Management of early neoplastic changes in the oesophagus in England

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Abstract

Oesophageal cancer is the 13th most common cancer in the UK, but 6th most common cause of cancer death with only 15% of patients surviving 5 years (1). The disparity between incidence and mortality is due to the fact that a large proportion of oesophageal cancers are diagnosed at a late stage (2).

This thesis aims to investigate the patterns of management and outcomes associated with the treatment of early neoplastic changes in the oesophagus in England, in order to try and identify areas where care may be improved. Four separate studies were performed on i) the management of high grade dysplasia (HGD) in England, ii) the proportion of oesophageal cancers missed at endoscopy, iii) the management and outcomes for early oesophageal cancer and iv) the safety and efficacy of radiofrequency ablation and complete endoscopic resection in the management of dysplastic Barrett's oesophagus . These studies (expect study iv, which is a systematic review) were performed by linking three national databases, the National Oesophago-Gastric Cancer database, Hospital Episode Statistics and Office for National Statistics mortality data.

The results of our studies highlight, that 1. a third of patients with HGD are managed by surveillance alone, with patients treated in low volume centres more likely to be managed in this manner, 2. a substantial proportion of cancers were missed at endoscopy, 3. only 6.8% of oesophageal cancers were diagnosed at an early stage, but two thirds of these patients survived 5 years if managed curatively 4. radiofrequency ablation should be used in preference to complete endoscopic resection in the management of dysplastic Barrett's. Therefore there is still substantial room to improve the quality of care received by patients with early neoplastic changes in the oesophagus in England.

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Declaration

The work contained in this thesis is my own and was performed by myself. In the process of carrying out this work, other individuals were involved. My supervisors, Dr Oliver Groene, Professor George Hanna, Dr Jonathan Hoare and Dr Stuart Riley provided direction and advice with conception, design and editing of the studies included in this thesis. While other members of the NOGCA project team including Dr David Cromwell, Mr Richard Hardwick and Dr Tom Crosby provided additional statistical and clinical input. Mr Sheraz Markar acted as second reviewer for the articles included in the systematic review.

A proportion of the NOGCA data was collected before I started as research fellow for the audit.

All other work is appropriately referenced.

Copyright Declaration

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Publications

Publications directly resulting from thesis

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Chadwick G, Groene O, Markar SR, Hoare J, Cromwell D, and Hanna GB. Systematic review comparing radiofrequency ablation and complete endoscopic resection in treating dysplastic Barrett's esophagus: a critical assessment of histologic outcomes and adverse events**.** **Gastrointestinal Endoscopy**. 2014;79(5):718-31.

Chadwick G, Groene O, Hoare J, Hardwick RH, Riley S, Crosby TD, et al. A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy. **Endoscopy.** 2014;46(7):553-60.

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Groene O, ***Chadwick G***, Riley S, Hardwick RH, Crosby T, Greenaway K, et al. Re-organisation of oesophago-gastric cancer services in England and Wales: a follow-up assessment of progress and remaining challenges. BMC research notes. 2014;7:24.

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Posters and Presentations (*Oral Presentations)

Chadwick G, Groene O, Riley S, Hardwick RH, Crosby T, Greenaway K, and Cromwell D. Outcomes after curative treatment for oesophago-gastric cancer in the elderly. DDF. London. 2015.

Chadwick G, Groene O, Riley S, Hardwick RH, Crosby T, Greenaway K, and Cromwell D. Management of dysphagia in patients with oesophageal cancer. DDF. London. 2015.

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Abbreviations

5- ALA – 5-aminolevulinic acid

ACA - Adenocarcinoma

AGA – American Gastroenterological Association

ASA – American Society of Anaesthesiologists

APC – Argon plasma coagulation

AUGIS - The Association of Upper Gastro-Intestinal Surgeons

BMI – Body mass index

BSG – British Society of Gastroenterologists

CaNISC - Cancer Network Information System Cymru

CE-D - Complete eradication of dysplasia

CE-IM – Complete eradication of intestinal metaplasia

CEMR – Complete endoscopic mucosal resection

CEU - Clinical Effectiveness Unit

CRG - Clinical Reference Group

CRT - Chemoradiotherapy

CT – Computer tomography

ECOG - Eastern Cooperative Oncology Group

EMR – Endoscopic mucosal resection

ESD - Endoscopic submucosal dissection

EUS – Endoscopic ultrasound

GI – Gastro-intestinal

GOJ – Gastro-oesophageal junction

GP – General Practitioner

HGD – High grade dysplasia

HRE – High resolution endoscopy

HQIP - Healthcare Quality Improvement Partnership

HSCIC – Health and Social Care Information Centre

ICD-10 - International Classification of Diseases, 10th edition

IM – Intestinal metaplasia

IMC – Intramucosal cancer

IQR – Inter-quartile range

ITT- Intention to treat

JAG - Joint Advisory Group

LGD – Low grade dysplasia

LSHTM - London School of Hygiene and Tropical Medicine

LVI - Lymphovascular invasion

MDT – Multi-disciplinary team meeting

NA – Not applicable

NCASP - The National Clinical Audit Support Program

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

NOGCA – National Oesophago-Gastric Cancer Audit

NR – Not reported

NSCJ – Neosquamous columnar junction

OG – Oesophago-gastric

OGD – Oesophago-gastro duodenoscopy

ONS – Office for National Statistics

OPCS - Office of Population Censuses and Surveys Classification

OR – Odds ratio

PDT – Photodynamic therapy

PET – Positron Emission Tomography

PPI – Proton pump inhibitor

RCR - The Royal College of Radiologists

RCS - The Royal College of Surgeons of England

RCT – Randomised controlled trial

RFA – Radio-frequency ablation

SCC – Squamous cell cancer

SCN – Strategic clinical network

SD – Standard deviation

SEER – Surveillance Epidemiology and End Results

SNOWMED - Systematized Nomenclature of Medicine

UGI – Upper gastro-intestinal

UICC - Union for International Cancer Control Classification

UK – United Kingdom

US – United States

95% CI – 95% confidence interval

1. Introduction

Oesophageal cancer is the 13th most common cancer in the UK, with 8,332 cases diagnosed in 2011 (1). Its incidence in the UK is the second highest in Europe for men and the highest for women (1). Furthermore the incidence of oesophageal cancer is rising steadily, such that between 1975-77 there were 8.8 cases per 100,000 population, but by 2006-8 this figure had increased to 14.5 per 100,000 (1). It is therefore concerning that in the UK only 15% of patients diagnosed with oesophageal cancer survive 5 years (1). The disparity between the incidence and mortality of oesophageal cancer in the UK is due to the fact that a large proportion of oesophageal cancers are diagnosed at a late stage (2). It is therefore very important that increased focus goes into the diagnosis and management of early stage oesophageal cancers.

In recent years a number of studies have raised concerns about overall cancer outcomes in the UK compared to other countries with similar health care systems and wealth (3-6). As a result the UK government has been taking steps to improve cancer outcomes (7, 9-11), including increasing GP access to diagnostic tests, improving timely access to specialist clinics and centralising cancer services, in order to try and reduce the inherent delays in diagnosis and treatment.

Nonetheless key to substantially improving outcomes for oesophageal cancer in England is increasing the proportion of patients diagnosed with oesophageal cancer at an early stage, and optimising the management of these patients. This thesis therefore aims to investigate in greater detail the patterns of management and outcomes associated with the treatment of early neoplastic changes in the oesophagus in England in order to try and identify areas where care may be improved in future.

This chapter aims to provide an overview of the current management of oesophageal cancer and high grade dysplasia of the oesophagus, and the organisation of oesophageal cancer services in England. The chapter concludes by identifying current gaps in the literature, and summarises the research that will be performed in this thesis to address these gaps.

1.1 Oesophageal cancer

1.1.1 Types of cancer

There are two main histological subtypes of oesophageal cancer, adenocarcinomas (ACA) and squamous cell cancers (SCC). Oesophageal ACAs currently account for over half of cases of oesophageal cancer in England, with SCCs accounting for a quarter, the remainder are made up of undifferentiated cancers, endocrine tumours, gastro-intestinal stromal tumours and a variety of other rarer tumours (1). These proportions are changing though, with a marked increase in the

incidence of oesophageal ACAs over the last 20 years, while the incidence of oesophageal SCCs has remained relatively stable (1).

The work in this thesis will focus on oesophageal adenocarcinomas specifically, because these have a defined pre-malignant stage and make up the majority of oesophageal cancers in England. There is therefore the greater scope to improve patient outcomes for oesophageal adenocarcinoma in England.

1.1.2 Tumour classification

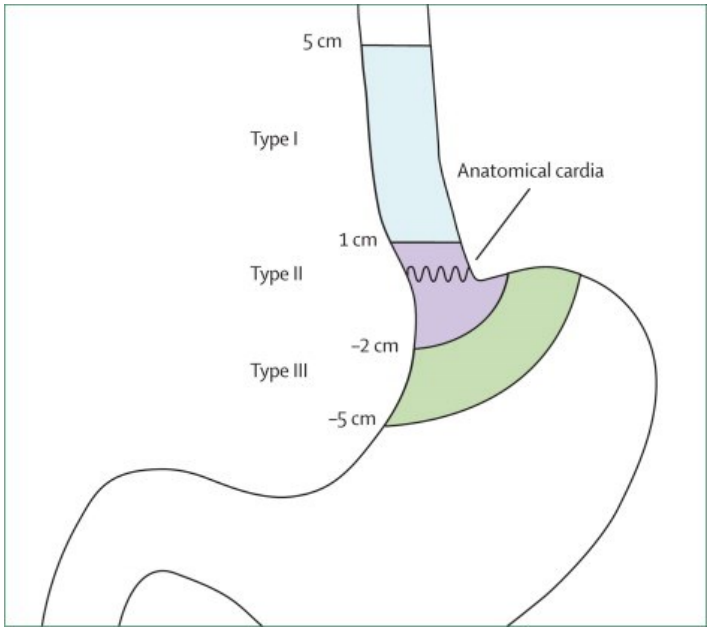
Oesophageal cancers can be sub-classified according to the site of the tumour using the International Classification of Diseases (ICD-10). This classifies oesophageal cancers based on either their anatomical site, or the third of the oesophagus in which they arise (**Table 1-1**) (12).

Table 1-1 ICD-10 classification for oesophageal and gastro-oesophageal junction cancers

ICD-10 code	Description
C15.0	Cervical part of oesophagus
C15.1	Thoracic part of oesophagus
C15.2	Abdominal part of oesophagus
C15.3	Upper third of oesophagus
C15.4	Middle third of oesophagus
C15.5	Lower third of oesophagus
C15.8	Overlapping lesion of oesophagus
C15.9	Oesophagus, unspecified

Gastro-oesophageal junction tumours can be further sub classified according to the Siewert classification (13). This assigns lesions into three groups, determined by the distance between the centre of the tumour and the anatomical cardia (**Figure 1-1**)(14).

Figure 1-1 Schematic illustration of the modified Siewert's classification (14)



The most recent National Oesophago-Gastric Cancer Audit (NOGCA) reported that in England and Wales, 64.9% of oesophageal cancers affect the lower oesophagus, with 27.2% affecting the middle third and only 7.9% affecting the top third (15).

1.1.3 Patient characteristics

Throughout most of the Western world the male to female sex ratio for oesophageal ACAs is in excess of 4:1 (16). There is also a strong association with age at diagnosis, such that between 2009-11 83% of patients were aged over 60 at diagnosis and 42% were over 75 (1) **(Table 1-2)**. Other patient characteristics associated with higher rates of oesophageal cancer include socio-economic deprivation (rates are over 40% higher in the most deprived areas compared the least deprived areas) (17) and white ethnicity (versus Asian and Black) (18).

Table 1-2 Summary of patient characteristics by tumour site

	Oesophageal ACA Upper	Oesophageal ACA Lower / Siewert I	GOJ ACA Siewert II/ III
Number of patients			
Total, n (%)	1,392 (8.8%)	7,171 (45.1%)	2,765 (17.4%)
Women, n	378	1,443	601
Men, n	1,012	5,717	2,155
Ratio women to men	1:2.7	1:4.0	1:3.6
Median age, years			
Women	78	74	74
Men	72	69	70
Performance Status[1] ≥3, %	16.3	11.8	10.4
Patient with ≥1 comorbidity, %	29.3	35.7	33.9

Data comes from the NOGCA 2014 Annual Report (2)

[1] European Cooperative Oncology Group (ECOG) score for performance status in cancer patients

1.1.4 Risk factors

Risk factors for oesophageal cancer can be divided into non-modifiable risk factors such as age and sex, and modifiable risk factors e.g. smoking.

In the UK it has been estimated that 89% of all oesophageal cancers are associated with potentially avoidable lifestyle factors including smoking, obesity and alcohol. These are reported to be linked to 65.5%, 21.7% and 20.6% of all cases of oesophageal cancer respectively (19).

Oesophageal cancer has also been linked to a number of specific diseases including Barrett's oesophagus, gastro-oesophageal reflux disease, gastric atrophy, diabetes and asthma (1). The next section goes on to explore Barrett's oesophagus in greater depth.

1.1.4.1 Barrett's oesophagus

Barrett's oesophagus can be defined as (20):

'..an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥1cm) above the gastro-oesophageal junction and confirmed histopathologically from oesophageal biopsies..'

It was first described in 1950 by Norman Barrett (21), and was soon shown to be an acquired condition which developed in the presence of chronic gastro-oesophageal reflux (22). By 1975 a link

with oesophageal cancer was established (23), and in 1978 Haggitt et al proposed that Barrett's oesophagus was a frequent precursor of oesophageal adenocarcinoma (24). Subsequent studies have shown that the risk of oesophageal cancer is up to 11 times higher in patients with Barrett's oesophagus compared to the general population (25).

It is difficult to accurately determine the true incidence and prevalence of Barrett's oesophagus, due to the need to perform an endoscopy to diagnose it. Two studies have attempted to establish the prevalence of Barrett's oesophagus in Europe. The first was conducted in Italy and recruited participants from two villages, this study had a 66.5% response rate and estimated the prevalence of Barrett's oesophagus was 1.3% (26). The other study was conducted in two small communities in Sweden and randomly selected 1 in 7 inhabitants to participate, this study had a 73% response rate and estimated the prevalence of Barrett's oesophagus to be 1.6% (27). Both studies acknowledged the risk of selection bias in their results, as symptomatic patients were more likely to have participated and agreed to undergo an endoscopy. Among populations with a history of reflux the prevalence of Barrett's oesophagus is much higher with one study reporting that 12.4% of patients with a history of reflux had Barrett's oesophagus (28), on the flip side it is important to realise that 46.2% of patients with Barrett's oesophagus have no history of reflux (26). Recent studies have suggested that the incidence of Barrett's oesophagus is rising, with one study performed in the UK reporting that the incidence had risen from 0.11 to 0.24/1000 population in men and from 0.06 to 0.11/1000 in women between 1996 and 2005 (29).

As discussed previously Barrett's oesophagus is a recognised pre-malignant condition for oesophageal adenocarcinoma (23, 24, 30). However, reported rates for the progression of non dysplastic Barrett's oesophagus to invasive cancer vary widely. While initial studies suggested rates of 4-5 per 1000 person years (31, 32), more recent studies have suggested much lower rates, 1.2-1.3 per 1000 patient years (0.1% per year) (25, 33).

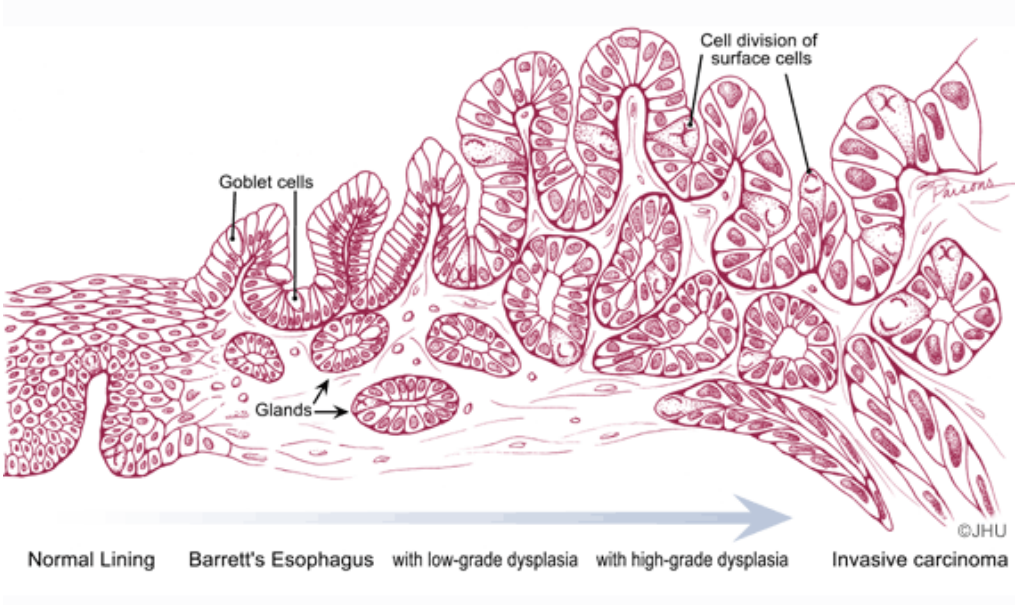
Extensive research has therefore gone into investigating the factors associated with an increased risk of progression to cancer. While there is little debate about the impact of some risk factors such as the presence of dysplasia, the relative importance of others remains controversial. Some of the key factors associated with the risk of progression are reviewed below.

Studies have consistently reported much higher risks of progression to cancer where there is evidence of more severe dysplasia within the Barrett's segment. Dysplasia is defined as the presence of unequivocal neoplastic epithelium strictly confined within the basement membrane of the gland from which it arises (34). The significance of increasing severity of dysplasia was

demonstrated in a study by Montgomery et al who asked 12 pathologists to each grade the degree of dysplasia present in 138 Barrett's oesophagus specimens on two occasions. They reported that the risk of progression to cancer during follow up increased from 0% for non dysplastic Barrett's oesophagus, to 15% for low grade dysplasia (LGD), to 61% for high grade dysplasia (HGD) (after a median of 38.5, 24 and 13 months follow up, respectively) (35).

A substantially lower risk of progression was reported in a recent systematic review, this reported that the risk of progression to cancer was 5.6% per year if HGD was present (36). This compares to a reported risk of progression of only 0.1% per year if there was no evidence of dysplasia (25). These differences in the rates of progression are thought to be due to the fact that Barrett's oesophagus progresses sequentially through a dysplasia-carcinoma sequence before developing into cancer (**Figure 1-2**) (35, 37).

Figure 1-2 The morphological development of Barrett's oesophagus
(http://pathology2.jhu.edu/beweb/Definition.cfm)



However, it is important to realise that the grading of the degree of dysplasia present by pathologists can be subjective, and depends on both architectural changes (e.g. glandular distortion and crowding), and cytological changes including nuclear alterations (38). In order to try and standardise the classification of gastrointestinal neoplasia, the Vienna classification was developed with the aim of improving the uniformity of dysplasia reporting (**Table 1-3**) (39). Studies have since shown that where the diagnosis of dysplasia is confirmed by two pathologists the risk of progression to cancer is significantly higher than in cases where the second pathologist does not confirm the

diagnosis (40-42). As a result the British Society of Gastroenterologists (BSG) recommends that all diagnoses of dysplasia are confirmed by two specialist gastro-intestinal (GI) pathologists (20).

Table 1-3 Revised Vienna classification of gastrointestinal neoplasia

Category	Diagnosis
1	Negative for neoplasia
2	Indefinite for neoplasia
3	Mucosal low grade neoplasia Low grade adenoma Low grade neoplasia
4	Mucosal high grade neoplasia 4.1 High grade adenoma/dysplasia 4.2 Non-invasive carcinoma (carcinoma in situ) 4.3 Suspicious for invasive carcinoma 4.4 Intramucosal carcinoma
5	Submucosal invasion by carcinoma

Other factors thought to increase the risk of malignant progression in Barrett's oesophagus include the presence of intestinal metaplasia (IM) in the Barrett's segment and the length of the Barrett's segment. Studies have demonstrated that patients with an endoscopic diagnosis of Barrett's oesophagus and evidence of IM on oesophageal biopsy are at three times greater risk of progression to cancer compared to patients with no evidence of IM (33). As a result the US American Gastroenterological Association (AGA) guidelines for the diagnosis of Barrett's oesophagus require the presence of IM on oesophageal biopsies to confirm the diagnosis (43). There is concern though that IM may have been missed at initial endoscopy, Gatenby et al reported that after 10-years follow up more than 90% of patients initially diagnosed with Barrett's oesophagus without IM were later found to have IM (44). As a result the current BSG guidelines do not require histological confirmation of the presence of IM to confirm the diagnosis Barrett's oesophagus (20).

One final factor thought to impact on the risk of progression of Barrett's oesophagus is the length of the Barrett's segment. Length of Barrett's oesophagus is traditionally classified as short segment if <3cm and long segment if ≥3cm. Studies investigating the effect of the length of Barrett's segment on the risk of progression to cancer have compared short versus long segment disease. Three recent meta-analyses all demonstrated a trend towards increased cancer risk in long segments of Barrett's oesophagus, however the difference was not statistically significant (45-47).

1.1.5 Diagnosis

In order to confirm a diagnosis of oesophageal cancer a histological specimen must be obtained. Endoscopy (oesophago-gastro duodenoscopy, OGD) and biopsy is currently regarded as the investigation of choice for this purpose (48, 49).

OGDs are readily available in the UK with 680,000 patients undergoing an endoscopy in England each year (50), this equates to around 1% of the population. However, difficulty arises in deciding who to investigate for oesophageal cancer, because symptoms are frequently non-specific and occur in many people without malignant disease. Current UK guidelines recommend that General Practitioners (GPs) send patients for an urgent OGD for suspected cancer if they present with any of the following: chronic gastrointestinal bleeding, dysphagia, progressive unintentional weight loss, persistent vomiting, iron deficiency anaemia, epigastric mass or a suspicious barium meal result (51). These are known as 'alarm' symptoms and signs. The National Institute for Health and Care Excellence (NICE) guidelines also note that patients aged 55 or older should be referred for an urgent OGD if they present with unexplained and persistent recent-onset dyspepsia (51).

When performing an endoscopy it is important that biopsies are taken of any suspicious lesions, in order to confirm or refute the diagnosis of cancer. Studies have clearly demonstrated that increasing the number of biopsies taken at endoscopy increases the sensitivity of cancer diagnosis (52). As a result the UK guidelines recommend that a minimum of 6 biopsies are taken to achieve a diagnosis of malignancy in areas of oesophageal or gastric mucosal abnormality (48).

Despite being the gold standard investigation for the diagnosis of oesophageal cancer, previous studies have suggested that around one in ten oesophago-gastric (OG) cancers are potentially missed at initial endoscopy (53-59). These studies have looked at the proportion of patients diagnosed with oesophago-gastric cancer within 2-3 years of an endoscopic examination, based on the fact that progression of early cancers is thought to be slow (60, 61). These studies have reported miss rates of between 5.0% (57) and 14.3% (56) within 3 years of previous endoscopy. To date only one study has focused on oesophageal cancer specifically. This was a single centre study conducted in the US which found that 10/110 (9.1%) patients diagnosed with oesophageal cancer had had an endoscopy within 2 years of diagnosis (54). The results of previous studies are summarised in **Table 1-4**.

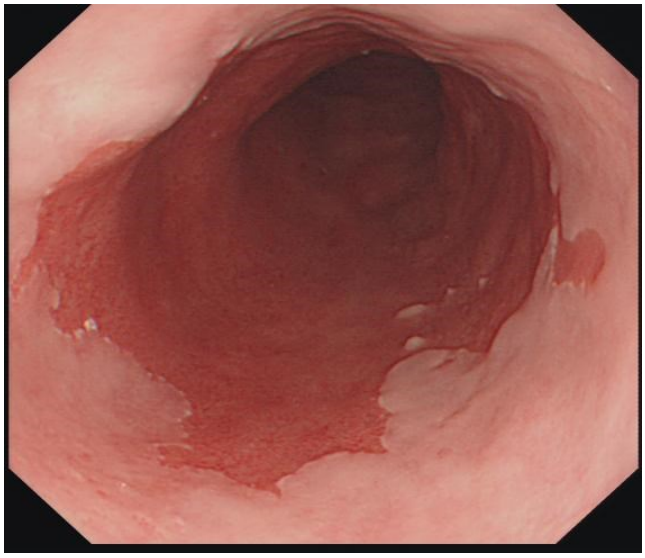
Table 1-4 Summary of results of previous studies looking at miss rates for oesophageal cancers

1st Author and Year	Country	Study Years	Study Design	Cancers identified	1 year miss rate	2 year miss rate	3 year miss rate
Raftopoulos 2010 (53)	Australia	1990-2004	Retrospective review of endoscopy database for all OG cancers at Sir Charles Gairdner Hospital in Perth	822	29/822 (3.5%)	NR	Additional 26/822 (3.2%) within 1-3 years. 55/822 (6.7%) within 3 years.
Bloomfield 2005 (54)	US	1997-2001	Retrospective review of tumour registry for oesophageal cancers only at Wake Forest University Baptist Medical Centre	110	6/110 (5.5%)	10/110 (9.1%)	NR
Yalamarthi 2004 (55)	Scotland	1994-2001	Retrospective review of endoscopy database for all OG cancers at Dumfries and Galloway Royal Infirmary	305	20/305 (6.6%)	NR	30/305 (9.8%)
Abstracts							
Cheung 2013 (56)	UK	1999-2007	Retrospective review of endoscopy database for all OG cancers at Sandwell General and City Hospital	524	42/524 (8.0%)	NR	Additional 33/524 (6.3%) within 1-3 years. 75/524 (14.3%) within 3 years.
Cheung 2013 (57)	UK	NR	Retrospective review of all oesophageal cancers submitted to UK Primary Care Database (THIN)	5354	NR	NR	266/5354 (5.0%)
Patel 2012 (58)	UK	2009-2010	Retrospective review of endoscopy database for OG cancers at Leeds Teaching Hospital	148	NR	NR	10/148 (6.8%) Excluded 6, diagnosed within 1 month of initial endoscopy.
Parsons 2010(59)	UK	2005-2009	Retrospective review of electronic hospital record for all cases OG cancer at Nottingham City Hospital	1075	NR	23/1075 (2.1%) Excluded 42, diagnosed within 3 months of initial endoscopy.	NR

1.1.5.1 Diagnosis of Barrett's oesophagus

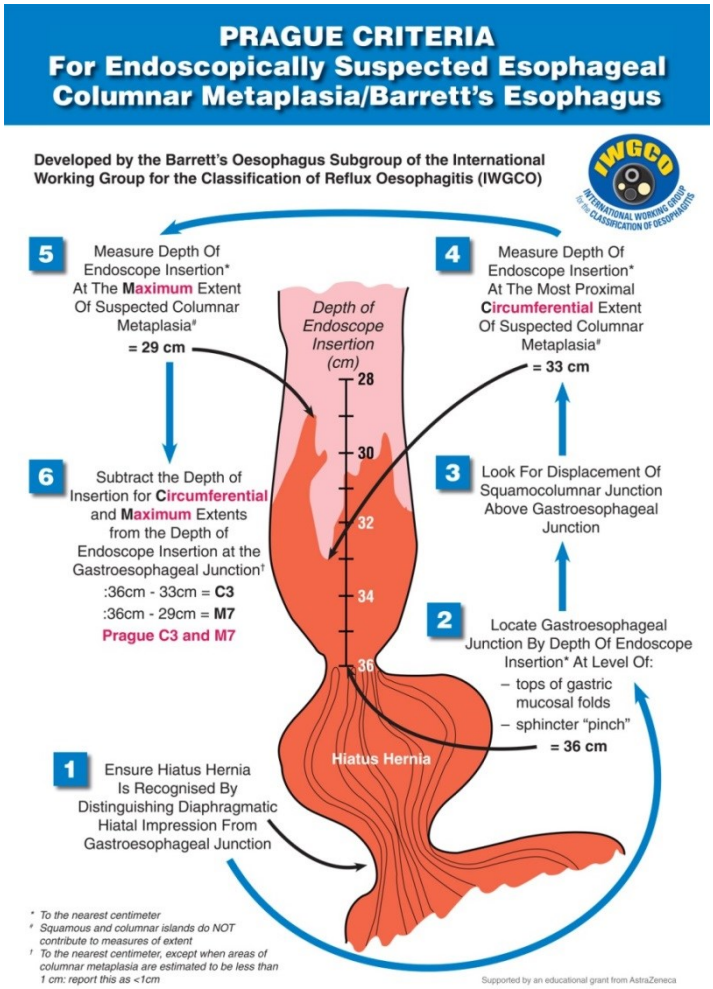
This can be identified at endoscopy as red velvety mucosa extending proximally from the gastro-oesophageal junction, replacing the normal squamous oesophageal mucosa which appears pale and shiny (**Figure 1-3**).

Figure 1-3 Barrett's oesophagus



Once identified, the extent of the Barrett's segment should be documented using the Prague criteria. This specifies both the circumferential ('C') length and the maximal ('M') length of endoscopically visible columnar lined oesophagus (62), and any more proximal islands of Barrett's oesophagus should also be noted separately (Figure 1-4).

Figure 1-4 Prague criteria for Barrett's oesophagus, developed by a Subgroup of the International Working Group for the Classification of Reflux Oesophagitis (IWGCO).
(http://www.iwgco.net/)



Having documented the extent of the Barrett's oesophagus it is important to assess whether there is any evidence of dysplasia. This is done in two stages, first the oesophagus needs to be carefully inspected for any visible nodules, then biopsies should be taken of any suspicious lesions with additional biopsies taken every 2cm from the segment of Barrett's oesophagus, in line with the 'Seattle protocol' recommended by the BSG (20). It is important to ensure this rigorous biopsy regimen is followed in order to optimise detection of dysplasia (63, 64).

Views of the mucosa need to be optimised to allow detection of subtle lesions, and numerous studies have looked at different approaches for improving this. A recent RCT showed that high resolution endoscopy (HRE) alone had 79% sensitivity in detecting HGD, and that the addition of indigo carmine chromoendoscopy or narrow band imaging increased the sensitivity to 93% and 86%, respectively (65). However, there are no RCTs comparing conventional endoscopy with high

resolution endoscopy in the detection of dysplastic Barrett's oesophagus. Current expert opinion suggests that HRE should be used as a minimum to inspect the mucosa in all patients with known Barrett's oesophagus (66), chromoendoscopy and narrow band imaging may provide useful adjuncts.

Most cases of HGD are diagnosed as a result of biopsies taken at routine endoscopy, performed either because the patient has developed new symptoms (52.9%) or as part of a Barrett's oesophagus surveillance program (39.4%) (15). Once a provisional diagnosis of HGD has been made, it is important to confirm the diagnosis with at least one other GI pathologist (20, 40) and consider performing a high-quality repeat endoscopy. The aim of this repeat endoscopy is to identify any additional lesions and plan further management. The importance of this repeat diagnostic endoscopy was highlighted by a study from Australia which demonstrated that a significant proportion of patients who were rescoped at a specialist centre were found to have additional lesions ($p<0.001$) and early cancers detected ($p=0.036$) at repeat endoscopy (67).

1.1.6 Staging

Once the initial diagnosis of oesophageal cancer has been made further staging investigations need to be performed to determine the extent of the disease, and assess whether it is potentially curable (48).

1.1.6.1 Staging Classification

Oesophageal cancers can be staged according the Union for International Cancer Control (UICC) TNM 6/7 Classification (68). This classification takes into account depth of tumour invasion (T stage), extent of lymph node involvement (N stage) and evidence of metastatic spread (M stage). This three pronged approach to staging is important because it reflects the fact that oesophageal cancer can spread via several different routes: direct invasion of adjacent structures, via the lymphatic channels, via the blood stream and by transcoelomic spread into the peritoneal cavity.

Table 1-5 outlines the current UICC classification and the slight differences between the two most recent versions, TNM 6 and TNM 7. One of the major changes seen with the introduction of TNM 7 was the ability to differentiate T1 tumours according to the degree of mucosal/submucosal invasion. This is very important when it comes to determining the most appropriate treatment regimen for early oesophageal cancers, as will be discussed later.

