Endoscopic Assessment and Treatment of Barrett's Oesophagus

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I, Gideon Lipman confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

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Abstract

Oesophageal cancer worldwide is the eighth commonest cancer and carries a poor prognosis. Barrett's oesophagus is the only known risk factor for oesophageal adenocarcinoma. Cancer progresses along a metaplasia-dysplasia pathway. Dysplastic changes may be seen on endoscopic assessment. This thesis presents evidence that *i*-Scan virtual chromoendoscopy together with acetic acid chromoendoscopy can improve dysplasia detection using a simple classification system.

Superficial lesions, without deeper invasion (low and high grade dysplasia, early cancers) have a low risk of distant metastasis. Endoscopic resection and ablation techniques have been demonstrated to have an excellent efficacy and safety profile. The current standard of care for early Barrett's neoplasia is endoscopic management rather than surgical intervention. Surgery for oesophageal cancer is centred in specialist units due to improved outcomes in high volume centres. The UK radiofrequency ablation registry collects outcomes for patients undergoing endoscopic therapy for Barrett's neoplasia. This thesis demonstrates that there is no difference in dysplasia or intestinal metaplasia resolution rates or dysplasia recurrence between low and high volume centres. Learning curve analysis suggests that there is a change point at 18 cases, when the observed successful treatment rate of the centre becomes better than the expected rate. Centres should complete 20 cases before competency can be achieved.

Treatment of Barrett's neoplasia involves endoscopic resection of visible lesions. Due to the high risk of metachronous lesions, the remaining Barrett's epithelium undergoes field ablation, commonly with radiofrequency ablation. Following successful treatment the risk of dysplasia recurrence is 6%. The risk increases with increasing length of the initial Barrett segment and with increasing age. The risk of untreated islands of Barrett's IM is unknown but this thesis demonstrates that it

does not seem to confer an increased risk of recurrence and may not require further ablation if unresponsive to treatment.

Impact Statement

The work from the chapter on the use of i-Scan technology with acetic acid forms the basis for the manuscript published in Endoscopy (*Lipman G, Bisschops R, Sehgal V, Ortiz-Fernández-Sordo J, Sweis R, Esteban JM, Hamoudi R, Banks MR, Ragunath K, Lovat LB, Haidry RJ.* Systematic assessment with I-SCAN magnification endoscopy and acetic acid improves dysplasia detection in patients with Barrett's esophagus. Endoscopy 2017). This is the first use of the narrow band imaging classification system in videos and using i-Scan technology. The work provides a structure for assessing Barrett's mucosa using a structured approach with virtual chromoendoscopy, acetic acid and magnification endoscopy.

The chapter on centre volumes and learning curves quantifies the number of cases required to achieve proficiency in treatment of Barrett's neoplasia. This is work from the UK that demonstrates that centre volume does not impact on treatment outcomes and these results have already been presented at the BSG Conference 2016. The work on learning curves will be prepared to form a manuscript for publication.

The work assessing risk from residual intestinal metaplasia at the end of treatment may change how we define treatment success and provide reassurance for patients who do not have complete resolution of IM following a yearlong treatment with radiofrequency ablation. The work again emphasises the risk factors for dysplasia recurrence being length of initial Barrett's and increasing age. However, residual islands may not be as worrying as previously thought. This work has been presented orally at Digestive Disease Week 2016. Further work assessing how we define treatment success and the need for 2 consecutive normal biopsies may shed further light on the issue of residual disease compared with recurrence.

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ABBREVIATIONS USED

AF	Autoflouresence
AGA	American Gastroenterological Association
ANOVA	Analysis of Variance
ASGE	American Society of Gastrointestinal Endoscopy
BAD CAT	BArrett's Dysplasia and CAncer Taskforce
BEACON (BEACON)	Barrett's and Esophageal Adenocarcinoma Consortium
BMI	Body mass index
BO	Barrett's Oesophagus
BSG	British Society of Gastroenterology
CCD	Couple charged device
CI	Confidence Interval
CLE	Columnar lined epithelium
CLE	Confocal Laser Endomicroscopy
CR-D	Complete resolution of dysplasia
CR-IM	Complete resolution of intestinal metaplasia
CUSUM	Cumulative sum
D-BO	Dysplastic Barrett's oesophagus
EMR	Endoscopic Mucosal Resection
ESD	Endoscopic submucosal dissection
ETMI	Endoscopic trimodal imaging
FICE	Fuji Intelligent Colour Enhancement
GORD	Gastro-oesophageal reflux disease
H. Pylori	Helicobacter Pylori
HD	High definition
HD-WLE	High definition white light endoscopy
HGD	High-grade dysplasia
IM	Intestinal metaplasia
IMC	Intramucosal cancer
KM	Kaplan–Meier
LGD	Low-grade dysplasia
MPEC	Monopolar Electrocoagulation
NAC	N-Acetyl cysteine
NBI	Narrow band imaging
ND-BO	Non-dysplastic Barrett's oesophagus
NPV	Negative predictive value
NSAID	Non-steroidal anti-inflammatory drug
OAC	Oesophageal adenocarcinoma
OCT	Optical coherence tomography
OGJ	Oesophagogastric junction
OR	Odds ratio
PDT	Photodynamic Therapy
PIVI	Preservation and Incorporation of Valuable endoscopic Innovations
PPV	Positive predictive value
PPI	Proton pump inhibitor
RA-CUSUM	Risk-adjusted cumulative sum

RFA	Radiofrequency ablation
RR	Relative Risk
SCC	Squamous cell carcinoma
SCJ	Squamo-columnar junction
SD	Standard definition
SEERS	Surveillance, Epidemiology and End Results
TNM	Tumour, Node, Metastases

DEDICATION

To all those who have given me encouragement and support, most especially my wife Leonora who inspires and challenges me. To my children, Carmelle, Gavriel, Max and Rafael and in memory of my father, Bobby Lipman, who died of oesophageal cancer before his time.

Contributions to this Thesis

I have received support from Professor Laurence Lovat and Dr Rehan Haidry throughout my research and acknowledge the following contributions made by others to the work presented in this thesis.

Chapter 3: Improving Dysplasia Detection in Barrett's Oesophagus

Dr Rehan Haidry developed the concept of a classification system. Dr Rehan Haidry, Professor Raf Bisschops and Professor Krish Ragunath provided endoscopic videos for assessment.

Dr Rifat Hamoudi provided statistical support to calculate sample size.

Chapter 4: Centre Volume and Outcomes in UK RFA Registry

Endoscopic treatment and data entry of the baseline demographics, procedures performed and subsequent results and complications were all entered into the RFA Registry by clinicians and research staff at their respective sites. I entered a small proportion of data at University College Hospital London and at the Glasgow Royal Infirmary.

Dr Sheraz Markar wrote the section entitled: Risk-Adjusted Cumulative Sum curve analysis and Hospital RA-CUSUM curve analysis and perfomed the analysis and provided the graphs demonstrating change points.

Dr Abhinav Gupta converted the data from the online RFA database to an Excel file before I reviewed all the data, removed erroneously entered data and analysed the data.

Chapter 5: Residual Intestinal Metaplasia Following Radiofrequency Ablation for Barrett's Oesophagus Related Dysplasia and the Risk of Dysplasia Recurrence

Endoscopic treatment and data entry of the baseline demographics, procedures performed and subsequent results and complications were all entered into the RFA Registry by clinicians and research staff at their respective sites. A small proportion of data was entered by myself at University College Hospital London and at the Glassgow Royal Infirmary.

Dr Rifat Hamoudi provided statistical support reviewing my statistical calculations.

1 Introduction

1.1 Oesophageal Cancer

1.1.1 Epidemiology

Oesophageal cancer is the eighth most common cancer worldwide (1) and carries a poor prognosis, with it being the sixth commonest cause of cancer related death (1). The two main histological types are adenocarcinoma and squamous cell carcinoma. Squamous cell carcinoma (SCC) accounts for 87% of oesophageal cancers worldwide (2), however, the UK has one of the highest incidences of oesophageal adenocarcinoma (OAC) in the world where it accounted for 55% of oesophageal cancers between 2008-2010 (3). Oesophageal cancer is the 14th most common cancer in the UK but in terms of mortality is the fourth and sixth commonest for men and women (3).

Over the last 40 years, the incidence of OAC in the Western World has continued to rise. A report in 2005 identified OAC as one the fastest growing cancers in the United States with an increase of 7.1%/year until the 1990s followed by 2%/year from 2000 to 2008 (4,5).

CRUK data demonstrate an increase in the observed age-standardised incidence rates of oesophageal cancer from 1979 to 2011 but have projected a fall of 3% by 2035 (Figure 1.1).

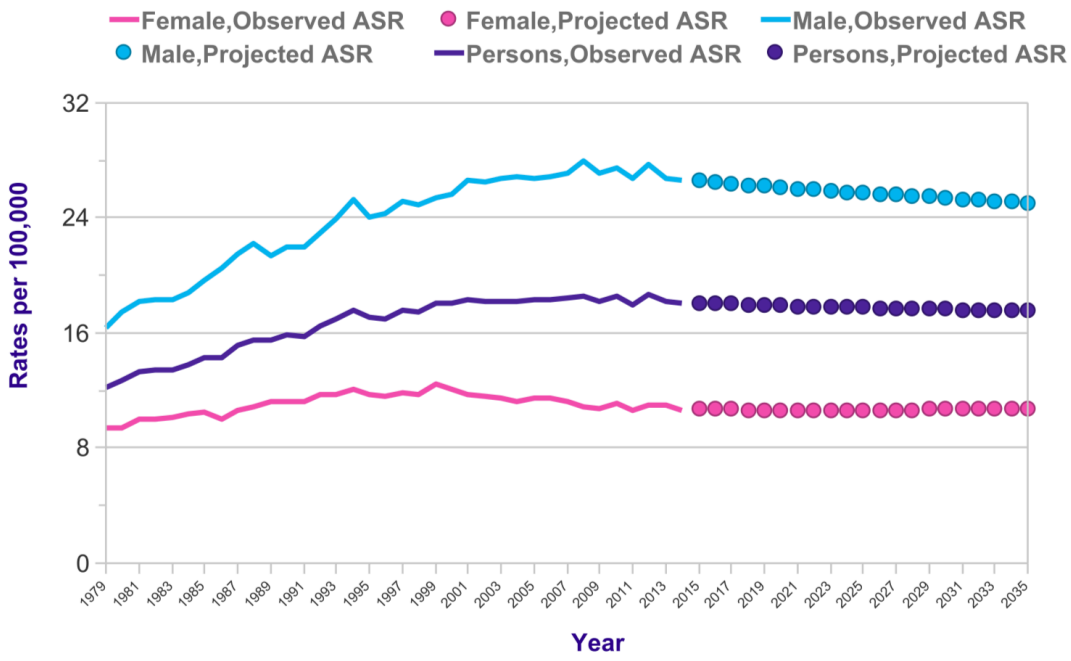


Figure 1.1: Oesophageal Cancer, Observed and Projected Age-Standardised Incidence Rates by Sex, UK 1979-2035 (6)

1.1.2 Survival

OAC has a poor prognosis, with 15.1% of patients surviving at 5 years (7). An important factor driving this poor survival is the late presentation of the disease. Over 40% of patients are diagnosed with metastatic disease, which carries an even more dismal 5-year survival of <3% (8).

1.1.3 Risk Factors for OAC

1.1.3.1 Age

The incidence of OAC increases with age. Data from the United States National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program reported a relative risk (RR) of 44.4 (95% confidence interval (CI) 41.8-47.1) of developing OAC if aged ≥70 years compared

with those under 50 (9). In 2015 in the UK, the crude incidence rate of oesophageal cancer was 14.1 per 100,000 (3).

1.1.3.2 Sex

OAC incidence is significantly higher in males than females, with a relative risk of 7.49 (95% CI 7.17-7.82) as reported by the SEER data (9). In the UK, the male to female incidence rate ratio for OAC is approximately 52:10 (3). This ratio does not appear to have changed with the rising incidence of the disease over the last 40 years (10).

1.1.3.3 Gastro-oesophageal reflux disease (GORD)

GORD is the presence of gastric acid or bile in the oesophagus. Although epidemiological studies have previously suggested an association between GORD and OAC, it was a 1999 study that reported an odds ratio (OR) of 7.7 (95% CI 5.3-11.4) for those with recurrent (at least weekly) reflux symptoms compared with those with less frequent symptoms (11). This association was stronger (OR 43.5, 95% CI 18.3-103.5) for those with a longer history of symptoms. A pooled analysis of 5 studies found an OR of 4.81 (95%CI 3.39-6.82) for developing OAC in those with recurrent reflux compared with those without symptoms (12).

