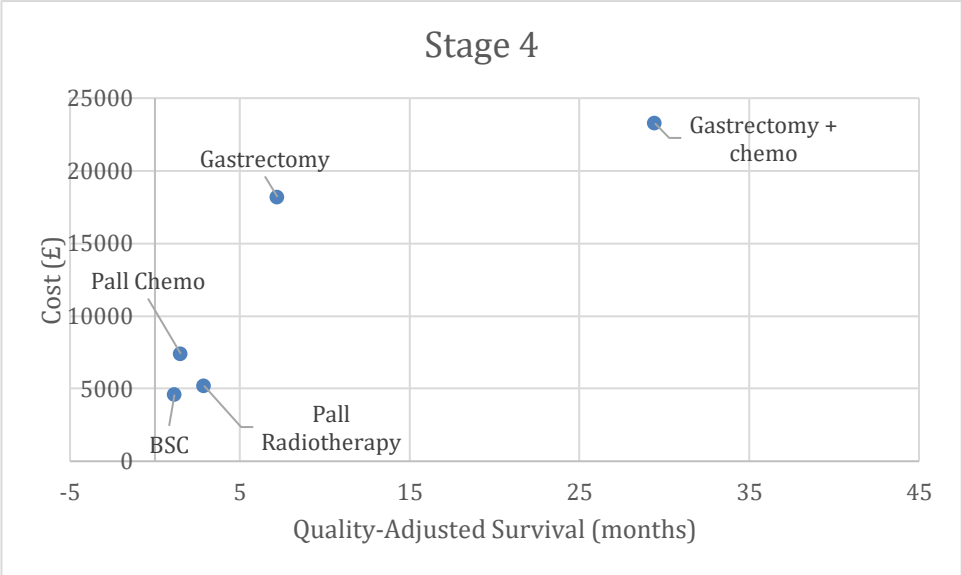

Stage 4
25000
20000
15000
10000
5000
0
Cost (£)
Gastrectomy + chemo
Gastrectomy
Pall Chemo
BSC
Pall Radiotherapy
-5
5
15
25
35
45
Quality-Adjusted Survival (months)