Table 1-5 TNM Classification for oesophageal cancers

	TNM 6	**TNM 7**
T	TX Primary tumour cannot be assessed. T0 No evidence of primary tumour. Tis Carcinoma *in situ* T1 Tumour invades lamina propria or submucosa T2 Tumour invades muscularis propria T3 Tumour invades adventitia T4 Tumour invades adjacent structures	TX Primary tumour cannot be assessed. T0 No evidence of primary tumour. Tis Carcinoma in situ /High-grade dysplasia T1 Lamina propria or submucosa T1a Lamina propria or muscularis mucosae T1b Submucosa T2 Muscularis propria T3 Adventitia T4a Pleura, pericardium, diaphragm, or adjacent peritoneum T4b Other adjacent structures, e.g. aorta, vertebral body, trachea
N	NX Regional lymph nodes cannot be assessed. N0 No regional lymph node metastasis N1 Regional lymph node metastasis	NX Regional lymph nodes cannot be assessed. N0 No regional lymph node metastasis N1 1 to 2 regional lymph nodes N2 3 to 6 N3 >6
M	MX Distant metastasis cannot be assessed. M0 No distant metastasis. M1 Distant metastasis For tumours of **lower thoracic** oesophagus: M1a Metastasis in coeliac lymph nodes M1b Other distant metastasis For tumours of **upper thoracic** oesophagus: M1a Metastasis in cervical lymph nodes M1b Other distant metastasis For tumours of **mid-thoracic** oesophagus: M1a Not applicable M1b Non-regional lymph node or other distant metastasis	MX Distant metastasis cannot be assessed. M0 No distant metastasis. M1 Distant metastasis

1.1.6.2 Staging Investigations

In order to accurately assess the stage of the disease, it is important to make good use of a variety of different staging investigations to assess the degree of both local and distant spread.

Investigations include:

- **Computed Tomography (CT)**

  A CT scan of chest and abdomen should be performed in all cases of oesophageal cancer to look for evidence of loco-regional and distant metastatic spread (48).

  However a CT is not generally considered useful in determining T-stage at diagnosis, other than in identifying T4 disease.

- **Endoscopic Ultrasound (EUS)**

  EUS combines the benefits of high frequency ultrasound with the ability to endoscopically visualise the tumour. This allows one to define the separate layers of the oesophageal wall thereby providing a more accurate T-stage than CT alone, while also allowing visualisation of local nodes to look for evidence of their involvement.

  A recent study reported that the sensitivity and specificity of EUS in assessing T stage was 82% and 91% for T1, 43% and 85% for T2; and 83% and 86% for T3, respectively. While the sensitivity and specificity in detecting N1 disease was 71% and 74%, respectively. (69).

- **Endoscopic mucosal resection (EMR)**

  EMR uses an endoscopic snare to remove sections of the mucosa endoscopically, providing a relatively large histological specimen. As a result EMR has now superseded EUS in the assessment of early oesophageal lesions, as it can clearly differentiate tumours involving just the mucosa from those involving the submucosal layer as well. This is particularly important if one is considering localised endoscopic therapy for an early cancer, because the risk of lymphatic spread rises rapidly once the submucosal layer is involved (70).

  It is now recommended that an EMR is performed when staging all T1 oesophageal tumours (48). Studies have shown that provision of a large EMR specimen can result in both up and down staging of the initial histological diagnosis, resulting in changes in the management plan in up to 30% patients (71-73).

- **Staging laparoscopy**

  A staging laparoscopy should be considered for all GOJ tumours to look for evidence of peritoneal or hepatic metastases. De Graaf et al found that performing a staging laparoscopy provided additional treatment information in 17% of lower oesophageal and

GOJ cancers (74). It is important to collect peritoneal cytology at the time of the staging laparoscopy, because 15% of patients with no overt peritoneal metastases have positive peritoneal cytology and this is associated with a worse prognosis (75).

- **Positron emission tomography (PET)-CT**

  A PET scan is a nuclear medicine imaging technique that allows you to look for changes in the activity of cells. In order to achieve this, the patient is usually injected with fluorodeoxyglucose, an analogue of glucose, which is taken up by cells. The patient is then scanned to detect the concentration of this tracer in different tissues. Malignant cells usually metabolise glucose at a faster rate and therefore show up more brightly.

  Combining PET and CT scans provides both functional and anatomical data and may improve detection of spread to regional and distant lymph nodes, thereby providing more accurate staging information than CT-EUS alone (76). However, PET-CT should not be relied upon for detecting spread to local nodes because high uptake of contrast by the adjacent tumour can obscure uptake by smaller volume local nodes (48). It is therefore important to ensure that EUS continues to be used for this purpose.

1.1.7 Management

Once patients with oesophageal cancer have had their disease staged, decisions need to be made as to whether the disease can be managed with curative intent and if so what the most appropriate treatment modality is. In England decisions about the management of both oesophageal HGD and oesophageal cancer are made at an upper gastro-intestinal (UGI) multidisciplinary team meeting (MDT) (20, 48). The MDT will usually consist of an interventional endoscopist, an UGI surgeon, a specialist gastro-intestinal pathologist, and a radiologist. Decision making is a two-step process, firstly in the case of oesophageal cancer the team need to establish whether the disease is localised with no evidence of distant spread in which case the patient can be considered for curative treatment. The focus then shifts towards determining the most appropriate treatment modality for the patient, taking into account both disease site and stage, and also patient characteristics (e.g. age, comorbidities, and performance status) and wishes.

Currently only around 35% of all oesophageal cancers diagnosed in England are managed with curative intent (77), but this proportion is significantly higher for patients who are diagnosed with early stage disease (75%) (2). Where the disease is potentially curable several different treatment options are available, and this section goes on to explore these options for both oesophageal adenocarcinomas and high grade dysplasia of the oesophagus.

1.1.7.1 Surgery

Until recently surgery has been considered the main stay of treatment for both oesophageal HGD and cancer (48, 78).

The previous recommendation of surgery for the treatment of HGD was based on literature suggesting that a concomitant focus of invasive cancer was found in up to 40% of oesophagectomy specimens taken from patients with a history of HGD alone (79, 80). However a more recent review found that while the overall incidence of invasive cancer in such specimens was still 13%, the incidence dropped to 3% once all patients with endoscopically visible lesions were excluded (81). With increased focus on performing high quality endoscopies for the assessment of HGD, along with the increased use of EMR to provide large histological specimens of any visible lesions it is likely this figure will fall further in future.

Furthermore it is also important to realise that oesophagectomy is associated with significant morbidity and mortality (82-84), and therefore careful consideration needs to be given to performing an oesophagectomy for HGD alone or early cancer. The 2010 NOGCA report found that the 90-day mortality post oesophagectomy for oesophageal cancer was 5.7% (85), this figure has fallen over recent years but was still reported to be 4.4% in the 2014 NOGCA report (2). In addition, a third of patients suffer significant post-operative complications post-oesophagectomy (such as respiratory 17.1%, cardiac 7.3% and anastomotic leak 7.1%) (2).

As a result over recent years localised endoscopic treatment options have superseded surgery as the treatment of choice for HGD (20), although surgery remains the mainstay of treatment for most oesophageal ACAs. Nonetheless localised endoscopic therapy may be considered where oesophageal ACA is diagnosed at a very early stage before there is evidence of submucosal invasion. The next section goes on to explore these endoscopic treatment options in greater detail.

1.1.7.2 Endoscopic treatment

Given that dysplastic changes are, by definition, limited to the mucosa, there is no concern about the risk of spread with HGD (as there is with cancer), consequently localised endoscopic therapy is now considered the treatment of choice for HGD, thereby avoiding the need for an oesophagectomy and its associated risks (20). When managing HGD endoscopically it is important to ensure the entire Barrett's segment is treated, to reduce the risk of future recurrence or development of a metachronous lesion in the remaining Barrett's segment (86, 87).

Localised endoscopic therapy can also be used to treat early oesophageal cancers limited to the mucosa, due to the very low risk of lymphatic spread in this situation (88, 89). It may also be considered for cancers invading the most superficial layer of the submucosa (sm1), if the tumour is well differentiated with no evidence of lymphovascular invasion, or if the patient is unfit or unwilling to undergo an oesophagectomy (20).

There are several different endoscopic treatment options available for the management of oesophageal HGD and cancer, and this section goes on to explore these options in greater detail.

Endoscopic Resection

Endoscopic resection is useful for treating both early oesophageal cancers and HGD if there is a visible nodule. There are two broad approaches to endoscopic resection, endoscopic mucosal resection and endoscopic submucosal dissection.

Endoscopic mucosal resection (EMR) uses an endoscopic snare to remove sections of mucosa endoscopically. The technique was first developed to treat gastric cancers in 1980 (90), and by 1990 was being used successfully to treat early oesophageal cancers (91). More recently it has been used to treat HGD of the oesophagus (92). EMR is now considered the treatment of choice for treating both visible dysplastic nodules and intramucosal cancers of the oesophagus (20).

The aim of EMR can be two fold, firstly to remove any obvious nodules of concern within the oesophageal mucosa, alternatively it can be used to remove the entire segment of Barrett's mucosa. The later approach is called complete endoscopic mucosal resection, and is performed to reduce the risk of cancer in future. Evidence regarding the outcomes that can be achieved with EMR in treating dysplastic Barrett's will be presented in Chapter 4.

When resecting an early cancer endoscopically it is important to try to achieve an enbloc resection, to allow accurate histological assessment of the lesion and reduce the risk of local recurrence (93). It is not always possible to achieve this using EMR, and as a result endoscopic submucosal dissection (ESD) was developed. ESD allows the en bloc resection of larger lesions and of lesions extending into the submucosa, this is achieved by injecting solution under the lesion of concern to allow the submucosa under the lesion to be dissected using a specialised knife. To date most studies using ESD for the treatment of oesophageal cancer have come from Japan and have focused on the treatment of oesophageal squamous cell cancers (94-96). Very few studies have reported on the use of oesophageal ESD in the West and in particular to treat oesophageal adenocarcinomas, and where these have been done initial studies reported disappointing results. A study from Germany reported

that a complete resection (R0) was only achieved in 38.5% (97), while another small study from the US reported that an R0 resection was only achieved in 2/4 (50%) oesophageal cancers treated with ESD (98). A more recent German study has produced more encouraging results, reporting a 95.4% R0 resection rate for oesophageal adenocarcinomas, with a recurrence rate of 2.4% over 2 years follow up (99). The variability in the results reflect the fact that ESD is a much more technically demanding technique than EMR, and studies have shown that outcomes after ESD are closely linked to the volume of cases managed at that institution, with increased rates of complications at lower volume centres (100). As a result the role of ESD in the management of oesophageal adenocarcinomas in Europe has not yet been clearly defined, and use is currently limited to a few specialist centres.

Endoscopic Ablation

An alternative approach for managing dysplasia within a segment of Barrett's oesophagus is to ablate the neoplastic mucosa, allowing regrowth of normal squamous mucosa in its place. This technique is useful for treating flat areas of dysplasia, and to treat residual Barrett's mucosa after endoscopic resection of any visible nodules.

There are several different ablative therapies available including radiofrequency ablation, photodynamic therapy, argon plasma coagulation, multipolar electro-coagulation, laser therapy, and cryotherapy. This section goes on to describe in more detail some of the more commonly used techniques.

Photodynamic therapy (PDT) was one of the earlier ablative treatments developed to treat dysplastic Barrett's oesophagus. Administration of PDT is a laborious process. First a photosensitizer (e.g. porfimer sodium or oral 5-aminolevulinic acid (5-ALA)) is administered systemically, and then at a later date an endoscopy needs to be performed to expose the oesophagus to a specific wave length of light which activates the photosensitiser which has been preferentially retained by the abnormal cells causing their delayed cell death. Studies looking at the success of PDT in eradicating Barrett's oesophagus have produced variable results and have been associated with a high risk of complications. For instance a randomised controlled trial (RCT) by Overholt et al found that while administration of porfimer sodium as a photosensitiser achieved significantly better rates of regression of HGD compared to omeprazole alone (77% vs 39%, $P<0.0001$), 13% of patients treated with PDT went on to develop cancer during follow up, and 94% developed complications associated with treatment (101). While another trial using 5-ALA as photosensitiser produced better results short term outcomes (97% of patients with HGD and 100%

of patients with early cancer achieved a complete response), but recurrence rates were still high affecting 2.8% of patients treated for HGD and 32% of patients treated for early cancers (102).

Argon plasma coagulation (APC) is an alternative treatment using ionised argon gas to conduct monopolar current into the tissue, causing cell death through electrocoagulation. Studies using APC to treat dysplastic Barrett's have produced poor results (103, 104), with only 65% of patients achieving complete eradication of intestinal metaplasia above the GOJ after a median of 3.8 treatment sessions (104). Furthermore the rates of buried Barrett's associated with APC are also high (103).

More recently radiofrequency ablation (RFA) has been developed; this technique uses high-frequency alternating current to destroy the mucosa. Before applying RFA it is important to ensure that any visible nodules are resected first using EMR, this is important for two reasons firstly RFA does not provide a histological specimen needed to look for evidence of deeper tissue invasion and secondly the mucosa needs to be flat in order to apply RFA effectively and evenly.

RFA can be applied using the HALO system (BARRX Medical, Sunnyvale, CA). There are two main types of HALO device available; HALO^{360} which provides circumferential treatment to the mucosa, and HALO^{90} which provides focal treatment to localised areas of disease. Patients usually require initial circumferential RFA, followed by focal RFA to treat any small areas of residual disease. However, short-segments of non-circumferential Barrett's oesophagus can often be treated with focal RFA alone.

Circumferential RFA is usually applied, using standard energy settings (12J/cm^2, 40W/cm^2). After initial application the probe is cleared of debris and the process is repeated again ablating the same segment for a second time. In contrast focal RFA is usually administered using a 'double-double' approach, here RFA is delivered twice in succession to each area (12-15J/cm^2, 40W/cm^2), before the probe is cleaned and the area is then ablated again twice.

Studies have consistently demonstrated that better outcomes can be achieved with RFA compared to older ablative techniques, consequently use of both PDT and APC has declined in recent years (105). Evidence regarding the use of RFA to treat dysplastic Barrett's will be reviewed in detail in Chapter 4.

1.1.7.3 Summary of treatment options

For locally advanced oesophageal adenocarcinoma surgery is still regarded as the curative treatment of choice. However, two recent reviews have shown that for patients with disease limited to the

most superficial layers of the oesophagus the morbidity and mortality is substantially lower for patients treated endoscopically than for those treated surgically (105, 106). As a result the current BSG guidelines advocate the endoscopic treatment of early oesophageal cancers limited to the mucosa and carefully chosen cases invading the most superficial layer of the submucosa (20). Endoscopic treatment options include endoscopic mucosal resection and endoscopic submucosal dissection. The choice of modality used depends on the tumour size and depth of invasion, as well as local expertise available.

Similarly for oesophageal HGD the BSG guidelines now recommend that this is treated endoscopically, in preference to either surgical resection or surveillance alone (20). There are two broad approaches to the endoscopic treatment of HGD, endoscopic resection and ablation, each approach has their own advantages and disadvantages. In Western countries RFA is now considered the ablative treatment of choice, associated with better outcomes and fewer complications than previous ablative techniques such as PDT and APC (105). Chapter 4 will go on to compare outcomes achieved with complete endoscopic resection with those achieved with RFA for treating dysplastic Barrett's oesophagus.

1.1.8 Survival

Despite being only the 13th most common cause of cancer in the UK, oesophageal cancer is currently the 6th most common cause of cancer death (1). The disparity between the incidence and mortality of oesophageal cancer is due to the fact that a large proportion of oesophageal cancers are diagnosed at a late stage (2). As a result only a third of patients are managed with curative intent (77) and only 15% of patients survive 5 years (1).

However the overall survival for oesophageal cancer does appear to be improving. A study from the US found that overall 5 year survival for oesophageal cancer had increased from 5% in 1974-1976, to 16% between 1995-2000 (107). Nonetheless UK outcomes are still far behind the rest of Europe (1), with several papers raising concerns about overall cancer outcomes in the UK compared to other countries with similar health care systems and wealth (3-6). One paper estimated that between 1985-1999 there were 6600-7500 excess deaths in Britain each year among cancer patients, which could have been avoided if the overall 5 year cancer survival was the same as the mean survival in Europe (108). As a result the UK government has been taking steps to improve cancer outcomes (7, 9, 10, 109).

Key to improving survival for oesophageal cancer is increasing the proportion of patients diagnosed at an early stage, but identifying these patients is difficult because symptoms of oesophageal cancer

frequently present at a late stage. In January 2015 the government launched a 'Be Clear on Cancer' campaign for oesophago-gastric cancer. The aim of this campaign was to improve early diagnosis of these cancers by raising public awareness of their symptoms and signs, and to encourage patients to see their GP without delay if they were concerned (9). The campaign targeted men and women aged 50 years and over with persistent heartburn for 3 weeks or more, or problems swallowing (9). However these symptoms are non-specific and frequently seen in individuals without cancer, so it will be important to investigate the impact this campaign has on both the proportion of cancers diagnosed at an early stage and the number of urgent endoscopies being performed.

1.1.8.1 Early oesophageal cancer outcomes

The outcomes associated with the treatment of early stage oesophageal cancer are much better. Wani et al reported that up to 90% of patients diagnosed with early oesophageal cancer who were managed with a curative oesophagectomy survived 5 years (110).

Until recently surgery had been considered the only curative treatment for oesophageal cancer, however with studies demonstrating the low risk of lymphatic spread with early stage disease and recent advances in endoscopic options have meant that endoscopic treatment options are being considered with increasing frequency for early cancer. Given the changing patterns of management for early oesophageal cancers it is important to ensure that comparable long term outcomes can be achieved with localised endoscopic therapy.

Several papers have attempted to compare outcomes for early oesophageal cancers managed surgically and endoscopically. Previous single centre studies from the US and Germany (111, 112) have reported similar outcomes for both therapies, but these studies were small and consequently underpowered to detect significant differences. These studies report that the risk of procedure-related mortality was higher after surgery, but that the risk of recurrence was higher for patients treated endoscopically. Population based studies performed in the US, using the Surveillance Epidemiology and End Results (SEER) database (113-115) reported no difference in cancer specific mortality at 5 years, but that patients treated surgically had better overall 5 year survival. However it is important to realise that there were differences in the baseline characteristics of the two groups which could not be accounted for.

1.2 Care provision in England

1.2.1 Organisation of cancer services in England

In 2000 the National Health Service (NHS) Cancer Plan was developed to provide a comprehensive strategy to tackle the disease (109). This aimed to target everything from disease prevention, to diagnosis, treatment and research.

As a result in 2001, the 'Improving Outcomes Guidance' document was published (7), this provided guidance on how NHS services should be organised resulting in the major reorganisation of oesophago-gastric cancer services in England. Its key recommendations included:

- Development of Cancer Networks. These were designed to provide specialist diagnostic services and curative therapies (including surgery and oncology) at a single specialist centre (Cancer Centre) to all patients living in a geographical area. While more general diagnostic services and most palliative services would continue to be provided by local NHS trusts (known as Cancer Units).
- Development of specialist treatment teams to treat OG cancer, with each serving populations of more than one million. Within this strategy they recommended the introduction of specialist UGI cancer MDTs, which met regularly to collectively decide on individual patient's management. There is good evidence to suggest use of the MDT approach to plan treatment improves overall survival for patients with oesophageal cancer (116).

When the NOGCA started in 2007 there were 30 Cancer Networks in England (117), since then there has been further centralisation of services. An organisational survey of OG cancer services in England was conducted in 2012, at that time there were 28 Cancer Networks providing services to the 151 trusts treating OG cancer, with 39 of these trusts designated as specialist Cancer Centres (77).

Further changes to the organisation of cancer services took place in 2013, resulting in the replacement of Cancer Networks by 12 Strategic Clinical Networks (SCNs) in England (118). It is the responsibility of these SCNs to provide clinical and managerial support to Clinical Commissioning Groups, Health and Wellbeing Boards and NHS England in order to improve regional healthcare (119).

1.2.2 Management of HGD in England

In the past several surveys have been conducted to investigate the services available for the management of HGD in England. These have reported significant variability in the management of HGD and poor adherence to published guidelines (Table 1-6) (120-123). This in part reflects the fact that new treatment options have become available over recent years resulting in substantial changes to national guidelines.

As recently as 2002 74% of clinicians considered surgery as the treatment of choice for HGD where active treatment was being considered (115), but surveillance alone was still considered the treatment of choice by 83% of clinicians in preference to active treatment as recently as 2004 (120). Since then there has been a dramatic shift in the treatment options available for HGD, such that endoscopic therapy is now considered the treatment of choice in preference to surgery or surveillance alone (20). As a result a recent study from the Netherlands reported that the proportion of patients treated endoscopically for HGD had risen rapidly over the last 15 years, from 18% between 1998-2003 to 42% between 2004-2008 (124). During this time frame there was a corresponding decline in the use of oesophagectomy from 82% to 56%. It is expected that a similar trend will have been seen in UK practice, but no recent studies have been done to investigate the current management of HGD in the UK.

Table 1-6 Summary of key findings of previous studies looking at the management of Barrett's oesophagus

1st Author and Year	Country	Study Years	Study Design	Key Findings
Ramus 2008 (120)	UK	2004-2005	Questionnaires on Barrett's oesophagus sent to endoscopy leads at 41 centres across the UK	33 (73%) of centres responded - 73% adhered to the Seattle protocol in biopsying Barrett's oesophagus - *Management of HGD*: 83% of centres adopted frequent surveillance of HGD, 7% made direct referral for surgery and 1 stated they would repeat biopsy and ask for the opinion of a second pathologist.
Das 2008 (121)	UK	2002	Questionnaires on Barrett's oesophagus sent all 387 consultant members of BSG and further 14 trainees across the UK	228 (57%) of clinicians responded - 55% adhered to the Seattle protocol in biopsying Barrett's oesophagus - 55% reported having access to a specialist GI pathologist - 50% always had diagnosis of HGD confirmed by 2nd pathologist, a further 23% reported this was frequently the case. - *Management of HGD*: 74% consider surgical resection as their preferred treatment option for HGD.
Mandal 2003 (123)	UK	2001	Questionnaires on Barrett's oesophagus sent to 300 members of BSG across the UK	203 (68%) of clinicians responded - 41% adhered to the Seattle protocol in biopsying Barrett's oesophagus - 55% had all diagnoses of HGD confirmed by 2nd pathologist, 23% did only if surgery considered - *Management of severe (HGD) dysplasia*: 23% referred directly for surgery without repeat endoscopy.
Smith et al 1999 (122)	UK	1997	Questionnaires on Barrett's oesophagus sent to 297 members of BSG across the UK	152 (51%) of clinicians responded - 8% adhered to the Seattle protocol in biopsying Barrett's oesophagus - 3% had diagnosis of HGD confirmed by 2nd pathologist - *Management of severe dysplasia*: 70% (74/106) considered surgery as their preferred treatment (some after repeated OGD to confirm diagnosis), 21% (22/106) continued regular surveillance.

In 2012 the NOGCA conducted an organisational survey to investigate the services available for the management of HGD in England at a local cancer network level, and reported on adherence to national guidelines for the management of HGD (20, 125). Valid responses were obtained from 137 out of 151 NHS trusts (90.7%). The results of the survey are summarised below:

- 26 out of 30 Cancer Networks (86.7%) had a policy for the management of HGD.
- 105 trusts (76.6%) reported that the diagnosis of HGD was confirmed by a second pathologist with an interest in GI pathology.
- 130 trusts (94.8%) reported that patients with HGD were discussed at the upper GI MDT, this could be either at their local hospital or the patient could be referred on to their local specialist centre for discussion at their UGI MDT. Mechanisms for referral to the MDT varied locally, with 11 (8.5%) trusts reporting that they had no specific mechanism for the referral of patients with HGD to their specialist MDT.
- 132 (96.4%) trusts reported having access to both endoscopic and surgical treatments for HGD within their Cancer Network. Further details on the proportion of trusts who reported access to different therapeutic modalities is shown in **Table 1-7**.

Table 1-7 Therapeutic procedures available for patients with HGD

	Available at local trust or another hospital with their Cancer Network, n (%)
Oesophagectomy	134 (97.8%)
Endoscopic mucosal resection	133 (97.1%)
Argon plasma coagulation	116 (84.7%)
Radiofrequency ablation	111 (81.0%)
Photodynamic therapy	100 (73.0%)
Laser therapy	75 (54.7%)

The results of this survey raised several areas requiring further investigation, firstly reported adherence to some of the BSG guidelines remains poor, for instance only 76.6% of trusts reported that the diagnosis of HGD was confirmed by a second pathologist, and secondly there was significant variation in availability of the difference HGD treatment modalities across the country.

One of the key new recommendations of the most recent BSG guidelines was that endoscopic treatment with EMRs should be centralised to high volume centres (20). This mirrors changes which have already been seen in OG cancer surgery services where care is centralised to a limited number

of specialist centres across England, based on a large body of evidence demonstrating that better outcomes can be achieved after oesophagectomy in high volume centres (126-128). The evidence base for centralising the endoscopic treatment of HGD treatment is currently limited, with only a few studies investigating the effect of treatment volumes on the outcomes of endoscopic interventions. A study by Van Vilsteren et al showed that EMRs performed in the hands of experienced therapeutic endoscopists were associated with very low complication rates, but that the risk of complications was significantly higher when procedures were performed by less experienced endoscopists performing their first 20 procedures (129). On the basis of this evidence, the most recent BSG guidelines for the management of Barrett's oesophagus suggest that EMRs should be performed in high volume tertiary referral centres (managing at least 15 cases per year) (20). A further recent study looked at the effect of the learning curve on RFA outcomes, this found that the number of RFA treatment sessions required to achieve complete eradication of intestinal metaplasia was significantly higher if the endoscopist/centre had performed less than about 30 RFA procedures (130). This was in contrast to an earlier study which had reported that performing RFA appeared to be associated with minimal learning curve (129). Finally a recent observational study from Australia investigated the effect of assessment in specialist centres on the detection and staging of oesophageal cancer within Barrett's oesophagus, and found this improved detection of lesions (67). This evidence suggests that further consideration should go into whether all management of patients with HGD should be centralised to a few specialist centres in England.

1.3 Conclusions from the literature search

The aim of this thesis is to investigate the patterns of management and outcomes associated with the treatment of early neoplastic changes in the oesophagus in England. As a result of the literature search performed in this Chapter several clear gaps in the literature were identified. These will be discussed in further detail in the next section, and will provide the focus for my research.

1.3.1 Management of HGD in England

As discussed earlier, previous studies have suggested that there is considerable variation in the management of patients with HGD in England (120-123). However these studies were conducted between 1997 to 2005, a period when endoscopic therapies were still relatively novel and were not widely available. Since these studies were performed there has been a dramatic shift in the treatment options available for the management of HGD, such that endoscopic therapy is now considered the treatment of choice for HGD in preference to either surgery or surveillance alone (20). Furthermore these surveys all relied on clinician reported management of patients with HGD, and did not have access to patient level data.

In April 2012 the NOGCA started collecting data on all patients with a new diagnosis of oesophageal HGD and this provides us with a unique opportunity to investigate the management of HGD at a national level using patient level data. The aim of Chapter 3 is to investigate current management of HGD in England and adherence to published guidelines. In addition it aims to investigate whether specific features in the patient's management pathway (e.g. confirmation of the diagnosis on repeat biopsy, discussion as the MDT and management of the patient in a high volume centre) impact on choice of treatment modality.

1.3.2 Choice of endoscopic treatment

When treating dysplastic Barrett's oesophagus it is important to ensure that both the dysplastic lesion of concern and the remaining Barrett's segment is effectively treated in order to reduce the risk of cancer developing in future (86, 87). There are two broad approaches that can be taken to achieve this, resection of the entire Barrett's segment endoscopically or ablation (with prior resection of any visible nodules).

Given that RFA is now the ablative treatment of choice in Europe for treating dysplastic Barrett's oesophagus, it is important to investigate its safety and efficacy and compare this to that of complete endoscopic resection. To date there has only been one RCT done directly comparing the two approaches (131), so Chapter 4 aims to address this gap in the literature by systematically reviewing the literature comparing the risks and benefits of each approach.

1.3.3 Are we missing the opportunity to diagnose some cases of oesophageal cancer at an early stage?

Although endoscopy is seen as the definitive investigation for the diagnosis of oesophageal cancer, several previous studies have suggested that a significant proportion of cancers are potentially missed at initial endoscopy (53-59).

However, these studies have been subject to significant limitations. Firstly, the majority of studies have been small single centre studies (53-56, 58), preventing meaningful investigation into patient factors that may be associated with a missed diagnosis. Secondly many of the studies were conducted over many years (up to 14 years (53)), during a period when there were significant advances in endoscopic equipment and imaging techniques, this may make their results less applicable to current practice. Finally very few studies had access to information on stage at diagnosis; this makes it difficult to be certain that lesions were missed at previous endoscopy. Prior endoscopies may have been performed as part of a planned surveillance programme, representing good practice by promoting early diagnosis of cancer rather than representing missed lesions. As a

result, previous studies may have overestimated the true value. Nonetheless, if the natural history of oesophageal cancer is long as previous studies have suggested (60, 61), then one should consider any cancers detected within three years of endoscopy as potentially missed. It is also important to realise that none of the previous studies have attempted to investigate the impact of a missed diagnosis on patient outcomes.

By linking data provided by the NOGCA on all patients diagnosed with oesophageal cancer in England over a 1 year period with data provided by Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality data, Chapter 5 aims to investigate the proportion of oesophageal cancers missed at endoscopy on a national level and address some of these limitations.

1.3.4 Management and outcomes for early oesophageal cancers

Over recent years endoscopic therapy has superseded surgery in the management of early oesophageal cancers (20, 132, 133). In the past several studies have attempted to investigate outcomes associated with both techniques, but these have been associated with significant limitations. Most importantly previous studies have collected data over many years (up to 14 years), over a period when significant advances were made in the endoscopic treatment of early stage disease. Previous national studies have also had limited access to details on patient characteristics which may potentially confound their results. Finally it is important to realise while most research comes from specialist research centres, no national population studies investigating outcomes for early oesophageal cancers have been performed outside of the US.

As a result it is important to investigate the patterns of management of early oesophageal cancer in England, looking at the use of surgery and endoscopic therapy and the associated long-term outcomes. This study was made possible by linking data from the NOGCA to HES and ONS, and the results are presented in Chapter 6.

2. Methods

The research presented in this thesis results from work done while I was Clinical Fellow for the National Oesophago-Gastric Cancer Audit (NOGCA). Data derived from the audit dataset was linked with other data sources, to provide the comprehensive dataset required for further analysis. The specific methodology for each study is detailed in the relevant chapter, while the more general methodology relevant to all chapters is outlined below.

2.1 Data sources

2.1.1 National Oesophago-Gastric Cancer Audit

The NOGCA was set up in October of 2006 with the aim of measuring the quality of care received by patients with oesophago-gastric (OG) cancer in England and Wales, and was funded for three years in the first instance. The long term goal was to identify areas where services could be improved in future and to provide a bench mark against which services could be compared.

The **first audit** collected data between 1st October 2007 and 30th June 2009. On the back of the success off the first audit, funding was secured for further five years. The **second audit** started collecting data again in April 2011 (after a gap in data collection of 21 months).

In April 2012 the audit was extended to include patients with high grade dysplasia (HGD) of the oesophagus. The aim was to assess whether patients with HGD were managed consistently with uniform access to different treatment modalities across the UK, and to assess whether management of these patients was adhering to current UK guidelines.

The audit is commissioned by Healthcare Quality Improvement Partnership (HQIP), and is a collaboration of:

- Clinical leadership from:
    - The Association of Upper Gastro-Intestinal Surgeons (AUGIS)
    - The British Society of Gastroenterology (BSG)
    - The Royal College of Radiologists (RCR)
- Project management and administrative support is provided by The National Clinical Audit Support Program (NCASP) of the Health and Social Care Information Centre (HSCIC).
- Audit design, analysis and reporting is performed by The Clinical Effectiveness Unit (CEU) of The Royal College of Surgeons of England (RCS) and London School of Hygiene and Tropical Medicine (LSHTM)

A project team made up of representatives from these organisations work together to run the audit. Additional clinical input is provided by the Clinical Reference Group (CRG), who meet on a bi-annual basis to discuss the progress of the audit and future plans.

2.1.1.1 Inclusion Criteria

The NOGCA is a national clinical audit that prospectively collects data. All patients aged 18 or over, diagnosed in England or Wales are eligible for inclusion in the audit if they meet the following criteria:

Oesophago-Gastric Cancer

- Invasive, epithelial cancer of the oesophagus, gastro-oesophageal junction (GOJ) or stomach (International Classification of Diseases (ICD-10) codes C15 and C16)
- Date of diagnosis
    - First audit: 1st October 2007 and 30th June 2009
    - Second audit: 1st April 2011 to present

The audit does not include patients with non-epithelial OG tumours (e.g. endocrine tumours, gastrointestinal stromal tumours or lymphomas), due to the different behaviour and management of these tumours.