1.1.3.4 Cigarette Smoking

Cigarette smoking has been reported to increase the risk of OAC in a dose responsive association, smoking $\geq$45 pack years carries an OR of 2.73 (95% CI 2.27- 3.29) for developing OAC compared with those who had never smoked (13).

1.1.3.5 Obesity

Obesity and particularly abdominal obesity are associated with OAC (14). Hoyo et al reported an OR of 2.39 (95% CI 1.86-3.06) of developing OAC with a BMI 30-34.9 kg/m^2 compared with a BMI of 20-24.9 kg/m^2. This risk was more pronounced with a BMI $\geq$40 kg/m^2 (OR 4.76, 95% CI 2.96-

7.66) (15). Obesity is also associated with GORD (16), however a 2014 study demonstrated that obesity, independent of GORD, is a risk factor for OAC (17).

1.1.3.6 Alcohol

Unlike for SCC, alcohol intake (duration nor frequency) does not appear to increase the risk of OAC according to a pooled analysis of 11 studies (18).

1.1.3.7 Non-steroidal anti-inflammatory drugs (NSAIDs)

A pooled analysis of 6 studies in the International Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) reported a significantly lower risk of developing OAC amongst those reporting any use of NSAIDs (OR 0.68, 95% CI 0.56-0.83). Increased frequency and duration of use were associated with lower risk (19). However, this study was a pooled analysis of 6 studies, 5 case-control studies and a single cohort study, which raises the possibility that the association is not causative but due to reverse causation. The UK based AspECT trial assessing the use of aspirin and proton pump inhibitors in patients with Barrett's Oesophagus may shed more light on this issue. It is due to report in 2019 (20).

1.1.3.8 Helicobacter Pylori (*H. Pylori*)

H Pylori, a gram-negative bacterium, is known to cause gastric cancer (OR =3.6, 95% CI 1.8-7.3) (21), however, a recent meta-analysis reported the presence of the bacteria in the stomach is associated with a lower risk of OAC (OR=0.57, 95% CI 0.44-0.73) (22).

1.1.3.9 Barrett's Oesophagus

The only known precursor to OAC is Barrett's Oesophagus (BO). It is estimated that up to 79% of OAC cases arise in an area of BO (23,24). This condition is discussed in more detail below.

1.2 Barrett's Oesophagus

1.2.1 Diagnosis

Barrett's Oesophagus (BO) is a precursor to OAC and is diagnosed during endoscopy of the upper gastrointestinal tract. The mucosa of distal oesophagus changes from a squamous lined epithelium to metaplastic columnar lined epithelium (CLE). The UK guidelines require these changes to be present more than 1cm above the top of the gastric folds but unlike guidelines from the United States, do not require the histological presence of goblet cells demonstrating intestinal metaplasia (IM) to confirm the diagnosis (25). Changes less than 1cm are classified as an irregular z-line and are not considered as BO.

To help standardise endoscopic reporting of BO, the Prague Classification was developed and validated in 2006, see Figure 1.2 (26). The consensus driven classification describes the circumferential (C) and maximal (M) extent of the columnar lined epithelium above the top of the gastric folds. Short segment BO is defined as CLE <3cm above the top of the gastric folds and long segment BO is >3cm in length.

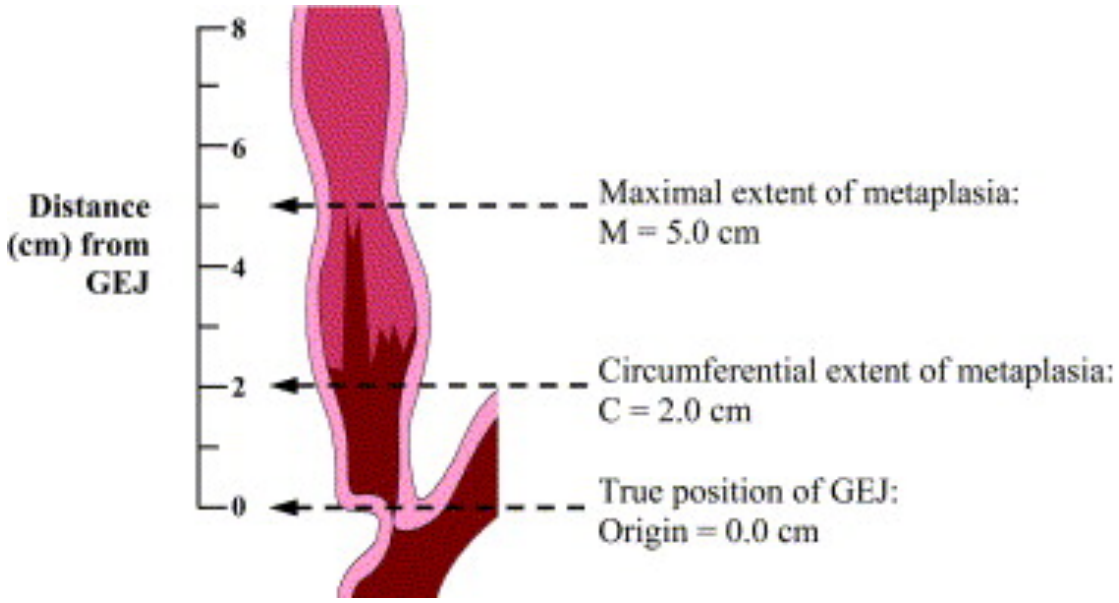


Figure 1.2: Diagrammatic representation of endoscopic Barrett's oesophagus showing an area classified as C2M5. C: extent of circumferential metaplasia; M: maximal extent of the metaplasia (C plus a distal "tongue" of 3 cm); GOJ: gastro-oesophageal junction (26)

1.2.2 Prevalence

A relatively small Swedish study of 1000 people (mean age 53.5, 51% female) undergoing upper gastrointestinal endoscopy reported a prevalence of 1.6% (27). A study of 300 patients attending for screening colonoscopy (median age 71.8, 54% male) reported an incidence of 16.7% (28). Of those suffering with chronic reflux, the prevalence of BO is though to be in the region of 6-14% of (29).

1.2.3 The Metaplasia, Dysplasia, Cancer Pathway

Inflammation has long been linked with the development of cancer (30) and chronic exposure of the lower oesophagus to acid and bile results in inflammation or oesophagitis. This chronic exposure to acid or bile refluxate injures the epithelium resulting in inflammation and cell proliferation. In combination with genetic instability, this refluxate driven

inflammation, is thought to trigger the development of Barrett's metaplasia, seen endoscopically as CLE (31).

Once the Barrett's metaplasia is present, continued exposure to acid and bile is thought to continue the inflammatory process and through a combination of transcription factors, chemokines, cytokines and prostaglandins increase cell proliferation, cell survival and activate epithelial-mesenchymal transition to the development of low-grade (LGD), high-grade dysplasia (HGD) and finally invasive OAC (31).

The Revised Vienna classification for the reporting of histological samples into distinct categories, namely; Negative for Dysplasia, Indefinite for Dysplasia, LGD, HGD (incorporating carcinoma in situ), Intramucosal Carcinoma (including suspicious for invasive carcinoma) and Submucosal Invasion by Adenocarcinoma (32).

Negative for Dysplasia includes normal and metaplastic epithelium with nuclear enlargement, nuclear hyperchromasia and prominent nucleoli (Figure 1.3).

Indefinite for Dysplasia is used for samples where there is uncertainty whether the changes seen are due to dysplasia or regenerative atypia (Figure 1.3).

LGD is defined as samples demonstrating preserved glandular architecture but there is evidence of cytological atypia, including an 'adenomatous' appearance such as elongated, slightly enlarged, hyperchromatic nuclei with inconspicuous nucleoli and loss of surface maturation (Figure 1.3).

HGD (incorporating carcinoma in situ) is based on architectural changes and nuclear atypia including atypical mitoses, mucin depletion and loss of nuclear polarity (Figure 1.3).

Intramucosal Carcinoma (including suspicious for invasive carcinoma) describes cases where neoplastic cells have penetrated the basement membrane into the lamina propria or muscularis mucosae, but not into the submucosal (Figure 1.3).

Submucosal Invasion by Adenocarcinoma includes neoplasm that invades into the submucosal layer (Figure 1.3)

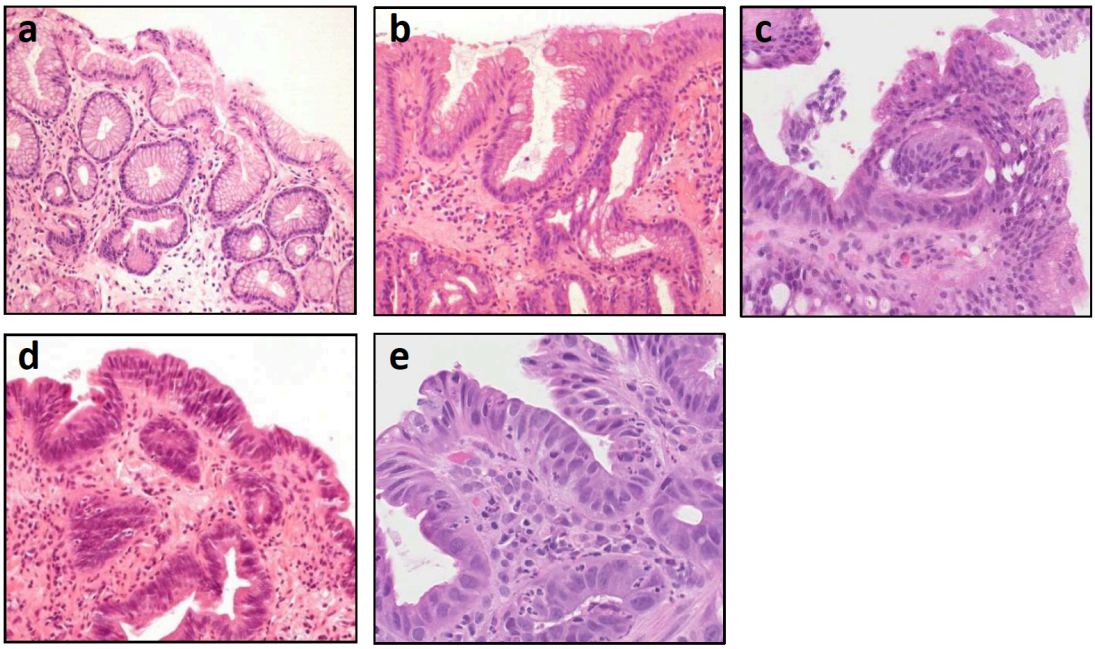


Figure 1.3: a. Barrett's oesophagus with gastric metaplasia only. b. Barrett's oesophagus with intestinal metaplasia. c. Barrett's oesophagus with indefinite for dysplasia. d. Barrett's oesophagus with LGD. e. Barrett's oesophagus with HGD

The risk of developing OAC following a diagnosis of non-dysplastic Barrett's is estimated between 0.12 and 0.48%/year (33–35), but please see section 1.2.5 for a more detailed discussion.. Once LGD has been diagnosed, the risk of progression to OAC has been reported as 5.1 per 1000 patient years (33). HGD and intramucosal cancer has a reported risk of OAC of over 10% per year (36–38).

1.2.4 Chemoprevention of Progression

There has been an observational study suggesting that patients with BO on proton pump inhibitor (PPI) medication had a lower rate of progression to dysplasia (39) and that aspirin is associated with a lower risk of developing OAC (40). The recent AspECT trial compared low dose aspirin and low and high dose PPI in a cohort of 2557 patients with BO. High dose PPI prolonged the composite end point (mortality, OAC and development of HGD) compared with low dos. Aspirin use was significant when those on NSAIDs were excluded from analysis (41).

1.2.5 Staging of dysplasia / early cancer

Staging of cancers allows the stratification of patients according to survival risk and allows appropriate modalities of treatment to be offered. OAC is staged according to the Tumour, Node, Metastases (TNM) model (8^{th} Edition) seen in Table 1.1 and Table 1.2 (42).