Figure (j): Kaplan-Meier plot for survival in months, stage 1 oesophageal cancer

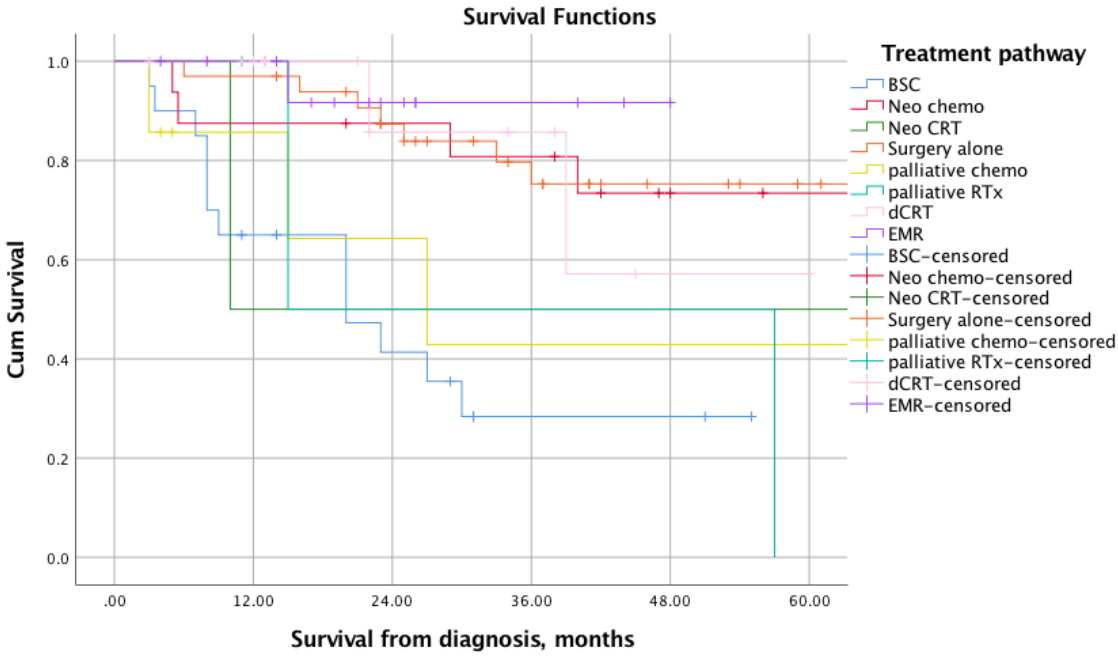


Figure (k): Kaplan-Meier plot for survival in months, stage 2 oesophageal cancer

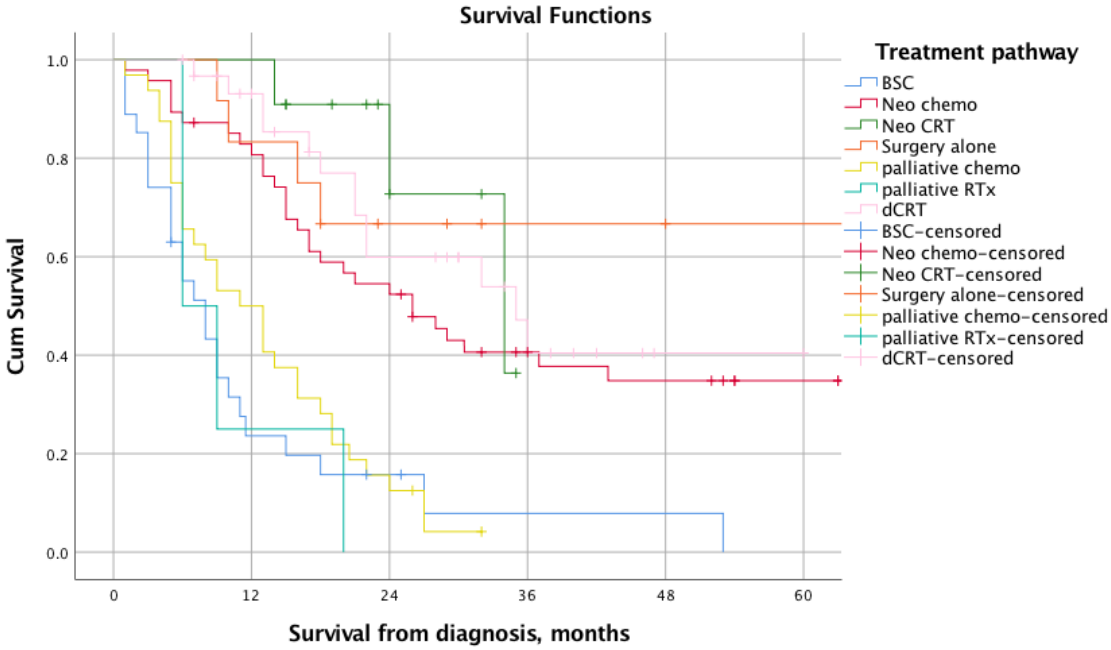


Figure (l): Kaplan-Meier plot for survival in months, stage 3 oesophageal cancer

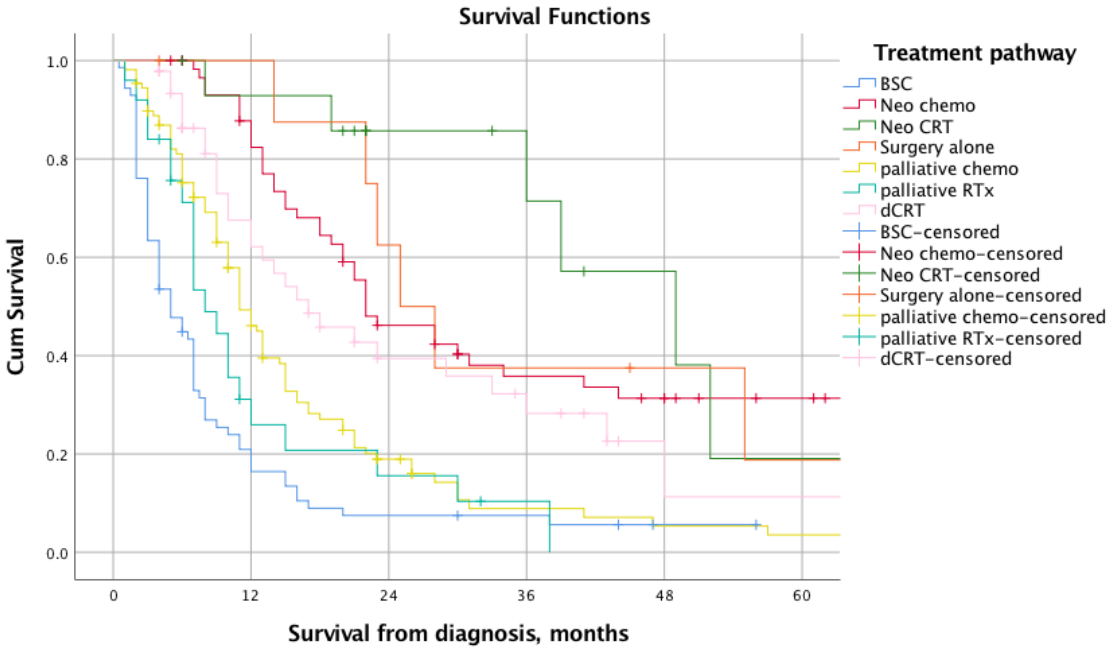


Figure (m): Kaplan-Meier plot for survival in months, stage 4 oesophageal cancer

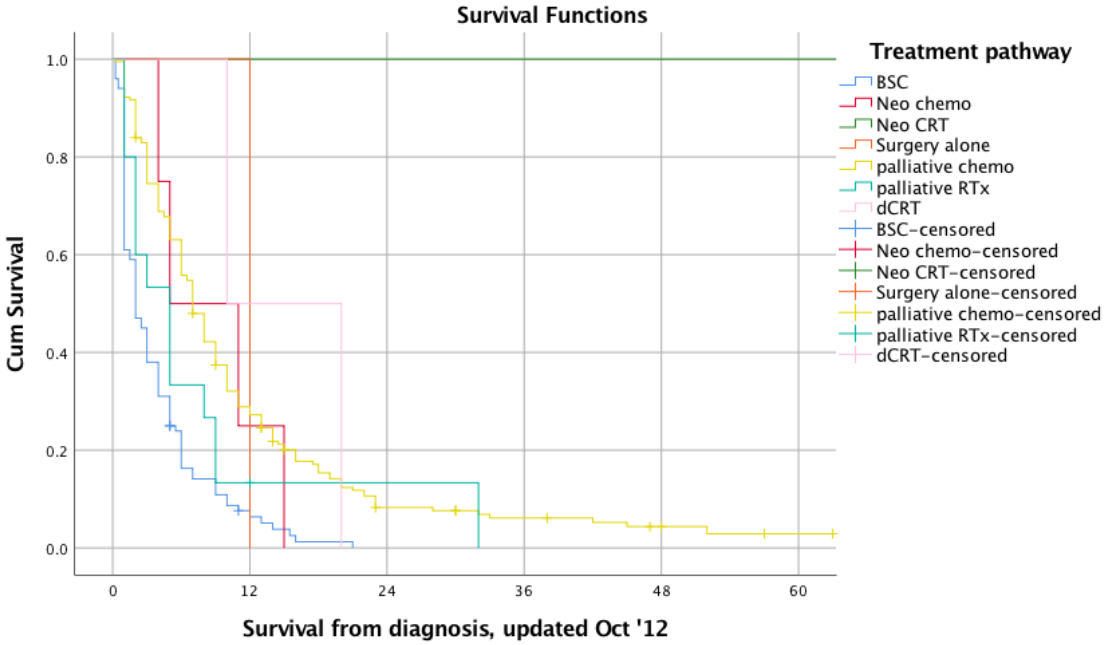
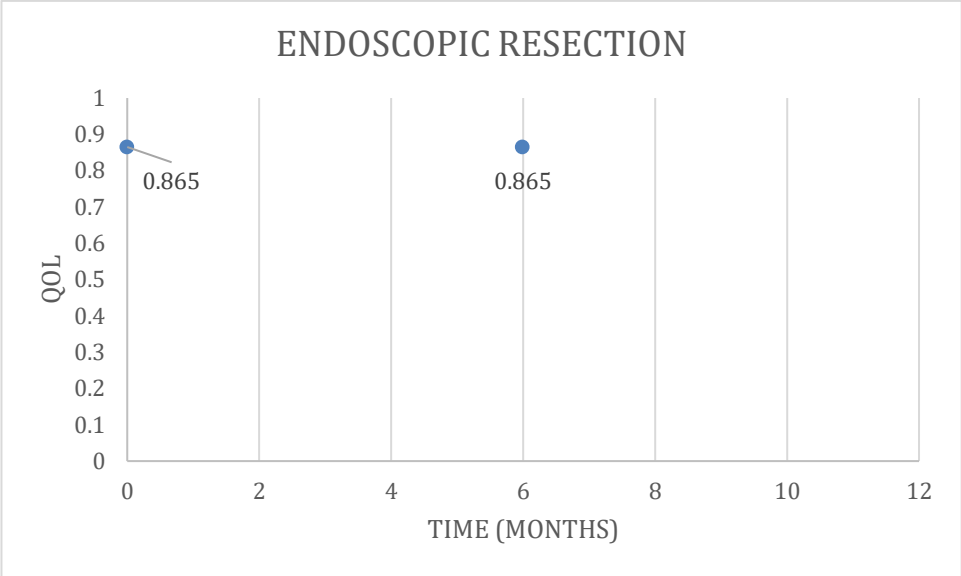
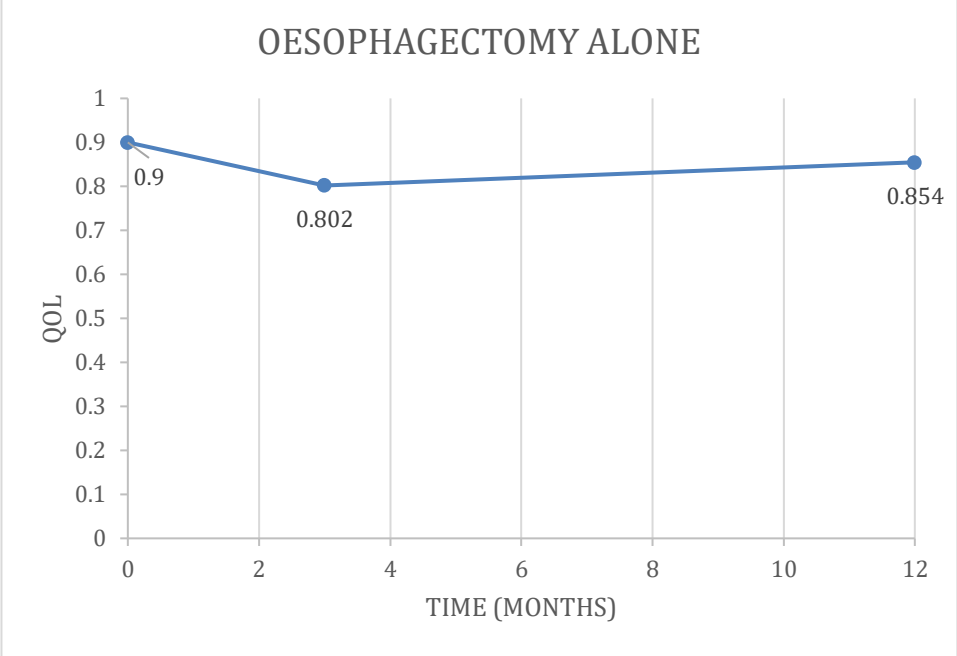
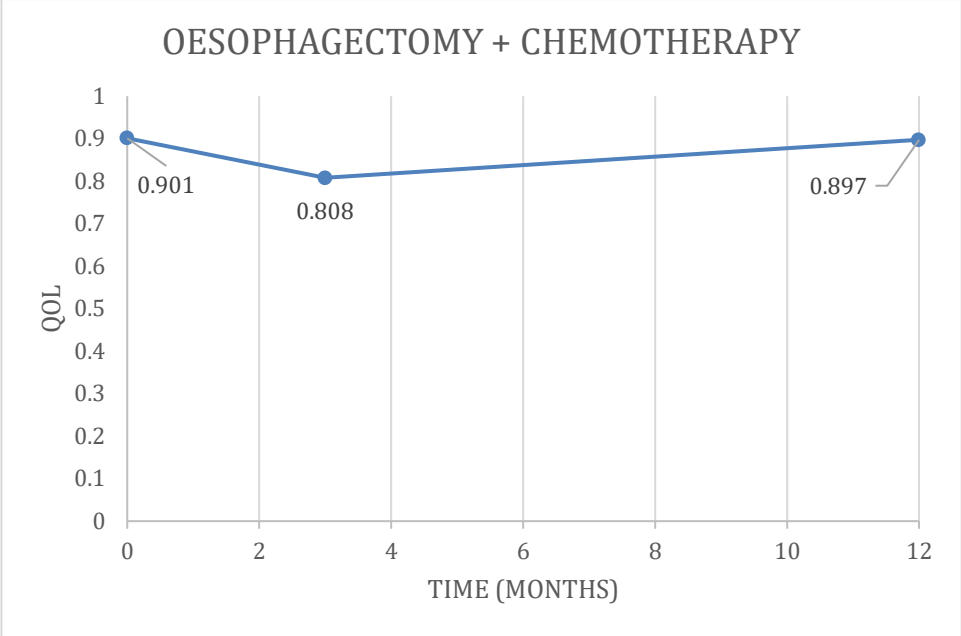
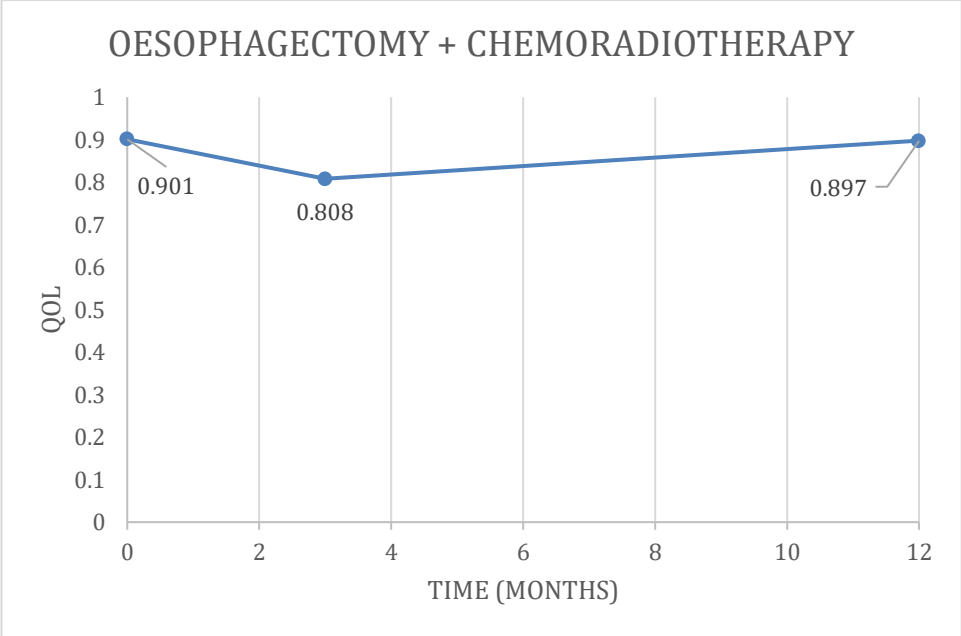


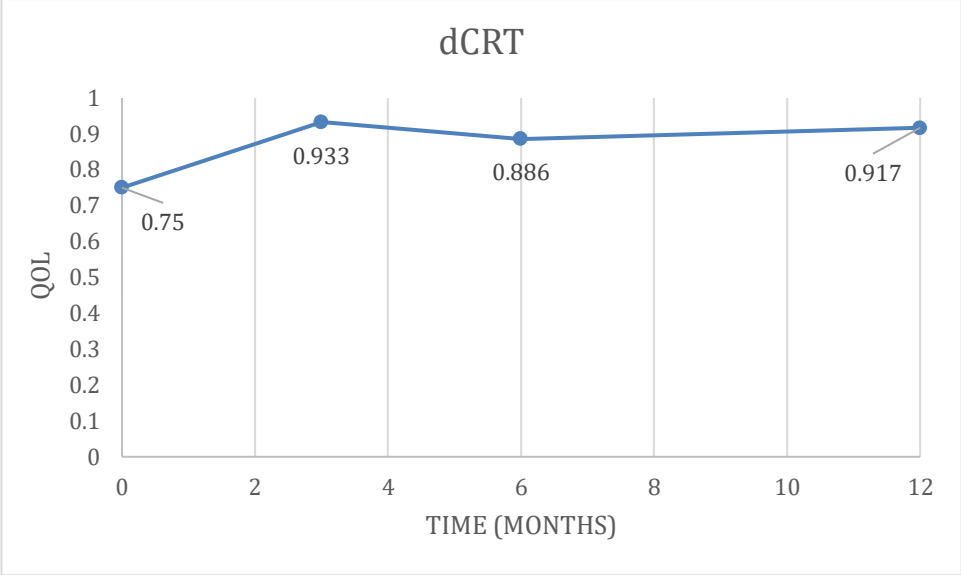
Figure (n): QOL-time profiles of oesophageal cancer treatments

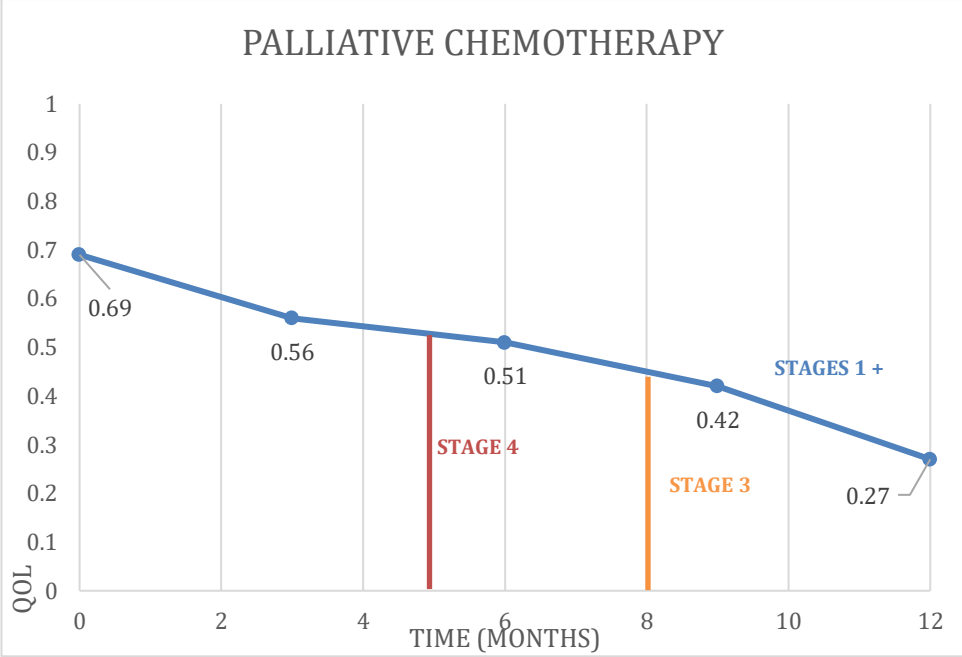


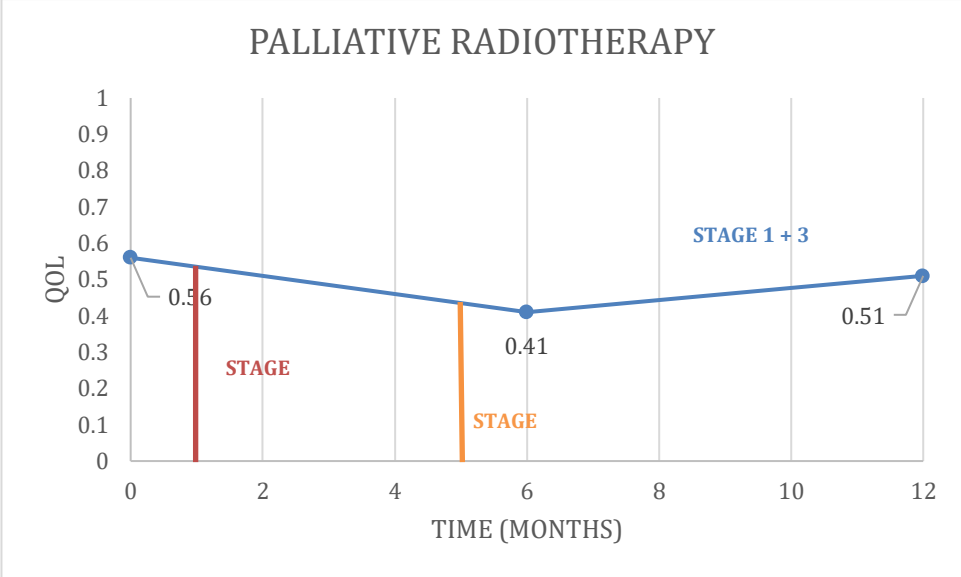



OESOPHAGECTOMY + CHEMOTHERAPY
QOL
TIME (MONTHS)
0.901
0.808
0.897
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12


OESOPHAGECTOMY + CHEMORADIOTHERAPY
QOL
TIME (MONTHS)
0.901
0.808
0.897
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12


dCRT
QOL
TIME (MONTHS)
0.75
0.933
0.886
0.917


PALLIATIVE CHEMOTHERAPY
QOL
TIME (MONTHS)
0.69
0.56
0.51
0.42
0.27
STAGE 4
STAGE 3
STAGES 1 +


PALLIATIVE RADIOTHERAPY
QOL
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.56
STAGE
0.41
STAGE
STAGE 1 + 3
0.51
0
2
4
6
8
10
12
TIME (MONTHS)