High grade glandular dysplasia of the oesophagus

- Diagnosed with high grade glandular dysplasia of the oesophagus
- First biopsy (either initial referral or as part of routine surveillance) which diagnosed HGD performed after 1st April 2012

The audit does not include patients with squamous dysplasia.

2.1.1.2 Dataset

The dataset was designed to collect information on all stages of the patient's management pathway. It was developed by the project team with input from the CRG.

The dataset collects information on a series of different forms:

- **Tumour Record:** Provides details on patient characteristics, site of cancer, staging investigations, pre-treatment tumour stage (according to the Union for International Cancer Control Classification (UICC) TNM classification) (68), comorbidities, performance status (Eastern Cooperative Oncology Group (ECOG) score for performance status in cancer

patients) (Appendix A)), treatment intent and management plan. It also collects data on date of diagnosis, hospital where diagnosis was made, and source of referral.

- **Surgery Record:** For patients undergoing surgery it collects details on surgical intent, pre-operative American Society of Anaesthesiologists (ASA) grade (Appendix B), surgical approach, postoperative complications, and length of stay.
- **Pathology Record:** A separate post-operative pathology record is collected for all surgical patients. This records information on final post-operative stage, status of the resection margins, and the number of lymph nodes examined and involved.
- **Oncology Record:** Provides details on any oncological treatments administered and their timing and treatment intent.
- **Endoscopic/Radiological Palliative Record:** Provides details on the first endoscopic procedure a patient undergoes post-diagnosis, including its timing, and any immediate complications.
- **Oesophageal High Grade Dysplasia Dataset (From April 2012 only):** Provides details on the initial diagnosis of HGD, initial endoscopic report, planned treatment and outcomes after endoscopic mucosal resection. Data items were pilot tested and selected to allow practice to be compared against current guidelines for the management of HGD (20, 78).

Data for both the first and second audits were collected using the same skeleton dataset, but revisions were made to the dataset in April 2012. Changes included removing some items that were poorly completed and not reported on in the 1st audit, and making some additional variables mandatory (in order to improve case-mix adjustment). Finally some data items were added to aid analysis of patient flow. The final dataset is detailed in Appendix C.

Data items were defined to be consistent with:

- The Scottish Upper GI cancer dataset (July 2005)
- The All Wales Oesophago-Gastric Cancer Minimum Reporting requirements (v. 2.0) including Core Reporting Items v5.0
- The Royal College of Pathologists Datasets for reporting oesophageal and gastric cancers
- The Royal College of Radiologists radiotherapy dataset (version 3.7)

All variable definitions are clearly outlined in the NOGCA Data Manual (134).

2.1.1.3 Data Collection

In England all National Health Service (NHS) hospitals are part of an NHS trust. NHS trusts consist of one or more hospitals that provide the required range of services to a particular patient population, but are managed by a single management structure. Each NHS trust was asked to prospectively identify all patients with a new diagnosis of oesophago-gastric cancer or HGD through their upper gastro-intestinal multidisciplinary team meetings (UGI MDT), and submit data on all patients via an online reporting system. Within each trust local audit coordinators were responsible for managing the input of their data into the audit, with clinical teams providing assistance where needed to clarify responses.

Participation in the NOGCA is mandatory for NHS trusts in England. It is a requirement of the Health Act 2009 that trusts demonstrate their participation in this and other National Clinical Audits via their Quality Accounts which are submitted to the Secretary of State. Since 2012 it has been a requirement that these Quality Accounts are externally audited.

Additional steps were taken by the HSCIC in order to optimise data submissions to the audit. Firstly the HSCIC provided trusts with an email address and contact details, so that trusts could contact them directly with any queries regarding data submission. In addition the HSCIC sent regular newsletters and updates to trusts regarding the audit's progress, highlighting any problems in either the quality of data submitted or low volumes of data submitted.

2.1.1.4 Data Submission

Data could be submitted to the audit in a variety of different ways, depending on where the patient was diagnosed.

English Patients

Data could be submitted to the audit in two ways:

- If data was already being collected locally, then the relevant fields could be extracted and uploaded to the audits secure database via a 'csv' file upload facility
- Alternatively data could be collected manually via a secure web-based data entry form

The majority of trusts submitted records to the audit via data extraction from local databases, these records were uploaded as a 'csv' file.

Data submitted to the audit was frequently analysed at a trust level.

Welsh Patients

Data was provided by the Cancer Network Information System Cymru (CaNISC). However, this data was limited and did not provide information on complications after surgery, or on patients with a new diagnosis of HGD. As a result this data is not reported on for Welsh patients.

2.1.1.5 Ethical Approval

As the audit involved analysis of data for service evaluation it was exempt from the UK National Research Ethics Committee approval. Section 251 approval was obtained for the collection of the personal health data from the Ethics and Confidentiality Committee.

2.1.1.6 My responsibilities within the audit

I started work as Clinical Research Fellow for the NOGCA in October 2012, and was based at the Royal College of Surgeons of England for the duration of this role. Within this role I was supported by my supervisors and members of the Project Team.

The work I performed in this role included:

- Analysing the prospective data collected for the audit and drafting the Annual Reports (2, 15, 77)
- Revision of the High Grade Dysplasia dataset in September 2015
- Communicating with clinical leads and audit coordinators at local NHS trusts to support data collection, addressing queries raised and providing feedback on the case-ascertainment and completeness of data submitted
- Drafting regular newsletters to NHS trusts to update them on the audit's progress
- Communicating with AUGIS, BSG and RCR providing regular updates for their websites
- Presenting the audit's findings at national conferences including Digestive Disease Federation, National Cancer Intelligence Network, National Awareness and Early Diagnosis Initiative.

2.1.2 Hospital Episode Statistics (HES)

NOGCA records were linked with patient's HES records to allow more in depth research to be performed. HES is a national administrative health database, which records information on all day cases and admissions to English NHS hospitals since 1987 (135).

Each record describes the period during which a patient is under a particular hospital consultant (an episode). Within HES it is possible for more than one episode to occur during an admission to hospital. For each episode routine administrative data is recorded (e.g. patient details, date of admission and discharge), as well as clinical data including information on comorbidities and complications and operative procedures that occur during an episode. The ICD-10 system is used to record a primary diagnosis and up to 19 secondary diagnoses for each episode (12). While up to 24 operative procedures are recorded using the UK Office of Population Censuses and Surveys Classification version 4, 4th revision (OPCS-4) (136).

Data was extracted from the HES database for all episodes relating to patients resident in England with an ICD-10 diagnostic code of C15 (oesophagus) or C16 (stomach), over a specified time frame.

It should be noted that HES data is not available for patients treated in Wales, and as such Welsh patients are excluded from all analysis involving HES.

2.1.3 Mortality database from the Office for National Statistics (ONS)

The ONS collects information on the date and cause of death for all deaths registered in the UK. The extract of ONS used for our work presented in this thesis was restricted to the date of death only.

2.2 Data Linkage

In order to provide the in depth analysis required to address the specific research questions raised in this thesis, data from the NOGCA was linked to HES and the ONS death register records for each patient. Data from the various data sources were linked using a hierarchical deterministic approach, using patient identifiers including NHS number, date of birth, sex and postcode. Overall linkage rates were very good.

By linking the NOGCA dataset to HES it was possible to estimate the overall case ascertainment for each audit. For the first audit it was estimated that 71% of cases of OG cancer were recorded in the audit (85), this figure had risen to 83% by the second audit with over 95% case ascertainment for patients undergoing curative surgery (77).

2.3 Statistical Analysis

Details on specific statistical methods used in each Chapter are included in the Methods section for that Chapter. Certain aspects were common throughout; STATA 11.2 (Statacorp, College Station, TX, USA) was used for all statistical calculations.

Patient characteristics were compared across the groups using the t-test and chi-square test as appropriate to test for statistically significant differences between the groups. All p-values were two sided and those <0.05 were considered statistically significant.

Multiple logistic regression models were used to examine the relationship between a previous endoscopy, planned treatment intent (curative vs palliative) and 1-year survival. Relative risks were adjusted for patient age, sex, and performance status, as well as type of cancer, tumour site and TNM stage at diagnosis. Missing values for these covariates were imputed using multiple imputation by chained equations (138). The imputation model included age at diagnosis, sex, type of cancer, tumour site, performance status and referral source. Ten imputation datasets were created. Logistic regression models were also used to investigate the effect of HGD treatment centre volume on treatment plan, this time adjusting for only the patient's age and sex.

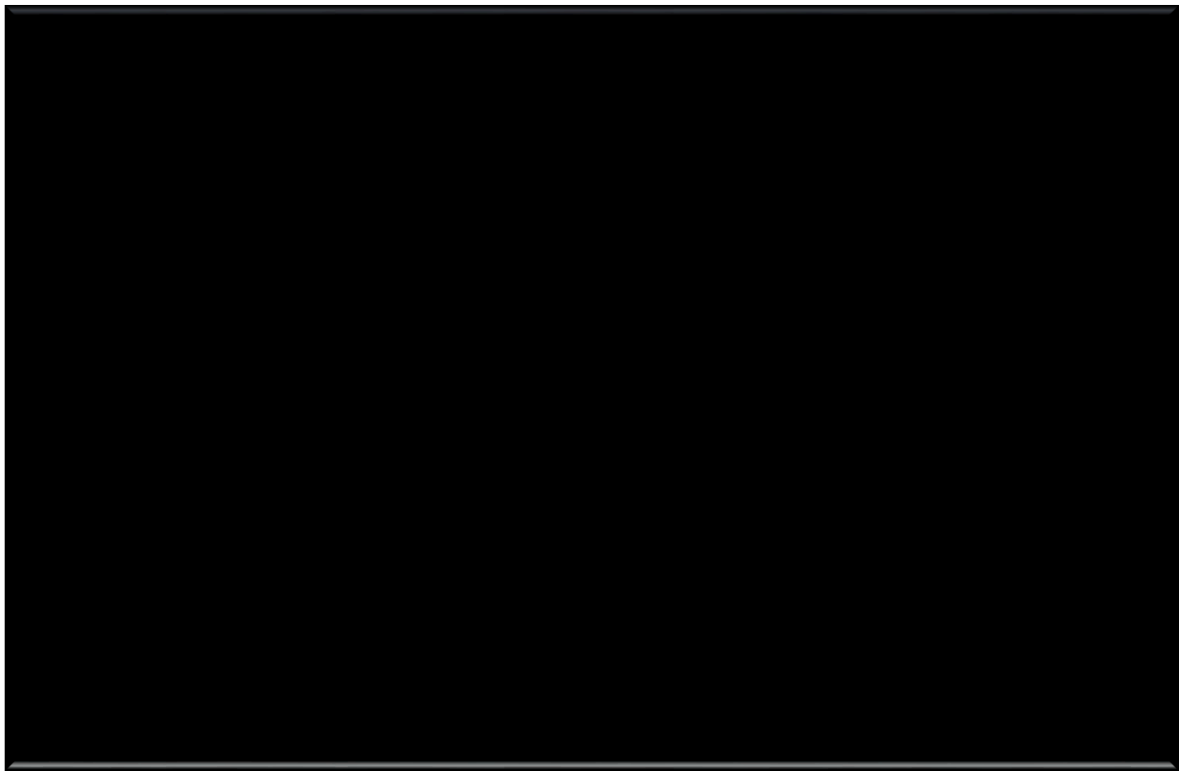
Kaplan-Meier graphs were used to present estimated 5 year survival rates for patients with early oesophageal cancer according to their primary treatment modality. The log rank test was used to test for significant difference between survival curves.

3. Management of Barrett's Oesophagus High Grade Dysplasia

3.1 Introduction

As discussed in Chapter 1, studies have shown that Barrett's oesophagus is a premalignant condition that progresses through a dysplasia-carcinoma sequence to oesophageal adenocarcinoma (37), as it does the risk of progression to cancer increases from 0.1% per year for non-dysplastic Barrett's oesophagus (25) to 5.6% per year if high grade dysplasia (HGD) is present (36).

It is therefore very important to ensure that patient's found to have HGD are managed optimally to minimise the risk of progression to cancer in future. As a result the BSG has made recently updated their guidelines for the management of HGD, and their key recommendations are highlighted below (20).



Previous studies have reported significant variation in the management of HGD on a national basis (120-123), although these studies have been subject to significant limitations (as discussed in Chapter 1).

3.2 Aims of this chapter

Since April 2012 the National Oesophago-Gastric Cancer Audit (NOGCA) has been prospectively collecting data on all patients newly diagnosed with HGD of the oesophagus in England. This provides us with the unique opportunity to examine the management of HGD in England using patient level data.

This study aims to:

- Provide an initial description of this cohort of patients
- Provide a summary of treatment modalities used to treat HGD in England
- Compare current practice with national guidelines (20)

3.3 Methods

This population based cohort study used data collected prospectively for the NOGCA. All patients with a new diagnosis of oesophageal HGD between 1st April 2012 and 31st March 2013 reported to the NOGCA were considered for inclusion in this study.

Trusts were asked to prospectively identify all patients with a new diagnosis of HGD through their upper gastro-intestinal (UGI) multi-disciplinary team meeting (MDTs), and submit data for these patients to the audit via the online reporting system (as discussed in Chapter 2). This was felt to be a secure method for identifying these patients because results from the previous NOGCA organisational survey in 2012 revealed that 92% of trusts had specific mechanisms in place to ensure all new cases of HGD were discussed at their MDT and had their data recorded in their MDT information system (125). As a result identification of new cases of HGD did not rely on the engagement of individual clinicians.

In order to optimise submissions to the audit for patients with HGD, the Health and Social Care Information Centre (HSCIC) sent out repeated newsletters to the audit leads at each NHS trust to ensure they were aware of the inclusion of patients with HGD in the audit. Furthermore, all pathologists with an interest in UGI pathology in England were contacted by the Royal College of Pathologists, to make them aware of the inclusion of patients with HGD in the NOGCA and to remind them of the requirement to refer such patients to the UGI MDT.

The NOGCA HGD dataset collected data on patient characteristics, the process of diagnosis, findings at initial endoscopy, treatment planning, and treatment provided (Appendix C). Within this dataset some variables were mandatory, and had to be entered by the trust in order for the record to

successfully upload onto the audit platform, but other variables were made optional in order to reduce the burden of data collection and maximise the case ascertainment of the audit. The option of 'not known' was also available for several of the data items. A summary of the variables used in this paper are shown in Table 3-1.

Table 3-1 NOGCA dataset variables analysed for patients with HGD, including whether the submission of the variable was mandatory

Mandatory	**Non-mandatory**
Date of endoscopic biopsy	Length of circumferential columnar lining
Hospital of first biopsy	Maximum length of columnar lining
Second biopsy	Date that the treatment plan was agreed
Second biopsy confirmed HGD	Treatment plan agreed at a specialist MDT meeting
Hospital at which treatment plan was made	
Planned treatment modality (Endoscopic mucosal resection, endoscopic submucosal dissection, photodynamic therapy, radiofrequency ablation, argon plasma coagulation, multipolar electrocautery, laser therapy, cryotherapy, no active treatment, surveillance)	
Option of 'not known'	
Route to referral	
Appearance of HGD (flat, nodular, depressed)	
Barrett's segment	
HGD lesion (uni- focal or multifocal)[$]	
Second pathologist confirmation of diagnosis	

[$] Focality of lesion was based on the patient's pathology report

At the analysis stage the cohort of patients with HGD was stratified by patient characteristics (e.g. age at diagnosis, route to referral), whether the diagnosis was confirmed by a second pathologist and whether the case was discussed at a specialist MDT to assess whether these characteristics were associated with the choice of treatment. In addition trusts where treatment was provided were classified as high or low volume (based on whether they managed 15 or more cases a year (20)), and analysis was performed to assess the effect of trust volume on treatment plan.

The chi-squared test was used to compare differences across patient groups, with p-values <0.05 considered statistically significant. Logistic regression models were used to investigate the effect of centre volume on treatment plan.

3.4 Results

3.4.1 Patient Characteristics

465 patients were diagnosed with HGD in England between 1st April 2012 and 31st March 2013, and had records submitted to the NOGCA. Table 3-2 summarises the characteristics of these patients. The mean age of patients at diagnosis was 71.3 years (SD ± 10.5 years), and 333 (71.6%) patients were male. 246 (52.9%) patients were diagnosed following investigation of symptoms, with the majority of the remainder being diagnosed as a result of Barrett's surveillance (n=183, 39.4%).

Table 3-2 Characteristics of patients diagnosed with HGD

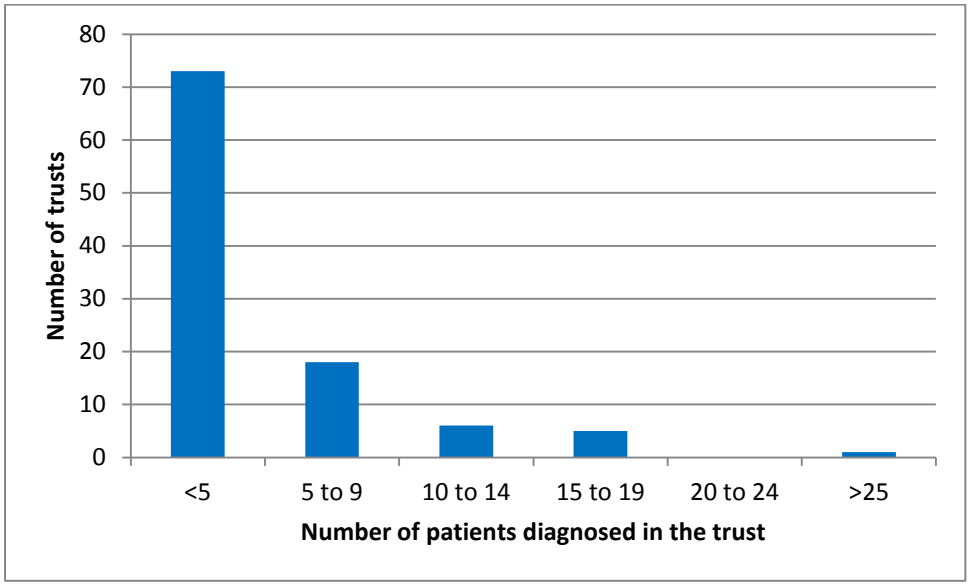
Patient Demographics	
Number of patients, n	465
Age, years (mean ±SD)	71.3 ± 10.5
Sex, n (%*)	
Male	333 (71.6)
Female	132 (28.4)
Source of Referral, n (%*)	
Symptomatic	246 (52.9)
Surveillance	183 (39.4)
Not known	36 (7.7)

* Column percentage

3.4.2 Diagnosis

Of the 154 NHS trusts participating in the NOGCA across England, 103 (67%) submitted data on patients newly diagnosed with HGD. The number of cases diagnosed at each trust varied hugely, median 3 (IQR 2-5) (Figure 3-1).

Figure 3-1 Number of patients diagnosed with HGD at each trust



Where a diagnosis of HGD was made 263 (56.6%) patients had the diagnosis confirmed on a repeat biopsy and 270 (79.4%) patients had the diagnosis of HGD confirmed by a second pathologist (for 125 patients this information was not recorded).

3.4.3 Endoscopic findings

It was not mandatory to submit details on the endoscopic findings to the NOGCA; as a result this information was missing for some cases. Where known the overall patterns of endoscopic findings are summarised in **Table 3-3**. In 112 (24.1%) cases the maximum circumferential length of Barrett's was recorded, the mean circumferential length (±SD) was 4.6cm (±3.7). 42 of these patients had a short segment of Barrett's oesophagus, less than 3cm.

Further details about the endoscopic appearance of the Barrett's segment were available for 245 patients, where this was known 139 (56.7%) cases had an endoscopically visible nodule, 98 (40.0%) had flat mucosa and in 8 (3.3%) cases there was a depressed lesion. The proportion of endoscopies done for symptomatic referrals did not vary according to the whether the lesion was nodular or flat.

Table 3-3 Endoscopic findings of patients diagnosed with HGD

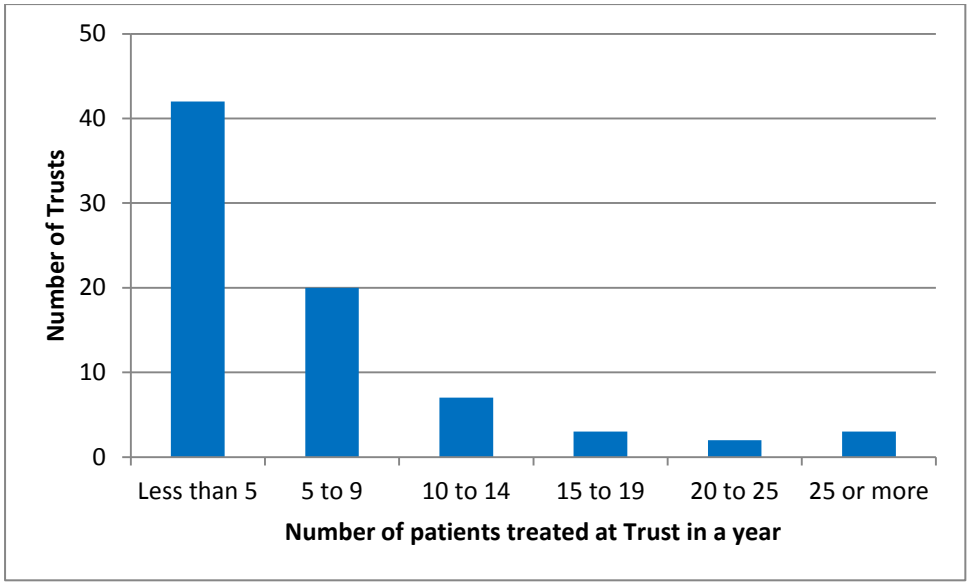
Endoscopic findings	
Length of circumferential Barrett's, n (%*)	
<3cm	42 (37.5)
3-10cm	55 (49.1)
>10cm	15 (13.4)
Missing	353
Endoscopic appearance, n (%*)	
Flat mucosa	98 (21.1)
Nodular lesion	139 (29.9)
Depressed lesion	8 (1.7)
Not known	220 (47.3)
Type of lesion, n (%*)	
Unifocal	136 (29.3)
Multifocal	100 (21.5)
Not known	229 (49.2)

* Column percentage

3.4.4 Management of HGD

30.0% of patients were referred onto a specialist centre for treatment; as a result only 77 trusts treated patients with HGD. Trusts treated between 1 and 34 cases over the year, with only 8 trusts treating 15 or more cases (**Figure 3-2**).

Figure 3-2 Number of patients who had treatment for HGD planned at each trust



Once a diagnosis of HGD was confirmed, 86.0% (374/435) of cases were discussed at an UGI MDT in order to plan their treatment. However, there were frequently significant delays between the date

when HGD was first diagnosed on biopsy and the date the treatment plan was agreed (Table 3-4). The median delay was 36 days (IQR 18-78), but 22 patients (6.3%) waited more than 6 months.

Table 3-4 Delay between date of diagnosis of HGD and date when treatment plan was made

Delay from diagnosis to treatment plan (n=465)	Frequency, n (%*)
< 30 days	156 (44.4)
30-90 days	123 (35.0)
90-180 days	50 (14.3)
>180 days	22 (6.3)
Missing	114

* Column percentage

Choice of primary treatment modality was investigated and is summarised in Table 3-5. Almost a third of patients were planned to receive no active treatment or undergo surveillance alone. This proportion increased significantly as the patient's age increased, such that while 19.5% of patients under 65 were managed by surveillance alone this figure increased to 63.8% for patients aged 85 or more at diagnosis. Patients with flat HGD lesions were more likely to have no planned active treatment than those with nodular lesions (26.5% vs 14.4%, p=0.02), but whether the lesion was multifocal or unifocal did not impact on choice of treatment.

Table 3-5 Management of patients with HGD

	Number of patients, n (%*)
Primary treatment modality (n=465)	
Endoscopic treatment	290 (62.4)
Surgery	26 (5.6)
Surveillance	138 (29.7)
No treatment[$]	11 (2.4)
Choice of endoscopic treatment (n=290)	
Endoscopic mucosal resection	184 (63.4)
Radiofrequency ablation	67 (23.1)
Endoscopic submucosal dissection	15 (5.2)
Other ablative therapy	24 (8.3)

* Column percentage
[$] Patient did not receive any treatment and had no further surveillance endoscopies planned

Additional factors associated with choice of treatment included whether the diagnosis of HGD was confirmed (either on repeat biopsy or by a second pathologist), whether the patient was referred to a specialist centre for treatment, whether the case was discussed at the UGI MDT and the volume of

patients treated at the trust. Patients who had had the diagnosis of HGD confirmed on second biopsy were significantly more likely to receive active treatment (76.8% vs 56.4%, p<0.001), as were patients who had the diagnosis confirmed by a second pathologist (78.2% vs 58.6%, p=0.001). Furthermore patients who had their case discussed at the UGI MDT (73.5% vs 44.3%, p<0.001), or who were referred to a specialist centre for treatment (83.0% vs 59.7%, p<0.001) were more likely to be actively treated. Finally patients managed in high volume NHS trusts (planning treatment for 15 or more cases a year) were more likely to receive active treatment (87.8% vs 55.4%, p<0.001). After adjusting for age and sex, our results showed that patients managed in high volume trusts were five times more likely to receive active treatment than patients managed in lower volume trusts (**Table 3-6**).

Table 3-6 Association between volume of patients who had treatment planned at trust and choice of treatment

Trust volume	N	N (%) who received active treatment	Odds Ratio (95 % CI)	Adjusted Odds Ratio (95 % CI)*
< 5	77	44 (57.1%)	1	1
5 – 9	124	70 (56.5%)	0.97 (0.56-1.73)	0.87 (0.48-1.58)
10 – 14	84	44 (52.4%)	0.82 (0.44-1.54)	0.76 (0.40-1.46)
>=15	180	158 (87.8%)	5.39 (2.86-10.16)	4.94 (2.57-9.51)
Total	465			

* Rates adjusted for patient age (treated as continuous) and sex

For 182 (91.5%) patients who had had an endoscopic resection the outcome of the resection was known. 120 (65.9%) patients had the lesion completely excised but for the remaining 62 (34.1%) patients the excision was incomplete. Where the excision was incomplete 13 patients went on to require an oesophagectomy, while 17 had a further endoscopic resection, and the remaining 32 were managed by surveillance alone. The final pathological diagnosis following endoscopic resection was altered in 89 (48.9%) cases, with 24 (13.2%) patients found to have no evidence of HGD or IMC in the resected specimen and 65 (35.7%) patients found to have evidence of more advanced disease.

3.5 Discussion

For the first time this study has explored the management of patients with oesophageal HGD using patient-level data in England. This study corroborates the findings of previous studies, reporting on clinician's perceptions of the management of HGD, by revealing considerable variation in its management. This study highlighted two key findings. Firstly, a third of patients received no active treatment for HGD. Secondly, patients were more likely to receive active treatment for HGD if they had been referred to a specialist centre or they were managed at a high volume trust. The later finding supports the new BSG recommendation that care of patients with HGD should be centralised (20).

Previous studies have reported that within a segment of Barrett's oesophagus dysplastic changes are frequently focal and microscopic (139, 140). This suggestion is supported by the fact that 57.6% patients in this study had a unifocal lesion and in 40.0% of cases the mucosa was flat. As a result diagnosis of HGD is difficult unless a rigorous biopsy regimen is followed. The BSG currently recommend that when surveying a segment of Barrett's oesophagus biopsies are taken of any visible nodules, with additional random quadrantic biopsies taken every 2 cm (20, 78). If only a few selective biopsies are taken there is an increased chance of a dysplastic lesion being missed (141, 142). In the past studies from both the UK and US have reported that adherence to this recommendation is poor, with the guidelines followed in only half of cases (121, 123, 141). The current NOGCA dataset did not allow further investigation into this, however changes were made to the dataset in September 2015 which will allow this to be studied in future.

Histological criteria for the classification of dysplastic Barrett's were developed in 1988 (143), despite this studies continue to demonstrate significant inter-observer variability in the diagnosis of dysplasia (144). As a result, the BSG guidelines recommend that where a diagnosis of HGD is made the diagnosis is confirmed by a second pathologist (20, 78). This is based on evidence showing that the risk of progression to cancer is higher where the diagnosis of HGD has been confirmed by two pathologists (40, 41). Compliance with this recommendation appears to be improving, in this study 79.4% of patients had the diagnosis of HGD confirmed by a second pathologist. In comparison, only 55% of clinicians reported having the diagnosis of HGD confirmed by a second pathologist in 2001 (123).

Once a diagnosis of HGD is confirmed it is recommended that all cases of HGD that are considered for active treatment are discussed at the UGI MDT to determine the most appropriate course of treatment (20, 78). Adherence to this recommendation was generally good in this study, with 86.0%

cases discussed at an MDT. However 44.3% of patients who had not been discussed at the MDT went on to receive active treatment as well. It is also concerning to note that there were frequently significant delays between diagnosis and discussion at the MDT, with a fifth of patients waiting more than three months. This may reflect 'surveillance by proxy' and puts the patient at risk of disease progression.

In terms of patient management a key finding of this study was that a third of cases of HGD were managed by surveillance alone, this is contrary to current recommended practice (20). The proportion of patients managed by surveillance alone increased as the age of the patient increased, but limitations of the dataset prevented us from investigating whether this was due to increased prevalence of comorbidities making them unfit for treatment or patient/clinician choice. This area needs further exploration and changes to the HGD dataset should make this possible in future. Finally patients who were managed in high volume centres were significantly more likely to receive active treatment, after adjusting patient's age and sex. While this could in part reflect the fact that patients referred on to these high volume centres were already identified as requiring endoscopic treatment, it is also possible that clinicians at non-specialist hospitals are not fully informed about the possible treatment options. As a result patients may be making choices about treatment without adequate information about endoscopic treatment options.

3.5.1 Strengths and limitations

Until now there have been no national databases available which collect data on all patients newly diagnosed with HGD of the oesophagus. This study is therefore unique in providing an insight into the management of HGD on a national level using patient level data, previous national surveys have relied on clinician reported management instead. In the long term it is hoped that by linking this dataset with Hospital Episode Statistics it will be possible to monitor further treatment and long-term outcomes for patients with HGD in England.

The most significant limitation of this dataset was the lack of certainty regarding the case ascertainment achieved by the audit. For patients diagnosed with oesophago-gastric (OG) cancer who have data submitted to the audit, the 2nd audit is consistently achieving around 80% case ascertainment (2, 77, 145). In contrast for HGD there is no unique International Classification of Diseases (ICD-10) code or Systematized Nomenclature of Medicine (SNOWMED) code which can be recorded in national data sources to identify patients with HGD. As a result it is not possible to calculate the actual case ascertainment of the NOGCA for HGD patients. Overall 67% of NHS trusts submitted data for patients with HGD to the NOGCA, while this suggests cases of HGD were missed in the NOGCA given the low incidence of HGD one would not expect all of the smaller trusts to have

diagnosed a case of HGD in a year. Furthermore, it is important to realise that data collection for patients with HGD is managed by the same procedures at a trust level as collection of data for patients with OG cancer, so there is no reason to believe that the case-ascertainment for HGD is not as high as it is for OG cancer.

Uncertainty about the study's case ascertainment does not impact on the major findings of this study, namely the high proportion of patients managed by surveillance alone and the considerable variation in its management across NHS trusts. While the magnitude of any selection bias cannot be quantified, it is possible to confidently infer the direction of any bias. Cases of HGD which were discussed at the UGI MDT were more likely to be considered for active treatment and have their data submitted to the audit. As a result our study is likely to have underestimated the proportion of patients managed by surveillance alone.

The final limitation of the NOGCA HGD dataset was the limited information available about the endoscopic findings and the lack of information about why a particular treatment modality was chosen. Several variables relating to endoscopic findings were not mandatory or had the option of unknown; as a result conclusions relating to the endoscopic findings are limited. In addition the dataset did not collect information on the reason why endoscopic surveillance was chosen. In order to address these limitations substantial changes have since been made to the HGD dataset (Appendix D).

Publication related to this work: Chadwick et al, Gastrointestinal Endoscopy 2016; 83(4): 736-42

4. Systematic Review comparing radiofrequency ablation and complete endoscopic resection in treating dysplastic Barrett's oesophagus

4.1 Introduction

Barrett's oesophagus has long been known to be a significant risk factor for the development of oesophageal cancer (23, 24, 30), with the risk of cancer increasing from 0.1% per year for non-dysplastic Barrett's oesophagus (25, 33) to 5.6% per year where there is evidence of high grade dysplasia (HGD) (36). As a result UK guidelines recommend that patients with HGD of the oesophagus should be considered for treatment to reduce the risk of progression to cancer in future, with the most recent guidelines favouring endoscopic therapy over surgery or surveillance alone (20).