Table 1.1: Oesophageal Adenocarcinoma TNM Classification (8TH Edition)

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as the aorta, vertebral body, and trachea
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 1.2: Anatomical Staging of Oesophageal Adenocarcinoma

Stage	T	N	M
0	Tis (HGD)	N0	M0
IA	T1	N0	M0
IIA	T1	N1	M0
IIB	T2	N0	M0
IIA	T2	N0	M0
III	T1	N2	M0
	T2	N1, N2	M0
	T3, T4a	N0, N1	M0
IVA	T4b	N0, N1	M0
	Any T	N2, N3	M0
IVB	Any T	Any N	M1

Once a tumour involves regional nodes or distant metastases, local treatment with endoscopic intervention will not be a curative option. It is therefore imperative in patients with Barrett's dysplasia or early OAC that treatment is offered when there is still curative intent. The depth of the cancer is correlated with the risk of lymph node metastases (43). The depth of mucosal or T1a cancer (also referred to as intramucosal cancer, IMC) can be subdivided into M1, M2 and M3 and sub-mucosal or T1b cancer can be further divided into SM1, SM2 or SM3 as seen in Figure 1.4 (44).

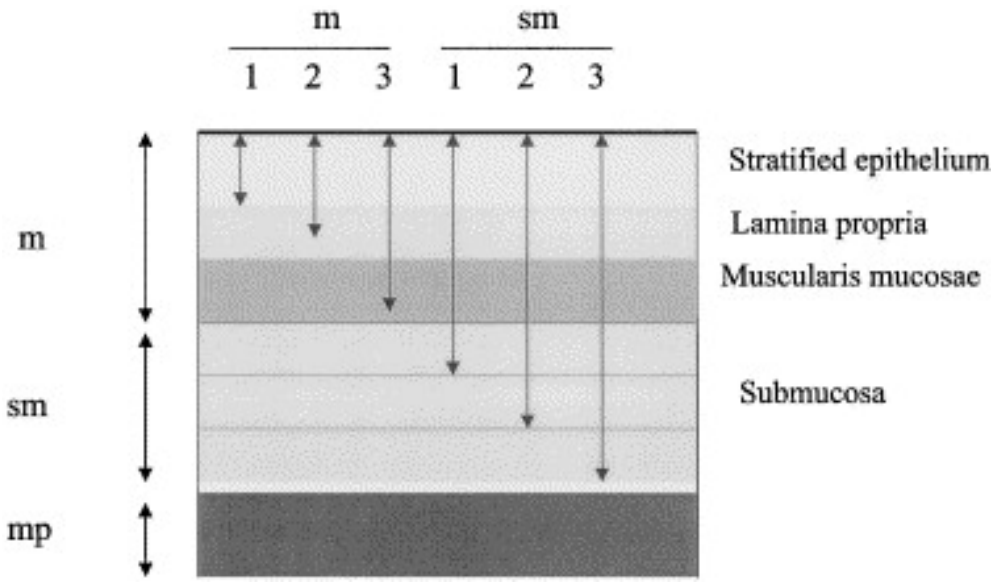


Figure 1.4: Mucosal carcinoma is divided into 3 groups: m1 (IMC / Tis), m2 or m3 (T1a). The depth of invasion in the submucosal (T1b) is divided into 3 sections of equivalent thickness: superficial (sm1), middle (sm2), and deep (sm3) (T1b). m; mucosa, sm; submucosal, mp; muscularis propria (45)

A retrospective review of 126 early OAC specimens reported lymph node metastasis in 1.3% of T1a cancers compared with 22% of T1b cancers (46). A further systematic review of 7645 patients with early OAC and SCC reported the risk of lymph node involvement for OAC T1b cancer with SM1, SM2 and SM3 disease as 6%, 23% and 58% respectively (47). Further risk factors for lymph node involvement include poorly differentiated tumour grade and lympho-vascular invasion (47).

Due to this risk of nodal disease, only LGD, HGD and tumours staged as T1a, or sm1-T1b with no poor prognostic markers for lymph node spread (poorly differentiated tumours and histological evidence of lympho-vascular invasion) are offered endoscopic treatment as recommended by current guidelines (25). The rationale for this, is that once there is evidence of lymph node spread of disease, endoscopic treatment will

only remove the primary lesion and will not treat nodal or metastatic disease.

1.2.6 Risk of Progression

Several population-based studies have reported a risk of progression to OAC or dysplasia for BO. A Spanish study found progression to OAC of 0.48% per year (95% CI 0.006-2.62) equating to an incidence of 1 case per 210 patient-years of follow-up (34). A large meta-analysis of 51 BO studies reported a pooled estimate of OAC of 6.3 per 1000 patient-years of follow-up (95% CI 4.7–8.4) with the risk of OAC in patients with dysplasia estimated at 10%/year (48). The largest study to date, from Denmark, of over 11,000 patients reported OAC progression of 1.2 per 1000 patient-years (95% CI 0.9-1.5) with a RR of 11.3 (95% CI 8.8-14.4) compared with the normal population. Overall there was an annual risk of 0.12% (0.09-0.15) of progression to OAC with BO (33).

Although OAC can arise in short and long segments of BO, length of the BO segment is a risk factor for dysplasia and OAC. Longer segments (>3cm) have been found to have a higher risk of OAC compared with shorter segment BO (0.33%/year versus 0.19%/year) (35). A Northern Ireland Registry reported a hazard ratio of developing OAC or HGD of 7.1 (95% CI 1.74-29.04) with long segment compared with short segment BO (49). A large cohort study reported that for every centimetre increase in the length of Barrett's, the risk of progression increased by an odds ratio or 1.19 (95% CI 1.09-1.30) (50).

The presence of IM (mucous cells or goblet cells) is associated with a higher risk of progression to HGD and cancer. A large population based study in Ireland reported annual incidence of HGD and cancer as 0.38% in those with IM compared with 0.07% in those without IM (51).

The overall risk of BO to progression to OAC is estimated 0.12-0.48% per year, whilst the risk for progression to either OAC or HGD is 0.26-0.63% per year (33,35,51–53).

1.2.7 Risk factors for progression in patients with Barrett's Oesophagus

1.2.7.1 GORD

Similar to the risk factors for OAC, GORD is the strongest risk factor for development of Barrett's (54,55). A younger age of the onset of recurrent reflux is associated with a higher risk of dysplasia progression, with those with onset of symptoms under 30 reporting an OR of 15.1 compared with those who had never experienced GORD symptoms (95% CI 7.91-28.8) (56).

1.2.7.2 Sex

Most patients with Barrett's are male. A meta-analysis reported a male to female ratio for non-dysplastic Barrett's of 1.96:1 (95% CI 1.77-2.17:1) (57). Several studies have identified male sex as a risk factor for progression (33,49,51,53). Data from Northern Ireland reported that the risk of progression to HGD or cancer in men was 0.28% per year compared with 0.13% per year for women (HR = 2.11, 95% CI = 1.41 - 3.16, P < .001) (51).

1.2.7.3 Age

The incidence of OAC increases with age and is diagnosed at a mean age of 68 (58). For patients with Barrett's, increasing age is associated with a higher risk of progression (53) and was notably highest in those over 70 according to a large Danish study (33).

1.2.7.4 Ethnicity

Barrett's is more commonly seen in Caucasians with a UK study reporting a higher incidence in Caucasians than South Asians (OR, 6.03; 95% CI, 3.56–10.22) (59). Within the United States the annual incidence was highest in Caucasians (39 per 100,000), then Hispanics (22 per 100,000), Asians (16 per 100,000) and lowest among Afro-Caribbeans (6 per 100,000) (60).

1.2.7.5 Obesity

Obesity is a risk factor for Barrett's with a positive correlation between increasing weight and development of Barrett's (61,62). However, waist to hip ratio may be a more accurate marker than obesity (63,64) as the BMI does not account for body fat distribution. Central obesity is correlated with insulin resistance. Higher levels of insulin promote carcinogenesis through anti-apoptotic and proliferative mechanisms and its effect on insulin-like growth factors (65).

A recent study by our group found that abdominal obesity was strongly associated with Barrett's (OR 1.65 p=0.02) and also with progression of dysplasia (OR 2.44) (66).

1.3 Barrett's Oesophagus Surveillance

1.3.1 Surveillance

The role of BE surveillance is to identify early pre-cancerous changes to allow an endoscopic intervention that will prevent development of cancer. Whilst white light endoscopy allows endoscopists a clear picture of the Barrett's segment, optimising the identification of early dysplastic changes requires a clean oesophagus, a compliant and comfortable patient and time to view the metaplastic mucosa in detail.

Current guidelines from the British Society of Gastroenterology recommend that those with >1cm of columnar lined epithelium are offered surveillance endoscopies with biopsies to detect dysplastic changes. Patients with long segment BO (>3cm) are offered 2-3 year intervals between endoscopic examinations. Surveillance aims to identify early changes in the metaplasia-dysplasia-cancer sequence to allow early endoscopic intervention with mucosal or sub-mucosal resection and ablative therapies, which carry a high success rate (25).

The current gold standard for the diagnosis of dysplasia remains histological assessment of samples obtained at endoscopy. Guidelines recommend targeted biopsies of suspected areas followed by random biopsy sampling of the BO segment. The Seattle protocol recommends obtaining random quadrantic biopsies every 1-2cm of the BO. However, dysplasia can be focal and therefore easily missed and this method only samples up to 5% of the segment (67,68). Compliance with the Seattle protocol has been reported as only 51% in the community setting with poorer adherence the longer the BE segment (69). A further drawback of the Seattle protocol is the cost of the histological processing and assessment of the large number of biopsies that are generated in the process with a relatively low yield for dysplasia.

1.3.2 Controversies with surveillance

Whilst the diagnosis of BO and its surveillance results in the earlier diagnosis of patients with OAC (70) and improved outcomes in those patients (71), no effect on overall survival has been demonstrated with surveillance programs (72). A 2010 meta-analysis of 51 papers reported OAC incidence of 6.3 per 1000 patient years (95% CI 4.7-8.4). OAC related mortality was 3.0 (95% CI 2.2–3.9). The authors concluded that most patients with Barrett's die of unrelated causes and further

questioned the role of surveillance for all patients, suggesting that high-risk patients should be identified for such programs (48). A further study of 8272 patients with Barrett's found surveillance had no effect in preventing cancer deaths (73).

However, surveillance for patients with BO is currently recommended by numerous guidelines and Gastroenterology Societies including the British Society of Gastroenterology (BSG), the American Society of Gastrointestinal Endoscopy (ASGE) and the American Gastroenterological Association (AGA) (25,74,75). The BOSS study aims to compare 2-yearly surveillance with endoscopic assessment and biopsies with endoscopy on an 'as needed' basis. The study has closed to recruitment and is due to report 10-year outcomes in 2022. It may give a definitive answer on the need for surveillance in BO.

1.4 Lesion Detection

The aim of surveillance is the detection of dysplasia at an early stage to permit endoscopic therapy. There are three essential diagnostic steps; recognition of a dysplastic lesion, characterisation of the lesion (in the form of size, location, nodularity, pit pattern, vasculature and type of dysplasia) and histological confirmation (either conventionally with a tissue sample or in vivo).

Until recently, the ability to identify lesions has depended on the quality of endoscopic images produced at endoscopy. From the original eye-piece endoscopes to standard definition and now high definition endoscopy there have been significant improvements in the quality of the images obtained at endoscopy.

Visualisation of subtle mucosal lesions can be enhanced with the application of dyes (such as acetic acid in Barrett's Oesophagus, Lugol's Iodine in oesophageal squamous dysplasia, Methylene blue and Indigo carmine for gastric and colonic lesions). The advent of virtual chromoendoscopy has reduced the need for these dyes through the manipulation of the while light images with either pre or post processing optical technologies to enhance the detection of small and subtle lesions that would otherwise be missed. These techniques include proprietary imaging techniques including Olympus Narrow band imaging, Pentax i-Scan and i-Scan OE and Fuji Intelligent Colour Enhancement, which are summarised in Table 1.3. A simple switch on the endoscope hand-piece to activate these imaging techniques instantaneously makes them simple and very convenient to use.

Table 1.3: Virtual chromoendoscopy technologies

Technology	Mechanism
Narrow Band Imaging Olympus Medical Systems (Olympus, Japan)	Optic filtering of reflected light from the mucosa, isolating blue (415nm) and green (540nm) bands of light to enhance visualisation
i-Scan and i-Scan OE PENTAX (HOYA Corporation, Japan)	Digital post-processing image enhancement to improve mucosal pattern and vascularity. New OE technology combines this with optic filtering.
FICE (Fujinon, Japan)	Post-processing technology that reconstructs a virtual image of a single wavelength in real time
Blue Light Imaging (BLI) and Linked Colour Imaging (LCI) (Fujinon, Japan)	Uses two monochromatic lasers and white light phosphor. Varying the intensity balance of the lasers results in varying contrasts. LCI utilese post-processing enhancement in addition to BLI

All these technologies allow for greater detection of subtle lesions. They also require specialist expertise to recognise these abnormalities. Recent research has shown that a longer procedure time to allow a detailed inspection of the mucosa using high quality white light imaging may yield just as accurate diagnosis (76). Nonetheless, most expert endoscopists agree that these extra imaging modalities enhance their diagnostic toolkit.