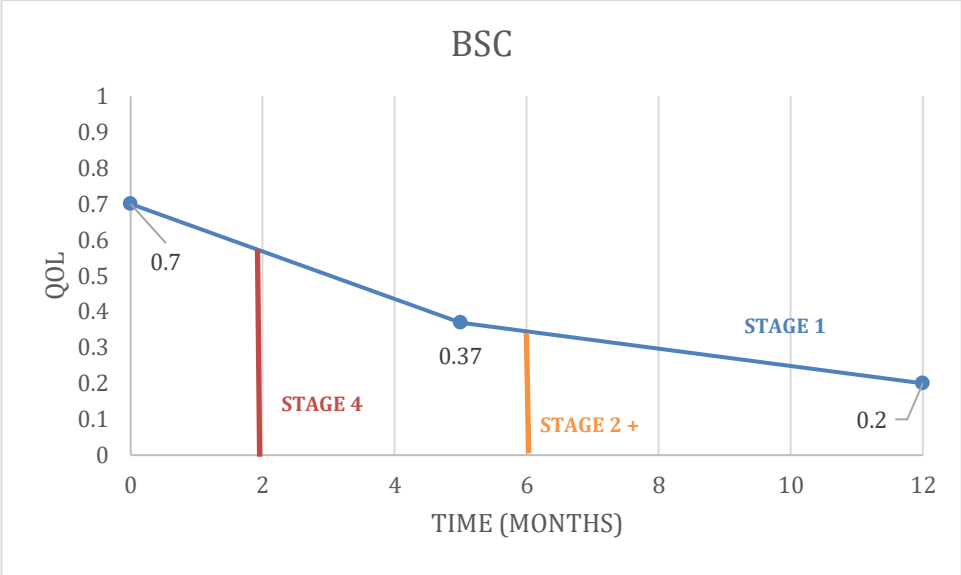
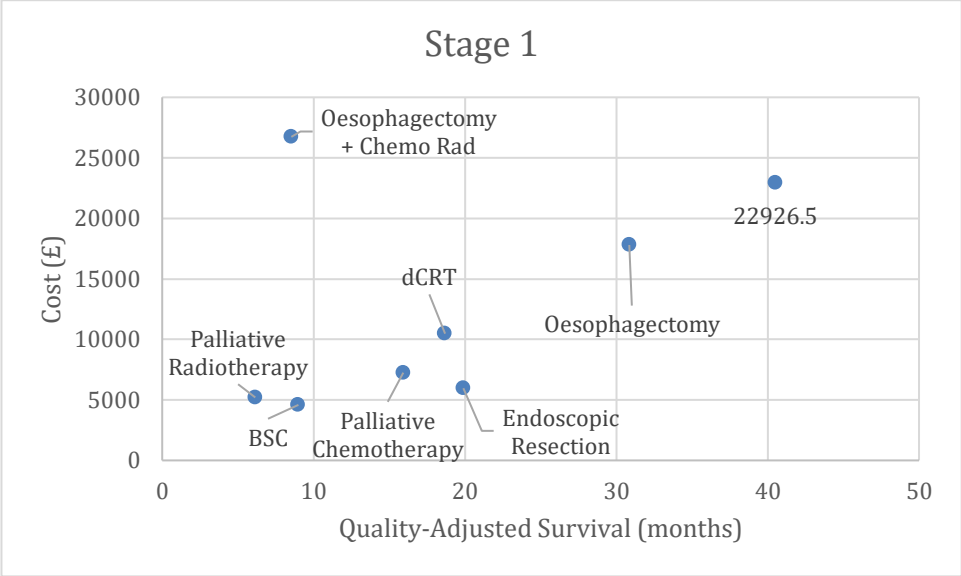
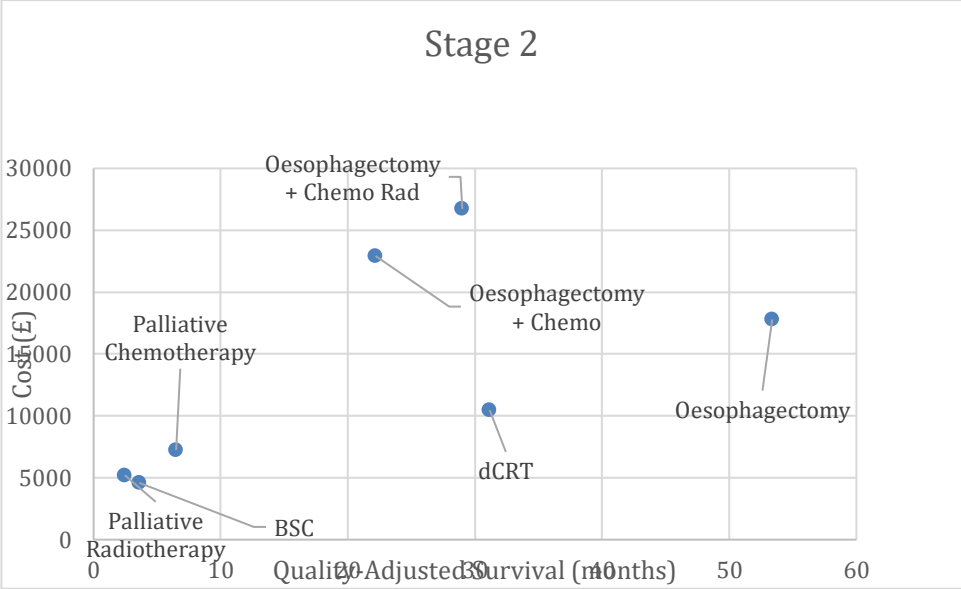
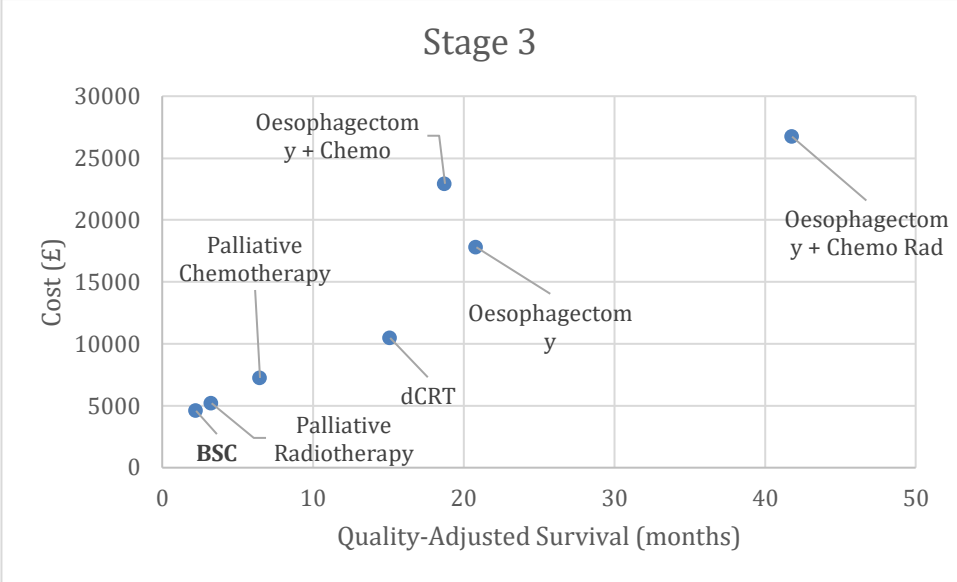

BSC
QOL
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.7
STAGE 4
0.37
STAGE 2 +
STAGE 1
0.2
0
2
4
6
8
10
12
TIME (MONTHS)

Figure (o): The cost per QALY of oesophageal cancer treatments, according to stage, represented on ICER charts






Stage 3
30000
25000
20000
15000
10000
5000
0
Cost (£)
0
10
20
30
40
50
Quality-Adjusted Survival (months)
Oesophagectomy + Chemo
Oesophagectomy + Chemo Rad
Palliative Chemotherapy
Oesophagectomy
dCRT
Palliative Radiotherapy
BSC

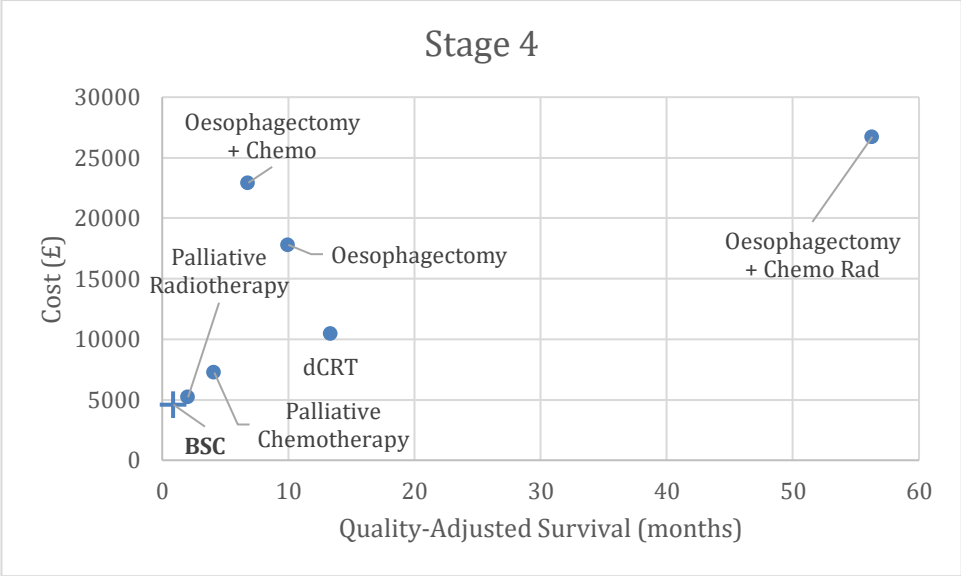
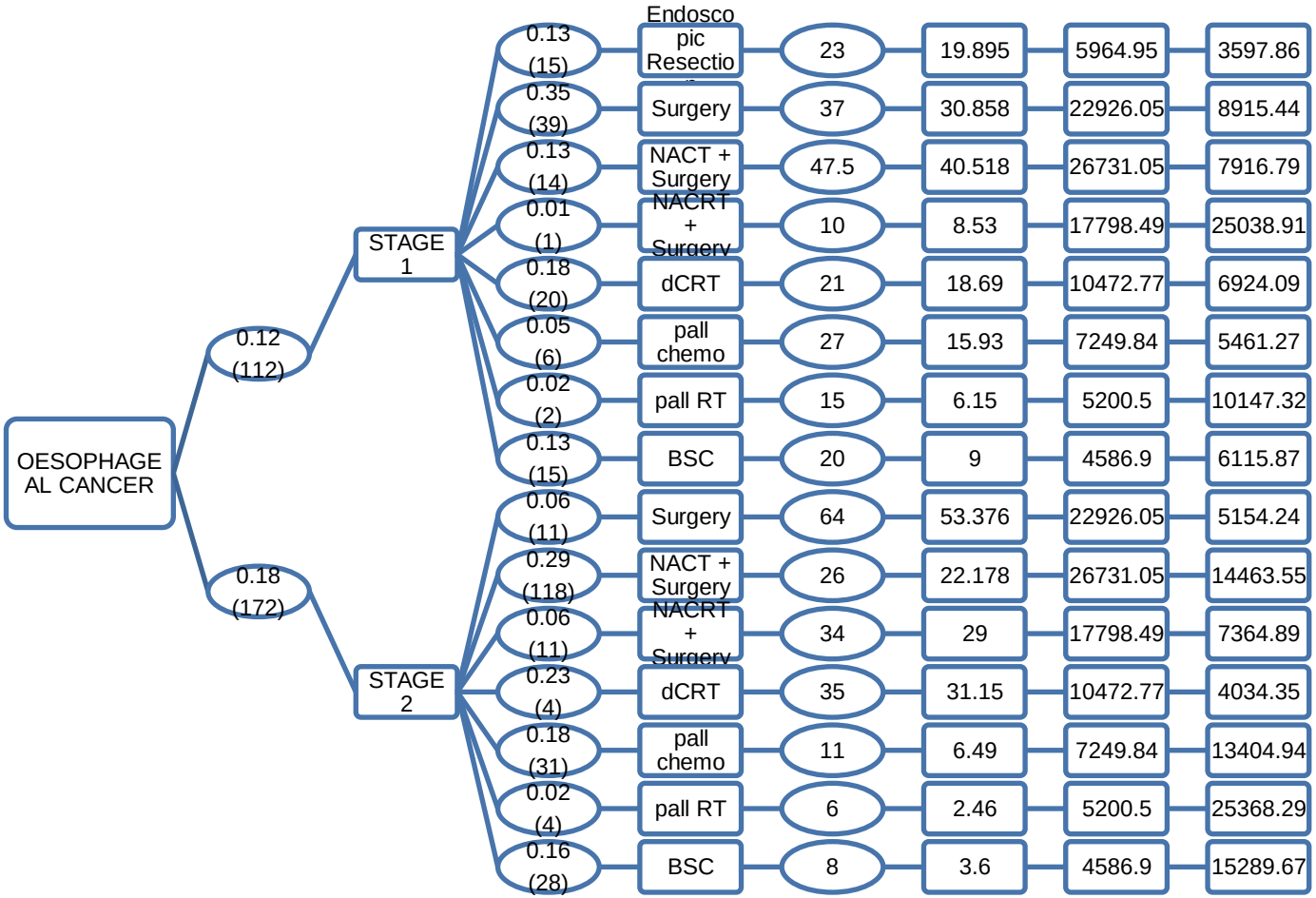
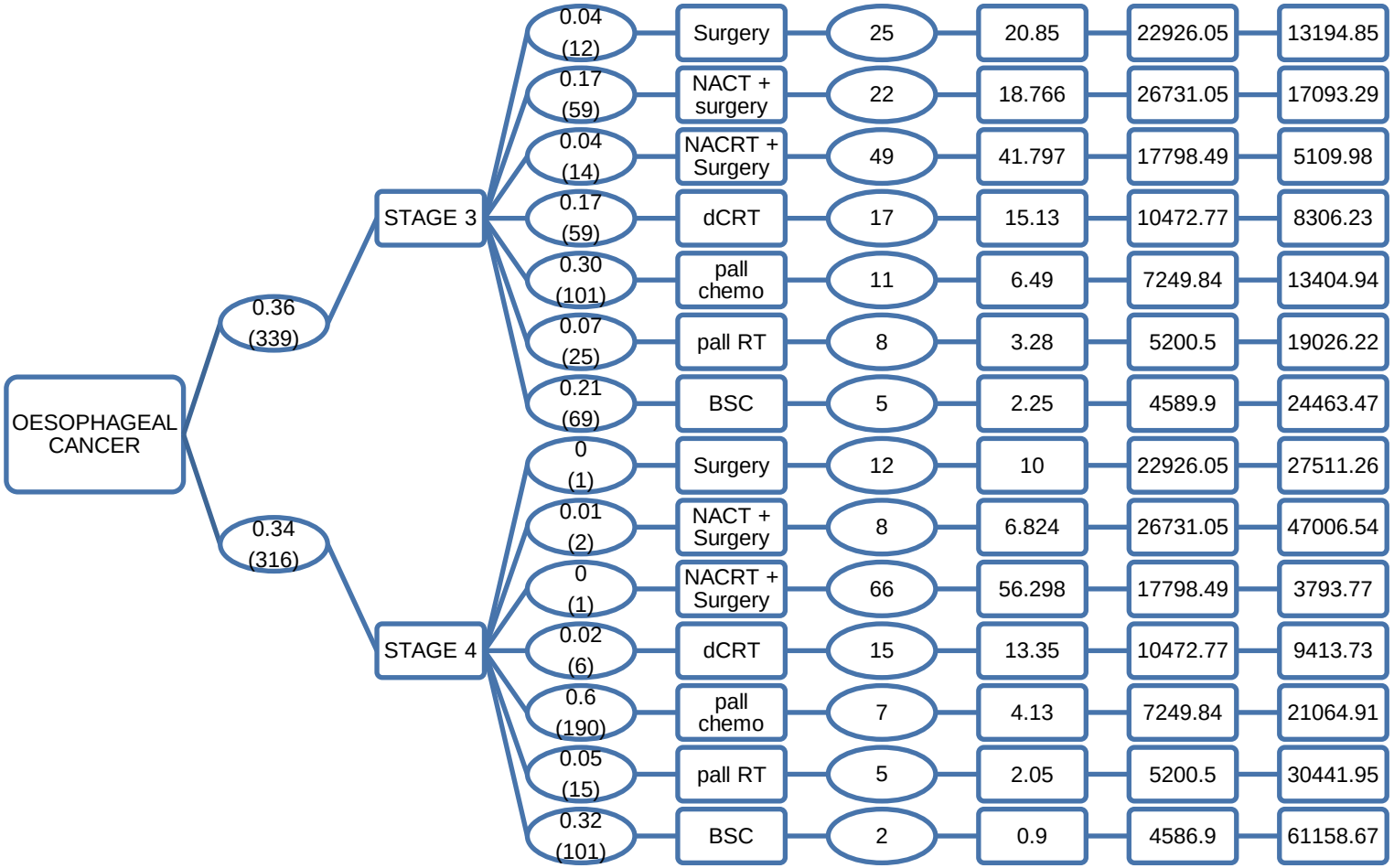