In considering the endoscopic treatment of dysplastic Barrett's oesophagus, it is important to ensure that the entire Barrett's segment is treated because localised resection of only the dysplastic lesion of concern at endoscopy can be associated with significant problems. Firstly, dysplasia is often an incidental finding on random biopsies with no visible lesion. Secondly, early studies demonstrated that localised endoscopic resection was associated with a significant risk of a metachronous lesion developing in the remaining Barrett's segment in future (86, 87). As such current best practice is to remove or ablate the entire Barrett's segment when treating an area of dysplasia. As briefly discussed in Chapter 1 two distinct endoscopic approaches can be used to achieve this endoscopically, complete endoscopic resection and ablation.

Complete endoscopic mucosal resection (CEMR)

Complete endoscopic mucosal resection of the entire Barrett's segment was first reported in humans by Seewald et al (146), with a report by Satodate et al going on to demonstrate the subsequent process of squamous reepithelialisation of the Barrett's segment (147). Since then several studies have been done to show that complete endoscopic resection can achieve complete eradication of Barrett's mucosa (71, 73, 148-155).

CEMR has the advantage of providing a large histological specimen, and may also result in the removal of the genetic alterations associated with neoplasia, which in turn may reduce the risk of progression to neoplasia in future (156). It is also hoped that by resecting the mucosa as deep as the submucosa, one may also be able to reduce the risk of 'buried Barrett's'. Buried Barrett's describes the presence of 'glandular epithelium beneath intact layer of squamous epithelium without communication to the surface' (157). These areas of Barrett's oesophagus are not visible endoscopically, so there is concern about the risk of malignant transformation without detection (158).

However complete endoscopic resection is associated with significant disadvantages, firstly concerns have been raised about the high risk of complications associated with this technique (131), there is also

uncertainty about whether this technique is appropriate when treating long segments of Barrett's oesophagus (146, 156).

Endoscopic Ablation

An alternative to CEMR is using endoscopic ablation to ablate the entire segment of Barrett's mucosa; this allows regrowth of normal squamous mucosa in its place. Ablation can be achieved using a variety of techniques including photodynamic therapy (PDT), argon plasma coagulation (APC), and more recently, radiofrequency ablation (RFA). As discussed in Chapter 1 studies using PDT and APC have reported relatively poor outcomes, with a high risk of future recurrence (101-104, 159). However, over the last decade radiofrequency ablation (RFA) has been developed, this approach uses high-frequency alternating current to destroy the neoplastic mucosa. A recent review has demonstrated superior efficacy and lower complication rates associated with RFA compared to previous ablative techniques (105), as a result RFA is now considered the ablative treatment of choice in Europe.

Ablation of the neoplastic mucosa rather than resection is also associated with several disadvantages. Firstly, this approach does not provide a histological specimen. It is therefore important to ensure that any visible nodules are resected prior to the application of RFA. Secondly there is concern that ablative therapy may allow the persistence of genetic alterations associated with Barrett's oesophagus in the mucosa, thus increasing the risk of future neoplasia (160).

4.2 Aims of this chapter

Despite numerous studies being done in the past to investigate the safety and efficacy of both complete endoscopic resection and radiofrequency ablation individually, only one randomised controlled trial (RCT) has attempted to directly compare the two techniques (131).

So the aim of this chapter is to provide a systematic review of the available of literature, and compare the efficacy and safety of these two techniques. This is important because RFA is substantially more expensive than complete endoscopic resection and may require multiple procedures over 6 months or more. Therefore, in order to justify the use of RFA in the future it must be convincingly proven to be superior to complete endoscopic resection, in terms of both efficacy and risk of complications.

4.3 Methods

The reporting of this systematic review follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (161).

4.3.1 Study selection criteria

For the purposes of this review the inclusion and exclusion criteria were defined as follows:

Inclusion criteria

- Original research papers published in the last 10 years, no language restrictions were in place
- Study population: Adults over 18, with evidence of HGD or intramucosal cancer (IMC) within a segment of Barrett's oesophagus at the point of inclusion
- Aim of treatment: Complete eradication of all dysplasia and intestinal metaplasia in the oesophagus
- Intervention: Complete endoscopic resection or RFA used to treat the neoplastic lesion and the remaining Barrett's mucosa.

Exclusion criteria

- Studies where participants had had previous endoscopic treatment for Barrett's oesophagus (e.g. use of APC or PDT), or previous reflux surgery
- Studies where the patient cohorts overlapped with other studies, these studies were excluded to avoid dual reporting of the same patient cohort. In this situation the paper with the longest follow up and most detailed results was included.

4.3.2 Search Process and Study Selection

In January 2013 a systematic literature search was performed to identify any published studies that met our inclusion and exclusion criteria.

An initial database search of PubMed (MEDLINE), EMBASE and the Cochrane Library was performed. The search strategy is outlined in **Table 4-1**. After removing duplicate records, a total of 251 references were identified.

Table 4-1 MEDLINE and EMBASE search strategy

#	Searches	Results
1	(barret* and (oesophagus or oesophagus)).mp.[mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]	16,967
2	(endoscop* or EMR or RFA or HALO or radiofrequ*).mp.[mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]	392,674
3	Complet*.mp.[mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]	1,726,898
4	1 and 2 and 3	1,213
5	Limit 4 to human	1,023
6	Limit 5 to yr=" 2002-Current"	817
7	Limit 6 to 'review articles' [Limit not valid in Embase; records were retained]	566
8	6 not 7	251

Bibliographies of included articles and the abstracts from the last 3 years of Digestive Disease Week were also reviewed to identify additional studies that should be considered for inclusion. Results from abstracts were only considered if there was sufficient information included in the abstract to demonstrate that the study met the review's inclusion criteria, and was of an acceptable methodological standard.

Two independent observers (myself (GC) and Sheraz Markar (SM)) then screened all the abstracts to determine eligibility for inclusion in the study. Finally full text of potentially relevant publications was reviewed to determine final inclusion in this review.

4.3.3 Summary Measures

The principal outcome measures assessed were complete eradication of dysplasia (CE-D) and intestinal metaplasia (CE-IM) at the end of planned treatment. This was defined as the absence of any dysplasia or intestinal metaplasia, respectively, on oesophageal biopsies taken within 12 months of completing treatment.

'Escape treatment' was allowed during the initial treatment stage. This was defined as any treatment deviation away from the pre-planned treatment regime prior to the completion of the initial treatment regimen. For instance, use of RFA to ablate small areas of residual Barrett's oesophagus after complete endoscopic resection. The frequency with which 'escape' treatment was needed was noted and recorded in **Table 4-3.**

Secondary outcomes assessed included:

- CE-D/CE-IM at follow-up endoscopy, more than 12 months after completion of treatment. During follow up, additional *'touch up'* treatment to treat small areas of recurrence was allowed, but it's use was again clearly documented and reported (Table 4-5, Table 4-6).
- Short term complications, related to the initial endoscopic treatment e.g. bleeding or perforation.
- Long term complications of treatment e.g. oesophageal stenosis, 'buried Barrett's'.
- Long term risk of cancer recurrence.

4.3.4 Data Extraction

Data was independently extracted from relevant publications by myself and SM, using a standardised extraction template (Table 4-2).

Table 4-2 Data extraction template

Study Details	
Where was study performed?	Country, type of hospital, single or multicentre.
Study years	
Specific inclusion and exclusion criteria	
Assessment of study quality	Guided by the Newcastle-Ottowa assessment scale.
Patient Characteristics	
Number of patients	
Age of patients	Including median or mean age, and range of ages.
Length of Barrett's treated	Including median or mean length, and range.
Presence of nodular lesion	
Intervention	
Planned Intervention	CEMR or RFA.
Number of treatment sessions	
Use of 'escape treatment'	Number requiring this and type of treatment used e.g. APC.
Use of acid suppressive medication	Use of proton pump inhibitors, hydrogen receptor antagonists and sucrulfate.
Outcome Assessment	
Pathology review	Number of pathologists who reviewed the sample, and access to specialist pathologists
Biopsy protocol	Details of where biopsies were taken from, including those taken from the neo-squamous columnar junction and just distal to it.

Table 4-2 Data extraction template (continued)

Results	
CE-D and CE-IM at completion of treatment	
Follow up duration	Time in months patient was followed up for, starting from once patient finishes planned treatment (time=0). Where follow up duration was only reported from the start of treatment this was also recorded.
CE-D and CE-IM at end of follow up	
Incidence of short term complications	Including details of management strategy
Incidence of long term complications	Including details of management strategy
Prevalence of Buried Barrett's	Were biopsies taken specifically looking for Buried Barrett's and if so what was the incidence?
Incidence of cancer recurrence or progression of HGD to cancer	

4.3.5 Presentation of Results

Results of the studies reviewed are presented on an intention to treat (ITT) basis. Patients were excluded from analysis if the initial endoscopy revealed the lesion was not amenable to endoscopic treatment (e.g. due to submucosal invasion) and the patient was subsequently referred for alternative treatment e.g. surgery.

Where patients were lost to follow up or did not complete treatment, they had success of treatment determined by most the recent histology results. Where this was unknown, they were considered to be treatment failures.

It is important to note that some of the retrospective studies did not report results on an ITT basis, and only reported results for patients who successfully completed treatment and follow up, these studies are highlighted in the results (Table 4-5, Table 4-6).

4.3.6 Statistical Methods

Summary estimates for effectiveness outcomes were generated by pooling results from the prospective studies to calculate an overall mean and 95% confidence intervals (95% CI). Retrospective studies were excluded from this analysis because a significant proportion of these did not report results on an ITT basis.

Overall means for all the studies were also calculated for the risks of short and long-term complications.

4.3.7 Assessment of study quality

The majority of studies were observational cohort studies (162), so the Newcastle-Ottawa Scale for cohort studies was chosen to assess the quality of included studies. Details of this assessment scale are provided in Appendix E.

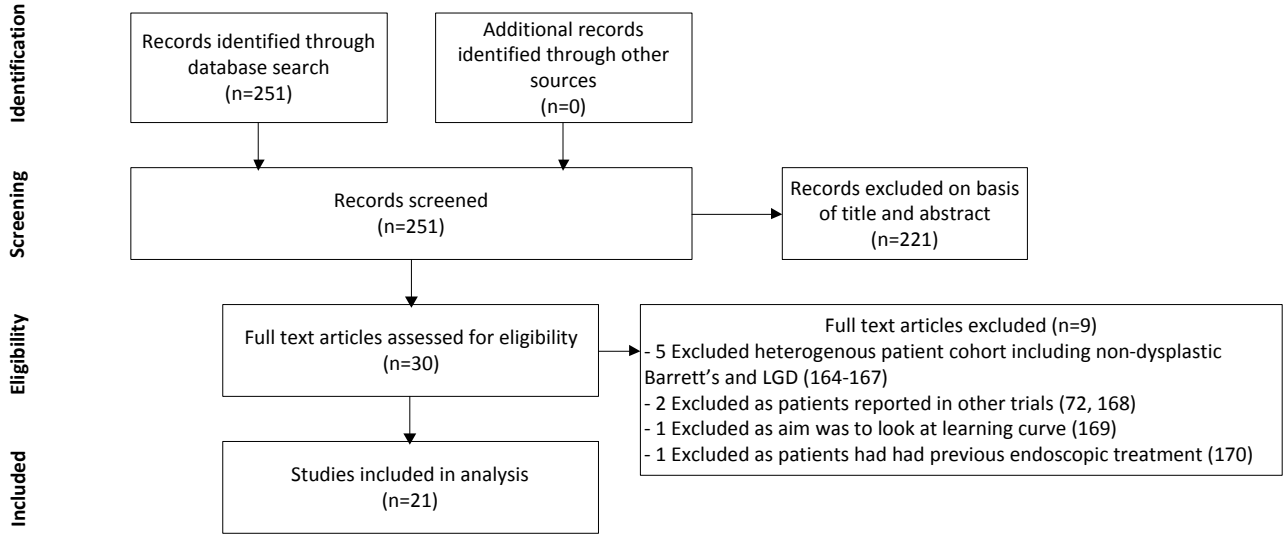
4.4 Results

4.4.1 Search Results

The initial search identified 1,213 potentially relevant papers (**Table 4-1**). In line with the study's exclusion criteria, 190 studies not conducted on humans and 206 papers published before 2002 were excluded from this review. A further 566 papers were review articles, and these were also excluded.

This left us with 251 papers to be considered for inclusion, each paper was reviewed independently by GC and SM to determine whether the study met this reviews inclusion and exclusion criteria. On the basis of the title and abstract 221 studies were excluded, and after full text review a further 9 papers were excluded (**Figure 4-1**) (72, 163-170). Repeating the search in October 2013 yielded one additional paper that met the study inclusion criteria (171). None of the abstracts identified included sufficient detail for inclusion in this review. There was no disagreement between the two reviewers with regard to which studies that should be included in this review.

Figure 4-1 PRISMA flow diagram of study selection process



This left 22 studies for inclusion in this review, including 18 cohort studies (10 evaluating complete endoscopic resection alone (71, 73, 146, 149-155), and 8 evaluating RFA alone (172-179)), and 2 RCTs (1 RFA vs Sham (180), and 1 RFA vs complete endoscopic resection (131)). The final two studies were follow up papers, providing longer term results from previous trials (171, 181). The design of individual studies is summarised in **Table 4-3**.

Table 4-3 Summary of study design and participant characteristics for all included studies

Study					Enrolled Patients			Planned Intervention				
1st Author	Country	Study Years	Study Design	No of centres in study	N	Median Age (Range or IQR) or mean* (± SD)	Median Length of Barrett's in cm (Range or IQR) or mean* (±SD)	Planned treatment	Overall Median no. treatment sessions (Range/IQR) or mean*	Reported use of 'escape' treatment		Use of acid suppressive medication after treatment
										N (%)	Type of treatment	
Van Vilsteren (131)	Netherlands and Germany	2006 - 2008	Randomised Control Trial	Two	22	69 (55-73)	C2M4 (IQR C1-3, M2-5)	RFA arm	3 (IQR 3-4)	4 (18%)	2 hot biopsy, 1 ER, 1 ER + APC	Triple therapy
					25	68 (45-88)	C2M4 (IQR C1-3, M2-5)	CEMR arm	2 (IQR 1-3)	8 (32%)	5 RFA, 3 APC	Triple therapy
Shaheen (181)	US	NR		Multicentre	61	66* (±8.8)	5.2* (±2.1)	RFA follow up trial	NR	NR	NR	PPI
Shaheen (180)	US	NR		Multicentre	42	66* (±9.1)	5.3* (±1.9)	RFA vs Sham	NR	NR	NR	PPI
Phoa (171)	Netherlands	NR	Prospective Cohort study	Multicentre	55	65* (±9.6)	C4M5 (IQR C1-5, M4-8)	RFA follow up trial	NR	NR	NR	Triple therapy
Chung (73)	Australia	2003 - 2010		Multicentre	77	65 (IQR 58-70)	C0M2 (IQR C0-1, M1-3)	CEMR	2 (IQR 1-3)	NR	NR	PPI
Pouw (172)	Europe	NR		Multicentre	24	65* (±9.8)	C6M8 (C2-9, M4-10)	RFA	3 (IQR 3-4)	2 (8%)	2 ER	Triple therapy
Sharma (173)	US	2006 - 2007		Single	24	73 (51-81)	6 (1-12)	RFA	2(IQR 3-4)	2 (8%)	2 ER	PPI
Gondrie (174)	Netherlands	2005		Single	11	60 (57-67)	5 (4-7)	RFA	5	1 (9%)	1 ER	Triple therapy
Gondrie (175)	Netherlands	2005 - 2006		Single	12	70 (IQR 53-76)	7 (IQR 6.5-8)	RFA	4	1 (8%)	1 ER	Triple therapy
Peters (149)	Netherlands	2003 - 2004		Single	39	65* (±7.9)	4 (3-5)	CEMR	3 (2-3)	34 (87%)	34 APC	Triple therapy
Giovannini (150)	France	1999 - 2002		Single	21	63* (42-75)	3.5*(2-5)	CEMR	2	2 (10%)	2 CRT	PPI
Seewald (146)	Germany	2000 - 2002		Single	12	64 (43-88)	5(1-10)	CEMR	2-3	NR	NR	PPI

Table 4-3 Summary of study design and participant characteristics for all included studies (continued)

Study					Enrolled Patients			Planned Intervention				
1st Author	Country	Study Years	Study Design	No of centres in study	N	Median Age (Range or IQR) or mean* (± SD)	Median Length of Barrett's in cm (Range or IQR) or mean* (±SD)	Planned treatment	Overall Median no. treatment sessions (Range/IQR) or mean*	Reported use of 'escape' treatment		Use of acid suppressive medication after treatment
										N, %	Type of treatment	
Kim (176)	US	2006 -2011	Retrospective Cohort	Single	65	69 * (±10)	4.4 * (±3.1)	EMR/RFA	3.5 *	NR	NR	PPI
					104	64 * (±11)	4.8 * (±3.4)	RFA only	2.8 *	NR	NR	PPI
Gerke (151)	US	2006 - 2010		Multicentre	41	70 (49-85)	3 (1-10)	CEMR	2 (1-6)	3 (7%)	3 APC	PPI
Pouw (152)	Europe	2000 - 2006		Multicentre	169	64 (57-71)	3 (2-5)	CEMR	2 (2-3)	103 (61%)	103 APC	PPI
Lyday (177)	US	2004 - 2008		Multicentre	31	NR	NR	RFA	NR	NR	NR	NR
Vassilou (178)	NR	2005 - 2009		Single	12	NR	NR	RFA	NR	NR	NR	PPI
Chennat (71)	US	2003 - 2008		Single	49	67 * (49-86)	2 (1-12)	CEMR	1-4	23 (47%)	19 APC, 4 RFA	PPI
Pouw (153)	Belgium	2001 - 2006		Single	34	67 * (±10)	C1M4 (C0-2, M2-5)	CEMR	2 (IQR 1-2)	27 (79%)	27 APC	PPI
Ganz (179)	US	2004 - 2007		Multicentre	92	68 (IQR 59-75)	6 (IQR 5-8)	RFA	NR	NR	NR	PPI
Larghi (154)	US	2001 - 2004		Two	24	64 * (±12)	2.5 (1-8)	CEMR	2 (1-5)	13 (54%)	13 APC	PPI
Lopes (155)	France	1999 - 2005		Single	41	66 * (±11)	4.9 * (±3.4)	CEMR	1.5 *	7 (17%)	6 APC, 1 CRT, 1 CRT + APC	PPI

IQR – Interquartile range, SD – Standard deviation of mean, NR – Not reported, NA – Not Applicable
US – United States, CxMx – Length of Barrett's according to Prague Criteria
ER – Endoscopic resection, APC- Argon Plasma Coagulation, CRT - Chemoradiotherapy
PPI – Proton Pump Inhibitor, Triple therapy – PPI and hydrogen receptor antagonist and sucrulfate

Overall the studies included 1,087 patients (532 treated with CEMR and 555 with RFA). Some patients included in these studies had not completed treatment, so these patients were only considered in analysis looking at the safety of the two techniques and not analysis looking at treatment efficacy. Individual studies were small, ranging from 11 to 77 patients for prospective studies and 12 to 169 patients for retrospective studies. The three largest studies were all retrospective (152, 176, 179).

Patient characteristics were similar across studies (**Table 4-3**), except for median length of Barrett's which varied between 2cm (73) and 10cm (178).

All studies using RFA as the primary treatment modality included some patients with nodular disease. In the study by Shaheen et al some patients had had an endoscopic resection performed just prior to inclusion in the study (180). Where RFA was the treatment modality of choice, the initial endoscopic resection did not extend beyond the nodule of concern and in nearly all cases a single specimen was removed and the resection was completed at a single session (Table 4-6). Only one study directly compared outcomes for patients with and without resections prior to RFA (176).

4.4.2 Methodological Quality

Methodological quality of included studies was formally assessed using the Newcastle-Ottawa scale for cohort studies (Table 4-4).

All studies included patients with confirmed HGD or IMC, and had a representative patient population. The papers all described the application of the two techniques clearly and in a reproducible manner.

The majority of included studies were observational in design, looking at patient outcomes after treatment. Only three studies had a control group (131, 180, 181), and only one of these studies directly compared the two techniques (131). These three studies scored highly on comparability, because patients were randomly allocated across the groups.

All studies assessed outcomes based on independent assessment of histological findings. There was most difference between the studies in relation to their follow period and how they accounted for patients lost to follow up. Follow up periods were generally short and inconsistently reported, with some studies reporting follow up duration from the start of treatment instead of completion, meaning that actual follow up period may have been considerably shorter (173, 177-179, 181). Several studies reported follow up periods of less than 1 year after completion of treatment (146, 149, 174, 176, 180), while four studies did not report results on an intention to treat basis (177-179, 181).

Table 4-4 Newcastle-Ottawa assessment of study quality

	Selection				Comparability	Outcome		
	Representiveness of the exposed cohort	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration outcome of interest not present at start**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was the follow up long enough for outcomes to occur**	**Adequacy of follow up cohorts**
Van Vilsteren (131)	1	1	1	1	2	1	1	1
Shaheen (181)	1	1	1	1	2	1	1	0 (Follow up not reported on ITT basis)
Shaheen (180)	1	1	1	1	2	1	0	1
Phoa (171)	1	No control	1	1	No control	1	1	1
Chung (73)	1		1	1		1	1	1
Pouw (172)	1		1	1		1	1	1
Sharma (173)	1		1	1		1	1	1
Gondrie (174)	1		1	1		1	1	1
Gondrie (175)	1		1	1		1	0	1
Peters (149)	1		1	1		1	0	1
Giovannini (150)	1		1	1		1	1	1
Seewald (146)	1		1	1		1	0	1
Kim (176)	1		1	1		1	0	1
Gerke (151)	1		1	1		1	1	1
Pouw (152)	1		1	1		1	1	1

Table 4-4 Newcastle-Ottawa assessment of study quality (continued)

	Selection				Comparability	Outcome		
	Representiveness of the exposed cohort	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration outcome of interest not present at start**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was the follow up long enough for outcomes to occur**	**Adequacy of follow up cohorts**
Lyday (177)	0 (Unknown for HGD subset)	No control	1	1	No control	1	1	0 (Follow up not reported on ITT basis)
Vassilou (178)	0 (Unknown for HGD subset)		1	1		1	1	0 (Follow up not reported on ITT basis)
Chennat (71)	1		1	1		1	1	1
Pouw (168)	1		1	1		1	1	1
Ganz (179)	1		1	1		1	Unknown	0 (Follow up not reported on ITT basis)
Larghi (154)	1		1	1		1	1	1
Lopes (155)	1		1	1		1	1	1

4.4.3 Treatment Outcomes

Treatment technique was evenly split between the studies, with 11 using complete endoscopic resection and 12 using RFA.

Where complete endoscopic resection was used, the median number of resection sessions required was two. However in 9 studies additional 'escape' treatment was required during the treatment stage, most commonly APC to treat small areas of residual Barrett's (**Table 4-3**).

Where RFA was the primary modality, both circumferential and focal ablation was available in all except one study by Ganz et al where focal RFA was not available (179). Standard energy settings and procedure protocols were used in all except two studies, one study by Lyday et al used lower energy settings for circumferential ablation (177), the other by Gondrie et al who only used the 'double-double' technique for focal ablation in the later part of their study (174). Patients received a median of 2 RFA sessions, one circumferential and one focal. 'Escape' treatment was only required in 5 studies, this commonly included resection of a residual nodule (131, 172-175) and APC (131).

The short term efficacy of treatment was assessed at the end of endoscopic therapy. Where complete endoscopic resection was used, complete eradication of dysplasia was achieved in 83-100% of patients, and complete eradication of intestinal metaplasia was achieved in 80-96% patients at the end of treatment (**Table 4-5**). Respective figures after RFA were 81-100% CE-D, and 55-100% CE-IM (**Table 4-6**).

Several of the retrospective studies did not present results on an intention to treat basis, so in order to calculate the overall mean results for treatment efficacy the results from only the prospective studies were pooled. On this basis, complete eradication of dysplasia was achieved in 95% (95% CI 87-99%) after complete endoscopic resection, and 92% (95% CI 85-96%) after RFA. The corresponding figures for complete eradication of intestinal metaplasia were 89% (95% CI 79-95%) and 88% (95% CI 81-93%).

Good long term treatment durability was seen with both complete endoscopic resection and RFA. Overall 85-100% of patients who received complete endoscopic resection had no evidence of dysplasia at follow up, compared to 79-100% of patients treated with RFA. Respective figures for eradication of intestinal metaplasia were more variable, 75-100% after complete endoscopic resection and 54-100% after RFA.

Reported follow up periods were relatively short, with a median follow up of 21 months (range 15-61) after RFA and 23 months (range 17-32) after complete endoscopic resection. Furthermore the range of follow up periods reported within studies varied hugely, for instance Lopes et al reported a median follow up of 32 months, but this ranged between 0-83 months for individual patients in this study (155). Nonetheless it reassuring to note that a recent study by Phoa et al reported good treatment durability after 5 years follow up,

with successful maintenance of CE-IM in 54/55 (98.2%) patients (with only 3 patients requiring additional 'touch up' treatment during follow up to achieve this level of response).

Use of 'touch up' treatment to maintain durability of successful eradication was more frequent among patients who had been treated with complete endoscopic resection than those treated with RFA (Table 4-5, Table 4-6). After complete endoscopic resection 27 patients required a repeat resection for a dysplastic lesion, while RFA and APC were also used in several studies to treat small areas of recurrence. In contrast use of 'touch up' treatment after RFA was limited to three studies, one used RFA to treat small areas of recurrence (although it was not reported how many patients required this) (180), while two studies used repeat endoscopic resection to treat IMC (171, 173), and one of these studies also treated a patient with recurrent low grade dysplasia using APC (171).

Table 4-5 Histological outcomes after complete endoscopic resection

Study	End of Treatment			Follow up				Buried Barrett's (%)
1st Author	No. patients	Intention to Treat (only oesophageal biopsies), n (%)		Median time from treatment end in (months)	Additional 'touch up' treatment during FU for recurrence	Intention to Treat (only oesophageal biopsies), n (%)		
		CE-D	CE-IM			CE-D	CE-IM	
Van Vilsteren (131) (CEMR arm)	25	25 (100%)	24 (96%)	20	1 IMC at NSCJ treated with ER	25 (100%)	24 (96%)	2 (8%)
Chung (73)	77	100% 'technical success', endoscopic absence of visible Barrett's but no biopsies taken		17	-	70/73 (96%)	68/73 (93%)	0 (0%)
Peters (149)	39	36 (92%)	33 (85%)	-	-	-	-	4 (11%)
Giovannini (150)	20	-	-	18	2 HGD treated ER	17 (85%)	15 (75%)	-
Seewald (146)	12	100% 'technical success', endoscopic absence of visible Barrett's but no biopsies taken		-	-	-	-	-
*Gerke (151)	41	34 (83%)	33 (80%)	24	2 1 LGD treated ER/RFA 1 IM treated ER	28/28(100%)	28/28 (100%)	-
**Pouw (152)	169	165 (98%)	146 (86%)	27	9 3 HGD/IMC at NSCJ treated ER, 6 IM treated ER/APC/biopsy	156/160 (98%)	146/160 (91%)	5 (3%)
Chennat (71)	32	-	-	17	-	32 (100%)	31 (97%)	1 (3%)
Pouw (153)	34	34 (100%)	31 (91%)	23	3 2 HGD treated ER 1 LGD treated APC	31 (91%)	26 (76%)	-
Larghi (154)	24	-	-	28	1 IMC at NSCJ treated ER	24 (100%)	22 (92%)	2 (8%)
Lopes (155)	41	-	-	32	10 Treated repeat ER, with APC in 2 & CRT in 1	-	37 (90%)	-

IMC – Intramucosal cancer, LGD – Low grade dysplasia
APC – argon plasma coagulation, CRT – chemoradiotherapy, ER – endoscopic resection, NSCJ – Neosquamous columnar junction
* Reported results at follow up for 32 patients where complete remission of IM initially, 4 of these dropped as only had LGD at initial endoscopy.
** Reported results at follow up for 160 patients who achieved CE-D at end of treatment and continued follow up.

Table 4-6 Histological outcomes after RFA

Study		Use of ER prior to RFA			End of Treatment		Follow up				Buried Barrett's (%)
1st Author	No. patients	Number (%)	Median number of resection sessions	Median number of resections per session	Intention to Treat (only oesophageal biopsies) CE-D	CE-IM	Median time from treatment end (months)	Additional 'touch up' treatment during FU for recurrence	Intention to Treat (only oesophageal biopsies) CE-D	CE-IM	
Van Vilsteren (131) (RFA arm)	22	18 (82%)	NR	NR	21 (95%)	21 (95%)	15	-	21 (95%)	21 (95%)	0
*Shaheen (181)		0	-	-	-	-	24 **	Some patients had touch up RFA	50/54 (93%)	48/54 (89%)	-
		0	-	-			36 **	Some patients had touch up RFA	23/24 (96%)	-	-
Shaheen (180)	42	0	-	-	34 (81%)	31 (74%)	-	-	-	-	-
Phoa (171)	55	40 (73%)	NR	NR	Not reported as patients followed up from other reported studies		61	3 1 LGD treated APC 2 IMC treated ER	54 (98%)	54 (98%)	0
Pouw (172)	24	23 (96%)	1	NR	24 (100%)	23 (96%)	22	-	24 (100%)	22 (92%)	0
Sharma (173)	24	2 (8%)	1	1	-	-	23 **	2 IMC found at 3 months treated with ER	19 (79%)	16 (67%)	0
Gondrie (174)	11	6 (55%)	1	1	11 (100%)	11 (100%)	14	-	11 (100%)	11 (100%)	0
Gondrie (175)	12	7 (58%)	1	2	12 (100%)	12 (100%)	-	-	-	-	0

IMC – Intramucosal cancer, LGD – Low grade dysplasia
APC – argon plasma coagulation, ER – Endoscopic resection, NR – Not reported
* Studies where results are not reported on ITT basis, as information regarding rest of cohort was not available.
** Studies in which follow up duration was recorded from the first endoscopic treatment, not the end of initial planned treatment.

Table 4-6 Histological outcomes after RFA (continued)

Study		Use of ER prior to RFA			End of Treatment		Follow up				Buried Barrett's (%)
1st Author	No. patients	Number (%)	Median number of resection sessions	Median number of resections per session	Intention to Treat (only oesophageal biopsies)		Median time from treatment end (months)	Additional treatment during FU	Intention to Treat (only oesophageal biopsies)		
					CE-D	CE-IM			CE-D	CE-IM	
Kim (176) (ER/RFA arm)	50	65 (100%)	1	1	47 (94%)	44 (88%)	-	-	-	-	-
Kim (176) (RFA only arm)	98	0	-	-	81 (83%)	76 (78%)	-	-	-	-	-
*Lyday (177)	31	7 (23%)	NR	NR	26 (84%)	17 (55%)	20 **	-	10/10 (100%)	8/10 (80%)	0
*Vassilou (178)	12	NR	NR	NR	-	-	20 **	-	10 (83%)	8 (67%)	0
*Ganz (179)	92	24 (26%)	NR	NR	-	-	12**	-	74 (80%)	50 (54%)	-

IMC – Intramucosal cancer, LGD – Low grade dysplasia
APC – argon plasma coagulation, ER – Endoscopic resection, NR – Not reported
* Studies where results are not reported on ITT basis, as information regarding rest of cohort was not available.
** Studies in which follow up duration was recorded from the first endoscopic treatment, not the end of initial planned treatment.

4.4.4 Short term complications

In order to calculate the short term complication rates associated with both techniques results from both the prospective and retrospective studies were pooled for each treatment modality. The most frequent complication reported after complete endoscopic resection was bleeding, reported in 57 patients (10.7%), while oesophageal perforation was only reported in 12 (2.3%) patients (with all except one of these cases were managed conservatively (152)) (Table 4-7). However reported complication rates did vary significantly across studies, with two studies reporting bleeding in a third of patients (146, 151), and several other studies not reporting any cases (71, 149, 152).

In contrast very few patients treated with RFA suffered an immediate complication of treatment (Table 4-8), with bleeding only reported in 6 (1.5%) patients and no reported perforations attributable to RFA.

4.4.5 Long term complications

The most common long term complication after complete endoscopic resection was stricture formation, affecting 38% (201/529) of patients. While most strictures were successfully treated with simple dilatation, some strictures were relatively resistant to treatment with 9 patients requiring a stent insertion and 6 patients requiring incision of a stricture. In contrast strictures were a relatively rare occurrence after RFA, affecting only 4% (16/403) of patients and most of these patients had had a previous endoscopic resection. Finally buried Barrett's was infrequently reported across all studies, with only 14 cases reported after complete endoscopic resection (3.8%) and no reported cases after RFA (Table 4-7, Table 4-8).