Lesions of the gastrointestinal tract are commonly descried according to the Paris Classification. This was born out of a Paris workshop in 2002 to assess the utility of the Japanese classification of mucosal lesions (Figure 1.5). The classification of lesions permits the endoscopist an accurate assessment of the risk of deeper disease and indicates whether or not a lesion should be resected endoscopically.

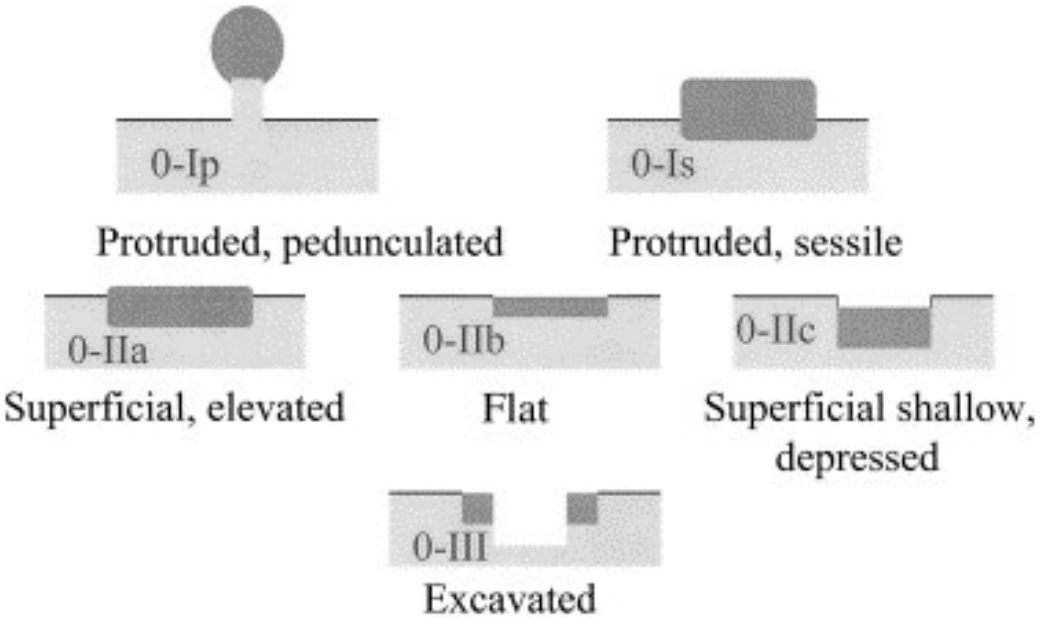


Figure 1.5: Classification of superficial neoplastic lesions according to their macroscopic morphological appearances (45)

1.4.1 Optimising the Mucosal View at Endoscopy with Adjuncts

1.4.1.1 Simethicone

An important feature of any endoscopic evaluation of the gastrointestinal mucosa is the adequate visualization of the target tissue. Techniques for this include washing the musoca at the endoscopic evaluation of the pre-medication with a detergent or mucolytic agent. The commonest agent used in the UK for both upper and lower GI endoscopy is a detergent, Simethicone (polydimethylsiloxane and silicon dioxide) suspension (Infacol, Teva UK Limited, UK). It is used to reduce foam and air bubbles and has mostly been studied in relation to capsule endoscopy visibility and colonoscopy studies. Three studies have investigated the use of a pre-procedure drink and its effect on visibility in the upper GI tract. Bertoni et al in 1992 and Banerjee et al in 1992 both demonstrated improvement in visibility (77,78). More recently, Ahsan et al 2011 (79) demonstrated significantly fewer gastric foam/air bubbles in the stomach with significantly shorter procedures following oral Simethicone prior to endoscopy, though no comment was made regarding oesophageal views and bubbles.

1.4.1.2 N-Acetyl cysteine

N-Acetyl cysteine (NAC) is a mucolytic agent commonly used prior to radiofrequency ablation of Barrett's epithelium to improve electrode contact with the targeted mucosa. NAC has also previously been reported to improve visibility at endoscopy (80,81) through the use of premedication with a pre-procedure drink. However, the effectiveness of NAC to improve visibility above that of Simethicone has been questioned by a 2014 study (82) that demonstrated no improvement in visibility or lesion detection between Simethicone alone and Simethicone with NAC.

However, the Simethicone and NAC combination did reduce the need for endoscopic flushing.

1.4.1.3 Distal Attachments and Caps

There has been considerable interest in distal attachments placed at the tip of endoscopes, particularly at colonoscopy to improve adenoma detection rates. A single trial assessing a transparent cap reported an increased detection rate of Barrett's (83).

1.4.2 High Definition White Light Endoscopy

A standard white light endoscope contains a couple charged device (CCD), which convert light received at the tip of the endoscope into an electronic signal that the video-processor converts to an image on a screen. Standard definition (SD) white light endoscopes CCDs contain 100,000-300,000 pixels to generate 480-576 lines on a screen. High definition (HD) endoscopes contain CCDs with 600,000 – 1.2 million pixels that generate up to 1080 scanning lines on a screen.

Curvers et al compared SD white light endoscopy with a combination of autofluorescence HD white light endoscopy and narrow band imaging. The combination of technologies including HD endoscopy improved dysplasia detection in BE (84). However, in 2015, Sami et al retrospectively compared SD and HD white light endoscopies over a 3-year period at a UK based teaching university hospital. HD endoscopy improved targeted detection of dysplasia (OR 3.27, 95% CI 1.27-8.40) and dysplasia detected on random biopsies (85).

1.4.3 Chromoendoscopy

Chromoendoscopy and virtual chromoendoscopy (discussed in the next section) are designed to improve lesion detection and recognition. This is important as endoscopic appearances of dysplasia can be characterised by the macroscopic type of lesion and changes seen in the mucosal and vascular pattern. Pech et al recorded 380 lesions and asked 6 experts to review the images and classify them according to the Japanese macroscopic classification for early gastric cancer (86). Of the 380 lesions, 42 were submucosal cancers, 308 were intramucosal cancers and 30 were HGD only. Using the Paris Classification system, Type IIb lesions were associated with early local tumour stage whereas Type IIa + c were more advanced and/or poorly differentiated. There was high agreement between experts (k = 0.89) (86).

Although the Paris classification allows the description of sessile polyps, further classification systems using chromoendoscopy have also been developed to characterise pit patterns in mucosal lesions.

Three classification systems were initially proposed using chromoendoscopy to identify pit patterns to differentiate Barrett's from gastric mucosa.

Guelrud assessed 48 patients with magnification endoscopy and acetic acid (see Figure 1.6) and observed 4 pit patterns. The classification reported a sensitivity of 97% and specificity of 89% for the detection of IM with patterns III and IV (87).

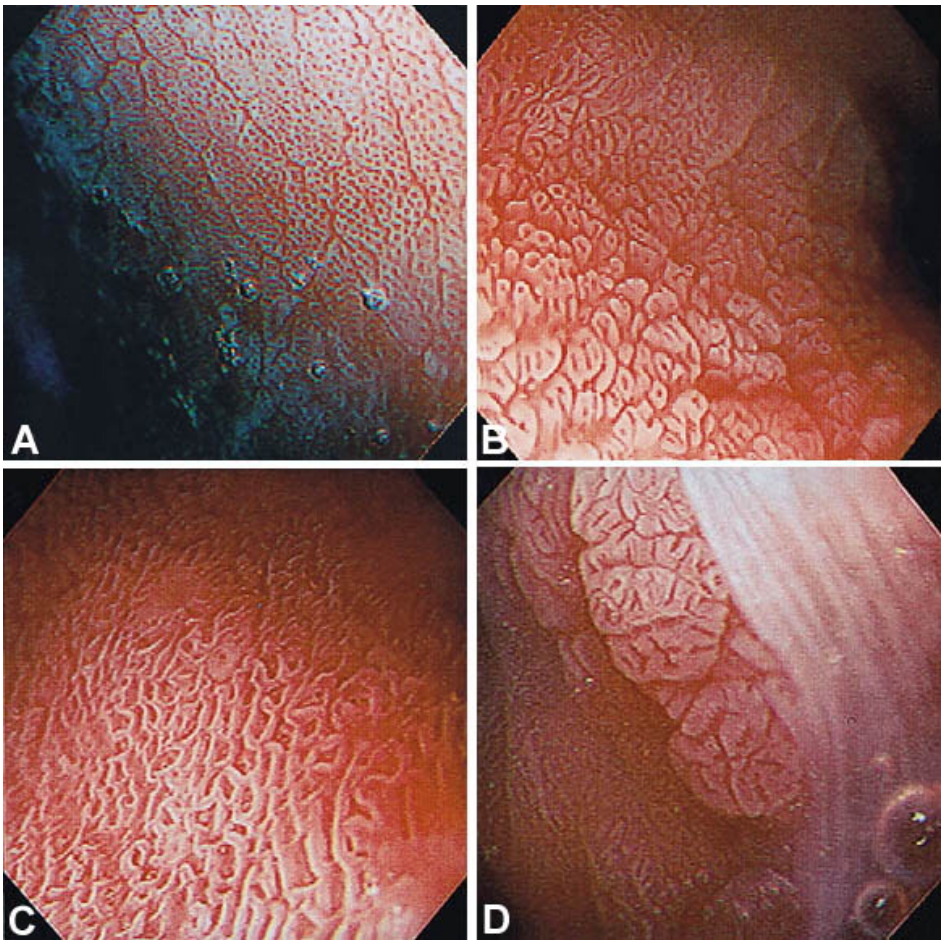


Figure 1.6: Endoscopic views after acetic acid instillation; 4 different patterns of the mucosal surface were observed. A, Pattern I: round pits with a characteristic pattern of regular and orderly arranged circular dots. B, Pattern II: reticular pits that are circular or oval and are regular in shape and arrangement. C, Pattern III: villous with no pits present but a fine villiform appearance with regular shape and arrangement is evident. D, Pattern IV: ridged with no pits present but a thick villous convoluted shape with a cerebriform appearance with regular shape and arrangement is evident (87).

Endo et al used magnification endoscopy with methylene blue into 5 pit patterns that predicted the presence of Barrett's with a sensitivity of 52% and a specificity of 100% (88).

A further classification system proposed by Sharma et al described mucosal patterns following the application of indigo carmine and magnification endoscopy (Figure 1.7).

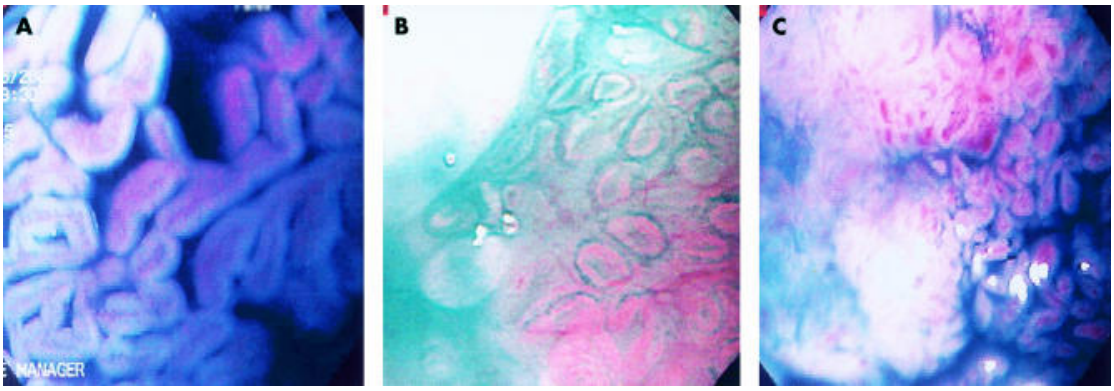


Figure 1.7: Three distinct mucosal patterns observed under magnification (115×) after spraying indigo carmine: ridge villous (A), circular (B), and irregular/distorted (C) (89).