Stage 4
30000
25000
20000
15000
10000
5000
0
Cost (£)
0
10
20
30
40
50
60
Quality-Adjusted Survival (months)
Oesophagectomy + Chemo
Oesophagectomy + Chemo Rad
Palliative Radiotherapy
Oesophagectomy
dCRT
Palliative Chemotherapy
BSC

Figure (p): Decision tree analysis of oesophageal cancer care





	Proportion (total no.)	Proportion (total no.)	Treatment pathway	Survival (months)	Quality-adjusted survival (months)	Cost (£)	Cost /QALY

Figure (q): The relationship between overall survival by team operating

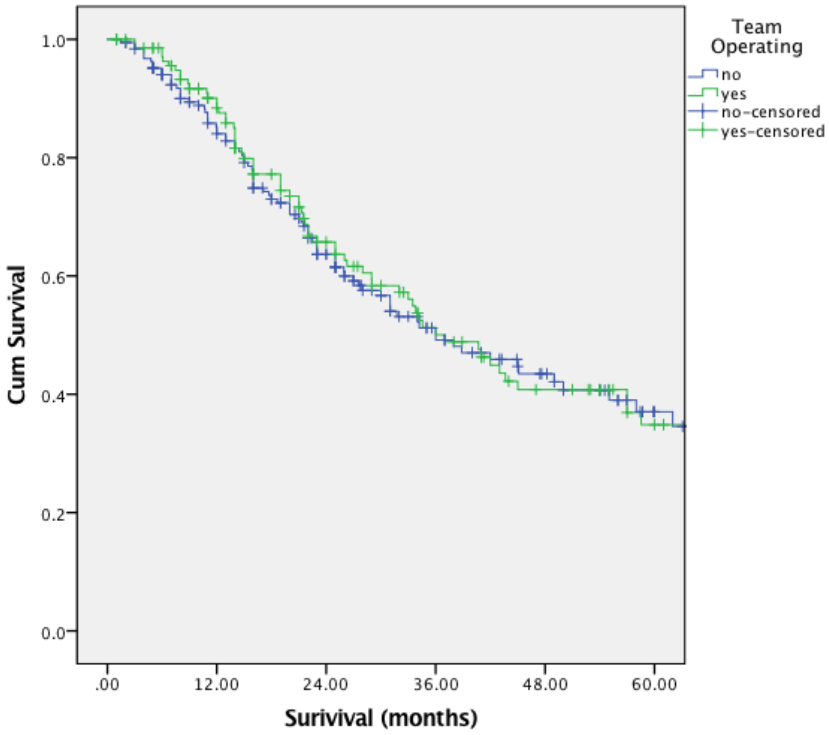


Figure (r): The relationship between disease free survival by team operating

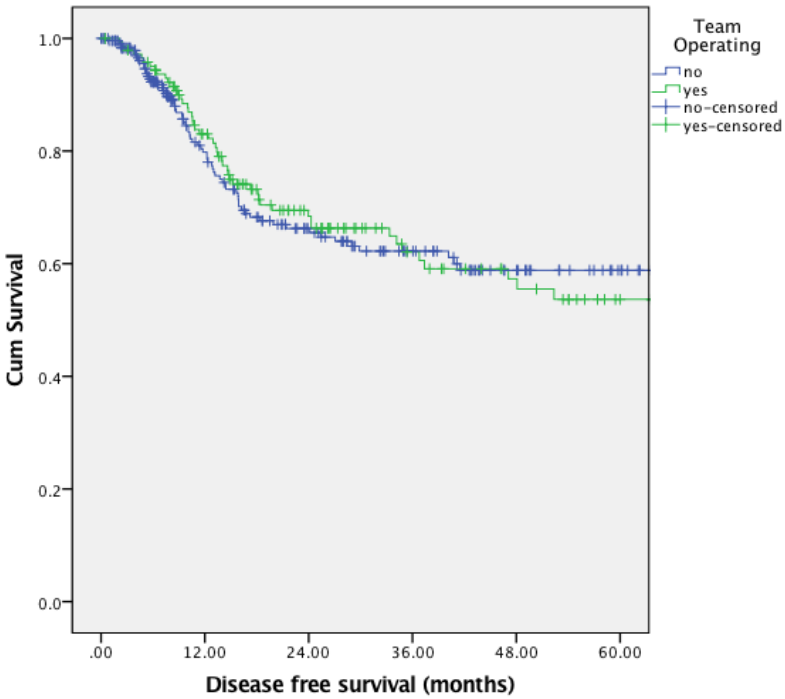
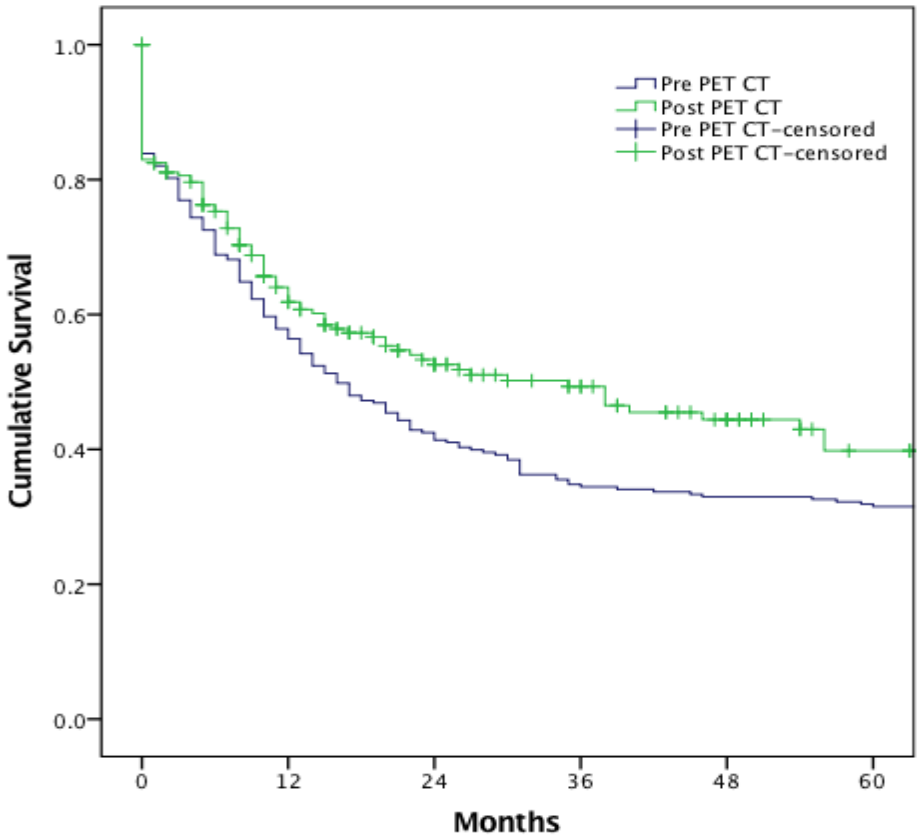


Figure (s): Cumulative disease-free survival related to introduction of PET-CT.

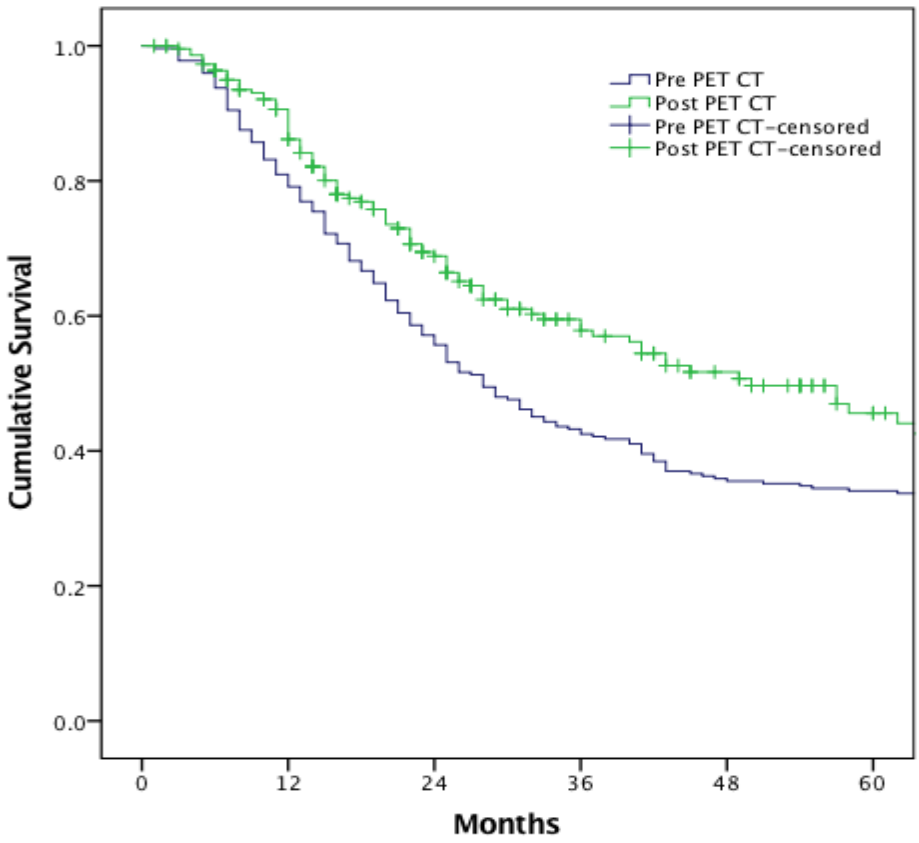


Number at risk

Time (months)	0	12	24	36	48
	60				
Pre PET CT	273	216	152	116	97
	92				
Post PET CT	223	174	113	71	51
	29				

Log Rank (Mantel-Cox) Chi Squared 3.964 df 1 p= 0.046

Figure (t): Cumulative overall survival related to inception of PET-CT.



Number at risk

Time (months)	0	12	24	36	48	60
Pre PET CT	273	154	113	94	90	86
Post PET CT	223	113	74	57	41	23

Log Rank (Mantel-Cox) Chi Squared 8.388 df 1 p= 0.004

Appendix 1

Appendix 1 (a): Costs of gastrectomy and perioperative chemotherapy

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	
	A&E admission	36-342	0			
Endoscopy	Open access	339	1	339	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	34.25	PSSRU	
	Specialist nurse	44	0.5	22	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
Staging CT		121	1	121	RD26Z	
Local MDT discussion		139	1	139	CMDTSPU	
O/P appt	Consultant-led	153	1	153	WF01B	
	CNS	44	0.3	13.2	PSSRU	
PET-CT		944	0	0	RN03A	
CPEX		347	0	0	DZ31Z	
EUS						
Staging laparoscopy		2907	1	2907	FZ27G	
Regional MDT discussion		139	1	139	CMDTSPU	
CNS phone call		44	0.25	11	PSSRU	
Outpatient clinic appt	Oncology, new patient	197	1	197	WF01B	
	Dietitian	33	0.5	16.5	PSSRU	
Medications	Dietetic supplements	6	30	180	BNF	£2 per drink, 3 per day
Chemotherapy	Epirubicin (E)	201.76	3	605.28	BNF	50mg/m2=92.5mg per dose

	Cisplatin (C)	56.12	3	**168.36**	BNF	60mg/m2=111mg per dose
	Fluorouracil (F)	96	3	**288**	BNF	200mg/m2/day for 21 days = 370mg/day, 7770mg over 21 days
	Antiemetics	23.38	3	**70.14**	BNF	
	Initial dose delivery	503	1	**503**	SB12Z+SB14Z	
	subsequent dose deliveries	212	2	**424**	SB15Z	
	PICC line insertion	329	1	**329**	YR42A	
	Bloods	7	3	**21**		
Re-staging CT		121	1	**121**	RD26Z	
MDT discussion		139	1	**139**	CMDTSPU	
Pre-operative assessment	CNS Assessment	44	2	**88**	PSSRU	
	Dietitian	33	0.5	**16.5**	PSSRU	
	Bloods	7	1	**7**	DAPS04,05, 08	
	ECG	40	1	**40**		
	Spirometry	112	0	**0**	DZ52Z	
Smoking cessation		22	0	**0**	DZ25Z	
Physiotherapist		33	0.5	**16.5**	PSSRU	
Gastrectomy	with 5 day stay	8440	1	**8440**	FZ80E	
excess bed days		244	6	**1464**	FZ80E	
Inpatient medications	Enoxaparin	3.03	10	**30.3**	BNF	
	AEStockings	10	1	**10**	Amazon	
	CHO loading	2.06	2	**4.12**	BNF	
Anaesthetic pre-op assessment	20 mins	137	0.3	**41.1**	PSSRU	
Intraoperative medications	Coamoxyclav	10.6	1	**10.6**	BNF	