Nonetheless if endoscopic treatment is to replace surgery in the management of dysplastic Barrett's oesophagus, then it is very important to establish the risk of progression to cancer in future. Given the limited and varied follow up periods reported in studies to date, it was not possible to calculate the incidence of recurrence per year. Despite these limitations reported rates of recurrence did appear to be low affecting only 9 (1.7%) patients treated with complete endoscopic resection and 11 (2.0%) patients treated with RFA. 6 of the cases detected after RFA may have been prevalent cancers, as they were detected within 3 months of starting treatment. If you consider this to be the case, the risk of cancer developing during follow-up after RFA was 0.9% (5/539).

Table 4-7 Complications after complete endoscopic resection

Study		Adverse Events				Rates of progression to cancer
		Short Term			Long Term	
1st Author and Year	Number Patients	Acute bleeds endoscopically treated (%)	Perforation (%)	Overall short term adverse event rate (%)	Stenosis requiring treatment (%)	
Van Vilsteren (131) (CEMR arm)	25	5 (20%)	1 (4%)	7 (28%)	22 (88%) Treated median 4 dilatations, 1 required incision	1/25 IMC at NSCJ treated ER
Chung (73)	77	7 (9%)	0	8 (10%)	24/74 (32%) Treated median 3 dilatations	0/77
Peters (149)	39	0	1 (3%)	3 (8%)	10 (26%) Treated median 5 dilatations	0/39
Giovannini (150)	21	4 (19%)	0	4 (19%)	0	0/21
Seewald (146)	12	4 (33%)	0	4 (33%)	2 (17%) Treated with dilatation	0/12
Gerke (151)	41	13 (32%)	2 (5%)	15 (37%)	18 (44%) Treated with median 3 dilatations, 1 required incision and 2 stents	0/41
Pouw (152)	169	0	4 (2%) (1 required surgery)	8 (5%)	84 (50%) Treated median 3 dilatations, 4 required incision and 2 stents	1/169 Persistent HGD progressed to cancer treated surgically
Chennat (71)	49	0	0	2 (4%)	18 (37%) Treated median 1.5 dilatations, 2 also required steroid injection and 1 stent.	0/49
Pouw (174)	34	14/55 (25%) sessions	2 (6%)	-	19 (56%) Treated median 2 dilatations, 4 required stents	1/34 Recurrent cancer treated surgically
Larghi (154)	24	2 (8%)	0	2 (8%)	3 (13%) Treated median 1 dilatation	1/24 HGD progressed to IMC treated ER
Lopes (155)	41	8 (20%) (1 with perforation)	2 (5%)	9 (22%)	1 (2%) Treated with dilatation	5/41 1 died of cancer 24mths after EMR, 1 treated surgically and 3 treated with repeat ER
OVERALL				**62/498 (12.5%)**	**201/529 (38.0%)**	**9/532 (1.7%)**

IMC – Intramucosal cancer, ER – Endoscopic resection, NSCJ – Neosquamous columnar junction

Table 4-8 Complications after RFA

Study		Adverse Events				Rates of progression to cancer (%)
		Short Term			Long Term	
1st Author	Number Patients	Acute bleeds endoscopically treated (%)	Perforation (%)	Overall short term adverse events rate (%)	Stenosis requiring treatment (%)	
Van Vilsteren (131) (RFA arm)	22	2 (9%) Occurred after ER	0	3 (14%)	3/21 (14%) Treated median 3 dilatations. All had had large ER prior to RFA.	0/22
Pouw (172)	24	0	1 (4%) After initial ER	2 (8%)	1 (4%) Treated with 5 dilatations, had had widespread ER prior to RFA	0/24
Sharma (173)	24	0	0	0 (0%)	0	2/24 Diagnosed at 3 months, likely prevalent cancer treated successfully with ER
Gondrie (174)	11	0	0	1 (9%)	0	0/11
Gondrie (175)	12	0	0	0	1 (8%) Treated with 1 dilatation, had had prior ER	0/12
*Kim (176) (ER/RFA arm)	65	2 (3%) Occurred after ER	0	2 (3%)	3 (5%) Treated with median 1 dilatation	0/65
Kim (176) (RFA only arm)	104	2 (2%)	0	2 (2%)	8 (8%) Treated with median 1 dilatation	2/104
*Ganz (179)	142	0	0	0	0	2/142 Diagnosed at 3 months, likely prevalent cancer
Shaheen (181)	63	Long term follow up trial				No additional cases
Shaheen (180)	42	Unknown heterogeneous group reported including HGD and LGD within Barrett's.				1/42 Diagnosed at 3 months, likely prevalent cancer treated successfully with ER
Phoa (171)	54	Long term follow up trial				2/54 Treated successfully with ER
*Lyday (177)	39	Unknown, heterogeneous group reported including HGD, LGD and non-dysplastic Barrett's.				2/39 1 Diagnosed at 2 months, likely prevalent cancer. 1 diagnosed at 4 months treated with CRT
Vassilou (178)	25	Unknown, heterogeneous group reported including HGD, LGD and non-dysplastic Barrett's.				0
OVERALL				**10/404 (2.5%)**	**16/403 (4.0%)**	**11/539 (2.0%)**

* Results from the safety cohort selected for inclusion in this review

LGD – Low grade dysplasia, ER – Endoscopic resection, CRT – Chemo radiotherapy

4.5 Discussion

With the publication of the most recent BSG guidelines for the management of Barrett's oesophagus, there has been a shift in the approach taken to manage the disease. Until recently oesophagectomy has been considered the treatment of choice for dysplastic Barrett's oesophagus, due to the risk of disease recurrence with localised endoscopic therapies (78). However significant advances in endoscopic techniques now allow the endoscopic treatment of dysplastic Barrett's and the remaining Barrett's segment, as a result endoscopic treatment is now replacing surgery as the treatment of choice for HGD (20).

This review aimed to determine whether there was a significant difference in the efficacy and safety of two commonly used endoscopic techniques, complete endoscopic resection and RFA, in the management of dysplastic Barrett's. Only one RCT which compared the two approaches directly was identified (131), with the rest of the evidence presented in this review coming from observational cohort studies and one RCT comparing RFA to sham treatment (180).

4.5.1 Success of Treatment

In reviewing the efficacy of both treatments it is important to consider both the initial treatment success, and the long term durability of treatment. Results from this review suggest that both complete endoscopic resection and RFA produce high rates of complete eradication of dysplasia and intestinal metaplasia at the end of treatment. However in order to achieve these results additional 'escape' treatment was required in 50% of patients treated with complete endoscopic resection, compared to only 11% of patients treated with RFA. This is important because it impacts on the overall number of treatment sessions required. Nonetheless it is encouraging to note that 'escape' treatment, with either resection or radiofrequency ablation, appears to be safe and effective. In this respect RFA is superior to other ablative approaches, which can cause deeper scarring preventing future endoscopic resection.

It has previously been suggested that resection of a nodule prior to RFA may impact on the efficacy of RFA, with Okoro et al reporting that this reduced the rate of CE-IM from 74% to 43% (164). However this study included patients with non-dysplastic Barrett's oesophagus, which may have resulted in selection bias causing baseline differences between the groups because it is likely that only more advanced cases required resection of a nodule prior to ablation. Only one study was identified in this review which compared outcomes for patients with dysplastic Barrett's with and without resection of nodule prior to RFA (176). This study reported no significant differences in treatment efficacy and complication rates between the two groups. This is important because the

proportion of patients who required resection of a nodule prior to RFA varied significantly between studies (between 8% (173) and 96% (152)), so it is reassuring to note that this is unlikely to have impacted on outcomes.

For patients treated with RFA there was significant variability in the success of treatment. This variability in part reflects different equipment available for the studies. If one considers the two studies with the lowest long term durability of CE-IM, in one study focal RFA was not available (179) and in the other focal RFA was only available in the later study years (180). This may have resulted in small areas of residual Barrett's oesophagus being left untreated, because further circumferential RFA was not justified. Lower rates of CE-IM were also seen where the regimen for washing the probe was less intensive (179), since then more intensive standardised washing regimens have been introduced.

In the past attempts have been made identify patient factors which predict the efficacy of RFA using sub-group analysis, but results have been variable. Shaheen et al showed that although patients who were younger, with shorter segments of Barrett's and shorter history of dysplasia were more likely to respond to RFA, none of these factors were significant on logistic regression analysis (181). A more recent study by Van Vilsteren et al found that poor response to RFA after 3 months of treatment may predict failure to successfully eradicate intestinal metaplasia (182). Active reflux oesophagitis has also been reported to be associated with lower success rates, this may account for the high rates of successful eradication in studies using triple acid suppression (131, 149, 152, 174, 175).

Finally it is important realise that studies followed variable biopsy regimens when assessing the success of treatment. Current UK guidelines recommend that quadratic biopsies are taken every 2cm from the entire Barrett's segment (20), but debates continue regarding the relevance of histology findings at and just distal to the neosquamous columnar junction (NSCJ) (183). Morales et al reported that 25% of the healthy population had evidence of intestinal metaplasia in the cardia, suggesting this finding is clinically irrelevant (184). However, other studies have suggested that the risk of recurrence of dysplasia was highest in this area (185, 186). For this review outcomes for treatment efficacy were reported based on the absence of intestinal metaplasia and dysplasia on oesophageal biopsies only. If one took the alternative approach and considered results of biopsies taken at and just distal to the NSCJ junction as well, this had minimal impact on rates of eradication of dysplasia but did reduce rates of eradication of intestinal metaplasia. However, it was interesting to note that several studies reported recurrence of cancers around the NSCJ (131, 154, 172). These

results suggest that while it is important to biopsy this area and treat dysplasia if found, the relevance of finding intestinal metaplasia is still questionable.

The study went on to evaluate the durability of treatment, this analysis was associated with several problems. Firstly follow up periods reported were short, and secondly there was lack of standardisation across studies in how follow up periods were reported. The durability of RFA in treating non-dysplastic Barrett's is well established, with Fleischer et al reporting that 92% of patients maintained CE-IM 5 years after treatment (187), however evidence with regard to the longer term durability of RFA in treating dysplastic Barrett's is more sparse. A recent study by Phoa reported good durability of RFA after 5 years follow up (171). The rest of the studies included in this review relied on outcomes after less than two years follow up, except a study by Shaheen et al who reported outcomes at three years but only for a select subgroup of patients who had achieved complete eradication of intestinal metaplasia at two years. In contrast durability of complete endoscopic resection efficacy in treating dysplastic Barrett's oesophagus has been reported more widely, with 4 studies (all retrospective) providing outcomes on an intention to treat basis after more than two years follow up (151, 152, 154, 155).

While acknowledging these limitations the review demonstrates that overall follow up outcomes were comparable for the two techniques, but clearly demonstrates that additional 'touch up' treatment for recurrent disease was required more frequently after complete endoscopic resection than after RFA. Allowing the use of 'touch up' treatment during follow up made the results more applicable to everyday clinical practice, but does affect comparability of results.

4.5.2 Complications

RFA appears to have significantly lower rates of both short and long term complications, compared to complete endoscopic resection. The most frequent long term complication associated with both complete endoscopic resection and RFA was stricture formation, but the rate was significantly higher for patients treated with complete endoscopic resection compared to RFA (38% vs 4%). This is concerning because strictures could be relatively resistant to treatment, in one recent study 5/22 patients treated with complete endoscopic resection required five or more dilatations (131). As a result some patients needed several therapeutic endoscopies to treat complications, this in turn increased their risk of further complications (e.g. perforation). While studies have suggested that pre-emptive dilation may reduce the incidence and duration of strictures, this is very resource intensive requiring frequent endoscopies (188).

Reasons for stenosis are multifactorial but may include both patient factors, such as pre- treatment luminal diameter and length of Barrett's, and technical factors such as diathermy settings and resection technique (the last two factors are particularly important because they are potentially modifiable). The relative importance of each factor is still debated and has been extensively explored, with several studies suggesting that increased overall length of Barrett's was associated with higher stricture rates (73, 149, 151, 177), while others have suggested that it is the circumferential length of Barrett's (154) or number of resection sessions required (71) which is important.

Buried Barrett's refers to the persistence of glandular epithelium beneath the new squamous epithelium, these buried glands are not visible endoscopically so there a risk of dysplastic progression without detection. Overall the risk of buried Barrett's reported in this review were very low, affecting 3-11% of patients treated with complete endoscopic resection, while there were no reported cases after RFA (although this has been reported elsewhere)(189). Where buried Barrett's was seen it was frequently associated with use of APC as an 'escape' treatment (71, 149, 154), suggesting use of APC should be avoided where possible.

If endoscopic therapy is to replace surgery as the treatment of choice for HGD, it is very important to monitor the rates of progression to cancer during follow up. A previous meta-analysis has reported that 5.6% of patients with untreated HGD progress to cancer each year (36). Given the relatively short and variable follow up periods reported here it was difficult to assess the impact of endoscopic treatment on this risk, despite this our results do tentatively suggest that both treatments reduce this risk. After a median follow up of just under 2 years the risk of progression to cancer was 1.7% after complete endoscopic resection and 0.9% after RFA. These results should be interpreted cautiously, given the relatively small study populations and short follow up periods reported.

4.5.3 Other treatment considerations

Decisions regarding the most appropriate choice of endoscopic treatment must also take into account the individual merits of each technique. Firstly complete endoscopic resection has the advantage of providing a large histological specimen, which can result in changes to the histological staging in up to 30% of cases (190). This in turn can impact on planned treatment, it is therefore important that any suspicious nodules are removed prior to RFA.

One also needs to consider the most appropriate treatment for a specific patient. None of the studies included in this review used complete endoscopic resection to treat segments of Barrett's with a median length >5cm, in contrast Vassiliou et al demonstrated the efficacy of RFA in Barrett's

up to 10cm long (178). It may therefore be sensible to restrict use of complete endoscopic resection to short segments of Barrett's, given that studies have shown that length of Barrett's is a significant factor in predicting the success of complete endoscopic resection (170), furthermore the risk of oesophageal strictures with complete endoscopic resection appears to increase when longer segments of Barrett's are treated (73, 149, 151, 172, 177).

Finally choice of treatment should be guided by endoscopist's expertise and experience. Studies have shown that there is a significant learning curve associated with learning complete endoscopic resection, and this is associated with a higher risk of complications when performing early procedures (129). As a result it may be sensible to restrict the use of CEMR to high volume centres. In contrast the learning associated with learning RFA is subject to debate, an early study by Zemlyak et al reported minimal learning curve associated with learning RFA (169), while a more recent study found that the number of RFA treatment sessions required to achieve CE-IM was significantly lower if the endoscopist/centre had performed 30 RFA procedures (130).

Publication related to this work: Chadwick et al, GI Endoscopy 2014; 79(5): 718-31

5. Cohort study of oesophageal cancer missed at endoscopy

5.1 Introduction

Oesophageal cancer is frequently diagnosed at a late stage, as a result only 30-40% of patients are considered suitable for treatment with curative intent at diagnosis (2) and only 1 in 7 patients survive more than 5 years (1). If one is going to make a significant impact on the overall survival from the disease, it is key to try and increase the proportion of oesophageal cancers diagnosed at an early stage. To this end the UK Department of Health has adopted various initiatives to try and promote symptom recognition and early diagnosis of the disease, including the launch of the 'Be Clear on Cancer' campaign for oesophago-gastric cancer in January 2015 (191).

In the meantime it is important to recognise the fact that a significant proportion of oesophageal cancers are potentially missed at initial endoscopy (53-59). This is concerning because many clinicians consider that if a patient has had a recent normal endoscopy the diagnosis of cancer has been ruled out, leading to further delays in investigation. It is therefore important to assess the impact a missed diagnosis may have on disease stage at diagnosis and patient outcomes.

5.2 Aims of this chapter

As discussed in Chapter 1 previous studies investigating the proportion of oesophageal cancers missed at endoscopy have been subject to significant limitations. This study aims to address some of these limitations by investigating at a national level the proportion of oesophageal cancers missed at endoscopy within three years of diagnosis. This analysis is made possible by linking data from three national databases. The study goes on to investigate clinical findings at previous endoscopy and patient factors associated with higher miss rates, before going on to investigate the impact of a missed diagnosis on planned treatment intent and 1-year survival.

5.3 Methods

This retrospective population-based cohort study used linked data from three national data sources: the second National Oesophago-Gastric Cancer Audit (NOGCA), mortality data from the Office for National Statistics (ONS), and data from the Hospital Episode Statistics (HES) database.

Patients were considered for inclusion in this study if they were diagnosed with oesophageal or gastro-oesophageal junction (GOJ) cancer between 1st April 2011 and 31st March 2012, and had a record submitted to the NOGCA which was successfully linked to HES. The extract of HES data used in this study covered admissions between January 2008 and March 2012. NOGCA records were linked to their HES and ONS records using the patient's National Health Service (NHS) number (a unique identifier for each UK resident). This resulted in 93% of NOGCA records being successfully linked to their corresponding HES

records. Over the period covered by this study, the audit achieved 83% case-ascertainment when compared to HES (77).

Having linked the three data sources it was important to verify consistency of key information across the datasets, in particular the accuracy with which 'date of diagnosis' was recorded in the audit. It was important to verify this date because 'date of diagnosis' was used as a reference date when calculating the timing of previous endoscopies. In order to do this all HES records in which a diagnosis of oesophageal or GOJ cancer was recorded were identified, by searching for the following International Classification of Diseases 10th edition (ICD-10) codes: C15 (malignant neoplasm of the oesophagus), C160 (malignant neoplasm of stomach cardia including gastro-oesophageal junction), and D001 (carcinoma in situ of the oesophagus) (136). Then, the first date a diagnosis of oesophageal or GOJ cancer was recorded in HES was identified (as HES does not record the date of cancer diagnosis) and this date was compared to the 'date of diagnosis' recorded in the NOGCA dataset. Patients were excluded from analysis if there was no record of oesophageal/GOJ cancer in HES, or if the diagnosis of oesophageal/GOJ recorded in HES was more than a month before the date of diagnosis in the NOGCA dataset.

Data required for this study was extracted from each of the three separate datasets. The NOGCA dataset provided information on patient demographics, route of referral, date of diagnosis, tumour site and stage, and treatment plan (Table 5-1).

Table 5-1 Summary of data extracted from the NOGCA dataset

Patient Demographics	
Age at diagnosis	
Sex	
History of Barrett's oesophagus	
Initial referral and diagnosis data	
Date of referral	
Source of referral	GP referral (non-emergency, to outpatient clinics). Further split into: - Urgent for suspected cancer - Non-urgent Referral after an emergency admission (via Accident & Emergency, Medical Admissions Unit, etc.) 'Other hospital referral' (patients referred by a hospital consultant from a non-emergency setting). Defined according to NOGCA data manual (192).
Date of diagnosis	
Diagnosis and Staging	
Type of cancer	Adenocarcinoma, squamous cell cancer, other
Tumour site	Upper oesophagus, mid oesophagus, lower oesophagus, gastro-oesophageal junction
Stage at diagnosis	Stage of cancer was defined using the Union for International Cancer Control (UICC) TNM 6 Classification (68).
Treatment Plan	
Treatment Intent	Curative, non-curative

While HES was used to identify previous endoscopic examinations (oesophago-gastric duodenoscopy (OGDs)), by searching for the following operation procedure codes in HES: G16 (diagnostic fibreoptic examination of the oesophagus) and G45 (diagnostic fibreoptic examination of the upper gastrointestinal tract)(136). In order to test the reliability of our coding algorithms and data linkage, we aimed to confirm that all patients included in analysis had had an endoscopy coded for in HES within one month of 'date of diagnosis' of cancer. This analysis demonstrated that 92.5% of patients had had one recorded.

Diagnostic codes recorded in HES relating to previous endoscopies were also analysed for common indications for endoscopy and common endoscopic findings (Table 5-2).

Table 5-2 ICD-10 diagnosis codes used to identify common indications for endoscopy and endoscopic findings.

ICD-10 Code	Indication for endoscopy
Alarm symptoms	
D500	Iron deficiency anaemia secondary to blood loss (chronic)
D508	Other iron deficiency anaemia
D509	Iron deficiency anaemia, unspecified
D649	Anaemia, unspecified
R11	Nausea and vomiting
R13	Dysphagia
R190	Intra-abdominal and pelvic swelling, mass and lump
R630	Anorexia
R634	Abnormal weight loss
Other gastro-intestinal symptoms	
K30	Dyspepsia
R07	Pain in throat and chest
R10	Abdominal and pelvic pain
R12	Heartburn
Gastrointestinal bleed	
K920	Haematemesis
K921	Melaena
K922	Gastrointestinal haemorrhage unspecified
	Findings at endoscopy
K20	Oesophagitis
K21	Gastro-oesophageal reflux disease
K221	Ulcer of oesophagus
K222	Oesophageal obstruction
K226	Gastro-oesophageal laceration haemorrhage syndrome
K228	Other specified diseases of oesophagus – Haemorrhage of oesophagus NOS

The principal outcome measures used to describe patterns of past endoscopy were:

- Patients who had had an endoscopy within 3 and 12 months of cancer diagnosis
- Patients who had had an endoscopy within 1 and 3 years before cancer diagnosis, but not in the year preceding diagnosis.

Endoscopies performed within 3 months of cancer diagnosis were excluded, because they may have formed part of the diagnostic work (e.g. where initial histology suspicious but non-diagnostic) or may have represented planned repeat endoscopies (e.g. follow up of an oesophageal ulcer). Endoscopies performed more than 3 years before the diagnosis of cancer were also excluded due to uncertainty regarding the natural history of the disease.

5.3.1 Data Analysis

Initial analysis calculated the proportion of patients from the complete cohort, who had had an endoscopy within 3-12 months of diagnosis or within 1-3 years. Rates of past endoscopy were then calculated and analysed by patient characteristics including age at diagnosis, sex, site and type of cancer, history of Barrett's oesophagus, stage at diagnosis, and route to diagnosis. The chi-square test was used to test the significance of differences across patient groups, and p-values less than 0.05 were considered statistically significant. Among patients who had had a previous endoscopy, the total number of endoscopies performed in the 3 years prior to diagnosis and the frequency with which particular conditions were recorded was also noted.

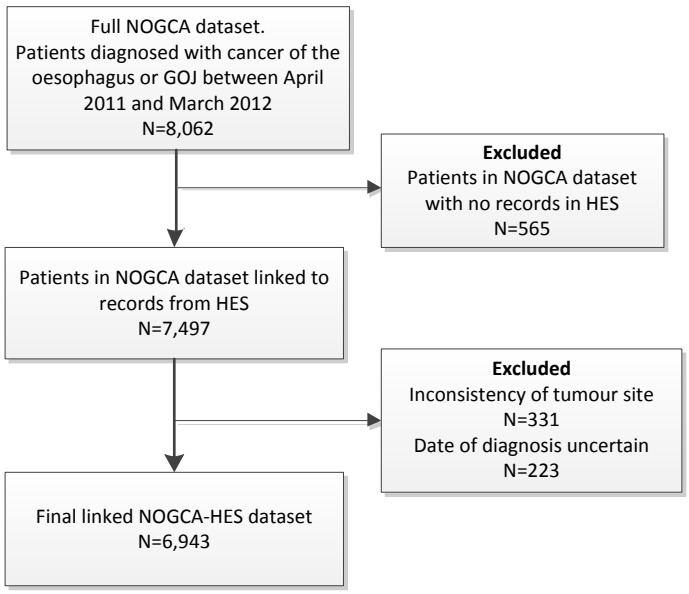
Finally, using multiple logistic regression models the relationship between a previous endoscopy, planned treatment intent (curative vs palliative) and 1-year survival was examined. This model was used to estimate the relative risk of having planned curative treatment and surviving 1-year, respectively, for patients who had an endoscopy in the previous 3-12 months, and previous 1-3 years compared to patients who had not had a recent endoscopy. Relative risks were adjusted for patient age, sex, and performance status, as well as type of cancer, tumour site and TNM stage at diagnosis. Missing values for these covariates were imputed using multiple imputation by chained equations (138). The imputation model included age at diagnosis, sex, type of cancer, tumour site, performance status and referral source. Ten imputation datasets were created.

5.4 Results

5.4.1 Selection of analysis cohort

The linked HES-NOGCA dataset identified 7,497 patients diagnosed with oesophageal or GOJ cancer between 1st April 2011 and 31st March 2012 in England. After excluding 331 (4.4%) patients who did not have a diagnosis of oesophageal/GOJ cancer recorded in HES (these patients frequently had a diagnosis of gastric cancer recorded instead) and 223 (3.0%) patients whose 'date of diagnosis' in the NOGCA dataset was not consistent with HES, 6,943 (92.6%) patients were left in the analysis cohort (Figure 5-1).

Figure 5-1 Flow diagram describing the inclusion of patients from the NOGCA dataset after linkage with data from HES dataset.



5.4.2 Summary of Patient Characteristics

The characteristics of the analysed cohort are summarised in **Table 5-3** (first column). The mean (SD) age at diagnosis was 70.6 (±11.5) years and 70.8% of patients were men. 74.6% of cancers were located in the lower oesophagus or GOJ. The majority (72.5%) of referrals came from General Practitioners (GPs), and three quarters of these referrals were urgent for suspected cancer. Of the remaining cases, 10.4% of referrals resulted from an emergency admission and 17.2% of patients had been referred by another hospital consultant. TNM stage at diagnosis was known for 4,787 patients (68.9%), and where this was known 72.1% of patients were diagnosed with stage 3 or 4 cancer and only 4.7% of cancers were diagnosed at stage 0 or 1.

Table 5-3 Characteristics of patients in the study cohort, and the proportion of patients who had undergone a previous endoscopy in the 3 years prior to diagnosis of oesophageal cancer

	Entire Cohort, n (%*)	Patients with no previous endoscopy, n (%*)	Patients endoscoped within 3-12 months of diagnosis, n (%**)		Patients endoscoped within 12-36 months of diagnosis, n (%**)	
			Number	Overall p-value	Number	Overall p-value
Patients	6,943	6,406	214 (3.1)		323 (4.7)	
Age Group, year						
<55	623 (9.0)	574 (9.0)	16 (2.6)	0.791	33 (5.3)	0.598
55-64	1,457 (21.0)	1,347 (21.0)	43 (3.0)		67 (4.6)	
65-74	2,110 (30.4)	1,936 (30.2)	72 (3.5)		101 (4.8)	
75-84	1,971 (28.4)	1,820 (28.4)	57 (2.9)		94 (4.8)	
≥85	782 (11.3)	729 (11.4)	25 (3.2)		28 (3.6)	
Sex, n (%)						
Male	4,915 (70.8)	4,538 (70.8)	149 (3.0)	0.671	228 (4.6)	0.935
Female	2,028 (29.2)	1,868 (29.2)	65 (3.2)		95 (4.7)	
Type of cancer						
Adenocarcinoma	4,827 (69.5)	4,458 (69.6)	152 (3.2)	0.814	217 (4.5)	0.514
Squamous cell	1,651 (23.8)	1,524 (23.8)	47 (2.9)		80 (4.9)	
Other	465 (6.7)	424 (6.6)	15 (3.2)		26 (5.6)	
Site of Cancer[1]						
Upper Oesophagus	351 (5.1)	315 (4.9)	19 (5.4)	**0.040**	17 (4.8)	0.099
Mid Oesophagus	1,411 (20.3)	1,303 (20.3)	37 (2.6)		71 (5.0)	
Lower Oesophagus	2,891 (41.6)	2,648 (41.3)	94 (3.3)		149 (5.2)	
GOJ	2,290 (33.0)	2,140 (33.4)	64 (2.8)		86 (3.8)	
History of Barrett's Oesophagus						
No	6,742 (97.1)	6,262 (97.8)	199 (3.0)	**<0.001**	281 (4.2)	**<0.001**
Yes	201 (2.9)	144 (2.3)	15 (7.5)		42 (20.9)	
T-Stage at Diagnosis						
Stage 0/1	302 (5.9)	203 (4.3)	47 (15.6)	**<0.001**	52 (17.2)	**<0.001**
Stage 2	848 (16.6)	753 (16.0)	36 (4.3)		59 (7.0)	
Stage 3	3,268 (63.9)	3,106 (65.9)	54 (1.7)		105 (3.2)	
Stage 4	694 (13.6)	654 (13.9)	16 (2.3)		24 (3.5)	
Missing values	1,831	1,690	58 (3.2)		83 (4.5)	
TNM Stage at Diagnosis						
Stage 0/1	227 (4.7)	150 (3.4)	36 (15.9)	**<0.001**	41 (18.1)	**<0.001**
Stage 2	1,106 (23.1)	995 (22.4)	44 (4.0)		67 (6.1)	
Stage 3	1,600 (33.4)	1,524 (34.3)	26 (1.6)		50 (3.1)	
Stage 4	1,854 (38.7)	1,775 (39.9)	26 (1.4)		53 (2.9)	
Missing values	2,156	1,962	82 (3.8)		112 (5.2)	
Route to diagnosis						
GP Routine	1,085 (17.5)	978 (17.0)	43 (4.0)	**<0.001**	64 (5.9)	**<0.001**
GP Urgent	3,418 (55.0)	3,307 (57.4)	32 (0.9)		79 (2.3)	
Emergency admission	645 (10.4)	594 (10.3)	22 (3.4)		29 (4.5)	
Other Hospital Referral	1,069 (17.2)	886 (15.4)	80 (7.5)		103 (9.6)	
Missing values	726	641	37 (5.1)		48 (6.6)	

1 Definitions of oesophageal cancer site: Upper <24cm from incisors, mid 24-32cm from incisors and lower >32cm from incisors. GOJ tumours included Siewert I/II and III cancers.
*Column percentage**Row percentage

5.4.3 Previous endoscopic examinations

Of the 6,943 patients considered for analysis, 537 (7.8%, 95% CI 7.1-8.4%) had had at least one endoscopy within three years of their cancer diagnosis. 214 patients (3.1%, 95% CI 2.7-3.5) had had an endoscopy within 3 and 12 months of diagnosis, and a further 323 (4.7%, 95% CI 4.2-5.2) had had one between 1 and 3 years before diagnosis.

Table 5-3 looks at the proportion of patients who had had a previous endoscopy according to various patient characteristics. This demonstrates that the rates of previous endoscopy were not associated with patient age, sex or cancer histology. However, the rate of previous endoscopy was significantly associated with TNM stage at diagnosis, such that the proportion of patients with early stage disease who had had a previous endoscopy was significantly higher than for those diagnosed with more advanced disease ($p<0.001$). Among patients with TNM stage 0/1 disease at diagnosis, 15.9% had had an endoscopy within 3-12 months and a further 18.1% had had one in the preceding 1-3 years. This compares to 4.0% and 6.1% respectively for stage 2 cancers, and 1.5% and 3.0% respectively for stage 3/4 cancers. This pattern was most closely linked to the size of the tumour (T-stage) at diagnosis. A significant association between tumour site and the rate of previous endoscopy was also demonstrated ($p<0.001$). So while only 3% of patients with lower oesophageal and GOJ cancers had had an endoscopy within 3-12 months, 5.4% of patients diagnosed with upper oesophageal cancers had had one ($p=0.040$).

Patients with a history or Barrett's oesophagus were also more likely to have had a previous endoscopy ($p<0.001$). Where stage at diagnosis was known for these patients the disease tended to be early stage, with 72.7% of patients who were diagnosed within 3-12 months of endoscopy and 33.3% of patients who were diagnosed within 1-3 years of endoscopy having stage 0/1 disease at diagnosis.

Patients referred by another hospital consultant were also roughly twice as likely to have had a previous endoscopy compared with those referred by a GP, for both of the primary outcome measures. Stage at of disease at diagnosis varied significantly depending on the route to diagnosis for patients who had had an endoscopy in the previous 1-3 years ($p<0.001$). While 34.7% of patients referred by another consultant had stage 0/1 disease at diagnosis, only 12.2% of patients referred by GP and 0% of patients referred as a result of an emergency admission were stage 0/1 at diagnosis. These findings would be consistent with a proportion of referrals from other consultants representing planned surveillance endoscopies.

Overall 75.9% of patients diagnosed with cancer who had been referred by their GP were referred urgently, but this proportion fell significantly to 42.7% ($p<0.001$) for patients who had had a previous non-diagnostic endoscopy in the last year. Furthermore, those patients who were referred by their GP and had had a prior endoscopy waited significantly longer between referral and diagnosis than those who had not had one before, irrespective of the urgency of referral. So while, 0.4% of urgent GP referrals with no history of a recent endoscopy waited more than 12 weeks from referral to diagnosis, 25.0% of those who had had an endoscopy in the preceding year waited more than 12 weeks ($p<0.001$).