Mucosal patterns were either ridged/villous (which correlated with non-dysplastic BE in 97%), circular (which correlated with cardiac mucosa in 87%) or irregular/distorted (which correlated with high grade dysplasia in 100%, though there were only 6 patients with this pattern) (89). Following these studies, dyes that highlight pit patterns have been further investigated.

1.4.3.1 Methylene Blue

Methylene blue inhibits nitric oxide synthase and guanylate cyclase. It was initially used for marking the intestinal lumen endoscopically before surgery but is often used for identifying lesions in the colon. Several

studies have assessed the use of methylene blue for the detection of dysplasia in Barrett's.

A meta-analysis of 450 patients across 9 trials found no incremental yield above white light endoscopy with methylene blue for the detection of dysplasia within BO (Incremental yield 9%, 95% CI -1%-20%)(90).

1.4.3.2 Acetic Acid

Acetic acid is a weak fatty acid, commonly used during colposcopy for the detection of dysplasia at the squamo-columnar junction. Its use has been appropriated into the diagnostic assessment of Barrett's oesophagus. Following the application of 2-3% acetic acid, the metaplastic (Barrett's) epithelium whitens, highlighting the mucosal pattern. Dysplastic lesions are thought to lose this white appearance faster than non-dysplastic areas, permitting targeted assessment and sampling of the noted areas.

The first reported use of acetic acid in Barrett's was in 1998 for the detection of Barrett's islands (91). However, its use for detecting dysplasia has been more extensively investigated. Longcroft-Wheaton et al demonstrated dysplasia detection with acetic acid had a sensitivity of 95.5% and specificity of 80% in 190 patients. There was significant improvement with the use of acetic acid compared with white light endoscopy and quadrantic biopsies every 2cm, p=0.001 (92). A recent meta-analysis of 9 studies, calculated a pooled sensitivity of 92% and specificity of 96% for the diagnosis of high grade dysplasia or intramucosal cancer (93).

1.4.3.3 Indigo Carmine

Indigo Carmine is an organic salt thought to highlight the pattern of the mucosal surface. Sharma et al reported on 80 patients using indigo carmine and magnification endoscopy and reported excellent outcomes

particularly in identifying high grade dysplasia, as described above (89). A further study by the same group in 2006, compared magnification and chromoendoscopy with random biopsies for the detection of dysplasia in BE. A ridged or villous mucosal pattern had a sensitivity of 71% for intestinal metaplasia without dysplasia and an irregular or distorted pattern had a sensitivity of 83% for high grade dysplasia (94).

1.4.3.4 Lugol's Iodine for Squamous Neoplasia

Detection of squamous dysplasia in the oesophagus can also be improved with chromoendoscopy using Lugol's iodine solution. The Lugol's iodine reacts with glycogen in the normal squamous mucosa and forms a brown colour, whereas dysplastic or malignant mucosa loses the glycogen-rich granules and is unstained, appearing white or pink. A drawback of the use of Lugol's iodine is the potential to cause acute oesophageal or gastric mucosal damage and in some cases severe retrosternal pain on application.

Lugol's iodine has been demonstrated to improve dysplasia detection in those at high risk of squamous dysplasia, due to existing head and neck cancer (95,96). A recent meta-analysis comparing Lugol's with NBI reported the sensitivity of Lugol's chromoendoscopy to be 92% compared with 88% with NBI. There was no statistical difference between either method (97).

1.4.4 Virtual Chromoendoscopy

1.4.4.1 Narrow Band Imaging

Narrow band imaging (NBI) mechanically filters the white light (400-700nm) to isolate blue (415nm) and green (540nm) light. These shorter wavelengths only penetrate the superficial layers of the mucosa (Figure 1.8). As a result of different absorptive and reflective properties of these

wavelengths, an image that enhances superficial mucosa and vascular structures can be generated. Haemoglobin found in the capillaries appears darker. Changes in blood vessel patterns associated with pre-malignancy and early cancer are more easily observed using this system (Figure 1.9).

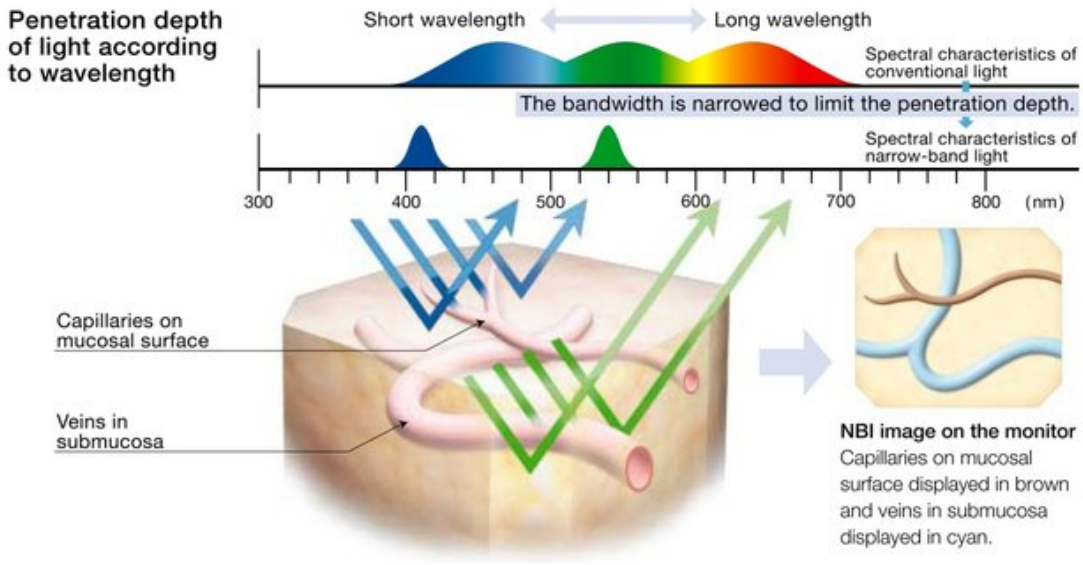


Figure 1.8: Schematic of NBI (98)

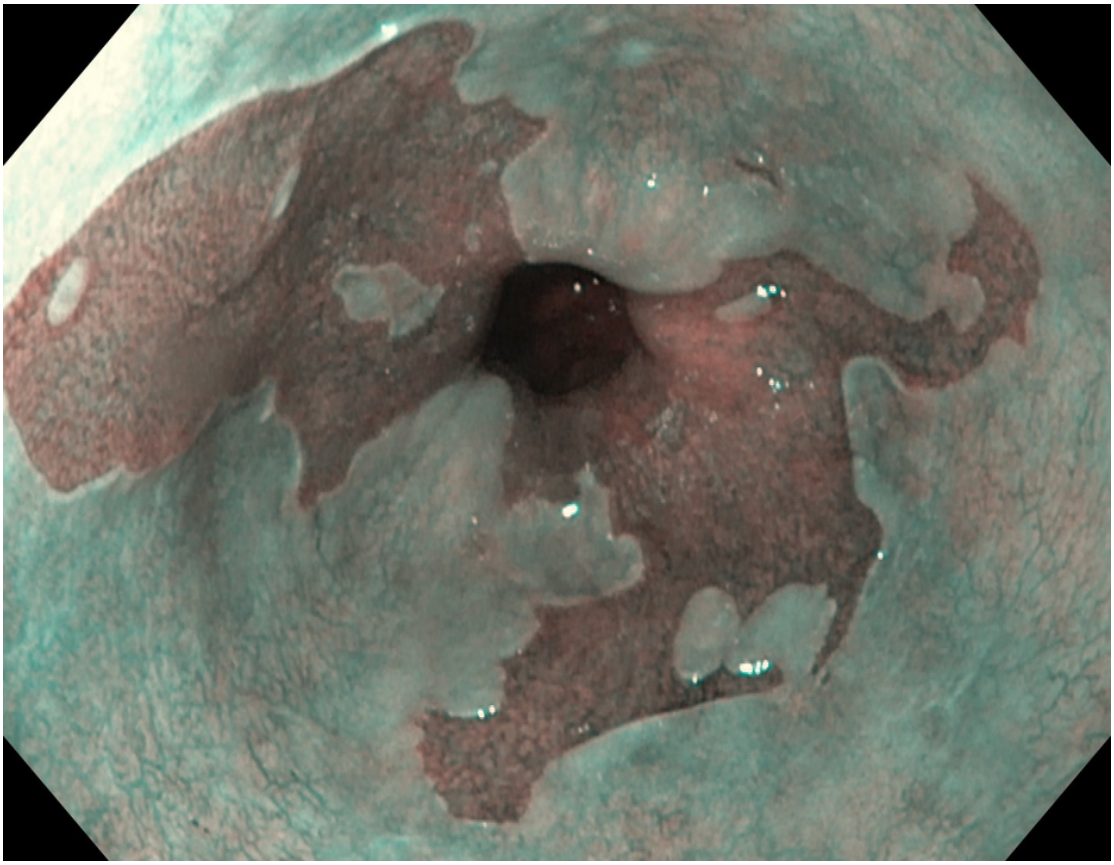


Figure 1.9: NBI image of Barrett's segment (99)

NBI is the most investigated technology offering virtual chromoendoscopy. Kara et al reported a sensitivity of NBI of 86% compared with 79% with high resolution endoscopy with targeted biopsies alone (100). Wolfsen et al reported that NBI targeted biopsies diagnosed higher grades of dysplasia than random biopsies alone (101) and Sharma et al found NBI detected a higher proportion of areas with dysplasia compared with standard random biopsies (30% versus 21%, p=0.01) (102).

NBI has been used to identify areas of mucosal and/or vascular irregularity that correspond to dysplasia, leading to the development of several classification systems (103–105). All classification systems using NBI have excluded nodular disease from analysis due to the presumption of dysplasia in these lesions and have focused attention on 'flat' dysplasia. Three systems have been proposed, each named after their respective centres (Table 1.4) (106).

Table 1.4: Summary of the 3 main scoring systems for NBI (Reproduced from Silva et al 2011)

Classification System		
Kansas	Amsterdam	Nottingham
Mucosal pattern: circular/ridge/villous/irregular/distorted	Mucosal pattern: regular/flat/irregular	Type A: round/oval pits with regular microvasculature
Vascular pattern: normal/abnormal	Vascular pattern: regular/irregular	Type B: villous/ridge/linear pits with regular microvasculature
	Abnormal blood vessels: absent/present	Type C: absent pits with regular microvasculature
		Type D: distorted pits with irregular microvasculature

1.4.4.1.1 The Kansas Classification System

The Kansas classification system was reported in 2006 and set out to classify both the presence of IM or dysplasia. The system identified a correlation between mucosal and vascular patterns and histological results. 51 patients were enrolled and in only 67% of images were both mucosal and vascular patterns identifiable. The system reported a sensitivity of 100%, a specificity of 98.7% and a positive predictive value (PPV) of 95.3% for the detection of HGD. No inter-observer agreement was reported and all scoring was performed on still images (103).

1.4.4.1.2 The Amsterdam Classification System

The Amsterdam classification system recruited 63 patients to identify features consistent with dysplasia. IM was characterized by either villous/gyrus-forming patterns (80%), which were mostly regular and had regular vascular patterns, or a flat mucosa with regular normal-appearing long branching vessels (20%). HGD was characterized by 3 abnormalities; irregular/disrupted mucosal patterns, irregular vascular patterns, and abnormal blood vessels. The system reported a sensitivity of 94%, a specificity of 76%, a PPV of 64% and a NPV of 98% for the detection of HGD. No inter-observer agreement was reported and all scoring was again performed on still images (104).

1.4.4.1.3 The Nottingham Classification System

The Nottingham classification system included magnification endoscopy and NBI to identify IM and dysplasia from still images of 109 patients. 4 patterns were identified; type A (columnar epithelium without IM), round pits with regular microvasculature; type B (IM), villous/ridge pits with regular microvasculature; type C (IM), absent pits with regular microvasculature; and type D (HGD), distorted pits with irregular microvasculature. For type D (HGD) the PPV was 81% and NPV 99%, based on 14 cases of HGD. Inter-observer agreement κ values were between 0.71 and 0.91 for expert and non-expert endoscopists (105).

1.4.4.1.4 Evaluation of NBI based Classification Systems with Still Images

Several studies have attempted to validate these systems using still images with varying degrees of success. Singh et al evaluated 22 images (8 with HGD) among expert and non-expert endoscopists to identify abnormal mucosal and/or vascular patterns. Each image was captured in high definition white light, NBI, following acetic acid application and also following indigo carmine application. There was no increase in diagnostic yield of dysplasia with NBI compared with WLE amongst expert and non-expert endoscopists. Agreement of the mucosal pattern ($\kappa = 0.53$) and vascular pattern ($\kappa = 0.52$) was moderate (107).