	Metronidazole	62	1	**62**	BNF	
Anaesthetic	Fentanyl	27.9	1	**27.9**	BNF	100mcg
	Muscle relaxant (Rocuronium)	4.8	1	**4.8**	BNF	42mg induction, up to 5mg maintenance
	Propofol	3.07	1	**3.07**	BNF	Induction 1.5mg/kg=105mg, 200mg (20ml)
	Ondansetron	11.69	1	**11.69**	BNF	8mg/4ml IV
	Dexamethasone	1.99	1	**1.99**	BNF	3.8mg/ml
	Morphine			**0**		
	Neostigmine/Glycopyronium	2.3	1	**2.3**	BNF	£1.15/ml, 2ml given
	Sevoflurane	30.75	1	**30.75**	BNF	123/250ml, lasts 4 days
Equipment	Central line	143	1	**143**	YR42A	
	Surgical disposables	696.72	1	**696.72**	ABC from theatre clinical leader	
Recovery	chest Xray	40	1	**40**		
Critical care (PACU)	Bed/day	718	1	**718**	XC07Z	
	SCP 20 mins	44	0.3	**13.2**	PSSRU	
	Cons r/v	137	0.3	**41.1**	PSSRU	
Post-op day 2-11	jej feed	16.97	7	**118.79**	BNF	Jevity 1.5kcal 1500ml, 2310kcal/day
	Dietetic R/v	8.25	8	**66**	PSSRU	33x0.25
	Paracetamol	4.8	11	**52.8**	BNF	1.2x4 doses per day=£4.80

	Tramadol	4	8	**32**		1x4 doses per day=£4
	Antiemetics	23	2	**46**	BNF	£7.67 per 4mg dose x 3/day= £23
	Pain team	10.5	6	**63**	PSSRU	35x0.3
	epidural (5 days)	21.78	5	**108.9**	BNF	bupivacaine only
	Bloods	7	8	**56**		
	CNS r/v	13.2	8	**105.6**		44x0.3=13.2
	Physio walk/respiratory exercises	9.9	7	**69.3**		33x0.3=9.9
	Cons r/v alt. day	34.25	6	**205.5**		137x0.25=34.25
Gastrograffin swallow		114	1	**114**	RD30Z	
Hospital discharge	Discharge advice CNS	44	0.25	**11**	PSSRU	
	Extended VTE	3.03	28	**84.84**	BNF	
	Jej feed training (SN/dietician)	33	0.25	**8.25**	PSSRU	
Follow up phone call	CNS	44	0.3	**13.2**	PSSRU	
Histology		31	1	**31**	DAPS02	
MDT discussion		139	1	**139**	CMDTSPU	
District nurse visit		38	1	**38**	PSSRU	
Outpatient clinic appt	at 2 weeks	122	1	**122**	WF01A	
Removal of feeding tube and clinic R/v	CNS	44	0.3	**13.2**	PSSRU	10 mins
Outpatient clinic appt	oncology or surgical	122	3	**366**	WF01A	3 appointments in first year
	CNS R/v in clinic	13.2	3	**39.6**	PSSRU	44x 0.3
Chemotherapy	Epirubicin (E)	201.76	3	**605.28**	BNF	50mg/m2=92.5mg per dose

	Cisplatin (C)	56.12	3	168.36	BNF	60mg/m2=111mg per dose
	Fluorouracil (F)	96	3	288	BNF	200mg/m2/day for 21 days = 370mg/day, 7770mg over 21 days
	Antiemetics	23.38	3	70.14	BNF	
	Initial dose delivery	503	1	503	SB12Z+SB14Z	
	subsequent dose deliveries	212	2	424	SB15Z	
	PICC line insertion	329	1	329	YR42A	
	Bloods	7	3	21		
			Total cost:	23270.63		

Appendix 1 (b): Costs of subtotal gastrectomy and perioperative chemotherapy

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	
	A&E admission	36-342	0			
Endoscopy	Open access	339	1	339	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	34.25	PSSRU	
	Specialist nurse	44	0.5	22	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
Staging CT		121	1	121	RD26Z	
Local MDT discussion		139	1	139	CMDTSPU	
O/P appt	Consultant-led	153	1	153	WF01B	
	CNS	44	0.3	13.2	PSSRU	

PET-CT		944	0		RN03A	
CPEX		347	0		DZ31Z	
EUS						
Staging laparoscopy		2907	1	2907	FZ27G	
Regional MDT discussion		139	1	139	CMDTSPU	
CNS phone call		44	0.25	11	PSSRU	
Outpatient clinic appt	Oncology, new patient	197	1	197	WF01B	
	Dietitian	33	0.5	16.5	PSSRU	
Medications	Dietetic supplements	6	30	180	BNF	£2 per drink
Chemotherapy	Epirubicin (E)	201.76	3	605.28	BNF	50mg/m2=92.5mg per dose
	Cisplatin (C)	56.12	3	168.36	BNF	60mg/m2=111mg per dose
	Fluorouracil (F)	96	3	288	BNF	200mg/m2/day for 21 days = 370mg/day, 7770mg over 21 days
	Antiemetics	23.38	3	70.14	BNF	
	Initial dose delivery	503	1	503	SB12Z+SB14Z	
	subsequent dose deliveries	212	2	424	SB15Z	
	PICC line insertion	329	1	329	YR42A	
	Bloods	7	3	21		
Re-staging CT		121	1	121	RD26Z	
MDT discussion		139	1	139	CMDTSPU	
Pre-operative assessment	CNS Assessment	44	2	88	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
	Bloods	7	1	7	DAPS04,05, 08	
	ECG	40	1	40		

	Spirometry	112	0		DZ52Z	
Smoking cessation		22	0		DZ25Z	
Physiotherapist		33	0.5	**16.5**	PSSRU	
Subtotal gastrectomy	with 5 day stay	8440	1	**8440**	FZ80E	
excess bed days		244	2	**488**	FZ80E	
Inpatient medications	Enoxaparin	3.03	10	**30.3**	BNF	
	AEStockings	10	1	**10**	Amazon	
	CHO loading	2.06	2	**4.12**	BNF	
Anaesthetic pre-op assessment	20 mins	137	0.3	**41.1**	PSSRU	
Intraoperative medications	Coamoxyclav	10.6	1	**10.6**	BNF	
	Metronidazole	62	1	**62**	BNF	
Anaesthetic	Fentanyl	27.9	1	**27.9**	BNF	100mcg
	Muscle relaxant (Rocuronium)	4.8	1	**4.8**	BNF	42mg induction, up to 5mg maintenance
	Propofol	3.07	1	**3.07**	BNF	Induction 1.5mg/kg=105mg, 200mg (20ml)
	Ondansetron	11.69	1	**11.69**	BNF	8mg/4ml IV
	Dexamethasone	1.99	1	**1.99**	BNF	3.8mg/ml
	Neostigmine/Glycopyronium	2.3	1	**2.3**	BNF	£1.15/ml, 2ml given
	Sevoflurane	30.75	1	**30.75**	BNF	123/250ml, lasts 4 days
Equipment	Central line	143	1	**143**	YR42A	
	Surgical disposables	696.72	1	**696.72**	ABC from theatre clinical leader	
Recovery	chest Xray	40	1	**40**		
Critical care (PACU)	Bed/day	718	1	**718**	XC07Z	
	SCP 20 mins	44	0.3	**13.2**	PSSRU	

	Cons r/v	137	0.3	**41.1**	PSSRU	
Post-op day 2-7	jej feed	16.97	6	**101.82**	BNF	Jevity 1.5kcal 1500ml, 2310kcal/day
	Dietetic R/v	8.25	5	**41.25**	PSSRU	33x0.25
	Paracetamol	4.8	7	**33.6**	BNF	1.2x4 doses per day=£4.80
	Tramadol	4	5	**20**		1x4 doses per day=£4
	Antiemetics	23	2	**46**	BNF	£7.67 per 4mg dose x 3/day= £23
	Pain team	10.5	6	**63**	PSSRU	35x0.3
	epidural (5 days)	21.78	5	**108.9**	BNF	bupivacaine only
	Bloods	7	7	**49**		
	CNS r/v	13.2	5	**66**		44x0.3=13.2
	Physio walk/respiratory exercises	9.9	5	**49.5**		33x0.3=9.9
	Cons r/v alt. day	34.25	4	**137**		137x0.25=34.25
Hospital discharge	Discharge advice CNS	44	0.25	**11**	PSSRU	
	Extended VTE	3.03	28	**84.84**	BNF	
	Jej feed training (SN/dietician)	33	0.25	**8.25**	PSSRU	
Follow up phone call	CNS	44	0.3	**13.2**	PSSRU	
Histology		31	1	**31**	DAPS02	
MDT discussion		139	1	**139**	CMDTSPU	
District nurse visit		38	1	**38**	PSSRU	
Outpatient clinic appt	at 2 weeks	122	1	**122**	WF01A	
Removal of feeding tube	CNS	44	0.3	**13.2**	PSSRU	10 mins
Outpatient clinic appt	6/52 or 3/12 (3 in first year post-op - onc or surg)	122	3	**366**	WF01A	

	CNS R/v in clinic	13.2	3	**39.6**	PSSRU	44x 0.3
Chemotherapy	Epirubicin (E)	201.76	3	**605.28**	BNF	50mg/m2=92.5mg per dose
	Cisplatin (C)	56.12	3	**168.36**	BNF	60mg/m2=111mg per dose
	Fluorouracil (F)	96	3	**288**	BNF	200mg/m2/day for 21 days = 370mg/day, 7770mg over 21 days
	Antiemetics	23.38	3	**70.14**	BNF	
	Initial dose delivery	503	1	**503**	SB12Z+SB14Z	
	subsequent dose deliveries	212	2	**424**	SB15Z	
	PICC line insertion	329	1	**329**	YR42A	
	Bloods	7	3	**21**		
				21972.81		

Appendix 1 (c): Costs of gastrectomy alone

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	**36**	PSSRU	
	A&E admission	36-342	0			
Endoscopy	Open access	339	1	**339**	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	**34.25**	PSSRU	
	Specialist nurse	44	0.5	**22**	PSSRU	
	Dietitian	33	0.5	**16.5**	PSSRU	
Staging CT		121	1	**121**	RD26Z	
Local MDT discussion		139	1	**139**	CMDTSPU	
O/P appt	Consultant-led	153	1	**153**	WF01B	

	CNS	44	0.3	**13.2**	PSSRU	
PET-CT		944	0	**0**	RN03A	
CPEX		347	0	**0**	DZ31Z	
EUS						
Staging laparoscopy		2907	1	**2907**	FZ27G	
Regional MDT discussion		139	1	**139**	CMDTSPU	
CNS phone call		44	0.25	**11**	PSSRU	
Outpatient clinic appt	Surgical consultant-led, new patient	197	1	**197**	WF01B	
	Dietitian	33	0.5	**16.5**	PSSRU	
Medications	Dietetic supplements	6	30	**180**	BNF	£2 per drink
Pre-operative assessment	CNS Assessment	44	2	**88**	PSSRU	
	Dietitian	33	0.5	**16.5**	PSSRU	
	Bloods	7	1	**7**	DAPS04,05, 08	
	ECG	40	1	**40**		
	Spirometry	112	0	**0**	DZ52Z	
Smoking cessation		22	0	**0**	DZ25Z	
Physiotherapy		33	0.5	**16.5**	PSSRU	
Gastrectomy	with 5 day stay	8440	1	**8440**	FZ80E	
excess bed days		244	6	**1464**	FZ80E	
Inpatient medications	Enoxaparin	3.03	10	**30.3**	BNF	
	AEStockings	10	1	**10**	Amazon	
	CHO loading	2.06	2	**4.12**	BNF	
Anaesthetic pre-op assessment	20 mins	137	0.3	**41.1**	PSSRU	

Intraoperative medications	Coamoxyclav	10.6	1	**10.6**	BNF	
	Metronidazole	62	1	**62**	BNF	
Anaesthetic	Fentanyl	27.9	1	**27.9**	BNF	100mcg
	Muscle relaxant (Rocuronium)	4.8	1	**4.8**	BNF	42mg induction, up to 5mg maintenance
	Propofol	3.07	1	**3.07**	BNF	Induction 1.5mg/kg=105mg, 200mg (20ml)
	Ondansetron	11.69	1	**11.69**	BNF	8mg/4ml IV
	Dexamethasone	1.99	1	**1.99**	BNF	3.8mg/ml
	Morphine			**0**		
	Neostigmine/Glycopyronium	2.3	1	**2.3**	BNF	£1.15/ml, 2ml given
	Sevoflurane	30.75	1	**30.75**	BNF	123/250ml, lasts 4 days
Equipment	Central line	143	1	**143**	YR42A	
	Surgical disposables	696.72	1	**696.72**	ABC from theatre clinical leader	
Recovery	CXR	40	1	**40**		
Critical care (PACU)	Bed/day	718	1	**718**	XC07Z	
	SCP 20 mins	44	0.3	**13.2**	PSSRU	
	Cons r/v	137	0.3	**41.1**	PSSRU	
Post-op day 2-11	jej feed	16.97	7	**118.79**	BNF	Jevity 1.5kcal 1500ml, 2310kcal/day
	Dietetic R/v	8.25	8	**66**	PSSRU	33x0.25
	Paracetamol	4.8	11	**52.8**	BNF	1.2x4 doses per day=£4.80
	Tramadol	4	8	**32**		1x4 doses per day=£4
	Antiemetics	23	2	**46**	BNF	£7.67 per 4mg dose x 3/day= £23