5.4.4 Association between previous endoscopy, treatment intent and 1-year survival

As **Table 5-3** demonstrates that there was marked variation in patient characteristics across the groups who had and had not had a previous endoscopy, such that patients who had not had a previous endoscopy were more likely to have advanced disease at diagnosis, and were less likely to have a history of Barrett's oesophagus and to have been referred by another hospital consultant. As a result, these patients had lower unadjusted rates of planned curative treatment (**Table 5-4**). However, this difference was not statistically significant after adjusting for patient characteristics such as age at diagnosis, sex, performance status, as well as type of cancer, tumour site and TNM stage at diagnosis. Similarly, the lower unadjusted 1-year survival rates among patients without a history of previous endoscopy improved after adjusting for confounding patient characteristics.

Table 5-4 Relationship between endoscopic examination, treatment plan, and 1-year survival among patients diagnosed with oesophago-gastric cancer in English National Health Service (NHS) trusts

Patient group	Total patients, n	Patients with outcome, n (%)	Unadjusted OR [95% CI]	Adjusted OR† [95% CI]
Patients with curative treatment intent	5,939*	2200 (37.0)		
Patients without previous endoscopy	5,493	1973 (35.9)	1	1
Patients endoscoped within 3–12 months of diagnosis	174	98 (56.3)	2.30 [1.68–3.14]	1.08 [0.66–1.75]
Patients endoscoped within 1–3 years of diagnosis	272	129 (47.4)	1.61 [1.24–2.08]	1.02 [0.68–1.54]
Patients who survived 1 year	6,943	3246 (46.8)		
Patients without previous endoscopy	6,406	2936 (45.8)	1	1
Patients endoscoped within 3–12 months of diagnosis	214	136 (63.6)	2.06 [1.56–2.72]	1.42 [1.02–1.99]
Patients endoscoped within 1–3 years of diagnosis	323	174 (53.9)	1.38 [1.10–1.72]	1.03 [0.80–1.33]

OR – Odds ratio

5.4.5 Findings reported at previous endoscopy

Table 5-5 describes the frequency with which specific diagnostic codes were recorded in HES at previous endoscopy. The most common diagnosis reported at previous endoscopy was that of an oesophageal ulcer (48%). Of the 22 patients diagnosed as result of an emergency admission within a year of previous endoscopy, 6 patients (27.3%) had had an oesophageal ulcer and 6 patients (27.3%) had had alarm symptoms recorded at their previous endoscopy.

Table 5-5 Common gastro-intestinal diagnoses recorded at previous endoscopic examinations that occurred prior to the cancer diagnosis

Diagnostic codes assigned to previous endoscopies	Patients endoscoped within 3-12 months of diagnosis (n=214)	Patients endoscoped within 12-36 months of diagnosis (n=323)
Oesophageal ulcer	109 (50.9%)	150 (46.4%)
Alarm symptoms	39 (18.2%)	81 (25.1%)
Oesophagitis	24 (11.2%)	33 (10.2%)
Gastrointestinal bleed	24 (11.2%)	30 (9.3%)
Oesophageal obstruction	16 (7.5%)	6 (1.9%)
Other gastrointestinal symptoms	18 (8.4%)	28 (8.7%)

Among the 537 patients who had had an endoscopy in the 3 years prior to diagnosis, 386 (71.9%) had only had one endoscopy, 101 (18.8%) had had two, and 50 had had three or more endoscopies (9.3%) (Table 5-4). 41 (82%) patients who had had 3 or more previous endoscopies had previously been diagnosed with an oesophageal ulcer.

Table 5-6 Number of endoscopies performed in the 3 years prior to cancer diagnosis

Number of Endoscopies	Patients endoscoped within 3-12 months of diagnosis (n=214)		Patients endoscoped within 12-36 months of diagnosis (n=323)	
1	125	58.4%	261	80.8%
2	57	26.6%	44	13.6%
≥3	32	15.0%	18	5.6%

Furthermore there was a strong association between disease stage at diagnosis and the number of previous endoscopic examinations that the patient had had in the last 3 years (p=0.014) (Table 5-7). So while 49.4% of patients with stage 0/1 disease had had more than one endoscopy in the previous three years, only 19.0% of stage 4 cancers had. Furthermore 22.1% of stage 0/1 cancers were diagnosed after 3 or more endoscopies in the previous three years.

Table 5-7 Number of endoscopies performed in the 3 years prior to diagnosis of cancer, stratified by pre-treatment stage at diagnosis

Total number of endoscopies in 3-36 months before diagnosis	Stage at Diagnosis							
	0/1 (n=77)		2 (n=111)		3 (n=76)		4 (n=79)	
	n	%	n	%	n	%	n	%
1	39	50.6	85	76.6	58	76.3	64	81.0
2	21	27.3	19	17.1	9	11.8	11	13.9
3	6	7.8	3	2.7	6	7.9	3	3.8
≥4	11	14.3	4	3.6	3	3.9	1	1.3

5.5 Discussion

Among this cohort of English NHS patients diagnosed with oesophageal cancer, 3.1% (95% CI, 2.7-3.5) of patients had had an endoscopy within 3-12 months of diagnosis, and a further 4.7% (95% CI, 4.2-5.2%) of patients had had one between 1-3 years before diagnosis. This suggests that 7.8% (95% CI, 7.1-8.4%) of cancers may have been missed at initial endoscopy within 3 years of diagnosis. This figure lies at the lower end of the range of rates reported in previous studies (5.0-14.3%) (53-56). By reporting results on a national basis this study is able to provide a more precise estimate of the likely miss rate in England, and reflects what is happening in everyday clinical practice. The study goes on to demonstrate that patients who had had a prior endoscopy were more likely to be diagnosed with early stage disease, and have an upper oesophageal cancer.

These results therefore suggest that a significant proportion of oesophageal cancers are being missed at endoscopy in England, unless these cancers progressed rapidly enough that they went from an early endoscopically invisible lesion to an advanced cancer over a short time frame. If one considers the later scenario to be the case, then a more conservative estimate of the miss rate may be 2.0% or 5.6%, representing stage 2-4 cancers diagnosed within 1 year or 3 years of endoscopy respectively. However, the initial overall figure may be more accurate because studies looking at the natural history of untreated early oesophageal cancer have suggested that progression of the disease is slow with some patients surviving more than 5 years after diagnosis (60, 61).

Nonetheless one reason to go with the more conservative estimate of miss rate and focus on only stage 2-4 cancers, was the inability to identify patients undergoing surveillance endoscopies in this study. Our results showed that patients with a history of Barrett's oesophagus or referred by another hospital consultant were more likely to have had a previous endoscopy, and it is likely that some of these previous endoscopies represent surveillance endoscopies. Unfortunately there was no record in the audit of surveillance endoscopies at that time (although the dataset has since been amended to address this (Appendix C)), and there is currently no national registry for Barrett's oesophagus which identifies all patients undergoing surveillance endoscopies.

Previous studies have come up with various different reasons for failing to diagnose a cancer at initial endoscopy (53-55). These include failure of the endoscopist to identify a potential lesion, or where a lesion is seen failing to recognise its significance resulting in the clinician deciding not to biopsy it or taking an insufficient number of biopsies. Raftopoulos et al found that where a cancer was potentially missed at endoscopy nearly three-quarters of patients had had abnormal findings

identified at the site where a cancer was subsequently reported (53). This suggests that the initial endoscopist may not have recognised the malignant potential of their finding. Raftopoulos et al went on to demonstrate that that if a patient had had an entirely normal endoscopy in the last year the risk of a missed cancer was 1.1%, but this risk rose to 3.5% if you considered all endoscopies done in the last year. It is therefore very important to ensure that all suspicious lesions are adequately biopsied, as this dramatically increases the diagnostic yield (52). This study found that early stage lesions were significantly more likely to be missed, this probably reflects the fact that they can present with very subtle changes in mucosal colour or contour (193). It is therefore important to consider using high-resolution endoscopy and enhanced endoscopic imaging techniques (e.g. narrow band imaging) to increase detection of these early lesions, although their use in preference to white light endoscopy is not recommended. An additional area to consider is the impact of proton pump inhibitors (PPIs) on endoscopy findings. PPIs promote mucosal healing, and in doing so may increase the chance that a lesion is missed at endoscopy in patients taking them (194). It is therefore important to ensure that PPIs are not be started where a diagnosis of cancer is suspected and the patient is being referred for urgent endoscopy, and to consider stopping PPIs prior to endoscopy where a patient is already on one.

Finally, previous studies have suggested that the mid and upper oesophagus may be less well inspected at endoscopy reducing the chance that subtle lesions are identified, this may be because the endoscope is often rapidly withdrawn during the final stages of the procedure (54). Our results were in line with this finding, as this study reported higher rates of previous endoscopy for patients diagnosed with upper oesophageal cancer than lower oesophageal and GOJ cancers (53, 54, 56). This highlights the need for careful inspection of this area.

Analysis of the diagnostic codes recorded in HES at the time of previous endoscopy, showed that the most common code recorded in HES was that for oesophageal ulcers, which was recorded at half of previous endoscopies. This compares to an incidence of oesophageal ulcers of 1.16% in unselected patients undergoing an endoscopy (195). Of the 259 patients previously diagnosed with an oesophageal ulcer, 20 (7.6%) patients required three or more endoscopies before a diagnosis of cancer was made. This finding could be interpreted in two ways, firstly it may reflect the fact that the endoscopists had a clinical suspicion of malignancy and patients were brought back for regular surveillance endoscopies. In which case our estimated miss rate would be a slight overestimate. An alternative explanation is that the original biopsies were insufficient for a diagnosis of cancer, and therefore a chance to diagnose the cancer at an earlier stage was missed. It is important to reflect

on the fact that although the risk of oesophageal cancer in patients previously diagnosed with oesophageal ulcers in Barrett's oesophagus is well recognised (66), there are currently no national guidelines for the surveillance of oesophageal ulcers. In contrast there are clear national guidelines for the management and follow up of gastric ulcers (49).

In summary it is important to ensure that clinicians are made aware of the risk of missing cancers at endoscopy, as results from this study showed that where a patient had had a recent endoscopy GPs were significantly less likely to re-refer the patient urgently ($p<0.001$). GPs should be encouraged to re-refer patients urgently for out-patient review and further investigation, where they feel a patient is still at high risk of malignancy.

Finally, while it is difficult to evaluate the consequences of a missed diagnosis, this study found no evidence that a history of previous endoscopy affected planned treatment intent. However this finding needs to be interpreted with caution, and does not imply that a missed diagnosis does not adversely affect patient outcomes. In order to formally evaluate the effect of the delay, one needs either information about the stage of the disease at the time of previous endoscopy or information on the speed of progression of the disease. Considering the first approach, future studies may be able to go back and re-examine previous histology results to look for errors in pathological interpretation, but this would not help in cases where insufficient biopsies were taken. Alternatively with information about the delay in diagnosis and speed of progression of oesophageal cancer, one could look at the impact of a missed diagnosis. This approach has been used to model the consequences of missed diagnoses for breast and cervical cancers (196), but further research is still needed on the natural history of oesophageal cancer.

5.5.1 Limitations

Specific limitations of this paper are discussed in detail here, while more general limitations associated with using national datasets for healthcare research are discussed in Chapter 7. There are three key limitations of this study which need to be considered.

Firstly neither the NOGCA nor the HES dataset recorded the indication for the initial endoscopy. Without this information it is not possible to be certain whether repeat endoscopies were planned follow up endoscopies investigating previous suspicious findings. In order to limit the impact these repeat endoscopies may have had on the miss rate, endoscopies performed within 3-months of diagnosis were excluded. It was also not possible to identify patients undergoing planned

surveillance endoscopies for Barrett's oesophagus, and this may have led to the overall miss rate being slightly overestimated.

Secondly, our calculation of missed cancer rates depended on complete coding of all endoscopies in HES. However a small proportion of patients will have had their initial endoscopy done either privately, or outside of England. In these cases the initial endoscopy will not have been recorded in HES, and this may mean that our calculated miss rate is a slight under-estimate.

Finally, there may have been residual confounding in the analysis looking at the association between previous endoscopy, treatment intent and 1-year outcomes. Within the dataset some of the data was missing for two variables, and multiple imputation models for these variables relied on the assumption that the data were 'missing at random'.

Publication related to this work: Chadwick et al, Endoscopy 2014; 46(7): 553-60

6. Management and survival of early oesophageal adenocarcinomas

6.1 Introduction

Oesophagectomy is the standard treatment for the majority of cases of oesophageal cancer, but is associated with significant morbidity and long-term impact on quality of life (83). However studies have shown that the risk of lymphatic spread is very low (0-2%) (88, 89) for oesophageal tumours limited to the mucosa, as a result focus has shifted towards using less invasive endoscopic treatment options (e.g. endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA)) for the management of these early cancers (20, 132, 133). Once there is evidence of submucosal invasion the risk of lymphatic spread can be as high as 20% (70, 89), consequently surgery remains the treatment of choice in the majority of these cases. Although endoscopic therapy may still be considered if tumour invasion is limited to the most superficial layer of the submucosa, the tumour is well differentiated and there is no evidence of lymphovascular invasion (20).

As discussed in Chapter 1 there is limited up to date research into the long term outcomes for early cancers treated endoscopically and surgically, with no large scale population studies performed outside of the US. Furthermore the studies that have been done have pooled data collected over many years, over a period when there were significant advances in endoscopic treatment options. This limits the applicability of their results to current practice. In addition no studies have been done to date to investigate the uptake of endoscopic therapy in England.

6.2 Aims of this chapter

This study aimed to investigate the treatment modalities used to treat early oesophageal cancer in England and associated 5 year survival outcomes, using data collected for the 1st National Oesophago-Gastric Cancer Audit (NOGCA) between 2007 and 2009.

6.3 Methods

This retrospective cohort study combined information from three national databases: the 1st NOGCA, Hospital Episode Statistics (HES), and the Office for National Statistics (ONS) death register. NOGCA records were linked to HES and ONS records using the patient's NHS number (a unique identifier for each UK resident), date of birth, sex and postcode. The extract of HES used for this study covered all hospital admissions between September 2007 and November 2009. While the ONS extract used covered deaths up to January 2015.

Patients were considered for inclusion in this study if they were diagnosed with oesophageal or gastro-oesophageal junction (GOJ) cancer between 1st October 2007 and 30th June 2009, and had a record submitted to the NOGCA. Over this time frame the NOGCA achieved 71% case ascertainment for English patients diagnosed with oesophago-gastric cancer and 82% for patients managed with a surgical resection (85). The cohort was then limited to those patients with a histological diagnosis of adenocarcinoma, to avoid histological heterogeneity.

The NOGCA dataset provided information on patient demographics, source of referral, date of diagnosis, tumour site and stage, treatment plan and finally surgical approach and outcomes (Table 6-1). Patients were defined as having early stage oesophageal cancer if their pre-treatment stage at diagnosis was T0/1 with no evidence of nodal or metastatic spread. Patients were excluded from all analysis where pre-treatment stage was unknown.

Table 6-1 Summary of data extracted from NOGCA dataset

Patient Demographics	
Age at diagnosis	
Sex	
Performance status	ECOG score for performance status in cancer patients (Appendix A).
Comorbidities	
Initial referral and diagnosis data	
Source of referral	GP referral (non-emergency, to outpatient clinics). Further split in: - Urgent for suspected cancer - Non-urgent Referral after an emergency admission (via Accident & Emergency, Medical Admissions Unit, etc.) 'Other hospital referral' (patients referred by a hospital consultant from a non-emergency setting). Defined according to NOGCA data manual (192).
Date of diagnosis	
Diagnosis and Staging	
Type of cancer	Adenocarcinoma, squamous cell cancer, other
Tumour site	Upper/mid oesophagus, lower oesophagus and GOJ
Stage at diagnosis	Stage of cancer, defined using the Union for International Cancer Control (UICC) TNM 6 Classification (68).
Treatment Plan	
Treatment Intent	Curative or palliative
Treatment modality	*Curative* Surgery $\pm$ oncology, definitive radiotherapy or chemoradiotherapy, endoscopic mucosal resection *Palliative* Surgery, oncology, endoscopic palliation, best supportive care
Surgery	
Surgical approach	
Complications	Defined according to the NOGCA data manual (134)
Pathological TNM stage	Stage of cancer

By linking the NOGCA dataset to HES, information was extracted on all endoscopic, surgical and oncological interventions the patient underwent after diagnosis by searching for specific operative procedure codes in HES using the Office of Population Censuses and Surveys Classification version 4 (OPCS) codes, as outlined in Table 6-2.

Table 6-2 OPCS codes used to identify primary treatment modality and therapeutic interventions after initial therapy

	Procedure	**Specific OPCS codes for procedures under endoscopic control**	**Non-specific OPCS codes for procedure, only considered if they occurred in the same episode as a definite endoscopic procedure**
Curative Surgery	Oesophagectomy	G01 G02 G03	
Endoscopic procedure	Diagnostic OGD	G16 G19.1/8/9 G21.4 G45	
	Ablation	G14.2/3/5/7 G17.2/3 G42.2 G43.2/3/4/5/7	Y08 Y11.4 Y13.1/4/6
	Resection	G14.1/6 G17.1 G42.1 G43.1	
	Other therapeutic OGD	G14.8/9 G15.8/9 G17.8/9 G18.8/9 G42.8/9 G43.8/9 G44.8/9 G46.8/9	
	Dilatation	G15.2/3/5 G18.2/3/5 G44.3/6	Y40
	Stent insertion	G15.4/6/7 G18.4 G21.5 G44.1	G11.2/8/9 Y02.1/2/8/9 Y14.1/2/3/4/8/9

Table 6-2 OPCS codes used to identify primary treatment modality and therapeutic interventions after initial therapy (continued)

	Procedure	**Specific OPCS codes for procedures under endoscopic control**	**Non-specific OPCS codes for procedure, only considered if they occurred in the same episode as a definite endoscopic procedure**
Oncological Treatment	Chemotherapy	X70 X71 X72 X73 X352	
	Radiotherapy	X65 X67 Y91 Y902 Y92 Y352	

At this stage, a HES-based definition of **primary treatment modality** was derived for each patient based on the OPCS intervention codes recorded after the date of diagnosis. Patients were grouped according to their most invasive treatment modality because using HES it is not possible to determine with certainty whether EMRs performed prior to surgery were performed with diagnostic or therapeutic intent. The derived HES-based treatment modality was then compared with the planned treatment modality recorded in the NOGCA dataset, to confirm consistency of information across the data sources. Patients were excluded from analysis where data was inconsistent or primary treatment modality was not recorded in HES.

Following any endoscopic procedure, the International Classification of Diseases (ICD-10) diagnostic codes related to that episode and any subsequent episode were searched to identify major endoscopic complications. While surgical complications and outcomes were derived from the NOGCA dataset.

The principal outcome measures assessed were:

- Choice of primary treatment modality for early oesophageal cancer, derived from HES.
- 5-year survival calculated based on date of diagnosis and then stratified by primary treatment modality.

6.3.1 Data Analysis

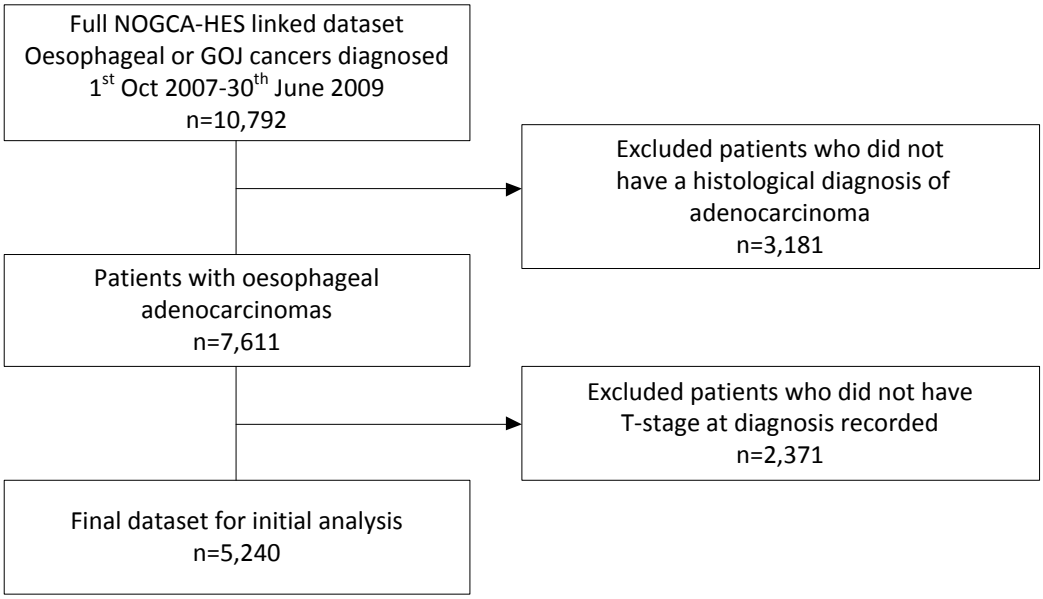
Initial analysis calculated the proportion of patients with a diagnosis of early oesophageal adenocarcinoma, this was calculated from all patients with known disease stage at diagnosis. Patient characteristics were then compared across the groups diagnosed with early and late stage disease to look for significant differences, using the t-test and chi-square test to test for statistical significance as appropriate. P-values less than 0.05 were considered statistically significant. Patients were later grouped according to their primary treatment modality, and patient characteristics were again compared across these groups.

Using data provided by the ONS death register, 5 year survival was estimated for patients according to their primary treatment modality and results were presented using Kaplan-Meier graphs. The log rank test was used to test for significant difference between survival curves.

6.4 Results

The linked dataset identified 10,792 patients diagnosed with oesophageal or GOJ cancer in England between 1st October 2007 and 30th June 2009. Of these, 7,611 patients had a histological diagnosis of adenocarcinoma and were considered for inclusion in this study. 2,371 patients were excluded from analysis due to incomplete staging details. This left 5,240 (68.8%) patients for analysis (**Figure 6-1**). However it should be noted that patients missing T stage at diagnosis were significantly more likely to be managed with palliative intent and had worse long term outcomes than those considered for analysis.

Figure 6-1 Flow diagram describing the selection of patients from the NOGCA-HES linked database for analysis



The characteristics of the analysed cohort are summarised in **Table 6-3** (first column). The mean (± SD) age of these patients at diagnosis was 69.8 (±11.6) years and 80.0% were men. 89.4% of cancers were located in the lower oesophagus or GOJ. Overall 1- and 5-year survival for the entire cohort was 53.6% (n=2,810) and 17.8% (n=934), respectively.

Table 6-3 Characteristics of patients in the overall study cohort and by the extent of disease (early or advanced cancer).

	Entire cohort n (%*)	**Early cancer n (%*)**	**Late stage cancer n (%*)**	**p-value**
Patients	5,240	354	4,886	
Age, years, mean (±SD)	69.8±11.6	69.1±11.2	68.4±11.0	1.0
Male	4,190 (80.0)	280 (79.1)	3,910 (80.0)	0.673
Tumour location				
Upper / Middle oesophagus	555 (10.6)	39 (11.0)	516 (10.6)	**0.001**
Lower oesophagus	3,442 (65.7)	260 (73.5)	3,182 (65.1)	
GOJ	1,245 (23.7)	55 (15.5)	1,188 (24.3)	
Performance status				
0/1	2,919 (74.2)	206 (80.5)	2,713 (73.8)	**0.018**
2/3/4	1,014 (25.8)	50 (19.5)	964 (26.2)	
Missing	1,307	98	1,209	
Any co-morbidity except Barrett's oesophagus				
No	3,009 (57.4)	193 (54.5)	2,816 (57.6)	0.252
Yes	2,231 (42.6)	161 (45.5)	2,070 (42.4)	
History of Barrett's oesophagus				
No	4,981 (95.1)	295 (83.3)	4,686 (95.9)	**<0.001**
Yes	259 (4.9)	59 (16.7)	200 (4.1)	
Source of referral				
Emergency	478 (10.0)	30 (9.7)	448 (10.1)	**<0.001**
GP	3,508 (73.7)	168 (54.2)	3,340 (75.0)	
Other Hospital Referral	775 (16.3)	112 (36.1)	663 (14.9)	
Missing	479	44	435	
Planned treatment intent				
Curative	2,440 (48.0)	260 (75.4)	2,180 (46.0)	**<0.001**
Palliative	2,643 (52.0)	85 (24.6)	2,558 (54.0)	
Missing	157	9	148	

* Column percentages

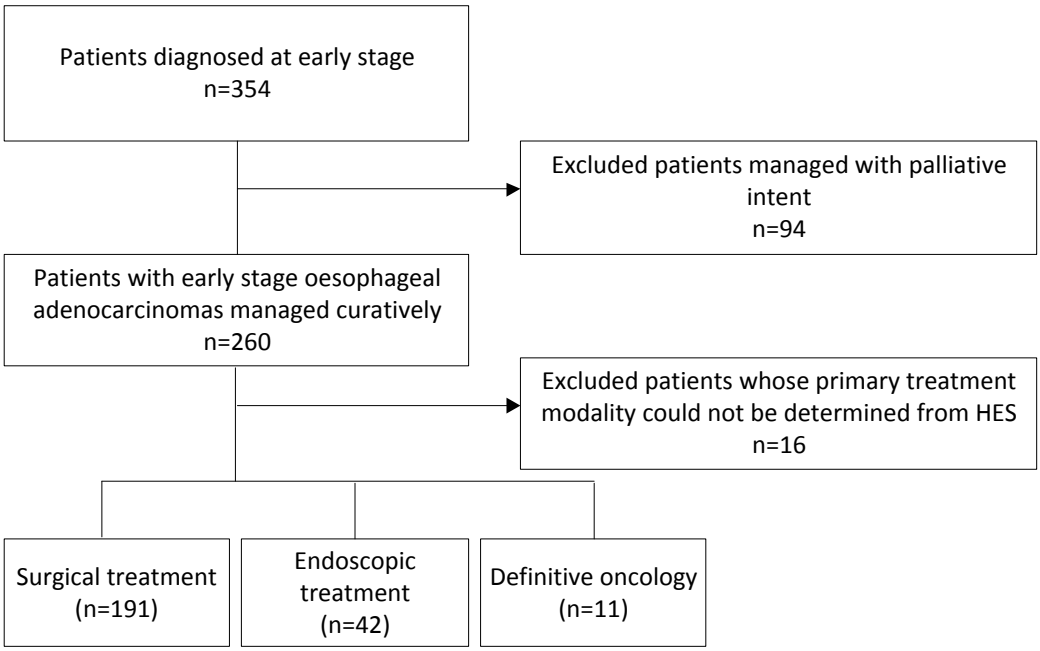
Where stage at diagnosis was known, 354 (6.8%) patients had early stage disease at diagnosis. Patient characteristics such as age at diagnosis and sex were not significantly different according to disease stage at diagnosis. However, patients diagnosed with early stage disease were more likely to have a history of Barrett's oesophagus (16.7% vs 4.1%, p<0.001), and they also tended to have a better performance status score (performance status 0/1 80.5% vs 2/3/4 73.8%, p=0.018). Finally, patients who were referred by another hospital consultant were more likely to have early stage disease at diagnosis (36.1% vs 14.9%, p<0.001).

As expected patients who were diagnosed with early stage disease were significantly more likely to be managed with curative intent compared to those diagnosed with more advanced disease (75.4% vs 46.0%, p<0.001). Further analysis of the subset of patients with early cancers who were managed with palliative intent revealed they were on average older (mean age at diagnosis 76.8 years vs 66.4 years, p<0.001) and/or had a worse performance status (performance status of 2 or more 51.0% vs 11.9%, p<0.001) than those treated with curative intent. All 59 patients diagnosed with early cancer who had a history of Barrett's oesophagus were managed with curative intent, compared to only 207 out of the 295 (70.2%) patients with no history of Barrett's oesophagus.

6.4.1 Primary treatment modality for early cancers managed curatively

Using HES, primary treatment modality was determined for 244 (93.8%) of the 260 patients diagnosed with early cancer who were managed with curative intent. Where this was known, 191 (78.3%) had a curative surgical resection, 42 (17.2%) were treated endoscopically, and 11 (4.5%) received definitive oncological treatment (Figure 6-2). Primary treatment modality could not be determined from HES for the remaining 16 patients, due to missing or non-specific data in HES (e.g. only diagnostic endoscopy recorded in HES where the planned treatment modality was endoscopic).

Figure 6-2 Primary treatment modality derived from HES, for patients with early oesophageal adenocarcinoma



10 patients who had a curative surgical resection had had an EMR performed at or soon after diagnosis and went on to have surgery within 3 months of diagnosis, it is likely that these represented diagnostic staging EMRs. For a further 4 patients who had an EMR before surgery the

intention of initial EMR was less certain, these patients had an EMR shortly after diagnosis and proceeded to have a subsequent diagnostic endoscopy before proceeding to surgery more than 3 months after diagnosis. These EMRs could therefore represent diagnostic EMRs with delayed surgery, or EMRs performed with curative intention where the resection failed and the patient proceeded to surgery. If one accepts the later interpretation, then 8.7% (4/46) of patients failed to have their disease controlled endoscopically where this was the initial treatment intent.

Table 6-4 examines the patient characteristics for patients who received the two main treatment modalities. Patients managed surgically were substantially younger (mean age at diagnosis 64.3 years vs 72.6 years, p<0.001) and were less likely to have a previous diagnosis of Barrett's oesophagus (21.5% vs 35.7%, p=0.05) than those managed endoscopically.

Table 6-4 Characteristics of patients with early oesophageal cancer who underwent curative treatment by treatment modality

	Surgery	**Endoscopic treatment**	**p-value**
Number of patients, n	191	42	
Age group, years, mean (±SD)	64.3±9.4	72.6±8.6	<0.001
Male, n (%*)	153 (80.1)	35 (83.3)	0.631
Tumour location, n (%*)			0.444
Upper / Middle oesophagus	14 (7.3)	5 (11.9)	
Lower oesophagus	154 (80.6)	34 (81.0)	
GOJ	23 (12.1)	3 (7.1)	
Performance status, n (%*)			0.158
0/1	138 (92.0)	26 (83.9)	
2/3/4	12 (8.0)	5 (16.1)	
Missing	41	11	
Any co-morbidity except Barrett's oesophagus, n (%*)			0.713
None	106 (55.5)	22 (52.4)	
One or more	85 (45.5)	20 (47.6)	
Barrett's oesophagus, n (%*)			0.050
No	150 (78.5)	27 (64.3)	
Yes	41 (21.5)	15 (35.7)	

* Column percentage

Treatment and outcomes of patients who had surgery as their treatment modality

Table 6-5 summarises the staging, treatment and outcomes for patients managed surgically.