Curvers et al (108) assessed the Amsterdam classification system of NBI and optical magnification images in 7 general gastroenterologists with no expertise in NBI or BO and a further 5 expert endoscopists. The yield of dysplasia detection was 81% for all endoscopists and did not improve with the addition of NBI. Baldaque-Silva et al evaluated NBI with optical magnification videos in 6 endoscopists with varying degrees of experience (109). Dysplasia detection varied from 62-90% with inter-observer agreement (κ) ranging 0.39-0.48.

1.4.4.1.5 Evaluation of NBI based Classification Systems with Videos

There has been a single reported study comparing these three classification systems using videos (106). Video clips were recorded with the endoscope in retroflexion, at lesions of interest and with the tip of the endoscope placed next to the surface of the mucosa at the 3 o'clock position on the left hand wall, every 2 cm from the GOJ until the squamo-columnar junction (SCJ). 32 patients yielded 209 videos and after quality assessment, 84 were used. Each video was viewed 3 times (one for each classification system) by each of the nine scoring endoscopists (3 international experts in magnification endoscopy NBI in BO, 3 users of magnification endoscopy NBI in the stomach but not in BO and 3 with

expertise in BO but not in magnification endoscopy NBI). The 84 videos contained 27 (32%) dysplastic lesions. The accuracy of 'experts' diagnosing IM across the three systems ranged from 0.53-0.57 and for dysplasia was 0.75-0.78. There was no significant difference in IM or dysplasia diagnosis across the scoring systems though the global κ agreement scores were moderate for the Kansas (0.44) and Amsterdam (0.47) systems and only fair for the Nottingham (0.34) classification system. The authors attributed the modest sensitivities and specificities reported in this study compared with previous studies to the difficulty in scoring videos rather than still images. One further limitation was the use of standard definition videos rather than high definition white light endoscopy and NBI.

1.4.4.1.6 Consolidation of the NBI Scoring Systems

A consortium of international experts in NBI, the BING consortium, developed a simplified consensus driven NBI classification system of BO, see Table 1.5 (110). The system was developed after review of 60 NBI images provided by several centres.

Table 1.5: The BING NBI magnification endoscopy classification system

	Morphological Characteristics	Classification
Mucosal pattern	Circular, ridged/villous, or tubular patterns	Regular
	Absent or irregular patterns	Irregular
Vascular pattern	Blood vessels situated regularly along or between mucosal ridges and/or those showing normal, long, branching patterns	Regular
	Focally or diffusely distributed vessels not following normal architecture of the mucosa	Irregular

The classification system was then validated on a further 50 images and the results discussed in a face-to-face meeting of experts. At this stage, inter-observer κ agreement of mucosal (0.48) and vascular (0.52) patterns was moderate. In the final assessment, a further 120 images were reviewed via a web-based survey with overall accuracy 0.85, sensitivity 0.80, specificity 0.88, PPV 0.81 and a negative predictive value (NPV) 0.88. Overall inter-observer agreement was substantial (κ =0.681).

1.4.4.2 i-Scan

i-Scan (Pentax Hoya, Japan), utilises post-processing technology to provide enhancement in 3 modes. The endoscopist can switch between modes in real-time whilst assessing the BE segment with a push of a button on the scope. *i*-Scan 1, surface enhancement, utilises the technology to detect the edge of a lesion by comparing the difference in pixels and then digitally enhancing the difference resulting in sharper contrast between structures (see Figure 1.10). *i*-Scan 2, contrast enhancement, detects darker areas of the image and includes blue colour before an algorithm enhances the image resulting in a blueish-white staining of depressed areas and vasculature (see Figure 1.11). *i*-Scan 3, tone enhancement, dissects and reconstructs the red, green and blue component of each image to provide enhancement of the mucosal structures, vascular patterns and changes in colour. *i*-Scan 1 is often the default setting in clinical practice for lesion detection. *i*-Scan 2 allows for assessment of mucosal and vascular structures in lesion characterization and *i*-Scan 3 enhances glandular structures and is used for lesion demarcation.

The modes available are summarised in Table 1.6 and representative images are shown in Figure 1.13.

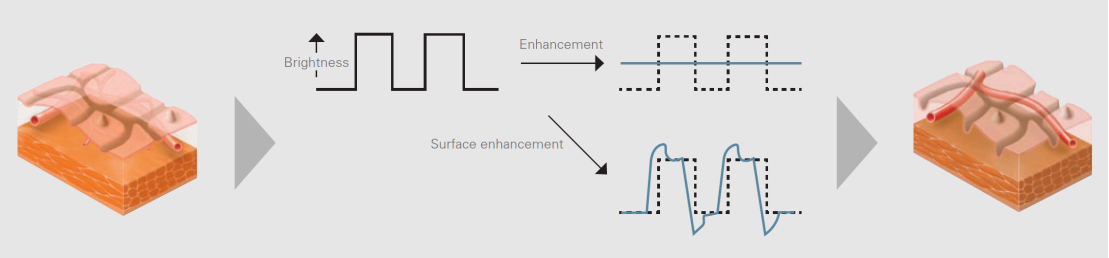


Figure 1.10: Schematic of *i*-Scan 1 mode

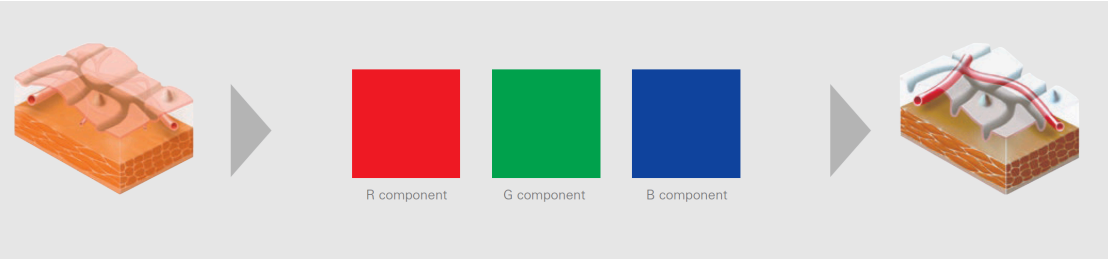


Figure 1.11: Schematic of *i*-Scan 2 mode

A new mode, Optical Enhancement (OE), combines optical filters together with digital post-processing with aim of overcoming the darkness seen with NBI. The technology aims to improve the visibility of the superficial mucosal and microvasculature structures (see Figure 1.12).

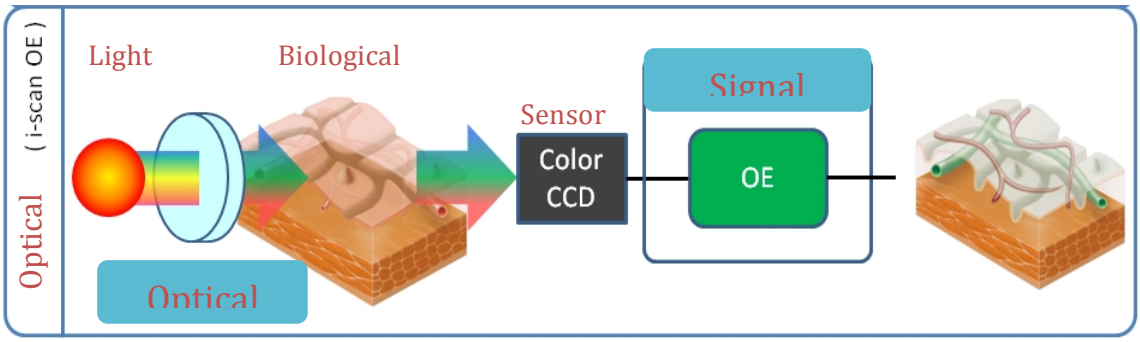


Figure 1.12: Schematic of *i*-Scan OE mode

Table 1.6: *i*-Scan modes and their uses

Mode	Enhancement
i-Scan 1	To improve surface enhancement
i-Scan 2	To improve contrast enhancement
i-Scan 3	To improve both surface and contrast enhancement
i-Scan OE	To improve surface enhancement and mucosal microvasculature visibility

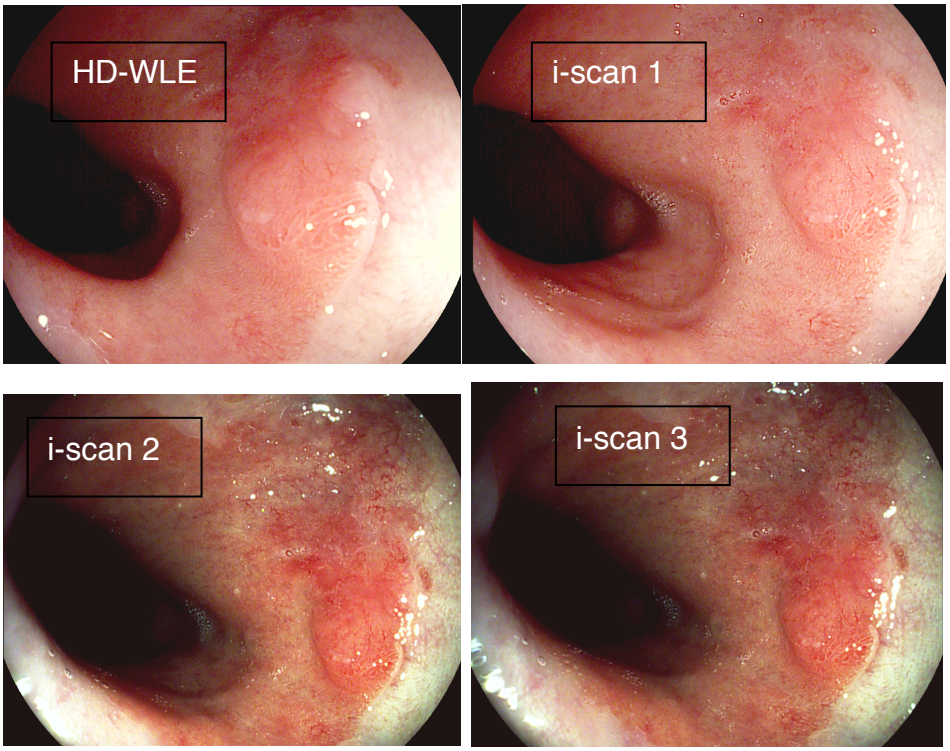


Figure 1.13: Pentax Images of a nodule in an area of Barrett's mucosa using different *i*-scan modes

i-Scan technology has been assessed in the colon and demonstrated to detect more adenomas than white light endoscopy alone, 618 adenomas in 1008 patients compared with 402 adenomas in 929 patients ($p<0.01$) (111). A meta-analysis for the use of i-Scan to diagnose colonic polyps reported a sensitivity of 90.4% (95% CI 85%-94.1%) and a specificity of 90.9% (95% CI 84.3%-94.9%) (112).

The use of i-Scan technology in the small bowel has also been investigated. I-Scan imaging has been shown to correlate the degree of villous atrophy with the histological grade of atrophy r=0.732, p<0.00001. The technology has been shown to have a sensitivity of 96% (95% CI 85-99%) and specificity of 63% (95% CI 26-90%) in diagnosing coeliac disease (113).

A single study in Barrett's demonstrated that i-Scan guided biopsies with acetic acid were superior to random quadrantic biopsies in identifying IM in patients with known columnar lined epithelium (114).

Further work from our centre, which was published in abstract form at UEGW 2014 proposed a classification system based on analysis of video recordings of endoscopy using post-processing I-Scan technology (115), Table 1.7.

Table 1.7: *i*-Scan London classification system for detecting dysplasia in BO

Mucosal Pattern	M1	Regular oval pits – Non-dysplastic Barrett's
	M2	Villous pits – Non-dysplastic Barrett's
	M3	Irregular or Featureless mucosa - dysplastic Barrett's
Vascular Pattern	V1	Regular vessels – Non-dysplastic Barrett's
	V2	Irregular (dilated, corkscrew) vessels - dysplastic Barrett's

47 patients were enrolled with 60 videos recorded, 47 pre-acetic acid and 13 post application of 2% acetic acid. The videos began with the scope

at the gastro-oesophageal junction and continued as the scope was withdrawn through the visible Barrett's segment in high definition white light. The pull-through was then repeated in each I-scan mode (1, 2 and 3). Three expert endoscopists scored the videos with a sensitivity and specificity of 68% in detecting dysplasia. Agreement between the experts was moderate, $\kappa = 0.42$. Inter-observer agreement was seen to improve with acetic acid ($\kappa = 0.70$), though this was only in respect to 13 videos. Acetic acid was also reported to improve the sensitivity (78%) and specificity (71%), though no statistical significance was reported (115).