	Pain team	10.5	6	63	PSSRU	35x0.3
	epidural (5 days)	21.78	5	108.9	BNF	bupivacaine only
	Bloods	7	8	56		
	CNS r/v	13.2	8	105.6		44x0.3=13.2
	Physio walk/respiratory exercises	9.9	7	69.3		33x0.3=9.9
	Cons r/v alt. day	34.25	6	205.5		137x0.25=34.25
Gastrograffin swallow		114	1	114	RD30Z	
Hospital discharge	Discharge advice CNS	44	0.25	11	PSSRU	
	Extended VTE	3.03	28	84.84	BNF	
	Jej feed training (SN/dietician)	33	0.25	8.25	PSSRU	
Follow up phone call	CNS	44	0.3	13.2	PSSRU	
Histology		31	1	31	DAPS02	
MDT discussion		139	1	139	CMDTSPU	
District nurse visit		38	1	38	PSSRU	
Outpatient clinic appt	at 2 weeks	122	1	122	WF01A	
Removal of feeding tube	CNS	44	0.3	13.2	PSSRU	10 mins
Outpatient clinic appt	6/52 or 3/12 (3 in first year post-op)	122	3	366	WF01A	
	CNS R/v in clinic	13.2	3	39.6	PSSRU	44x 0.3
				18193.07		

Appendix 1 (d): Costs of subtotal gastrectomy alone

Column1	Column2	Unit cost 2017	No. of units	Total cost (£)	Code/Source	Notes

Mode of presentation	GP referral	36	1	**36**	PSSRU	
	A&E admission	36-342	0			
Endoscopy	Open access	339	1	**339**	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	**34.25**	PSSRU	
	Specialist nurse	44	0.5	**22**	PSSRU	
	Dietitian	33	0.5	**16.5**	PSSRU	
Staging CT		121	1	**121**	RD26Z	
Local MDT discussion		139	1	**139**	CMDTSPU	
Outpatient appt	Consultant-led	153	1	**153**	WF01B	
	CNS	44	0.3	**13.2**	PSSRU	
PET-CT		944	0	**0**	RN03A	
CPEX		347	0	**0**	DZ31Z	
Staging laparoscopy		2907	1	**2907**	FZ27G	
Regional MDT discussion		139	1	**139**	CMDTSPU	
CNS phone call		44	0.25	**11**	PSSRU	
Outpatient appt	surgical, follow-up	153	1	**153**	WF01B	
	Dietitian	33	0.5	**16.5**	PSSRU	
Medications	Dietetic supplements	6	30	**180**	BNF	£2 per drink
Pre-operative assessment	CNS Assessment	44	2	**88**	PSSRU	
	Dietitian	33	0.5	**16.5**	PSSRU	
	Bloods	7	1	**7**	DAPS04,05, 08	
	ECG	40	1	**40**		
	Spirometry	112	0	**0**	DZ52Z	
Smoking cessation		22	0	**0**	DZ25Z	

Physiotherapy		33	0.5	**16.5**	PSSRU	
Subtotal gastrectomy	with 5 day stay	8440	1	**8440**	FZ80E	
excess bed days		244	2	**488**	FZ80E	
Inpatient medication	Enoxaparin	3.03	10	**30.3**	BNF	
	AEStockings	10	1	**10**	Amazon	
	CHO loading	2.06	2	**4.12**	BNF	
Anaesthetic pre-op assessment	20 mins	137	0.3	**41.1**	PSSRU	
Intraoperative medication	Coamoxyclav	10.6	1	**10.6**	BNF	
	Metronidazole	62	1	**62**	BNF	
Anaesthetic	Fentanyl	27.9	1	**27.9**	BNF	100mcg
	Muscle relaxant (Rocuronium)	4.8	1	**4.8**	BNF	42mg induction, up to 5mg maintenance
	Propofol	3.07	1	**3.07**	BNF	Induction 1.5mg/kg=105mg, 200mg (20ml)
	Ondansetron	11.69	1	**11.69**	BNF	8mg/4ml IV
	Dexamethasone	1.99	1	**1.99**	BNF	3.8mg/ml
	Morphine			**0**		
	Neostigmine/Glycopyronium	2.3	1	**2.3**	BNF	£1.15/ml, 2ml given
	Sevoflurane	30.75	1	**30.75**	BNF	123/250ml, lasts 4 days
Equipment	Central line	143	1	**143**	YR42A	
	Surgical disposables	696.72	1	**696.72**	ABC from theatre clinical leader	
Recovery	Chest Xray	40	1	**40**		
Critical care (PACU)	Bed/day	718	1	**718**	XC07Z	
	SCP 20 mins	44	0.3	**13.2**	PSSRU	
	Cons r/v	137	0.3	**41.1**	PSSRU	

Post-op day 2-7	jej feed	16.97	6	**101.82**	BNF	Jevity 1.5kcal 1500ml, 2310kcal/day
	Dietetic R/v	8.25	5	**41.25**	PSSRU	33x0.25
	Paracetamol	4.8	7	**33.6**	BNF	1.2x4 doses per day=£4.80
	Tramadol	4	5	**20**		1x4 doses per day=£4
	Antiemetics	23	2	**46**	BNF	£7.67 per 4mg dose x 3/day= £23
	Pain team	10.5	6	**63**	PSSRU	35x0.3
	epidural (5 days)	21.78	5	**108.9**	BNF	bupivacaine only
	Bloods	7	7	**49**		
	CNS r/v	13.2	5	**66**		44x0.3=13.2
	Physio walk/respiratory exercises	9.9	5	**49.5**		33x0.3=9.9
	Cons r/v alt. day	34.25	4	**137**		137x0.25=34.25
Hospital discharge	Discharge advice CNS	44	0.25	**11**	PSSRU	
	Extended VTE	3.03	28	**84.84**	BNF	
	Jej feed training (SN/dietician)	33	0.25	**8.25**	PSSRU	
Follow up phone call	CNS	44	0.3	**13.2**	PSSRU	
Histology		31	1	**31**	DAPS02	
MDT discussion		139	1	**139**	CMDTSPU	
District nurse visit		38	1	**38**	PSSRU	
Outpatient clinic appt	at 2 weeks	122	1	**122**	WF01A	
Removal of feeding tube	CNS	44	0.3	**13.2**	PSSRU	10 mins
Outpatient clinic appt	6/52 or 3/12 (3 in first year post-op - onc or surg)	122	3	**366**	WF01A	
	CNS R/v in clinic	13.2	3	**39.6**	PSSRU	44x 0.3

				16851.25		

Appendix 1 (e): Costs of ESD for gastric cancer

		Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	
	A&E admission	36-342	0			
Endoscopy	Open access	339	1	339	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	34.25	PSSRU	
	Specialist nurse	44	0.5	22	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
Staging CT		121	1	121	RD26Z	
Local MDT discussion		139	1	139	CMDTSPU	
Outpatient appt	Consultant-led	153	1	153	WF01B	
	CNS	44	0.3	13.2	PSSRU	
Pre-operative assessment	CNS Assessment	44	2	88	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
	Bloods	7	1	7	DAPS04,05, 08	
	ECG	40	1	40		
	Spirometry	112	0	0	DZ52Z	
ESD	with 2 day stay	2618	1	2618	FZ89Z	
Inpatient medications	Enoxaparin	3.03	2	6.06	BNF	
	AEStockings	10	1	10	Amazon	
Anaesthetic pre-op assessment	20 mins	137	0.3	41.1	PSSRU	

Intraoperative medications	Coamoxyclav	10.6	1	10.6	BNF	
	Metronidazole	62	1	62	BNF	
Anaesthetic	Fentanyl	27.9	1	27.9	BNF	100mcg
	Muscle relaxant (Rocuronium)	4.8	1	4.8	BNF	42mg induction, up to 5mg maintenance
	Propofol	3.07	1	3.07	BNF	Induction 1.5mg/kg=105mg, 200mg (20ml)
	Ondansetron	11.69	1	11.69	BNF	8mg/4ml IV
	Dexamethasone	1.99	1	1.99	BNF	3.8mg/ml
	Morphine			0		
	Neostigmine/Glycopyronium	2.3	1	2.3	BNF	£1.15/ml, 2ml given
	Sevoflurane	30.75	1	30.75	BNF	123/250ml, lasts 4 days
Equipment	Central line	143	0	0	YR42A	
	Surgical disposables		1	0		
Day 1 and 2 post op	SCP 20 mins	44	0.6	26.4	PSSRU	0.3x2=0.6
	Cons r/v	137	0.3	41.1	PSSRU	
	Paracetamol	4.8	2	9.6	BNF	1.2x4 doses per day=£4.80
	Tramadol	4	1	4		1x4 doses per day=£4
	Antiemetics	23	1	23	BNF	£7.67 per 4mg dose x 3/day= £23
	Bloods	7	1	7		
	Omeprazole infusion	5.2	5	26	BNF	8mg/hour for 24 hours
Follow up phone call	CNS	44	0.3	13.2	PSSRU	
Take home	omeprazole	2.64	6	15.84	BNF	40mg BD for 3/12, £2.64 for 28 tablets
Histology		31	1	31	DAPS02	
MDT discussion		139	1	139	CMDTSPU	
Outpatient clinic appt	at 2 weeks	122	1	122	WF01A	

UGI endoscopy at 6 months		339	1	339	FZ61Z	
Outpatient clinic appt	6/52 or 3/12 (3 in first year post-op)	122	3	366	WF01A	
	CNS R/v in clinic	13.2	3	39.6	PSSRU	44x 0.3
				5058.45		

Appendix 1 (f): Costs of palliative chemotherapy for gastric cancer

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	
	A&E admission	36-342	0			
Endoscopy	Open access	339	1	339	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	34.25	PSSRU	
	Specialist nurse	44	0.5	22	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
Staging CT		121	1	121	RD26Z	
Local MDT discussion		139	1	139	CMDTSPU	
Outpatient appt	Consultant-led	153	1	153	WF01B	
	CNS	44	0.3	13.2	PSSRU	
Medications	Dietetic supplements	6	120	720	BNF	£2 per drink, 4 months
Chemotherapy	Epirubicin (E)	201.76	4	807.04	BNF	50mg/m2=92.5mg per dose
	Cisplatin (C)	56.12	4	224.48	BNF	60mg/m2=111mg per dose
	Fluorouracil (F)	96	4	384	BNF	200mg/m2/day for 21 days = 370mg/day, 7770mg over 21 days
	Antiemetics	23.38	4	93.52	BNF	

	Initial dose delivery	503	1	503	SB12Z+SB14Z	
	subsequent dose deliveries	212	2	424	SB15Z	
	PICC line insertion	329	1	329	YR42A	
	Bloods	7	4	28	DAPS04,05,08	
Medications	Analgesia	4.54	30	136.2	BNF	Diamorph £4.54/10mg
	Antiemetics	8.12	30	243.6	BNF	cyclizine £8.12 for 150mg
	Anxiolytic	0.585	30	17.55	BNF	midazolam 58.5p/10mg
	Syringe driver pump hire					£1000-1500 initial cost
Community palliative care	Initial visit	52	0.5	26	PSSRU	Band 7 nurse
	monthly	52	1.2	62.4	PSSRU	4 x 0.3
	twice/week in last month	52	2.4	124.8	PSSRU	8 x 0.3
District nurse visit	twice a day for last month	38	60	2280	PSSRU	
GP home visit		236	0.5	118	PSSRU	
				7395.54		

Appendix 1 (g): Costs of palliative radiotherapy for gastric cancer

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	
	A&E admission	36-342	0			
Endoscopy	Open access	339	1	339	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	34.25	PSSRU	

	Specialist nurse	44	0.5	22	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
Staging CT		121	1	121	RD26Z	
Local MDT discussion		139	1	139	CMDTSPU	
Outpatient appt	Consultant-led	153	1	153	WF01B	
	CNS	44	0.3	13.2	PSSRU	
Medications	Dietetic supplements	6	120	720	BNF	£2 per drink, 4 months
Palliative radiotherapy	Preparation	462	1	462	SC48Z	
	administration	108	1	108	SC22Z	
	Bloods	7	4	28	DAPS04,05,08	
Medications	Analgesia	4.54	30	136.2	BNF	Diamorph £4.54/10mg
	Antiemetics	8.12	30	243.6	BNF	cyclizine £8.12 for 150mg
	Anxiolytic	0.585	30	17.55	BNF	midazolam 58.5p/10mg
	Syringe driver pump hire			0		£1000-1500 initial cost
Community palliative care	Initial visit	52	0.5	26	PSSRU	Band 7 nurse
	monthly	52	1.2	62.4	PSSRU	4 x 0.3
	twice/week in last month	52	2.4	124.8	PSSRU	8 x 0.3
District nurse visit	twice a day for last month	38	60	2280	PSSRU	
GP home visit		236	0.5	118	PSSRU	
				5200.5		

Appendix 1 (h): Costs of Best Supportive Care for gastric cancer

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	

	A&E admission	36-342		0			
Endoscopy	Open access		339	1	**339**	FZ61Z	Included biopsy processing
Counselling/diagnosis	Endoscopist		137	0.25	**34.25**	PSSRU	
	Specialist nurse		44	0.5	**22**	PSSRU	
	Dietitian		33	0.5	**16.5**	PSSRU	
Staging CT			121	1	**121**	RD26Z	
Local MDT discussion			139	1	**139**	CMDTSPU	
Outpatient clinic appt	Consultant-led		153	1	**153**	WF01B	
	CNS		44	0.3	**13.2**	PSSRU	
Medications	Dietetic supplements		6	120	**720**	BNF	£2 per drink, 4 months
Medications	Analgesia		4.54	30	**136.2**	BNF	Diamorph £4.54/10mg
	Antiemetics		8.12	30	**243.6**	BNF	cyclizine £8.12 for 150mg
	Anxiolytic		0.585	30	**17.55**	BNF	midazolam 58.5p/10mg
	Syringe driver pump hire						£1000-1500 initial cost
Community palliative care	Initial visit		52	0.5	**26**	PSSRU	Band 7 nurse
	monthly		52	0.9	**46.8**	PSSRU	3 x 0.3
	twice/week in last month		52	2.4	**124.8**	PSSRU	8 x 0.3
District nurse visit	twice a day for last month		38	60	**2280**	PSSRU	
GP home visit			236	0.5	**118**	PSSRU	
					4586.9		