Table 6-5 Details of surgery and associated outcomes

	Surgery (n=191)
Pre-operative EUS, n (%)	143 (74.9)
Use of pre-operative chemotherapy, n (%)	18 (9.4)
Times from diagnosis to surgery, days (IQR)	
No neo-adjuvant treatment	62 (46-91)
Neo-adjuvant treatment first	134 (100-161)
Length of stay from, days (IQR)	16 (12-26)
Surgical approach, n (%*)	
Left Thoracic	23 (13.8)
2-Phase (Ivor-Lewis)	109 (65.3)
3-Phase (McKeown)	22 (13.2)
Trans-hiatal	13 (7.8)
Missing	24
Planned MI/Hybrid surgery, n (%)	56 (32.2)
Any post-operative complication, n (%)	64 (33.5)
Return to theatre, n (%)	20 (12.0)
Post-operative endoscopic treatment e.g. dilatation or stent, n (%)	45 (23.6)
Pathology stage (available for n=171), n (%*)	
T0/T1, N0, M0	119 (69.6)
T1, N1, M0	11 (6.4)
T1, N1, M1	1 (0.6)
T2, N0, M0	10 (5.8)
T2, N1/2, M0	15 (8.8)
T3, N0, M0	4 (2.3)
T3, N1/2, M0	11 (6.4)

* Column percentage
EUS – Endoscopic ultrasound, MI – Minimally invasive

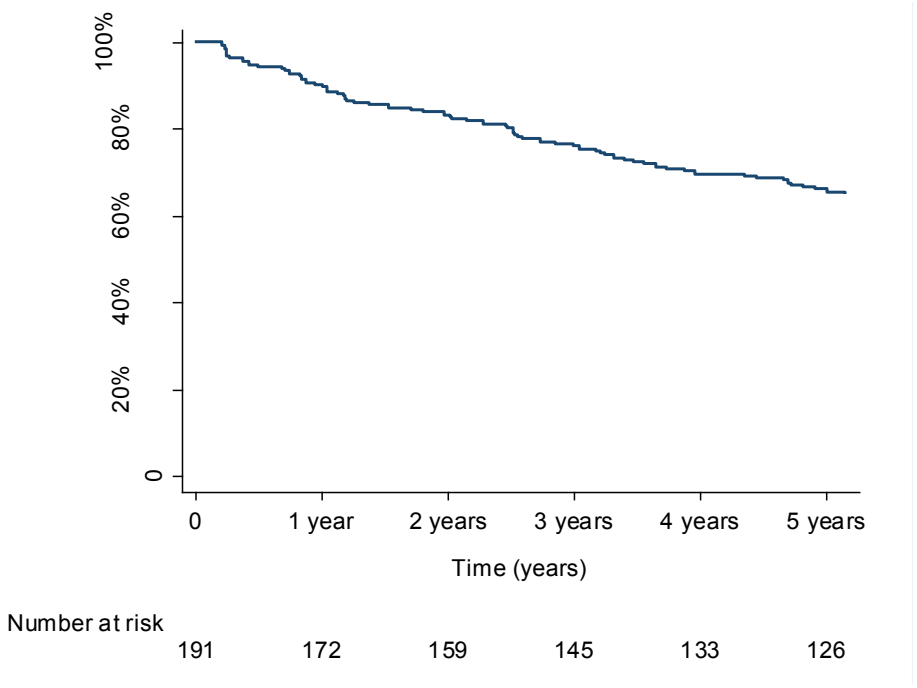
Analysis of NOGCA dataset revealed that 64 (33.5%) patients suffered at least one post-operative complication, with 20 (12%) patients requiring a further unplanned operation. Other frequent complications included respiratory complications affecting 36 (18.8%) patients and cardiac complications affecting 9 (4.7%) patients. Further analysis of the HES episodes after surgery revealed that 45 (23.6%) patients needed a further endoscopic intervention, including 11 stents and 39 dilatations (with 5 patients requiring both). 12 patients required ≥3 dilatations.

Where the patient had had a surgical resection, a separate pathology report was recorded for 171 patients (89.5%). In 52 cases (30.4%) the disease was upstaged post-operatively, with 25 tumours subsequently found to be T2 and 15 found to be T3, a few patients were also found to have evidence of lymphatic and metastatic spread (Table 6-5). Given that almost a third of patients had their disease upstaged post-operatively it was important to assess the adequacy of pre-operative staging investigations, our analysis demonstrated that a pre-operative EUS significantly reduced the proportion of patients found to have more advanced disease post-operatively, from 47.6% to 24.8% (p=0.005).

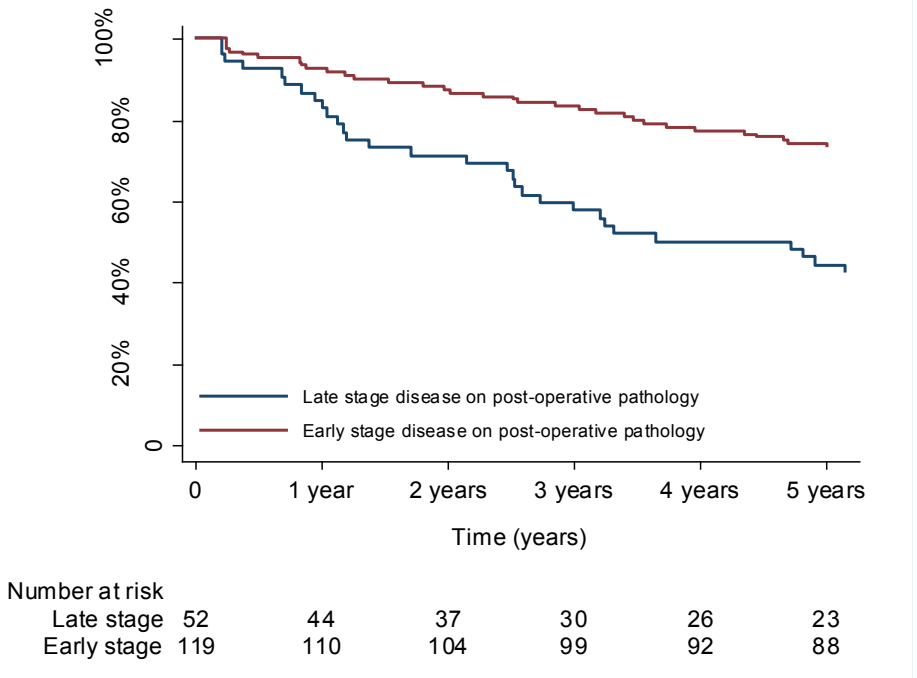
Overall survival rates were calculated for all patients managed surgically, 90.1% (95% CI 84.9 to 93.9) survived 1 year post diagnosis and 66.0% (95% CI 58.8 to 72.7) survived 5 years (Figure 6-3). However, only 84.0% of patients with an ASA (American Society of Anesthesiologists) grade of 3 or more survived 1 year. As may be expected patients who were found to have more advanced disease on their post-operative specimen were significantly less likely to survive (Log-rank test, p<0.001) (Figure 6-3).

Figure 6-3 Kaplan-Meier survival curves for patients who had curative surgery for early oesophageal adenocarcinoma, overall (A) and stratified according to post-operative pathology results (B)

(A)



(B)



Treatment and outcomes of patients who had endoscopic therapy as their treatment modality

42 patients received endoscopic therapy for their early cancers, their treatment modality and outcomes are summarised in Table 6-6. The vast majority of endoscopic procedures were performed as a day case (78.6%), with only 6 (14.3%) patients requiring overnight admission and 3 (7.1%) patients requiring admission for 2 nights. Analysis of HES codes associated with these episodes did not reveal any complications that would account for these overnight stays.

Table 6-6 Characteristics and outcomes of patients managed endoscopically

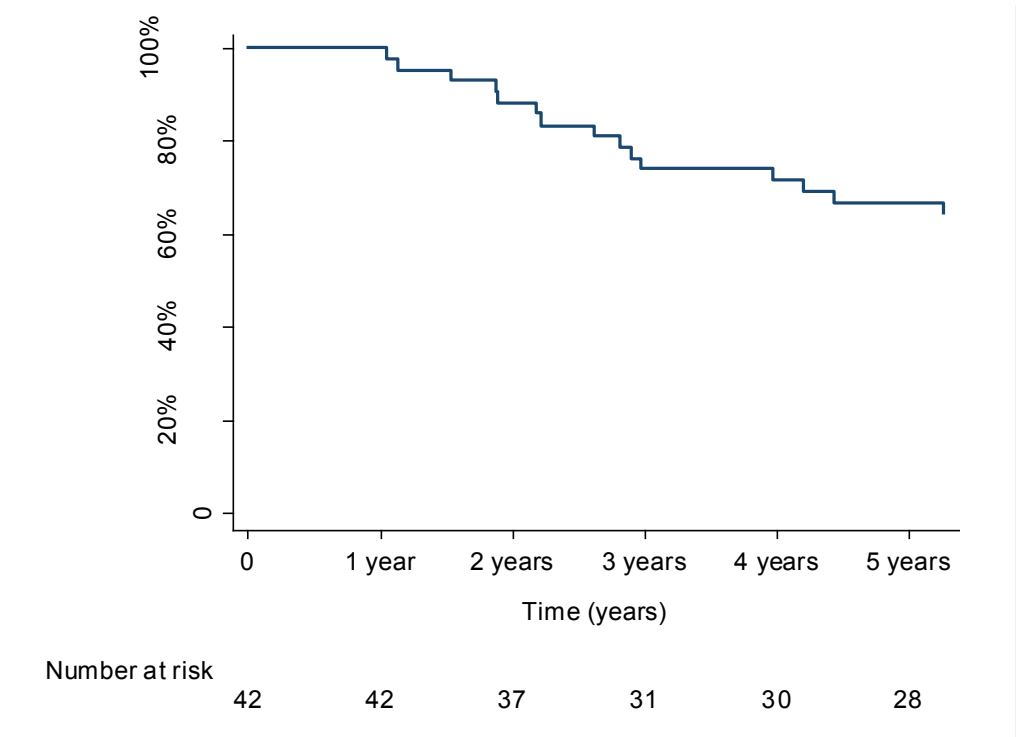
	Endoscopic treatment (n=42)
Pre-treatment EUS, n (%)	15 (35.7)
Time from diagnosis to EMR, days (IQR)	56 (0-81)
Endoscopic treatment, n (%*)	
EMR alone	28 (66.7)
EMR and Ablation	13 (31.9)
Ablation alone	1 (2.4)
Repeat endoscopic treatment required, n (%)	23 (54.8)
Stricture post treatment requiring further treatment, n (%)	2 (8.7)

* Column percentage

The risk of complications appeared to be low after endoscopic therapy with no reported perforations, and only 2 patients (4.8%) required a stent or dilatation at a later date. However 23 (54.8%) patients required further endoscopic treatment, including 8 patients (19.1%) who required ≥ 3 treatment sessions.

Overall survival for patients managed endoscopically was 100% (95% CI 91.6 to 100* (one-sided test)) at 1 year and 66.7% (95% 50.5 to 80.4) at 5 years (Figure 6-4).

Figure 6-4 Kaplan-Meier survival curves for patients who had endoscopic therapy for early oesophageal adenocarcinoma



6.5 Discussion

Using the NOGCA dataset this study identified 354 patients in England who had been diagnosed with early stage oesophageal adenocarcinomas between 2007 and 2009. This equates to 6.8% (95% CI 6.1-7.5) of all oesophageal adenocarcinomas diagnosed in England over this time frame. Although this figure appears low, it probably reflects the upper estimate of the true incidence of early stage disease in England, because a significant number of patients were missing information on stage at diagnosis and these patients were more likely to have more advanced disease at diagnosis.

Early diagnosis of oesophageal cancer was significantly associated with a history of Barrett's oesophagus and referral by another hospital consultant. This probably reflects the fact that a proportion of these cancers were detected as a result of surveillance endoscopies performed for Barrett's oesophagus. Unfortunately limitations of the dataset prevented further investigation into this, but changes to the dataset will allow this to be investigated in future.

Given the changing treatment options available for the treatment of early oesophageal cancer and the shift in guidelines towards recommending endoscopic therapy in preference to surgery (20), it was important to investigate current use of endoscopic therapy in England. This study found that only 17.2% of patients with early cancers were managed endoscopically, much lower than the 29% reported to have been managed endoscopically over a similar timeframe in a study from the US using the Surveillance Epidemiology and End Results (SEER) national database (114).

However if endoscopic therapy is to replace surgery as the treatment of choice for early cancer then it is important to produce more conclusive evidence regarding the long term outcomes associated with its use. The current literature base is sparse and previous studies have been subject to significant limitations. One of the main limitations of previous studies is that they have relied on data pooled data over long periods (ranging between 5 and 13 years), and collected as early as 1998 (111-115). It is important to realise that in 1998 endoscopic therapy was a relatively novel technique and use would have been limited to very few specialist centres. Since then the treatment options and outcomes for oesophageal cancer have changed considerably (20, 48, 78), as a consequence results from previous studies may not provide an accurate representation of current practice and outcomes. Finally previous studies have attempted to directly compare outcomes of patients managed endoscopically and surgically, but these comparisons were limited for to two main reasons. Firstly previous single centre studies have relied on small sample sizes, and consequently may have been underpowered to detect significant differences in outcomes (111, 112). In addition their

results reflect the outcomes achieved in tertiary research centres, and therefore may not be generalizable to the wider population. Secondly previous national studies have lacked some of the details required to make accurate comparisons across patient groups, for instance information on treatment intent, ASA grade and performance status (113-115). As a result their reported outcomes are subject to bias from unmeasured confounders making it difficult to draw valid conclusions about the relative effectiveness of each treatment modality. These differences may account for the variability in reported outcomes, with US population-based studies reporting better overall 5 year survival for patients managed surgically and no difference in cancer specific mortality (113, 114), while previous single centre studies have reported no difference in outcomes (111, 112). In this study outcomes for both groups are reported, however in contrast to previous studies the decision was made not to directly compare their outcomes using a multivariable cox regression, because baseline characteristics of the two groups differed significantly. While some of these differences could be adjusted for (e.g. age), limitations of our dataset meant other potential confounders (e.g. depth of mucosal/submucosal invasion) could not be adjusted for and as a result it was felt to be inappropriate to attempt to make direct comparisons across the two groups.

This study reported that 66.7% of patients managed endoscopically survived 5 years after diagnosis. However, our results also suggest that 8.7% of patients who were initially managed endoscopically later went on to require a salvage oesophagectomy. Previous national studies have been unable to estimate this failure rate for endoscopic therapy, because they have relied on the SEER database which only records the most invasive treatment modality (113-115).

Other secondary outcomes reported included the use of pre-operative staging investigations. This study found that a quarter of patients did not undergo a staging EUS, and these patients were significantly more likely to have their disease upstaged post-operatively compared to those who had had a pre-operative EUS (47.6% vs 24.8%, p=0.005). This in turn had a direct impact on patient outcomes, only 44.2% of patients who had their disease upstaged post-operatively survived five years compared to 74.0% of those with confirmed early stage disease on post-operative pathology.

Finally previous studies have reported higher rates of recurrence after endoscopic therapy compared to surgery (6-20% vs 0-2% surgery group) (111, 112, 197), and that a significant proportion of patients were lost to follow up 3 years after endoscopic treatment (197). As a result this study investigated the proportion of patients managed endoscopically who required repeated therapeutic endoscopies, and demonstrated that 54.8% of patients managed endoscopically required further endoscopic treatment.

This highlights the important of achieving high levels of patient compliance in endoscopic follow up if endoscopic therapy is to be used as the treatment of choice for early cancers.

Strengths and weakness of the study

The major strength of this study comes from the fact that is the largest cohort of patients with early oesophageal cancer identified in England and all patients were diagnosed over a relatively short time frame (21 months). As a result this study should not be prone to some of the limitations affecting previous studies which relied on data collected over many years, over a period of time when there were substantial advances in the treatment options available. Furthermore the study had access to data on key prognostic factors (e.g. ASA grade) which were not available in previous national studies and which were shown to impact significantly on treatment outcomes in this study. Finally for the first time this study was also able to examine the use of staging investigations and the impact this had on post-operative histology results on a national level.

The study did have several limitations though. Firstly HES is designed primarily as an administrative dataset which aims to capture details relating to all NHS hospital admissions in England, as a result it is subject to coding errors. Of particular concern is the fact that it is likely that a proportion of therapeutic endoscopies were non-specifically coded for in HES and were therefore not picked up this study. This limitation is highlighted by the fact that for the 16 patients where primary treatment modality could not be established from HES, 6 (37.5%) had been planned to undergo an endoscopic resection. Consequently, the study may have underestimated both the frequency of repeat endoscopic interventions and the proportion of patients undergoing endoscopic resections as primary treatment modality.

This study did not attempt to compare outcomes across patients managed endoscopically and surgically for two main reasons. Firstly the extract of ONS used for this study did not provide cause of death, this is important because it is likely that patients managed endoscopically had a higher all cause mortality than those managed surgically, as they were older and frailer (114). Secondly the dataset did not distinguish between tumours invading the mucosa and submucosa, this is important because surgery remains the mainstay of treatment where there is submucosal invasion. As a result there were baseline characteristics between the two groups that could not be adjusted for.

Publication related to this work: Chadwick et al, British Journal of Surgery, 2016; 103(5): 544-52

7. Discussion and Conclusions

The aims of this thesis were to further investigate the management of early neoplastic changes in the oesophagus in England. Having reviewed the current literature in the Chapter 1, several keys gaps in the literature were identified which this thesis aims to address by performing several separate studies, including:

- Investigation into the current management of high grade dysplasia (HGD) of the oesophagus in England.
- Systematic review comparing the safety and efficacy of complete endoscopic resection and radiofrequency ablation in the treatment of dysplastic Barrett's oesophagus.
- Investigation into the proportion of oesophageal cancers missed at endoscopy in England.
- Investigation into the management and 5 year survival outcomes associated with the treatment of early oesophageal adenocarcinoma in England.

7.1 Implications for clinical practice

The results of these studies raise several salient findings which may have important implications for clinical practice, and which will be discussed in greater detail in the next section.

Over the last few years, national guidelines have been updated to recommend endoscopic treatment instead of surgery as the treatment of choice for oesophageal HGD (20). It is therefore important to establish the best endoscopic treatment, in terms of both treatment efficacy (short and long term) and risk of complications. As discussed in the Introduction (Chapter 1) two broad approaches exist for the endoscopic treatment of dysplastic Barrett's oesophagus, complete endoscopic mucosal resection (EMR) and ablation. With radiofrequency ablation (RFA) now considered the ablative approach of choice in Europe, our review sought to compare outcomes after RFA and complete EMR. To date the evidence base comparing the two techniques is limited, with only one randomised control trial (RCT) directly comparing their outcomes (131), highlighting the need to systematically review the available literature in order to be able to draw any firm conclusions, as done in Chapter 4.

This review demonstrated that while there is extensive evidence regarding the short term efficacy of both techniques, the body of literature regarding their longer term efficacy is limited. Pooling results from prospective studies found that complete eradication of dysplasia at the end of treatment was achieved in 95% (95%CI 87-99%) of patients treated with complete endoscopic resection and 92% (95%CI 85-96%) treated with RFA. It is equally important, if not more important,

to investigate the longer term durability of treatment if endoscopic therapy is to replace surgery as the treatment of choice for HGD. Unfortunately assessment of long term treatment durability was difficult for two reasons i) follow up periods were variably reported and ii) overall follow up periods were relatively short with a median follow up of under two years. Overall 85-100% of patients treated with complete endoscopic resection and 79-100% of patients who received RFA were reported to have maintained complete eradication of dysplasia at follow up endoscopy. However, it was not possible to accurately calculate the risk of progression to cancer due to the limited and varied follow up periods reported. Nonetheless overall rates of progression did appear to be low, with only 1.7% of patients treated with complete endoscopic resection and 0.9% of patients treated with RFA developing cancer during follow up. These figures are substantially lower than the 5.6% per year reported risk of progression to cancer if HGD is left untreated (36). Another important consideration of treatment is the risk of complications, and this varied substantially by treatment modality. Overall 38% of patients treated with complete endoscopic resection developed an oesophageal stricture, compared to only 4% treated with RFA.

So, the results of our systematic review conclude that while both complete EMR and RFA have proven short term efficacy in the treatment of HGD, complication rates were significantly higher after complete EMR. Further studies need to be done to demonstrate the longer term (5-10 year) durability of both approaches. It is also important to appreciate that the results of this review demonstrate the ongoing risk of recurrence of dysplasia after endoscopic treatment and therefore the need for continuing endoscopic surveillance.

The remaining studies in this thesis used data collected for the National Oesophago-Gastric Cancer Audit (NOGCA), which provided us with a unique opportunity to explore the management of early neoplastic changes in the oesophagus in England using patient level data.

Until now studies looking at the management of HGD in England have had significant limitations. Firstly previous studies have relied on the results from surveys of clinicians looking at the reported management of patients with HGD (120-123), without access to patient level data. These studies reported considerable variability in the management of HGD in England and lack of adherence to national guidelines. Secondly these studies were conducted many years ago (between 1997-2005), at a time when treatment options for HGD were much more limited and endoscopic therapy was a relatively novel approach, with use limited to a few specialist centres. Since then there has been a dramatic shift in the management of HGD, with the most recent BSG guidelines recommending that all patients with HGD of the oesophagus are considered for endoscopic therapy in preferences to either surgery or surveillance alone (20). It is therefore important to investigate current

management of HGD in England and adherence to national guidelines, in order to ensure any gaps in care are identified and improve care of patients in the future.

In April 2012 the NOGCA started collecting information on all patients newly diagnosed with HGD of the oesophagus in England, providing us with a unique opportunity to investigate their management further. This is the first national database in the world collecting data on this subgroup of patients. The detailed results of our study are presented in Chapter 3 which highlights several key findings. Firstly, there is significant variation in the management of oesophageal HGD across England, with a third of patients managed by surveillance alone. Factors associated with this management plan were investigated, and our study found that patients who had not had the diagnosis of HGD confirmed (either on repeat biopsy or by a second pathologist) and had not had their case discussed at the UGI MDT were more likely to be managed by surveillance alone. Further our analysis demonstrated that there is a significant association between the volume of patients treated for HGD at a particular NHS trust and the proportion of patients managed by surveillance alone, such that patients managed in low volume trusts were five times more likely to be managed by surveillance alone than patients managed in high volume trusts. Currently the majority of trusts in England treat less than 5 cases of HGD each year. These two findings highlight the lack of centralisation of HGD services in England currently. It is therefore important to consider whether the management of patients with HGD should be centralised in future, to ensure that all patients get equal access to these newer endoscopic therapies. The most recent NOGCA report (198) makes the following recommendation based on this finding:

> *'A significant proportion of cases of HGD are still managed by surveillance alone, despite the BSG recommending that all patients should be considered for active treatment. It is important that NHS Trusts and Health Boards consider referral of patients with HGD to a specialist centre which has experience of treating HGD'*

It will therefore be interesting to see whether care of patients with HGD does undergo a process of centralisation over the coming years.

The thesis then turned to look at the management of oesophageal cancer in England. The overall prognosis for patients diagnosed with oesophageal cancer is dismal with only 15% of patients surviving 5 years (1). This is down to the fact that a substantial proportion of patients have their cancers diagnosed at a late stage, and as a result only a third of patients are considered for curative therapy (2). It is therefore important to try to increase the proportion of patients diagnosed with early stage disease and optimise their management.

Endoscopy and biopsy is widely regarded as the investigation of choice for the diagnosis of oesophageal cancer (48), Nonetheless previous studies have reported that a significant proportion of oesophageal cancers may have been missed at initial endoscopy (53-59), however these studies have been subject to significant limitations. Firstly, all previous studies have been single centre (except one (57)), and as a result they have relied on data collected over many years (up to 14 years (53)) in order to achieve reasonable patient numbers. Despite the long study inclusion periods examined, these single centre studies still had relatively small patient numbers, between 110 (54) and 1075 (59), making it difficult to investigate associations between patient characteristics and miss rates. Secondly previous studies have lacked access to key information such as stage at diagnosis, and treatment plan following diagnosis. These factors are important to investigate in order to establish the potential impact of a missed diagnosis.

In order to address some of these limitations Chapter 5 used data collected for the NOGCA, linked to Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality data, to investigate the proportion of oesophageal cancers that were potentially missed at endoscopy and the impact a missed diagnosis may have had on patient outcomes. This study identified 6,943 cases of oesophageal/or junctional cancer diagnosed over one year in England. 537 (7.8%, 95% CI 7.1-8.4) patients had had an endoscopy in the previous 3 years including 214 (3.1%, 95% CI 2.7-3.5) patients who had had one in the previous 3-12 months. Further analysis went on to demonstrate that early cancers ($p<0.001$) and cancers located in the upper oesophagus (0.004) were significantly more likely to have been missed at endoscopy in the preceding 12 months. The study went on to examine diagnostic codes associated with previous endoscopies and revealed that 50.9% of patients who had had an endoscopy in the previous three years had previously been diagnosed with an oesophageal ulcer. Finally the study investigated the potential impact of a missed diagnosis on treatment plan and 1 year survival. While this study established no clear impact on outcomes, it is important to realise that this was difficult to evaluate given the poor evidence base regarding the natural progression of untreated oesophageal cancer and the inability to review initial endoscopy and pathology findings. Furthermore important differences in outcomes may not have been detected within the 1 year follow up time frame.

This is the first time that the problem of missed oesophageal cancers at endoscopy has been investigated on a national level and our results raise key areas that could be targeted in order to improve practice in future. Firstly, it highlights the importance of careful visualisation of the upper oesophagus on both intubation and extubation in order to reduce the risk of missing lesions in this region. Secondly, where an oesophageal ulcer is identified it is important to ensure adequate

biopsies are taken and the patient is considered for a repeat endoscopy at 6-8 weeks to confirm ulcer healing (as is common practice for gastric ulcers). This is a key finding, because there are currently no national guidelines focusing on the management and follow up of oesophageal ulcers, and suggests that development of such guidelines should be considered with incorporation of oesophageal ulcer follow up into the auditable outcomes assessed by Joint Advisory Group (JAG). Finally, it is crucial that clinicians are made more aware of the risk of cancer in patients who have had a previous non-diagnostic endoscopy, and are encouraged to re-refer patients urgently for review and investigation where they feel the risk of malignancy is still high.

The final study presented in this thesis investigated the management and long term outcomes of patients diagnosed with early oesophageal cancer in England. As previously stated, survival for oesophageal cancer is closely linked to the disease stage at diagnosis and once diagnosed careful consideration needs to go into the most appropriate treatment option. Until recently oesophagectomy has been considered the treatment of choice for such lesions, but this is major surgery and associated with significant mortality and complication rates (2). Given the low risk of lymphatic spread where the cancer is localised to the mucosa or most superficial layer of the submucosa (88, 89), localised endoscopic therapy is now considered the treatment of choice for these early lesions (20). It is therefore important to monitor the long term outcomes associated with this approach, to ensure these are comparable to those achieved through a surgical resection.

Current evidence regarding the long term outcomes associated with the endoscopic and surgical management of early oesophageal cancers is limited. Previous studies have been subject to significant limitations, including small sample sizes, use of data pooled over many years and the potential impact of on unmeasured confounders on outcomes when comparing the two techniques. These limitations may account for some of the variability in results reported.

Chapter 6 aims to overcome some of these limitations by investigating the patterns of management of early oesophageal cancer in England, using linked data from three national databases collected over 21 months between 2007-2009. This study identified 10,792 patients diagnosed with oesophageal cancers, 5,240 of these were selected for analysis as they had been diagnosed with oesophageal adenocarcinomas and had complete staging information submitted to the NOGCA. 354 (6.8%) of these patients were diagnosed with early stage oesophageal adenocarcinoma. Three quarters were managed with curative intent, with the majority of these patients having a curative resection and only 1 in 5 patients were treated endoscopically. In contrast to previous studies this study did not attempt to directly compare outcomes for patients managed endoscopically and surgically, due the observational nature of the study and clear differences in the baseline

characteristics of the two groups. However, 5-survival rates associated with both therapies were reported, 66.7% (95% CI 50.5 to 80.4) after endoscopic treatment and 66.0% (95% CI 58.8 to 72.7) after surgery. It is important to appreciate that endoscopic treatment options were in their infancy in 2007, and as a result it is likely that practice and outcomes will have changed since then. Nonetheless it is still crucially important to monitor the longer term (5 year) outcomes associated with treatment as this study does.

One key area that this study addressed that has not been investigated in previous studies was the use of staging investigations in the diagnosis of early oesophageal cancer. This study found a quarter of patients managed surgically had not had a pre-operative staging endoscopic ultrasound (EUS). Our analysis demonstrated that these patients were significantly more likely to have their disease upstaged post-operatively (47.6% vs 24.8%, p=0.005) and as expected patients who were upstaged post-operatively had significantly worse outcomes (only 44.2% survived 5 years compared to 74.0% of those who had confirmed early stage disease on post-operative pathology).

In conclusion this study highlights several areas where care of patients with oesophageal cancer can be improved in England. Firstly, only 6.8% of oesophageal adenocarcinomas are diagnosed at an early stage and a quarter of these patients are managed with palliative intent. The UK government is taking steps to try and increase the proportion of cancers diagnosed early by increasing the public's awareness of sinister symptoms, with the launch of the 'Be Clear on Cancer' campaign for oesophago-gastric cancer in January 2015 (191). Secondly, the high proportion of patients with early cancer managed with palliative intent may reflect the relatively low uptake of endoscopic therapy in England 5 years ago. Future studies need to investigate whether the proportion of patients with early cancer managed endoscopically has increased in light of the changes to the BSG guidelines (20) and the impact this has had on the proportion of patients with early cancer managed with palliative intent. Finally our results suggest that staging investigations are currently being underutilised, and as a result a significant proportion of patients are upstaged post-operatively. NHS trusts therefore need to review their practice and improve staging of cancers in future.

7.2 Methodological considerations

A degree of caution always needs to be employed when interpreting the results of any study and this section aims to highlight the more general methodological considerations which may impact on the validity of the results presented in each chapter. Given the nature of a systematic review, the limitations of this type of work differed from those of the other chapters which present original research, and these two types of research are therefore considered separately.

7.2.1 Systematic review

7.2.1.1 External validity

In considering the external validity of the results of this review, the inclusion criteria for the review were broad including all studies published in any language in the last ten years, and only excluding studies where patients had had previous endoscopic treatment for their HGD or previous reflux surgery. Furthermore patients included in each study were broadly representative of patients with Barrett's oesophagus including all patients over the age of 18 with any length of Barrett's oesophagus.

The studies identified in this review came from a number of different countries. However, it is important to note that all of the prospective RFA studies came from two research groups in Europe, and this may limit the validity of their results if applied to less specialised centres. In contrast the retrospective studies came from a far greater spectrum of centres, including a community centre in the US (177), making their results more generally applicable. Nonetheless given that dysplastic Barrett's is a relatively rare condition it may be preferable to limit its management to high volume specialist centres.

7.2.1.2 Limitations

Narrative reviews are associated with specific limitations, such as relying on a limited search of the literature and making recommendations strongly based on opinions. In contrast a systematic review, as performed in Chapter 4, aims to summarise all the available evidence and provide an unbiased presentation of the literature with some kind of precise estimate of the magnitude of any treatment effect.

However this reliance on previously published literature is the major limitation of any systematic review. Publication bias can substantially affect the results of any review, because it is likely that only studies with more favourable results will have been published. As a result it is likely that the

benefits of any treatment effect are over-estimated, and this factor needs to be considered when interpreting the outcomes of our review.

In considering the quality of studies included in this review it important to ensure this is formally assessed, as was done in Chapter 4 using the Ottawa-Newcastle assessment scale. This assessment highlighted some of the limitations of available literature. Firstly the majority of previous studies were observational in design and therefore lacked a control arm. Secondly studies were generally small and provided limited longer term follow up data, with several studies providing less than 1 year follow up data (146, 149, 175, 176) and others only reporting follow up outcomes on subsets of their study group (181). Given the limited data available on follow up outcomes from prospective studies, the decision was made at the start to include retrospective studies in this review as well. Inclusion of these studies had the advantage of providing more data on long term follow up results, but was associated with limitations. Most importantly, several of the retrospective studies did not present results on an intention to treat basis, which may mean that the results presented are over optimistic due to preferential drop out of treatment failures. In order to overcome this limitation, pooled results from only the prospective studies were present separately as well. Despite this our conclusions about the longer term durability of both treatments remain tentative.

7.2.2 Original research papers

All three of the original research papers presented in this thesis (Chapters 3, 5 and 6), used data collected on a national basis, including both routinely collected administrative data and data collected specifically for the NOGCA. The main advantage of using national datasets is that the results are more representative than those from single-centre studies, and provide more precise estimates of the outcomes considered.

However use of national datasets to address specific research questions is associated with significant limitations. Firstly, individual studies in this thesis may have benefited from more detailed information in specific areas, for instance the study into missed oesophageal cancer would have benefited from access to the indication for initial endoscopy and results from the initial endoscopy report. However, this would have required access to patient records which was not feasible in the context of a National Clinical Audit. Secondly, with any research using national databases, one must accept that the accuracy of the results of these studies rely on the quality of data submitted. As a result steps were taken throughout our analysis to limit our patient cohorts to those patients whose data was consistent across the different databases. This limited the impact any coding errors may have had on overall results.

Overall it was felt that the benefits of using these national datasets to address our specific research questions outweighed these limitations. The next section goes on to review in greater detail the specific advantages and disadvantages of each national dataset.

7.2.2.1 National-Oesophago Gastric Cancer Audit

The primary dataset used in this thesis was the NOGCA dataset. This data is comprehensively collected and submitted by all NHS trusts. The NOGCA aims to collect data on all patients with a new diagnosis of invasive epithelial oesophago-gastric cancer in England and Wales, and more recently HGD of the oesophagus in England.

Participation in the NOGCA is mandatory for NHS trusts in England, with inclusion of participation levels in trusts Quality Accounts which are externally audited and submitted to the Secretary of State. As a result the quality and robustness of data collected from this source should be very high. The case ascertainment for the second NOGCA was 83% for patients diagnosed with oesophago-gastric cancer in England, and over 90% for patients undergoing a curative resection (77). The results of our studies should therefore be truly representative of current management of oesophageal cancer and HGD in England. Although it is important to appreciate that within individual studies there was the possibility of selection bias, as data entry was not mandatory in all fields. For instance in Chapter 6 patients who had incomplete staging information submitted to the audit were found to more likely to be managed with palliative intent and have worse outcomes, it is therefore likely that our study overestimated the proportion of cancers diagnosed at an early stage. Nonetheless significant benefits are gained from having such a large cohorts of patients to study, including having the statistical power to perform additional subgroup analysis which has been limited in previous single centre studies addressing similar research questions.