1.4.4.3 FICE, BLI and LCI

Fuji Intelligent Colour Enhancement (FICE) or optical band imaging limits the wavelength range of the light and offers images with brilliant colour and light quality. A proprietary algorithm makes it possible to select from a large number of wavelength combinations to alter the display of the mucosa depending on location and aim. In this way, FICE gives flexibility to formulate a diagnosis. The post processing technology converts images into individual wavelengths and reconstructs them to generate real time enhanced images. A single study of 20 patients using acetic acid and FICE reported irregular mucosal patterns in 14% of cases with FICE alone but in 100% of cases with FICE and acetic acid and irregular vascular patterns in 0% with FICE alone but 86% in FICE with acetic acid (116).

Fujifilm Corporation (Tokyo, Japan) has developed blue laser imaging (BLI) and Linked Colour Imaging (LCI).

BLI uses 2 lasers instead of the usual xenon lamp. One of the lasers stimulates the phosphor at the tip of the scope and the other produces a short wavelength light. The BLI light is a combination of the 410 nm and 450 nm wavelength lasers and fluorescent light. The wavelengths use

green and blue colour that provides a contrast similar to that of NBI, see Figure 1.14. In a small study assessing the use of BLI diagnosing short segment BO, BLI did not improve visibility among experts or trainees (117).

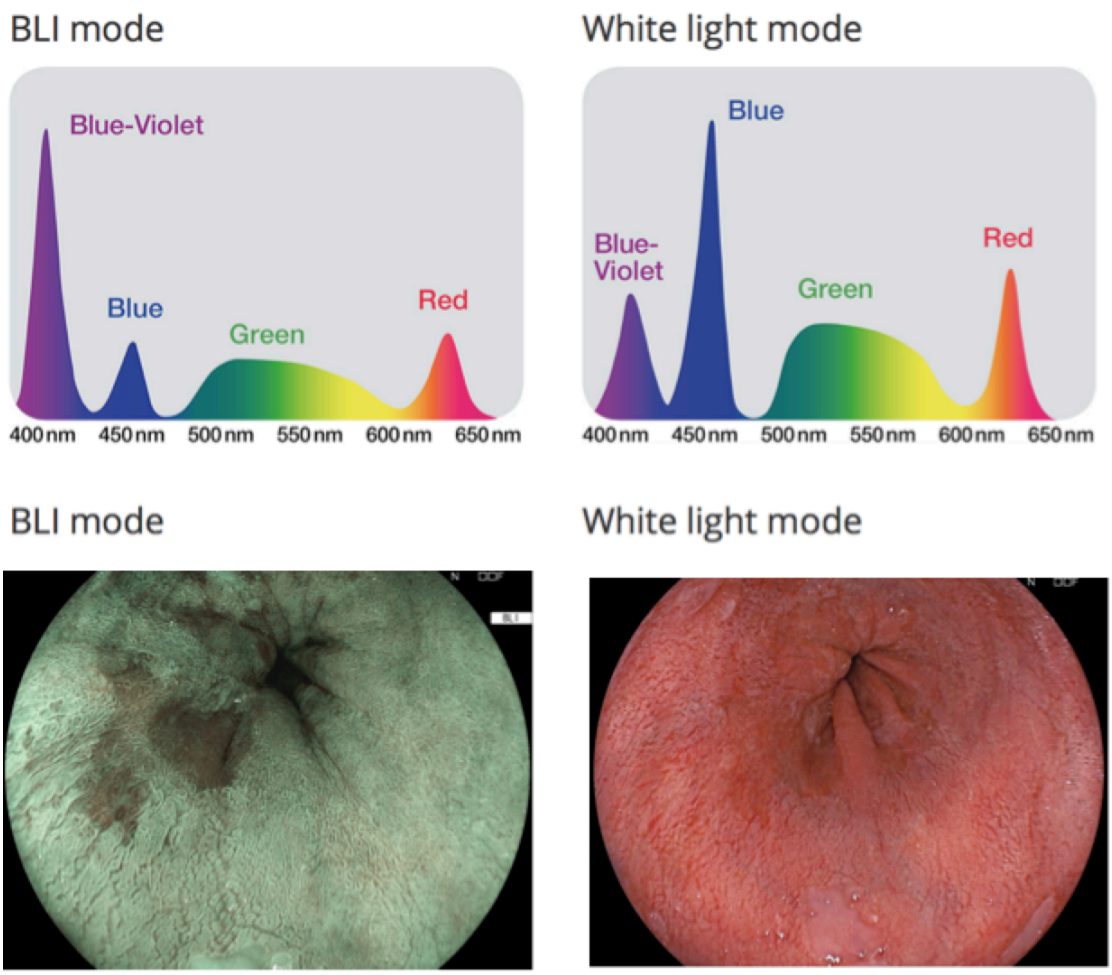


Figure 1.14: Schematic and Images of BLI (118)

LCI is a post processing technology of colour separation and enhancement. Similar to BLI, two lasers and a white laser light enable to the system to enhance red and white making red appear redder and white, brighter. This helps differentiate red tones with the aim of improving lesion detection and delineation, see Figure 1.15. A small study reported an improvement in short segment BO detection with the

use of LCI compared with white light endoscopy particularly for trainees (117).

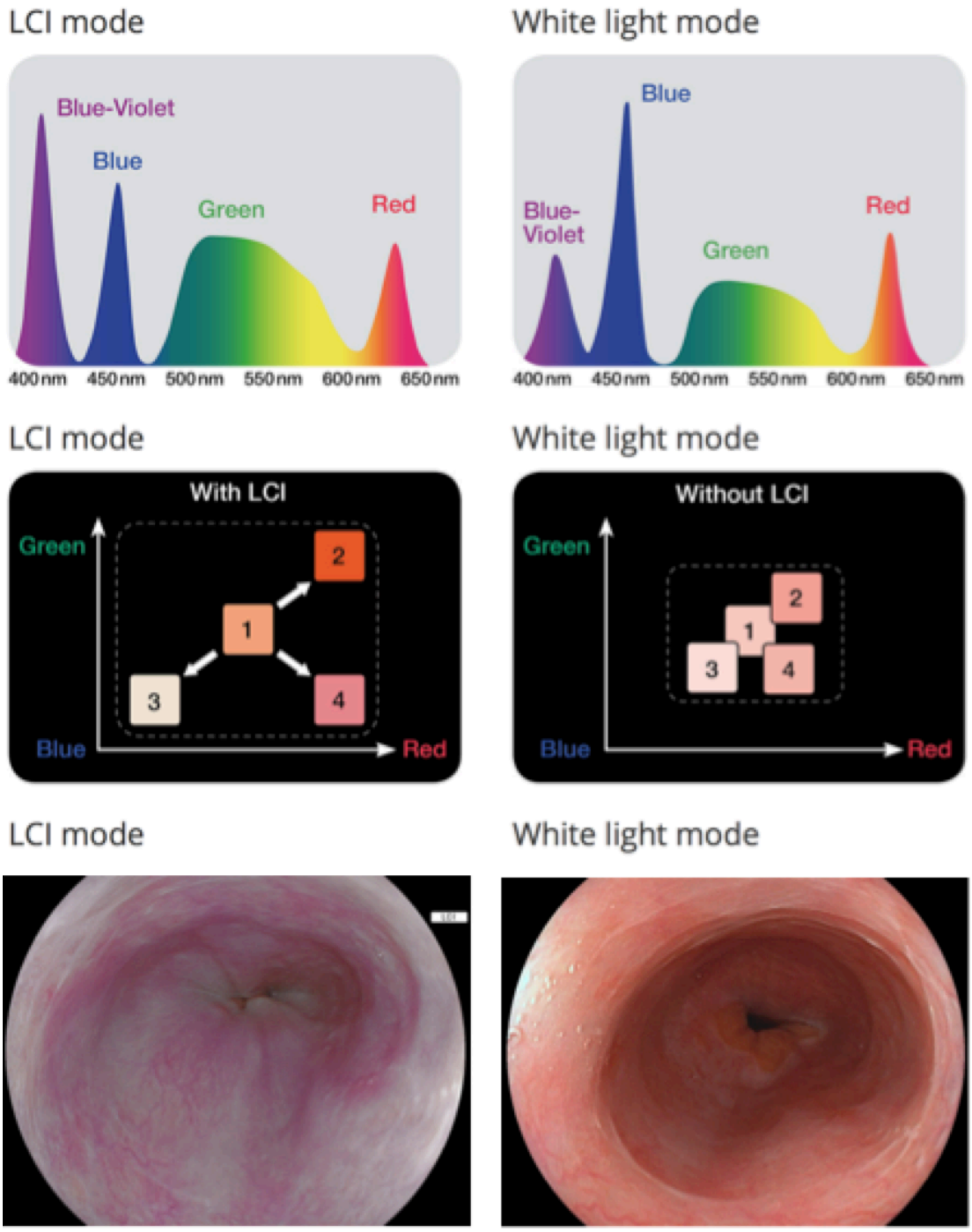


Figure 1.15: Schematic and Images of LCI (118)

1.4.5 Real time in vivo diagnosis

Specialised technologies, which aim to achieve in vivo diagnosis, now exist. These have been developed as both point techniques for virtual histology and as wide-field techniques to examine the entire lumen of the organ in question. Technologies include confocal laser endomicroscopy, auto-flouresence endoscopy and optical coherence tomography.

1.4.5.1 Confocal Laser Endomicroscopy

Confocal Laser Endomicroscopy (CLE) is performed with a probe passed through the working channel of an endoscope (pCLE, Cellvizio; Mauna Kea Technologies, Paris, France). Focused infra red light is reflected through a pinhole and generates grey-scale images once the tissue is made to fluoresce with topical or intravenous agents. High resolution of microstructures can be visualized in similar detail to histological sections, see Figure 1.16. The probe can be used in the upper and lower gastrointestinal tract as well as the biliary tree and produces images with a resolution of less than 10 microns. This makes it possible to see individual cells as well as tissue architecture. A 2014 meta-analysis of dysplasia detection using CLE reported a per-patient sensitivity of dysplasia detection of 89% with a specificity of 75% (119). However, a further study comparing high definition white light endoscopy with random biopsies with high definition white light endoscopy with CLE and targeted biopsies found CLE tripled the diagnostic yield of dysplasia (22% vs 6%; P = .002) and would have removed the need for any biopsies in 65% of patients. The addition of CLE improved the sensitivity of dysplasia detection form 40% to 96% ($p<0.0001$) with significantly reducing the specificity (120).

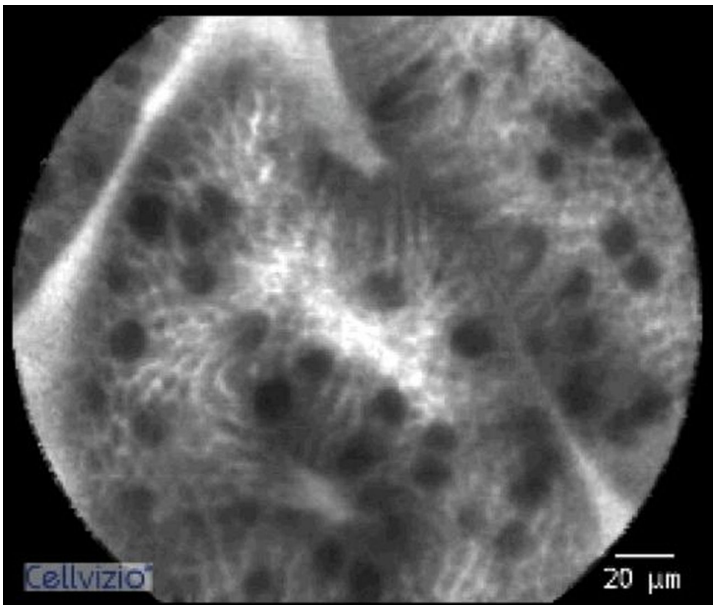


Figure 1.16: pCLE image of IM (121)

1.4.5.2 Autoflouresence

Autoflouresence (AF) is a virtual endoscopy technique utilising the variable quantities of fluorophores (substances that emit fluorescent light after exposure to short, blue light wavelengths). Alterations in the autofluorescence pattern of neoplastic tissue have been attributed to alter metabolic activity as well as haemoglobin content and a breakdown of collagen fibre cross-links. This results in a shift toward the red spectrum when such tissue is excited with blue light. The altered autofluorescence signal is translated into false colour images, usually depicting neoplasia in purple against a green background of healthy mucosa as seen in Figure 1.17.