Appendix 2

Appendix 2 (a): Costs of EMR for oesophageal cancer

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	
	A&E admission	36-342	0	0		
Endoscopy	Open access	339	1	339	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	34.25	PSSRU	
	Specialist nurse	44	0.5	22	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
Staging CT		121	1	121	RD26Z	
Local MDT discussion		139	1	139	CMDTSPU	
O/P appt	Consultant-led	153	1	153	WF01B	
	CNS	44	0.3	13.2	PSSRU	
EUS		604	1	604	GB13Z	
Regional MDT discussion		139	1	139	CMDTSPU	
Outpatient clinic appt	Surgical, new patient	147	1	147	WF01B	
	Dietitian	33	0.5	16.5	PSSRU	
Pre-operative assessment	CNS Assessment	44	2	88	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
	Bloods	7	1	7	DAPS04,05, 08	
	ECG	40	1	40		
	Spirometry	112	0	0	DZ52Z	
EMR	with 2 day stay	2618	1	2618	FZ89Z	
Drug chart	Enoxaparin	3.03	2	6.06	BNF	

	AEStockings	10	1	**10**	Amazon	
Anaesthetic pre-op assessment	20 mins	137	0.3	**41.1**	PSSRU	
Intraoperative medications	Coamoxyclav	10.6	1	**10.6**	BNF	
	Metronidazole	62	1	**62**	BNF	
Anaesthetic	Fentanyl	27.9	1	**27.9**	BNF	100mcg
	Muscle relaxant (Rocuronium)	4.8	1	**4.8**	BNF	42mg induction, up to 5mg maintenance
	Propofol	3.07	1	**3.07**	BNF	Induction 1.5mg/kg=105mg, 200mg (20ml)
	Ondansetron	11.69	1	**11.69**	BNF	8mg/4ml IV
	Dexamethasone	1.99	1	**1.99**	BNF	3.8mg/ml
	Neostigmine/Glycopyronium	2.3	1	**2.3**	BNF	£1.15/ml, 2ml given
	Sevoflurane	30.75	1	**30.75**	BNF	123/250ml, lasts 4 days
Day 1 and 2 post op	SCP 20 mins	44	0.6	**26.4**	PSSRU	0.3x2=0.6
	Cons r/v	137	0.3	**41.1**	PSSRU	
	Paracetamol	4.8	2	**9.6**	BNF	1.2x4 doses per day=£4.80
	Tramadol	4	1	**4**		1x4 doses per day=£4
	Antiemetics	23	1	**23**	BNF	£7.67 per 4mg dose x 3/day= £23
	Bloods	7	1	**7**		
	Omeprazole infusion	5.2	5	**26**	BNF	8mg/hour for 24 hours
Follow up phone call	CNS	44	0.3	**13.2**	PSSRU	
Take home	omeprazole	2.64	6	**15.84**	BNF	40mg BD for 3/12, £2.64 for 28 tablets
Histology		31	1	**31**	DAPS02	

MDT discussion		139	1	139	CMDTSPU	
Outpatient clinic appt	at 2 weeks	122	1	122	WF01A	
UGI endoscopy at 6 months		339	1	339	FZ61Z	
Outpatient clinic appt	6/52 or 3/12 (3 in first year post-op)	122	3	366	WF01A	
	CNS R/v in clinic	13.2	3	39.6	PSSRU	44x 0.3
				5964.95		

Appendix 2 (b): Costs of oesophagectomy with perioperative chemotherapy

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	
	A&E admission	36-342	0			
Endoscopy	Open access	339	1	339	FZ61Z	includes biopsy processin
Counselling/diagnosis	Endoscopist	137	0.25	34.25	PSSRU	
	Specialist nurse	44	0.5	22	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
Staging CT		121	1	121	RD26Z	
Local MDT discussion		139	1	139	CMDTSPU	
O/P appt	Consultant-led	153	1	153	WF01B	
	CNS	44	0.3	13.2	PSSRU	
PET-CT		944	1	944	RN03A	
CPEX		347	1	347	DZ31Z	
EUS		604	1	604	GB13Z	
Regional MDT discussion		139	1	139	CMDTSPU	
CNS phone call		44	0.25	11	PSSRU	
Outpatient clinic appt	Oncology, new patient	197	1	197	WF01B	
	Dietitian	33	0.5	16.5	PSSRU	

Medications	Dietetic supplements	6	30	180	BNF	£2 per drink
Chemotherapy	Epirubicin (E)	201.76	3	605.28	BNF	50mg/m2=92.5mg per do
	Cisplatin (C)	56.12	3	168.36	BNF	60mg/m2=111mg per dos
	Fluorouracil (F)	96	3	288	BNF	200mg/m2/day for 21 day
	Antiemetics	23.38	3	70.14	BNF	
	Initial dose delivery	503	1	503	SB12Z+SB14Z	
	subsequent dose deliveries	212	2	424	SB15Z	
	PICC line insertion	329	1	329	YR42A	
	Bloods	7	3	21		
Re-staging CT		121	1	121	RD26Z	
MDT discussion		139	1	139	CMDTSPU	
Pre-operative assessment	CNS Assessment	44	2	88	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
	Bloods	7	1	7	DAPS04,05, 08	
	ECG	40	1	40		
	Spirometry	112	0		DZ52Z	
Smoking cessation		22	0		DZ25Z	
Physiotherapist		33	0.5	16.5	PSSRU	
Oesophagectomy	with 5 day stay	8440	1	8440	FZ80E	
excess bed days		244	8	1952	FZ80E	
Inpatient medications	Enoxaparin	3.03	10	30.3	BNF	
	AEStockings	10	1	10	Amazon	
	CHO loading	2.06	2	4.12	BNF	
Anaesthetic pre-op assessment	20 mins	137	0.3	41.1	PSSRU	
Intraoperative medications	Coamoxyclav	10.6	1	10.6	BNF	
	Metronidazole	62	1	62	BNF	

Anaesthetic	Fentanyl	27.9	1	**27.9**	BNF	100mcg
	Muscle relaxant (Rocuronium)	4.8	1	**4.8**	BNF	42mg induction, up to 5m
	Propofol	3.07	1	**3.07**	BNF	Induction 1.5mg/kg=105n
	Ondansetron	11.69	1	**11.69**	BNF	8mg/4ml IV
	Dexamethasone	1.99	1	**1.99**	BNF	3.8mg/ml
	Neostigmine/Glycopyronium	2.3	1	**2.3**	BNF	£1.15/ml, 2ml given
	Sevoflurane	30.75	1	**30.75**	BNF	123/250ml, lasts 4 days
Equipment	Central line	143	1	**143**	YR42A	
	Surgical disposables	1056.96	1	**1056.96**	ABC from theatre clinical leader	
Recovery	chest Xray	40	1	**40**		
Critical care (PACU)	Bed/day	718	1	**718**	XC07Z	
	SCP 20 mins	44	0.3	**13.2**	PSSRU	
	Cons r/v	137	0.3	**41.1**	PSSRU	
Post-op day 2-7	jej feed	16.97	6	**101.82**	BNF	Jevity 1.5kcal 1500ml, 231
	Dietetic R/v	8.25	5	**41.25**	PSSRU	33x0.25
	Paracetamol	4.8	7	**33.6**	BNF	1.2x4 doses per day=£4.8
	Tramadol	4	5	**20**		1x4 doses per day=£4
	Antiemetics	23	2	**46**	BNF	£7.67 per 4mg dose x 3/d
	Pain team	10.5	6	**63**	PSSRU	35x0.3
	epidural (5 days)	21.78	5	**108.9**	BNF	bupivacaine only
	Bloods	7	7	**49**		
	CNS r/v	13.2	5	**66**		44x0.3=13.2
	Physio walk/respiratory exercises	9.9	5	**49.5**		33x0.3=9.9
	Cons r/v alt. day	34.25	4	**137**		137x0.25=34.25

Contrast swallow		141	1	**141**	RD30Z	
Days 8 to 13	at excess bed day cost					
Hospital discharge	Discharge advice CNS	44	0.25	**11**	PSSRU	
	Extended VTE	3.03	28	**84.84**	BNF	
	Jej feed training (SN/dietician)	33	0.25	**8.25**	PSSRU	
Follow up phone call	CNS	44	0.3	**13.2**	PSSRU	
Histology		31	1	**31**	DAPS02	
MDT discussion		139	1	**139**	CMDTSPU	
District nurse visit		38	1	**38**	PSSRU	
Outpatient clinic appt	at 2 weeks	122	1	**122**	WF01A	
Removal of feeding tube	CNS	44	0.3	**13.2**	PSSRU	10 mins
Outpatient clinic appt	6/52 or 3/12 (3 in first year post-op - onc or surg)	122	3	**366**	WF01A	
	CNS R/v in clinic	13.2	3	**39.6**	PSSRU	44x 0.3
Chemotherapy	Epirubicin (E)	201.76	3	**605.28**	BNF	50mg/m2=92.5mg per do
	Cisplatin (C)	56.12	3	**168.36**	BNF	60mg/m2=111mg per dos
	Fluorouracil (F)	96	3	**288**	BNF	200mg/m2/day for 21 day
	Antiemetics	23.38	3	**70.14**	BNF	
	Initial dose delivery	503	1	**503**	SB12Z+SB14Z	
	subsequent dose deliveries	212	2	**424**	SB15Z	
	PICC line insertion	329	1	**329**	YR42A	
	Bloods	7	3	**21**		
				22926.05		

Appendix 2 (c): Costs of oesophagectomy with perioperative chemoradiotherapy

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	
	A&E admission	36-342	0			
Endoscopy	Open access	339	1	339	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	34.25	PSSRU	
	Specialist nurse	44	0.5	22	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
Staging CT		121	1	121	RD26Z	
Local MDT discussion		139	1	139	CMDTSPU	
O/P appt	Consultant-led	153	1	153	WF01B	
	CNS	44	0.3	13.2	PSSRU	
PET-CT		944	1	944	RN03A	
CPEX		347	1	347	DZ31Z	
EUS		604	1	604	GB13Z	
Regional MDT discussion		139	1	139	CMDTSPU	
CNS phone call		44	0.25	11	PSSRU	
Outpatient clinic appt	Oncology, new patient	197	1	197	WF01B	
	Dietitian	33	0.5	16.5	PSSRU	
Medications	Dietetic supplements	6	30	180	BNF	£2 per drink
Chemotherapy	Epirubicin (E)	201.76	3	605.28	BNF	50mg/m2=92.5mg per dose
	Cisplatin (C)	56.12	3	168.36	BNF	60mg/m2=111mg per dose

	Fluorouracil (F)	96	3	**288**	BNF	200mg/m2/day for 21 days = 370mg/day, 7770mg over 21 days
	Antiemetics	23.38	3	**70.14**	BNF	
	Initial dose delivery	503	1	**503**	SB12Z+SB14Z	
	subsequent dose deliveries	212	2	**424**	SB15Z	
	PICC line insertion	329	1	**329**	YR42A	
	Bloods	7	3	**21**		
Radiotherapy (as outpatient)	planning	655	1	**655**	SC51Z	
	cost per fraction	126	25	**3150**	SC23Z	
Re-staging CT		121	1	**121**	RD26Z	
MDT discussion		139	1	**139**	CMDTSPU	
Pre-operative assessment	CNS Assessment	44	2	**88**	PSSRU	
	Dietitian	33	0.5	**16.5**	PSSRU	
	Bloods	7	1	**7**	DAPS04,05, 08	
	ECG	40	1	**40**		
	Spirometry	112	0		DZ52Z	
Smoking cessation		22	0		DZ25Z	
Physiotherapist		33	0.5	**16.5**	PSSRU	
Oesophagectomy	with 5 day stay	8440	1	**8440**	FZ80E	
excess bed days		244	8	**1952**	FZ80E	
Inpatient medications	Enoxaparin	3.03	10	**30.3**	BNF	
	AEStockings	10	1	**10**	Amazon	
	CHO loading	2.06	2	**4.12**	BNF	
Anaesthetic pre-op assessment	20 mins	137	0.3	**41.1**	PSSRU	

Intraoperative medications	Coamoxyclav	10.6	1	**10.6**	BNF	
	Metronidazole	62	1	**62**	BNF	
Anaesthetic	Fentanyl	27.9	1	**27.9**	BNF	100mcg
	Muscle relaxant (Rocuronium)	4.8	1	**4.8**	BNF	42mg induction, up to 5mg maintenance
	Propofol	3.07	1	**3.07**	BNF	Induction 1.5mg/kg=105mg, 200mg (20ml)
	Ondansetron	11.69	1	**11.69**	BNF	8mg/4ml IV
	Dexamethasone	1.99	1	**1.99**	BNF	3.8mg/ml
	Neostigmine/Glycopyronium	2.3	1	**2.3**	BNF	£1.15/ml, 2ml given
	Sevoflurane	30.75	1	**30.75**	BNF	123/250ml, lasts 4 days
Equipment	Central line	143	1	**143**	YR42A	
	Surgical disposables	1056.96	1	**1056.96**	ABC from theatre clinical leader	
Recovery	chest Xray	40	1	**40**		
Critical care (PACU)	Bed/day	718	1	**718**	XC07Z	
	SCP 20 mins	44	0.3	**13.2**	PSSRU	
	Cons r/v	137	0.3	**41.1**	PSSRU	
Post-op day 2-7	jej feed	16.97	6	**101.82**	BNF	Jevity 1.5kcal 1500ml, 2310kcal/day
	Dietetic R/v	8.25	5	**41.25**	PSSRU	33x0.25
	Paracetamol	4.8	7	**33.6**	BNF	1.2x4 doses per day=£4.80
	Tramadol	4	5	**20**		1x4 doses per day=£4
	Antiemetics	23	2	**46**	BNF	£7.67 per 4mg dose x 3/day= £23
	Pain team	10.5	6	**63**	PSSRU	35x0.3
	epidural (5 days)	21.78	5	**108.9**	BNF	bupivacaine only
	Bloods	7	7	**49**		
	CNS r/v	13.2	5	**66**		44x0.3=13.2