Use of the NOGCA dataset did have its own limitations. Firstly, as discussed in Chapter 3 there is no unique International Classification of Diseases (ICD-10) code or Systematized Nomenclature of Medicine (SNOWMED) code used to record the diagnosis of HGD in the national administrative datasets. As a result it is not possible to establish the case ascertainment for HGD cases submitted to the audit. Although there is no reason to believe this will have affected the major findings of the study, it may mean that the study underestimated the proportion of patients managed by surveillance alone.

Secondly, the NOGCA dataset did not collect data on some variables which would have provided additional weight to our study's results. For instance in the paper looking at missed oesophageal cancers at endoscopy, it was not possible to identify patients who had undergone planned

surveillance endoscopies. As a result our estimate of the miss rate may be a slight overestimate. While the paper on the management of early cancer would have benefited from additional information on the depth of tumour invasion, in order to better risk stratify patients. In addition several data items were not mandatory for the NOGCA dataset, particularly in the HGD dataset. This reduced the quality of the data available in certain fields e.g. length of Barrett's was missing for a high proportion of patients. This may have introduced the risk selection bias, as patients with this data entered in these fields in the NOGCA may have differed systematically from the rest of the cohort, although there is no reason to believe this to be the case. In order to reduce the effect of this problem in the future, the HGD dataset has been substantially modified to make more variables mandatory for the next data collection year (Appendix D).

7.2.2.2 Hospital Episode Statistics

HES was designed as an administrative database, but is increasingly being used in health care research. As a result previous studies have raised questions about the reliability with which data was recorded in HES. The accuracy of data being submitted to HES has since been well validated, with recent studies showing that the quality of coding has improved substantially over time (199).

Linking the NOGCA data to HES allowed more in depth research questions to be addressed, which would not have been possible using the NOGCA dataset alone. For instance it provided information about previous endoscopic and surgical procedures that the patients had underdone. This allowed investigation into both the proportion of oesophageal cancers potentially missed at endoscopy, and the management of early oesophageal cancers on a national basis.

Linkage of the two datasets also allowed for substantial data validation to occur, thus reducing the risk of coding errors impacting on results. For instance in Chapter 5, the accuracy of 'date of diagnosis' submitted to the audit was validated using HES data, and patients were dropped from analysis where this data was inconsistent because this date was crucial for determining the timing of previous investigations. Furthermore using NOGCA data the quality of coding of endoscopic procedures in HES was confirmed. For instance in Chapter 5 it was very important to ensure all endoscopies were accurately recorded in HES, this was demonstrated by the fact that 92.5% of patients with a new diagnosis of oesophageal cancer had had an endoscopy recorded in HES within one month of diagnosis.

It is important to realise that use of HES does still have limitations attached. Firstly HES only collects data on hospital admissions in NHS hospitals in England. As a result any procedures performed in private hospitals or in Scotland/Wales will not have been picked up. However, these figures are

expected to be low and the impact of this limitation is expected to be extremely small when considering data on such a large scale. Furthermore the coding of some endoscopic procedures was non-specific and ambiguous, this may have caused under-reporting of endoscopic resections in Chapter 6. As a result this study may have underestimated both the proportion of patients treated endoscopically, and the frequency of repeat endoscopic interventions.

7.2.2.3 Office for National Statistics

Finally the NOGCA dataset was linked to ONS mortality data. This data linkage allowed us to define outcomes such as survival after diagnosis without increasing the burden of data collection for participating units, and also ensured complete follow up of patients. This had the advantage that one could look at 5 year survival outcomes for patients diagnosed with early oesophageal cancer on a national level.

While ONS data can also provide access to cause of death, the extract of ONS used in our studies did not provide this information. This limited the analysis that could be performed looking at outcomes for patients managed endoscopically versus surgically for early cancers, because it was likely that patients managed endoscopically had a higher all cause mortality than those managed surgically, as they were older and frailer. In order to combat this limitation, future extracts of ONS received in this unit will include details on cause of death as well.

7.3 Conclusions

Use of linked national datasets in the studies performed in this thesis provided a unique insight into the current management of HGD and oesophageal cancer in England. In doing so it highlighted several key areas where care can be improved in future.

Firstly, there is currently huge variation in the management of HGD in England with a significant proportion of patients managed by surveillance alone. Further analysis showed that this proportion was higher for patients managed in low volume centres. It is therefore important that careful consideration goes into the centralisation of HGD treatment services in England, in order to optimise the management of these patients.

Secondly in order to improve the outcomes for oesophageal cancer in future it is important to try and improve the proportion of patients diagnosed at an early stage. Our analysis showed that currently only 6.8% of oesophageal cancers are diagnosed at an early stage, and that a substantial proportion of cancers were potentially missed at prior endoscopy. This highlights an area where care of patients could potentially be improved, in order to achieve this it is important that any suspicious lesions are adequately biopsied and appropriately followed up.

Finally in treating Barrett's oesophagus with HGD it is important to consider treatment using RFA in preference to complete endoscopic resection, given that our review demonstrated that while the efficacy of both treatment approaches was similar the risk associated with complete endoscopic resection were much higher.

7.4 Future work

The development of the NOGCA dataset and linkage with other administrative databases provides a number of unique opportunities for research in the future. Areas that may warrant further investigation include:

7.4.1 Analysis of the impact of the 'Be Clear on Cancer' campaign

Currently only 15% of patients diagnosed with oesophago-gastric (OG) cancer survive 5 years post diagnosis (1), but this is related to the high proportion of cancers diagnosed at a relatively late stage. As a result only 30-40% of OG cancers are suitable for curative treatment at diagnosis (2). The government has therefore been taking steps to try and increase the proportion of these cancers diagnosed at early stage. This resulted in the launch of the 'Be Clear on Cancer campaign' for OG cancer, which aimed to improve early diagnosis of these cancers by raising public awareness of their signs/symptoms, and to encourage patients to see their GP without delay if they had concerns (191).

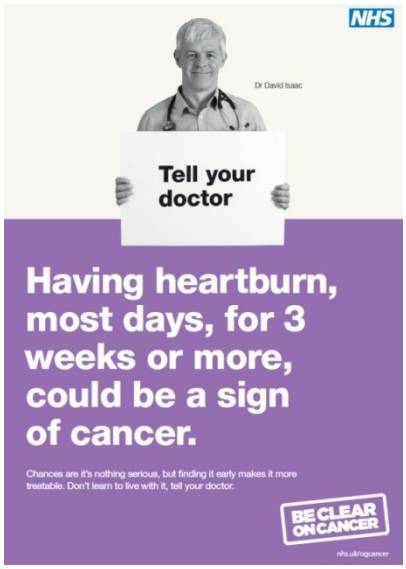
This national campaign was run based on evidence collected from seven local campaigns which ran between April and July 2012 and were extended into regional pilots which ran from February to March 2014. Cancer Research UK evaluated the success of these local and regional pilots by analyzing the effect the campaign had on symptom awareness, referrals rates from GP to secondary care, cancer detection rates and endoscopy to cancer diagnosis conversion rates (200). They reported the following, an increase in spontaneous awareness of the symptom 'difficulty swallowing' in those aged 55 and over (7% to 14%, statistically significant). This resulted in a 17% increase (statistically significant) in the number of GP visits for dysphagia in patients over 55 during the campaign. A significant increase in the number of urgent referrals for suspected upper GI cancer in pilot areas compared with control areas, from 26% to 16%, which they estimated would equate to approximately 16 extra endoscopies referrals each week for an average size trust. Finally they showed that although there was a 20% increase in the number of oesophageal cancers diagnosed following a 2 week-wait referral for suspected upper GI cancer following the campaign, this difference was not statistically significant and there was also no significant change in the conversion rate.

The 'Be clear on cancer' OG campaign ran from 26 January to 22 February 2015 (in England). The campaign was aimed at men and women aged 50 years and over and focused on two key messages:

- **'**Having heartburn, most days, for 3 weeks or more could be a sign of cancer – tell your doctor.' **Figure 7-1** shows an example of some of the campaign material.
- **'**Food sticking when you swallow could be a sign of cancer – tell your doctor.**'**

Figure 7-1 Media image from the 'Be clear on cancer' campaign

http://www.cancerresearchuk.org/health-professional/early-diagnosis-activities/be-clear-on-cancer/oesophago-gastric-cancers-campaign/resources-and-tools



It is therefore important to determine the success of the campaign on a national level, which can be done by investigating the following, (i) the number of cancers diagnosed at an early stage and therefore suitable for treatment with curative intent, (ii) the number of patients referred for endoscopy during campaign period and the conversion rate to OG cancer. These questions can be addressed by linking data from the NOGCA to HES and ONS, to compare endoscopy activity and oesophageal cancer outcomes between 26th Jan to 22nd March 2015 'campaign' period with the same 8 week period in 2014 'control' period.

Several key outcomes need to be assessed to do this. Firstly HES can be used to compare the number of cancers diagnosed in the 'campaign' vs the 'control' period. Then NOGCA data can be used to investigate changes in the patterns of referrals in greater detail, looking specifically for changes in the proportion of patients diagnosed after a GP referral and after an emergency hospital admission. It is then important to look at the impact the campaign had on cancer diagnosis and outcomes using NOGCA and ONS data, this analysis could look at changes in the proportion of cancers diagnosed at an early stage, and changes in the proportion of patients managed with curative intent and the proportion of patients who survive 1 year. Finally using HES data one could assess the impact of the campaign on hospital resources, in particular the total number of endoscopies done over the relevant time frame and the overall endoscopy to cancer diagnosis conversion rate.

7.4.2 Variation in OGD referral rates in English GP practices and effect on outcomes

GPs have had direct access OGDs since the 1980s, with introduction of 2 week-wait referrals in 2000. In 2013 Shawihdi et al used HES to demonstrate that there was significant variation in GP referral practices across England, including within PCTs (201). They went on to demonstrate that patients belonging to GP practices with lower referral rates had worse outcomes, with a lower proportion of patients undergoing a major resection, a higher proportion of patients being diagnosed as a result of an emergency admission and a lower proportion of patients surviving one year after diagnosis.

However, this paper had several limitations. Firstly it was unable to reliably distinguish between oesophageal and gastric cancer using HES. This is important because gastric cancers typically present with vaguer symptoms, and are therefore less likely to be referred for early investigation. Secondly they did not access to date of diagnosis or route to referral, these details had to be inferred from HES. As a result they could only determine which referrals were as a result of an emergency admission, and they were unable to look at use of routine and urgent GP referrals. This is important in order to look at whether GP with low referral rates refer a greater proportion of patients as two week wait referrals, suggesting the GPs had a higher threshold for referrals. Finally this paper was unable to establish important tumour characteristics (e.g type of cancer, site of cancer, stage at diagnosis) and initial treatment plan using HES data. Stage at diagnosis is important to determine whether patients belonging to GP practices with low referral rates were more likely to have their disease diagnosed at a later stage. While the lack of information on treatment plan including both treatment intent and treatment modality meant they could not identify surgical resections performed with non-curative intent or patients treated with alternative curative treatment options such as definitive oncology or a localised endoscopic resection for early cancer

Linking NOGCA data with HES allows some of these limitations to be addressed. In order to do this analysis the NOGCA dataset will need to be linked to the overall HES dataset managed by the Royal College of Surgeons in order to detect all OGDs done within a specified time frame.

7.4.3 Investigation into the long term outcomes of patients diagnosed with HGD of the oesophagus

Current follow up data looking at the long term outcomes for patients with HGD is limited, with studies coming primarily from specialist research centres. It is important to realise that outcomes achieved in these specialist centres may not be representative of those achieved in lower volume non-research centres.

The national cohort of patients with newly diagnosed HGD established by the NOGCA is unique worldwide. This provides us with an exciting opportunity to explore both the natural progression of the disease on a large scale, and the outcomes achieved with different treatment option. By linking this dataset to HES for patients with HGD it will be possible to investigate this is greater detail.

In particular this study aims to investigate the proportion of patients requiring further endoscopic therapy, the proportion of patients who go on to require a surgical resection at a later date and the risk of progression to cancer in future. It will also be possible to investigate whether the outcomes of patients with HGD managed in high volume treatment centres differ from those managed in lower volume centres. This will be the first time this type of study has been performed at a national level for this group of patients.

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Appendix

(A) ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group (202).

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

(B) ASA Grade

The ASA physical status classification system is a system for assessing the fitness of cases before surgery.

	ASA Grade
1	Healthy person.
2	Mild systemic disease.
3	Severe systemic disease.
4	Severe systemic disease that is a constant threat to life.
5	A moribund person who is not expected to survive without the operation.

(C) Dataset for the 2nd NOGCA

National Oesophago-Gastric Cancer Audit
New Patient Registration sheet –
Patients with Oesophageal High Grade Glandular Dysplasia

Patient Details

Surname: _____ Forename: _____

NHS number: _____ Postcode: _____

Sex: Male ☐ Female ☐ Not specified ☐ Date of birth: _____

Initial Referral to Local Oesophago-gastric Team and Diagnostic Process

Source of referral

From surveillance service: ☐ Symptomatic referral ☐ Not known ☐

Date of endoscopic biopsy in which HGD was first diagnosed: _____

Hospital where the endoscopic biopsy was taken: _____

Was a second biopsy performed? Yes ☐ No ☐

Did the second biopsy show HGD? Yes ☐ No ☐

Endoscopic Report

HGD appearance

Flat mucosa ☐ Nodular lesion ☐ Depressed lesion ☐ Not known ☐

Barrett's Segment

Present ☐ Absent ☐ Not known ☐

Length of Barrett's Segment, if present

Length of ***Circumferential*** Columnar Lining (nearest 0.5 cm): C ____.___cm

Maximum length including tongues/islands of Columnar Lining (nearest 0.5 cm): M ____.___cm

HGD Lesion (based on pathology report)

Unifocal ☐ Multi-focal ☐ Not known ☐

Was diagnosis confirmed by second pathologist? Yes ☐ No ☐ Not known ☐

[PTO]

Planned Treatment

Hospital at which treatment plan made _____

Date treatment plan agreed _____

Was the treatment plan agreed at an MDT meeting? Yes ☐ No ☐

Will the patient be referred to a specialist hospital for treatment? Yes ☐ No ☐ Not applicable ☐

Planned treatment modality

Surveillance	☐	Radiofrequency ablation	☐
Oesophagectomy	☐	Argon plasma coagulation	☐
Photo dynamic therapy	☐	Multipolar electrocautery	☐
Endoscopic Mucosal Resection (EMR)	☐	Laser therapy	☐
Endoscopic Submucosal Dissection (ESD)	☐	Cryotherapy	☐

Use of Endoscopic Mucosal Resection (EMR) / Endoscopic Submucosal Dissection (ESD)

EMR/ESD was not performed: ☐ Performed for diagnostic purpose: ☐

Performed for therapeutic purpose: ☐ Performed for both diagnostic and therapeutic purpose: ☐

Date of EMR/ESD: _____

Results of EMR/ESD:

Complete excision:	☐	Incomplete, follow up Oesophagectomy	☐
Incomplete, follow up surveillance	☐	Incomplete, follow up EMR/ESD	☐

Post-treatment Histology (pathology results based on EMR/ESD)

No high-grade dysplasia or carcinoma	☐
High-grade dysplasia confirmed	☐
Intramucosal carcinoma identified	☐
Submucosal carcinoma or worse	☐

National Oesophago-Gastric Cancer Audit

New Patient Registration datasheet (Oesophageal Gastric Cancer Patients)

Patient Details

Surname: _____ Forename: _____

NHS number: _____ Postcode: _____

Sex: Male ☐ Female ☐ Not specified ☐ Date of birth: _____

Initial Referral and Diagnosis Data

Source of referral: Direct from GP ☐ Barrett's Surveillance ☐ Emergency admission ☐

Open access endoscopy ☐ From other consultant ☐ Not known ☐

Priority of referral: (GP referral only) Urgent ☐ 2-week wait ☐ Routine referral ☐

Date of first referral to local oesophago-gastric team for investigation: _____

Date of diagnosis: _____

Local cancer unit where cancer was diagnosed: _____

Diagnosis - Site

Oesophagus: Upper $^1/_3$ ☐ Middle $^1/_3$ ☐ Lower $^1/_3$ ☐ ***NB: cervical oesophageal tumours are NOT included in this audit***

Gastro-Oesophageal Junction (adenocarcinomas only) Siewert classification:

1 ☐ 2 ☐ 3 ☐

Stomach: Fundus ☐ Body ☐ Antrum ☐ Pylorus ☐

Diagnosis - Histology

Invasive adenocarcinoma ☐ Squamous cell carcinoma ☐

Adenosquamous carcinoma ☐ Small-cell carcinoma ☐

Undifferentiated carcinoma ☐ Other epithelial carcinoma ☐

Unspecified malignant neoplasm (histology not done) ☐

NB: Non-epithelial tumours (GIST, sarcomas or melanomas) are NOT included in this audit

Staging investigations (please tick all that apply)

None ☐

CT scan ☐ PET / PET – CT scan ☐

Endoscopic ultrasound (EUS) ☐ EUS Fine needle aspiration ☐

Staging laparoscopy ☐ Other investigation ☐

Pre – Treatment Stage

Which TNM version do you use: TNM v6 ☐ TNM v7 ☐

T: 0☐ Tis☐ 1☐ 1a☐ 1b☐ 2☐ 2a☐ 2b☐ 3☐ 4☐ 4a☐ 4b☐ x ☐

N: 0☐ 1☐ 2☐ 3☐ 3a☐ 3b☐ x ☐

M: 0☐ 1☐ x☐

ECOG (WHO) Performance Status

0 Carries out all normal activity without restriction ☐

1 Restricted but walks/does light work ☐

2 Walks, full self-care but no work. Up and about >50% of the time ☐

3 Limited self-care, confined to bed or chair for >50% waking hours ☐

4 Fully disabled, confined to bed/chair ☐

Comorbidities (please tick all that apply)

None ☐

Cardiovascular disease ☐

Chronic renal impairment ☐

Cerebro/periph vascular ☐

Other significant condition ☐

Liver failure or cirrhosis ☐

Barrett's oesophagus ☐

Diabetes ☐

Mental illness ☐

Chronic respiratory disease (including COPD/asthma) ☐

Treatment Plan

Date final care plan agreed: _____

Treatment intent:

Curative: ☐

Non-curative (palliative) ☐ (i.e. surgery, chemotherapy, radiotherapy, endoscopy)

No active treatment (supportive care) ☐ (i.e. non -specific symptomatic treatments)

Details of planned treatment

<u>Curative modality</u>

Surgery only ☐

Chemotherapy and surgery (any combination) ☐

Chemo-radiotherapy and surgery (any combination) ☐

(Definitive) Radiotherapy only ☐

Definitive chemo - radiotherapy ☐

Endoscopic mucosal resection ☐

<u>Palliative modality</u>

Palliative surgery ☐

Palliative oncology (unspecified) ☐

Endoscopic palliation therapy ☐

No active treatment (supportive care) ☐

<u>Treatment part of a clinical trial</u>:

Patient eligible, consented and entered trial ☐

Patient eligible, declined trial ☐

Reasons for palliative treatment (please tick all that apply)

Patient declined treatment ☐

Unfit, because of advanced stage cancer ☐

Unfit, because significant co-morbidity ☐

Unfit, because poor performance status ☐

Not known ☐

National Oesophago-Gastric Cancer Audit
Postoperative Datasheet (Oesophageal Gastric Cancer and HGD Patients)

Patient details (for patient identification only)

Surname _____ Forename _____

NHS number _____ Date of birth _____

Admission and Surgical Details (Main procedure only)

Hospital name: _____

Date of admission: _____ Date of operation: _____

Pre-operative intent of surgery: Palliative ☐ Curative ☐

Fitness for Surgery (ASA grade): 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Height (in cm) _____ (to calculate body mass index)

Weight (in kg) _____ (to calculate body mass index)

Smoking: current smoker ☐ ex-smoker ☐ non-smoker (history unknown) ☐

never smoked ☐ not known ☐

Procedure

Surgical Access (thoracic) – the approach used for the thoracic phase of the operation (if applicable)

Open operation ☐ Thoracoscopic converted to open ☐ Thoracoscopic completed ☐ Not applicable ☐

Surgical Access (abdominal) - the approach used for the thoracic phase of the operation

Open operation ☐ Laparoscopic converted to open ☐ Laparoscopic completed ☐

Oesophageal

- Oesophagectomy:
  - Left thoraco-abdominal approach ☐
  - 2 – Phase (Ivor-Lewis) ☐
  - 3 – Phase (McKeown) ☐
  - Transhiatal ☐
  - Thoracotomy (Open & Shut) ☐

Gastric

- Gastrectomy:
  - Total ☐ Extended total ☐
  - Proximal ☐ Distal ☐
  - Completion ☐ Merendino ☐
  - Wedge/localised gastric resection ☐
  - Bypass procedure / Jejunostomy only ☐
  - Laparotomy (Open and Shut) ☐

Nodal Dissection

Oesophagectomy: None ☐ 1 – field ☐ 2 – field ☐ 3 – field ☐

Gastrectomy: D0 (peri-gut resection) ☐ D1 ☐ D2 ☐ D3 ☐

Postoperative complications and course (please tick all that apply)

None	☐	Respiratory:	
Anastomotic leak	☐	Pneumonia	☐
Chyle leak	☐	ARDS	☐
Haemorrhage	☐	Pulmonary embolism	☐
Cardiac complication	☐	Pleural effusion	☐
Acute renal failure	☐	Wound infection	☐
Other	☐		

Unplanned return to theatre? Y ☐ N ☐ Death in hospital? Y ☐ N ☐

Date of discharge or death: _____

Postoperative pathology and staging

Length of tumour _____

Site:

Oesophagus: Upper $^1/_3$ ☐ Middle $^1/_3$ ☐ Lower $^1/_3$ ☐

NB: cervical oesophageal tumours are NOT included in this audit

Gastro-Oesophageal Junction (adenocarcinomas only) Siewert classification:

1 ☐ 2 ☐ 3 ☐

Stomach: Fundus ☐ Body ☐ Antrum ☐ Pylorus ☐

Histology:

Invasive Adenocarcinoma	☐	Squamous cell carcinoma	☐
Adenosquamous carcinoma	☐	Small-cell carcinoma	☐
Undifferentiated carcinoma	☐	Other epithelial carcinoma	☐
Malignant Neoplasm	☐		

Proximal resection margin involved? Yes ☐ No ☐

Distal resection margin involved? Yes ☐ No ☐

Circumferential resection margin involved? (<1mm) Yes ☐ No ☐ N/A ☐

Number of lymph nodes examined: _____

Number of lymph nodes positive: _____

Postoperative stage

Which TNM version do you use: TNM v6 ☐ TNM v7 ☐

T: 0☐ Tis☐ 1☐ 1a☐ 1b☐ 2☐ 2a☐ 2b☐ 3☐ 4☐ 4a☐ 4b☐ x ☐

N: 0☐ 1☐ 2☐ 3☐ 3a☐ 3b☐ x ☐

M: 0☐ 1☐ x☐

Patient had neoadjuvant therapy prior to surgery: Yes ☐ No ☐

National Oesophago-Gastric Cancer Audit

Chemotherapy/Radiotherapy Datasheet (Oesophageal Gastric Cancer Patients)

Please fill in this datasheet for every course of oncological treatment received by a patient with oesophago-gastric cancer. Most patients will only require one datasheet to be completed. For patients who have both neoadjuvant and adjuvant therapy, complete two separate datasheets.

Patient details (for patient identification only)

Surname _____ Forename _____

NHS number _____ Date of birth _____

Hospital of treatment

Hospital where oncology treatment took place _____

Treatment details

Treatment intent:

Neoadjuvant ☐ Adjuvant ☐ Curative ☐ Palliative ☐

Intended treatment modality:

Chemotherapy ☐ Radiotherapy ☐ Chemo-radiotherapy ☐

Details of therapy

Chemotherapy details (if applicable)		**Radiotherapy details (if applicable)**	
Date first cycle started: _____		Date first fraction started: _____	
Outcome of treatment:		**Outcome of treatment:**	
Treatment completed as prescribed	☐	Treatment completed as prescribed	☐
Reason if incomplete		**Reason if incomplete**	
Patient died	☐	Patient died	☐
Progressive disease during treatment	☐	Progressive disease during treatment	☐
Acute chemotherapy toxicity	☐	Acute radiotherapy toxicity	☐
Technical or organisational problems	☐	Technical or organisational problems	☐
Patient choice (interrupted or stopped treatment)	☐	Patient choice (interrupted or stopped treatment)	☐
Not known	☐	Not known	☐

Post oncology fitness (for neoadjuvant therapy only)

Patient proceeded to planned curative surgery: Yes ☐ No ☐ Not applicable ☐

National Oesophago-Gastric Cancer Audit
Endoscopic / Radiological Palliative Therapy Datasheet
(Oesophageal Gastric Cancer Patients)

Please fill in this datasheet for every patient with oesophago-gastric cancer on the occasion of their FIRST PALLIATIVE endoscopic / radiological therapeutic intervention.

Patient details (for patient identification only)

Surname _____ Forename _____

NHS number _____ Date of birth _____

Treatment details

Hospital name: _____

Date of endoscopic / radiological procedure: _____

Dysphagia Rating Scale

0 ☐ No dysphagia
1 ☐ Able to eat solids
2 ☐ Able to eat semi-solids only
3 ☐ Able to consume liquids only
4 ☐ Complete dysphagia
9 ☐ Not known

Procedure details

Type of procedure (tick all that apply)

Insertion of stent ☐ Laser therapy ☐ Argon plasma coagulation ☐
Photodynamic therapy ☐ Gastrostomy ☐ Brachytherapy ☐
Dilatation ☐ *(Tick dilatation if it was the only procedure or if required to facilitate treatment)*
Other ☐

Is this procedure part of a planned course of multiple interventions? Yes ☐ No ☐ Not known ☐

Anaesthesia: Sedation ☐ Local anaesthetic spray ☐ General anaesthesia ☐
Sedation and local anaesthetic spray combined ☐ Not known ☐

Details of stent procedure, if inserted

Type of stent:

Plastic: expandable ☐ Metal: covered ☐ Metal: Anti-reflux ☐ Not known ☐
Biodegradable ☐ Metal: uncovered ☐ Other ☐

Method of stent placement:

Fluoroscopic control ☐ Endoscopic control ☐ Fluoroscopic & Endoscopic ☐ Not known ☐

Did the stent deploy successfully? Yes ☐ No ☐ Not known ☐

Immediate complications following stent insertion (tick all that apply)

No complication ☐ Postoperative stricture ☐ Perforation ☐
Haemorrhage ☐ Other complications ☐

(D) Updated HGD Dataset for the 2nd NOGCA

National Oesophago-Gastric Cancer Audit
New Patient Registration sheet –
Patients with Oesophageal High Grade Glandular Dysplasia

Patient Details

Surname: _____ Forename: _____

NHS number: _____ Postcode: _____

Sex: Male ☐ Female ☐ Not specified ☐ Date of birth: _____

Initial Referral to Local Oesophago-gastric Team and Diagnostic Process

Source of referral

From surveillance service: ☐ Symptomatic referral ☐ Not known ☐

Date of endoscopic biopsy in which HGD was first diagnosed: _____

Hospital where the endoscopic biopsy was taken: _____

Was the original diagnosis of HGD confirmed by a second pathologist? Yes ☐ No ☐ Not known ☐

Was a repeat biopsy taken to confirm the diagnosis of HGD? Yes ☐ No ☐ Not known ☐

Did the repeat biopsy confirm the diagnosis of HGD? Yes ☐ No ☐ Not known ☐

Was the second biopsy diagnosis of HGD confirmed by a second pathologist? Yes ☐ No ☐ Not known ☐

Comorbidities? None ☐ Cardiovascular disease ☐ COPD / Asthma ☐ Chronic Renal Impairment ☐

Liver Failure / Cirrhosis ☐ Diabetes ☐ Mental Illness ☐

Cerebro / peripheral vascular disease ☐ Significant other ☐

Endoscopic Report

At the initial endoscopy where a diagnosis of HGD was made:

- Were quadrantic biopsies taken every 2cm from the entire segment of Barrett's?
  Yes ☐ No ☐ Not known ☐
- Were additional biopsies taken of any visible nodule?
  Yes ☐ No ☐ Not known ☐

HGD appearance

Flat mucosa ☐ Nodular lesion ☐ Depressed lesion ☐ Not known ☐

Barrett's Segment

Present ☐ Absent ☐ Not known ☐

Endoscopic Report (continued)

Length of Barrett's Segment

Is the length of circumferential columnar lining recorded in the endoscopy report? Yes ☐ No ☐
Length of ***Circumferential*** Columnar Lining (nearest 0.5 cm): C___.___ cm

Is the maximum length of columnar lining recorded in the endoscopy report? Yes ☐ No ☐

Maximum length including tongues/islands of Columnar Lining (nearest 0.5 cm): M___.___ cm

HGD Lesion (based on pathology report)

Unifocal ☐ Multi-focal ☐ Not known ☐

Planned Treatment

Hospital at which treatment plan made _____

Date treatment plan agreed _____

Was the treatment plan agreed at an MDT meeting? Yes ☐ No ☐

Hospital where initial treatment was given _____

Date initial treatment was given _____

Planned treatment modality

Surveillance (follow up endoscopy)	☐	Radiofrequency ablation	☐
Oesophagectomy	☐	Argon plasma coagulation	☐
Photo dynamic therapy	☐	Multipolar electrocautery	☐
Endoscopic Mucosal Resection (EMR)	☐	Laser therapy	☐
Endoscopic Submucosal Dissection (ESD)	☐	Cryotherapy	☐
Other	☐	No active treatment	☐

Use of surveillance or no active treatment as planned treatment	
What was the reason for this treatment plan?	
Patient choice	☐
Patient unfit for endoscopic or surgical treatment	☐
Lack of access to endoscopic treatment or surgery	☐
Unknown	☐

Use of surveillance	
If plan was surveillance, when was the next surveillance endoscopy planned for?	
≤ 3 months	☐
3-6 months	☐
7-12 months	☐
>12 months	☐
Unknown	☐

Use of Endoscopic Mucosal Resection (EMR) / Endoscopic Submucosal Dissection (ESD)

Date of EMR/ESD: _____

Was excision complete? Yes ☐ No ☐ Not known ☐

If yes, what was the ongoing plan?

Further endoscopic treatment of the remaining Barrett's segment ☐
Surveillance (follow up endoscopy) only ☐
No further surveillance or treatment ☐
Not Known ☐

If no, what was the ongoing plan?

Further EMR/ESD ☐
Further ablative endoscopic treatment e.g. RFA, APC ☐
Refer for oesophagectomy ☐
Surveillance (follow up endoscopy) only ☐
No further surveillance or treatment ☐
Not Known ☐

Post-treatment Histology (pathology results based on EMR/ESD)

No high-grade dysplasia or carcinoma ☐
High-grade dysplasia confirmed ☐
Intramucosal carcinoma identified ☐
Submucosal carcinoma or worse ☐

(E) Newcastle-Ottawa Quality Assessment Scale for Cohort studies

A study can be awarded a maximum of one start for each numbered item within the Selection and Outcome categories. A maximum of two stars for Comparability.

Selection	
1. Representativeness of the exposed cohort	
Truly representative of the community	*
Somewhat representative of community	*
Selected group of users	
No description of derivation of cohort	
2. Selection of the non-exposed cohort	
Drawn from same community as exposed cohort	*
Drawn from a different source	
No description of derivation of the non-exposed cohort	
3. Ascertainment of exposure	
Secure record	*
Structured interview	*
Written self-report	
No description	
4. Demonstration that outcome of interest was not present at the start	
Yes	*
No	
Comparability	
1. Comparability of cohorts on the basis of the design or analysis	
Study controls for _____(select most important factor)	*
Study controls for any additional factor	*
Outcome	
1. Assessment of outcome	
Independent blind assessment	*
Record linkage	*
Self-report	
No description	
2. Was the follow up long enough for outcomes to occur	
Yes	*
No	
3. *Adequacy of follow up of cohorts*	
Complete follow up – all subjects accounted for	*
Subjects lost to follow up unlikely to introduce bias - >___% follow up	*
Follow up rate <___% and no description of those lost	
No statement	