	Physio walk/respiratory exercises	9.9	5	**49.5**		33x0.3=9.9
	Cons r/v alt. day	34.25	4	**137**		137x0.25=34.25
Contrast swallow		141	1	**141**	RD30Z	
Days 8 to 13	at excess bed day cost					
Hospital discharge	Discharge advice CNS	44	0.25	**11**	PSSRU	
	Extended VTE	3.03	28	**84.84**	BNF	
	Jej feed training (SN/dietician)	33	0.25	**8.25**	PSSRU	
Follow up phone call	CNS	44	0.3	**13.2**	PSSRU	
Histology		31	1	**31**	DAPS02	
MDT discussion		139	1	**139**	CMDTSPU	
District nurse visit		38	1	**38**	PSSRU	
Outpatient clinic appt	at 2 weeks	122	1	**122**	WF01A	
Removal of feeding tube	CNS	44	0.3	**13.2**	PSSRU	10 mins
Outpatient clinic appt	6/52 or 3/12 (3 in first year post-op - onc or surg)	122	3	**366**	WF01A	
	CNS R/v in clinic	13.2	3	**39.6**	PSSRU	44x 0.3
Chemotherapy	Epirubicin (E)	201.76	3	**605.28**	BNF	50mg/m2=92.5mg per dose
	Cisplatin (C)	56.12	3	**168.36**	BNF	60mg/m2=111mg per dose
	Fluorouracil (F)	96	3	**288**	BNF	200mg/m2/day for 21 days = 370mg/day, 7770mg over 21 days
	Antiemetics	23.38	3	**70.14**	BNF	
	Initial dose delivery	503	1	**503**	SB12Z+SB14Z	
	subsequent dose deliveries	212	2	**424**	SB15Z	
	PICC line insertion	329	1	**329**	YR42A	
	Bloods	7	3	**21**		

				26731.05		

Appendix 2 (d): Costs of oesophagectomy alone

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	
	A&E admission	36-342	0	0		
Endoscopy	Open access	339	1	339	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	34.25	PSSRU	
	Specialist nurse	44	0.5	22	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
Staging CT		121	1	121	RD26Z	
Local MDT discussion		139	1	139	CMDTSPU	
O/P appt	Consultant-led	153	1	153	WF01B	
	CNS	44	0.3	13.2	PSSRU	
PET-CT		944	1	944	RN03A	
CPEX		347	1	347	DZ31Z	
EUS		604	1	604	GB13Z	
Regional MDT discussion		139	1	139	CMDTSPU	
CNS phone call		44	0.25	11	PSSRU	
Outpatient clinic appt	Surgical, new patient	147	1	147	WF01B	
	Dietitian	33	0.5	16.5	PSSRU	
Medications	Dietetic supplements	6	30	180	BNF	£2 per drink

Pre-operative assessment	CNS Assessment	44	2	**88**	PSSRU	
	Dietitian	33	0.5	**16.5**	PSSRU	
	Bloods	7	1	**7**	DAPS04,05, 08	
	ECG	40	1	**40**		
	Spirometry	112	0	**0**	DZ52Z	
Smoking cessation		22	0	**0**	DZ25Z	
Physiotherapist		33	0.5	**16.5**	PSSRU	
Oesophagectomy	with 5 day stay	8440	1	**8440**	FZ80E	
excess bed days		244	8	**1952**	FZ80E	
Inpatient medications	Enoxaparin	3.03	10	**30.3**	BNF	
	AEStockings	10	1	**10**	Amazon	
	CHO loading	2.06	2	**4.12**	BNF	
Anaesthetic pre-op assessment	20 mins	137	0.3	**41.1**	PSSRU	
Intraoperative medications	Coamoxyclav	10.6	1	**10.6**	BNF	
	Metronidazole	62	1	**62**	BNF	
Anaesthetic	Fentanyl	27.9	1	**27.9**	BNF	100mcg
	Muscle relaxant (Rocuronium)	4.8	1	**4.8**	BNF	42mg induction, up to 5mg maintenance
	Propofol	3.07	1	**3.07**	BNF	Induction 1.5mg/kg=105mg, 200mg (20ml)
	Ondansetron	11.69	1	**11.69**	BNF	8mg/4ml IV
	Dexamethasone	1.99	1	**1.99**	BNF	3.8mg/ml
	Neostigmine/Glycopyronium	2.3	1	**2.3**	BNF	£1.15/ml, 2ml given
	Sevoflurane	30.75	1	**30.75**	BNF	123/250ml, lasts 4 days

Equipment	Central line	143	1	143	YR42A	
	Surgical disposables	1056.9 6	1	1056.96	ABC from theatre clinical leader	
Recovery	chest Xray	40	1	40		
Critical care (PACU)	Bed/day	718	1	718	XC07Z	
	SCP 20 mins	44	0.3	13.2	PSSRU	
	Cons r/v	137	0.3	41.1	PSSRU	
Post-op day 2-7	jej feed	16.97	6	101.82	BNF	Jevity 1.5kcal 1500ml, 2310kcal/day
	Dietetic R/v	8.25	5	41.25	PSSRU	33x0.25
	Paracetamol	4.8	7	33.6	BNF	1.2x4 doses per day=£4.80
	Tramadol	4	5	20		1x4 doses per day=£4
	Antiemetics	23	2	46	BNF	£7.67 per 4mg dose x 3/day= £23
	Pain team	10.5	6	63	PSSRU	35x0.3
	epidural (5 days)	21.78	5	108.9	BNF	bupivacaine only
	Bloods	7	7	49		
	CNS r/v	13.2	5	66		44x0.3=13.2
	Physio walk/respiratory exercises	9.9	5	49.5		33x0.3=9.9
	Cons r/v alt. day	34.25	4	137		137x0.25=34.25
Contrast swallow		141	1	141	RD30Z	
Days 8 to 13	at excess bed day cost			0		
Hospital discharge	Discharge advice CNS	44	0.25	11	PSSRU	
	Extended VTE	3.03	28	84.84	BNF	
	Jej feed training (SN/dietician)	33	0.25	8.25	PSSRU	
Follow up phone call	CNS	44	0.3	13.2	PSSRU	
Histology		31	1	31	DAPS02	

MDT discussion		139	1	139	CMDTSPU	
District nurse visit		38	1	38	PSSRU	
Outpatient clinic appt	at 2 weeks	122	1	122	WF01A	
Removal of feeding tube	CNS	44	0.3	13.2	PSSRU	10 mins
Outpatient clinic appt	6/52 or 3/12 (3 in first year post-op - onc or surg)	122	3	366	WF01A	
	CNS R/v in clinic	13.2	3	39.6	PSSRU	44x 0.3
				17798.49		

Appendix 2 (e): Costs of definitive chemoradiotherapy for oesophageal cancer

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	
	A&E admission	36-342	0			
Endoscopy	Open access	339	1	339	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	34.25	PSSRU	
	Specialist nurse	44	0.5	22	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
Staging CT		121	1	121	RD26Z	
Local MDT discussion		139	1	139	CMDTSPU	
O/P appt	Consultant-led	153	1	153	WF01B	
	CNS	44	0.3	13.2	PSSRU	
PET-CT		944	1	944	RN03A	

EUS		604	1	**604**	GB13Z	
Regional MDT discussion		139	1	**139**	CMDTSPU	
CNS phone call		44	0.25	**11**	PSSRU	
Outpatient clinic appt	Oncology, new patient	197	1	**197**	WF01B	
	Dietitian	33	0.5	**16.5**	PSSRU	
Medications	Dietetic supplements	6	30	**180**	BNF	£2 per drink
	Oramorph	0.378	35	**13.23**	BNF	5ml 4 times a day for 5 weeks
	Omeprazole	0.7	35	**24.5**	BNF	
	Mucilage			**0**		
	Chlorhexidine mouthwash	1.99	1	**1.99**	BNF	
Chemotherapy	Epirubicin (E)	201.76	0	**0**	BNF	50mg/m2=92.5mg per dose
	Cisplatin (C)	56.12	4	**224.48**	BNF	60mg/m2=111mg per dose
	Fluorouracil (F)	96	4	**384**	BNF	200mg/m2/day for 21 days = 370mg/day, 7770mg over 21 days
	Antiemetics	23.38	4	**93.52**	BNF	
	Initial dose delivery	503	1	**503**	SB12Z+SB14Z	
	subsequent dose deliveries	212	3	**636**	SB15Z	
	PICC line insertion	329	1	**329**	YR42A	
	Bloods	7	4	**28**		
	Outpatient review	163	4	**652**		
Radiotherapy (as outpatient)	planning	655	1	**655**	SC51Z	
	cost per fraction	126	25	**3150**	SC23Z	
CT scan at 3 months		121	1	**121**	RD26Z	
Outpatient clinic appt	after CT	163	1	**163**	WF01A	

Outpatient clinic appt	6/52 or 3/12 - 3 in first year post-dCRT	163	3	489	WF01A	
	CNS R/v in clinic	13.2	3	39.6	PSSRU	44x 0.3
				10472.77		

Appendix 2 (f): Costs of palliative chemotherapy for oesophageal cancer

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	
	A&E admission	36-342	0			
Endoscopy	Open access	339	1	339	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	34.25	PSSRU	
	Specialist nurse	44	0.5	22	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
Staging CT		121	1	121	RD26Z	
Local MDT discussion		139	1	139	CMDTSPU	
O/P appt	Consultant-led	153	1	153	WF01B	
	CNS	44	0.3	13.2	PSSRU	
Outpatient clinic appt	Oncology, new patient	197	1	197	WF01B	
	Dietitian	33	0.5	16.5	PSSRU	
Medications	Dietetic supplements	6	30	180	BNF	£2 per drink
Palliative chemotherapy	Epirubicin (E)	201.76	4	807.04	BNF	50mg/m2=92.5mg per dose

	Cisplatin (C)	56.12	4	224.48	BNF	60mg/m2=111mg per dose
	Fluorouracil (F)	96	4	384	BNF	200mg/m2/day for 21 days = 370mg/day, 7770mg over 21 days
	Antiemetics	23.38	4	93.52	BNF	
	Initial dose delivery	503	1	503	SB12Z+SB14Z	
	subsequent dose deliveries	212	3	636	SB15Z	
	PICC line insertion	329	1	329	YR42A	
	Bloods	7	4	28		
Medications	Analgesia	4.54	30	136.2	for 1 month	Diamorph £4.54/10mg
	Antiemtics	8.12	30	243.6	"	cyclizine £8.12 for 150mg
	Anxiolytic	0.585	30	17.55	"	midazolam 58.5p/10mg
	Syringe driver pump hire			0		£1000-1500 initial cost
Community Palliative care	Initial visit	52	0.5	26	Band 7 nurse	
	Monthly	52	0.6	31.2		0.3 x 2
	twice/week in last month	52	2.4	124.8		0.3 x 8
District nurse visit	twice/day for last month	38	60	2280	PSSRU	
GP home visit		236	0.5	118	PSSRU	
				7249.84		

Appendix 2 (g): Costs of palliative radiotherapy for oesophageal cancer

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	36	PSSRU	

	A&E admission	36-342	0			
Endoscopy	Open access	339	1	339	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	34.25	PSSRU	
	Specialist nurse	44	0.5	22	PSSRU	
	Dietitian	33	0.5	16.5	PSSRU	
Staging CT		121	1	121	RD26Z	
Local MDT discussion		139	1	139	CMDTSPU	
O/P appt	Consultant-led	153	1	153	WF01B	
	CNS	44	0.3	13.2	PSSRU	
Medications	Dietetic supplements	6	120	720	BNF	£2 per drink
Palliative radiotherapy (as outpatient)	planning	462	1	462	SC48Z	
	cost per fraction	108	1	108	SC22Z	
	Bloods	7	4	28		
Medications	Analgesia	4.54	30	136.2	for 1 month	Diamorph £4.54/10mg
	Antiemetics	8.12	30	243.6	"	cyclizine £8.12 for 150mg
	Anxiolytic	0.585	30	17.55	"	midazolam 58.5p/10mg
	Syringe driver pump hire			0		£1000-1500 initial cost
Community Palliative care	Initial visit	52	0.5	26	Band 7 nurse	
	Monthly	52	1.2	62.4		0.3 x 4
	twice/week in last month	52	2.4	124.8		0.3 x 8
District nurse visit	twice/day for last month	38	60	2280	PSSRU	
GP home visit		236	0.5	118	PSSRU	
				5200.5		

Appendix 2 (h): Costs of Best Supportive Care for oesophageal cancer

Column1	Column2	Unit cost 2016	No. of units	Total cost (£)	Code/Source	Notes
Mode of presentation	GP referral	36	1	**36**	PSSRU	
	A&E admission	36-342	0			
Endoscopy	Open access	339	1	**339**	FZ61Z	includes biopsy processing
Counselling/diagnosis	Endoscopist	137	0.25	**34.25**	PSSRU	
	Specialist nurse	44	0.5	**22**	PSSRU	
	Dietitian	33	0.5	**16.5**	PSSRU	
Staging CT		121	1	**121**	RD26Z	
Local MDT discussion		139	1	**139**	CMDTSPU	
O/P appt	Consultant-led	153	1	**153**	WF01B	
	CNS	44	0.3	**13.2**	PSSRU	
Medications	Dietetic supplements	6	120	**720**	BNF	£2 per drink
Medications	Analgesia	4.54	30	**136.2**	for 1 month	Diamorph £4.54/10mg
	Antiemetics	8.12	30	**243.6**	"	cyclizine £8.12 for 150mg
	Anxiolytic	0.585	30	**17.55**	"	midazolam 58.5p/10mg
	Syringe driver pump hire			**0**		£1000-1500 initial cost
Community Palliative care	Initial visit	52	0.5	**26**	Band 7 nurse	
	Monthly	52	0.9	**46.8**		0.3 x 3
	twice/week in last month	52	2.4	**124.8**		0.3 x 8

District nurse visit	twice/day for last month	38	60	2280	PSSRU	
GP home visit		236	0.5	118	PSSRU	
				4586.9		

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