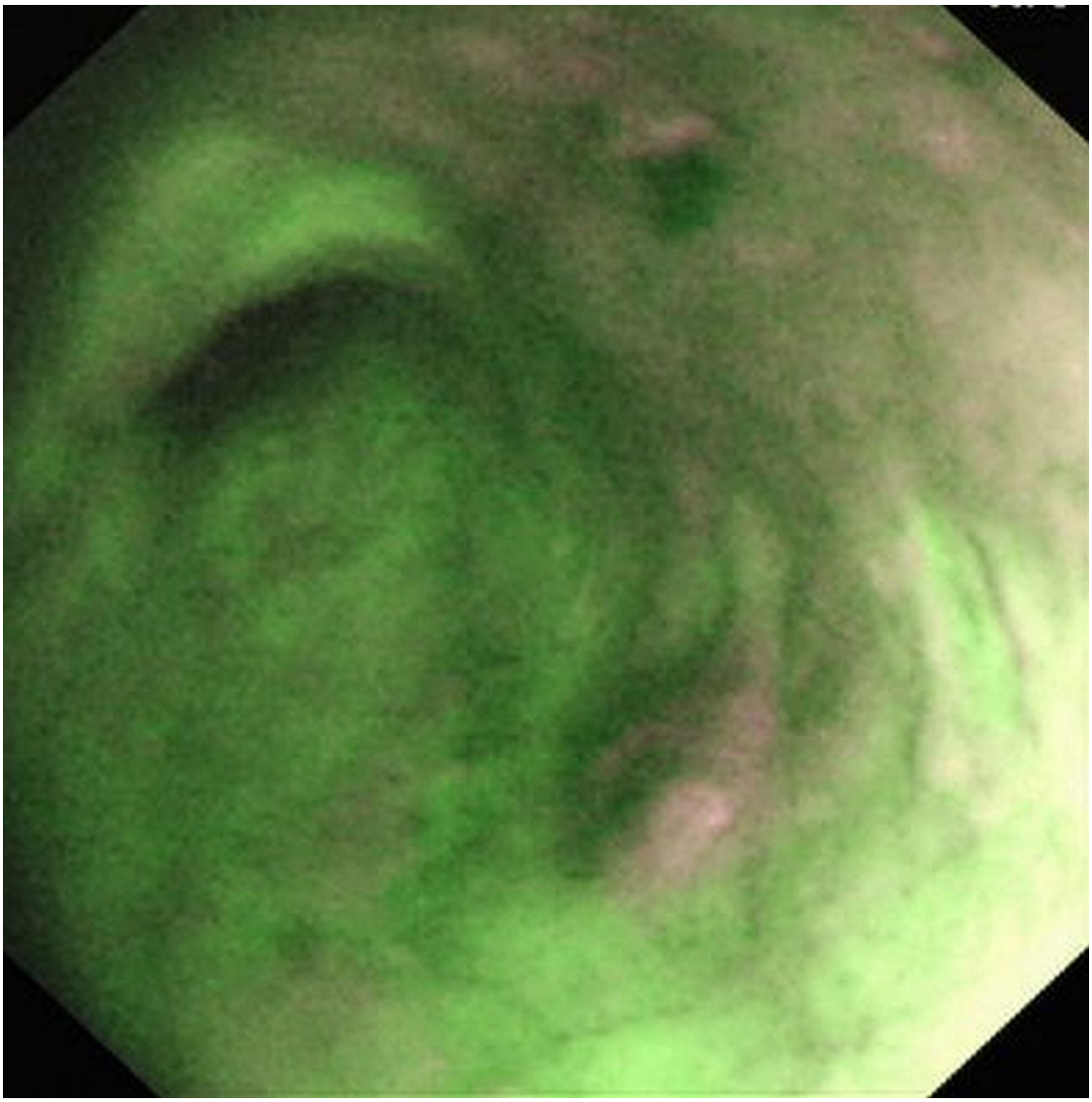


Figure 1.17: AF image of lesion within Barrett's oesophagus (121)

AF has been integrated with HD-WLE and NBI as part of the 'endoscopic trimodal imaging' (ETMI) system, with evidence of use differentiating adenomatous polyps in the colon (122). Giacchino et al evaluated AF alone and with the addition of magnification endoscopy and NBI in the detection of dysplasia within Barrett's. AF alone had a sensitivity of 50%, specificity of 61%, NPV of 71% and overall accuracy of 57%. The addition of NBI and magnification endoscopy improved the sensitivity to 71% and NPV to 76% but reduced the specificity to 46% and accuracy to 55%. Inter-observer agreement was moderate (123).

1.4.5.3 Molecular Imaging

Molecular imaging can help identify disease-specific morphological or functional changes in individual cells with an altered molecular signature. Wheat germ agglutinin (lectin), once fluorescently conjugated, has been found to improve dysplastic lesion detection and opens a new discipline within endoscopic diagnostics (124). No clinical trials have reported sensitivity or accuracy of molecular imaging for the detection of dysplasia in BO.

1.4.5.4 Optical coherence tomography and Volumetric Laser Endomicroscopy

Optical coherence tomography (OCT) uses reflected light in a manner similar to acoustic ultrasound to generate high-resolution 3-dimensional images. This allows 'visualisation' of the mucosa to a depth of 1-2mm. Currently performed with a probe through the working channel of an endoscope, the future may involve tethered capsule technology and rapid assessment of the tubular oesophagus. An early study of the technology in 2005 reported 314 OCT images with correlating histological biopsies, which were reviewed by 4 histopathologists. Detection of dysplasia by OCT had a sensitivity of 68%, specificity of 82% and an accuracy of 78% (125). More recent studies have suggested a role for OCT for surveillance after ablation therapy with radio-frequency ablation, where the detection of buried glands has been reported in up to 63% of patients with no endoscopically visible residual CLE (126,127).

Volumetric laser endomicroscopy (VLE) is a second-generation OCT technology with a balloon to provide circumferential images of the oesophagus to a depth of 3mm. Using a computer-aided algorithm, the system reported a sensitivity of 90% and specificity of 93% for detecting neoplasia (128). A case series of 6 patients undergoing VLE assessment

reported that all 6 were upstaged including one to intramucosal cancer (129).

1.4.6 Thresholds for the Introduction of New Technologies

The Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) initiative of the ASGE has set thresholds that any new technology should meet before the existing practice of random biopsies can be replaced (130). These include a per-patient sensitivity of ≥90%, specificity ≥80% and a NPV ≥98% for detecting dysplasia.

A recent systematic review and meta-analysis was performed (131) to assess new technologies that may eliminate the need for random biopsies to detect dysplasia within BO. Pooled sensitivities, specificities and NPV were calculated for acetic acid chromoendoscopy, NBI and CLE. The results can be seen in Table 1.8. Although several technologies have met PIVI thresholds according this met-analysis, *i*-scan technology was not assessed due to the limited number of studies published in the field of BO.

Table 1.8: Results of the meta-analysis of new technologies for the detection of BO associated dysplasia, from Thosani et al (131)

Technology	No. of studies	Sensitivity (95% CI)	NPV (95% CI)	Specificity (95% CI)	Meets ASGE PIVI threshold
All Chromo-endoscopy	7	91.9 (89.4-93.8)	95.5 (90.8-97.9)	89.9 (80.1-95.2)	No
Acetic acid	4	96.6 (95.2-97.7)	98.3 (94.8-99.4)	84.6 (68.5-93.2)	Yes
Methylene blue	2	64.2 (36.2-84.7)	69.8 (30.6-92.3)	95.9 (76.5-99.4)	No
NBI	9	94.2 (82.6-98.2)	97.5 (95.1-98.7)	94.4 (80.5-98.6)	Yes
NBI AF	4	80.6 (62.0-91.3)	88.7 (41.5-98.9)	46 (31.7-61.0)	No
CLE	5	90.4 (75.7-96.6)	96.2 (93.1-97.9)	89.9 (83.8-93.9)	No
eCLE	2	90.4 (71.9-97.2)	98.3 (94.2-99.5)	92.7 (87.0-96.0)	Yes
pCLE	3	90.3 (54.1-98.7)	95.1 (90.7-97.5)	77.3 (54.3-90.7)	No

1.4.7 Future Directions

Technology continues to evolve and there are new developments on the horizon that may change the detection of dysplasia within BO.

Wide-area transepithelial sampling with computer-assisted three-dimensional analysis (WATS 3-D brush) (CDx Diagnostics, NY, USA) is a new method of sampling the tissue from a Barrett's segment. An abrasive brush is passed through the working channel of an endoscope and a full thickness sample of epithelium is collected over a wide area. The collected tissue is then analysed using a computer assisted to identify abnormal cells. The system does not allow for targeting of lesions, which still require a targeted biopsy but does allow sampling of the seeming normal Barrett's segment. The system has been shown to increase the detection of Barrett's dysplasia by 42% (95% CI 20.7%–72.7%) in a high risk population (132). In a population of 211 patients undergoing surveillance, WATS 3-D increased the detection of LGD by 200%, by detecting a further 6 cases that targeted biopsies had not identified. No HGD cases were identified by either method (133).

As with WATS 3-D, computer aided diagnostics and artificial intelligence may help identify dysplasia. Recent work by the Amsterdam group and UCL has identified promise in this area. The Amsterdam group described an automated computer algorithm that was taught with a 100 images from 44 patients. The system achieved a sensitivity and specificity of 83% on a per-image basis (134). The UCL team developed decision trees through machine using endoscopic videos. Experts viewed the videos and had an accuracy of 88% when diagnosing dysplasia. When the expert views were fed into the decision tree, the decision tree had 92% accuracy (mean sensitivity 97% and mean specificity 88%), demonstrating that machine learning can define rules learnt from expert endoscopists (135). This technology may open the way for artificial intelligence to change our management practice in detecting dysplasia.

1.5 Treatment options for Barrett's associated dysplasia and early OAC

Historically, treatment for early gastrointestinal neoplasm required major surgery, with associated morbidity and mortality. Early neoplasms confined to the superficial layers of the mucosa and sub-mucosa can now be treated endoscopically with minimal risk of nodal and metastatic spread (47).

1.5.1 Monitoring and Oesophagectomy for HGD

The 2002 American College of Gastroenterology guidelines recommended (136) that:

> *"If multiple HGD foci are confirmed, then the patient should undergo either surgical therapy (esophagectomy) or endoscopic surveillance every 3 months."*

The option of en bloc oesophagectomy with regional lymph node dissection for patients with HGD carried a mortality risk of 4-19% (137) and a post-operative morbidity of 20-47% (138) 10 years ago. However, given that 6-20% of patients with HGD would progress in 17-34 months to OAC (36,139) and 30-40% of those undergoing surgery for HGD were found to have invasive OAC (140), this risk was felt to be acceptable.

Treatment of dysplasia arising in BO has significantly changed over the last 10 years with high success rates of eradication of dysplasia and intestinal metaplasia in BO with endoscopic treatment. Despite these advances in endoscopic therapy available for patients with dysplasia arising in Barrett's and the latest BSG guidelines, the most recent National Oesophago-Gastric Cancer Audit from 2015 reported that of 930 patients with HGD, 26.2% underwent surveillance alone with no therapy. The remaining patients received either endoscopic treatment (67.5%) or

surgical resection (6.3%) (141). That over a quarter of patients with HGD remain in surveillance, receiving no active treatment is a key point highlighted in the report.

1.5.2 Photodynamic Therapy

Photodynamic Therapy (PDT) uses a chemical to sensitise the target tissue before a light is shone and a photochemical reaction occurs, damaging the tissue. 5-aminolevulinic acid or Photofrin have been used as photosensitising agents. A randomized controlled trial compared Photofrin PDT with omeprazole versus omeprazole alone and found PDT achieved CR-D in 77% compared with 39% in the omeprazole only group. The durability of PDT was reported in the same study, with 15% progressing to cancer at 5 years compared with 29% in the omeprazole only group (142). Our group published work comparing 5-Aminolaevulinic acid with Photofrin and reported CR-D of 47% with 5-Aminolaevulinic acid and 40% with Photofrin. For patients with shorter segments of Barrett's (<6cm), 5-Aminolaevulinic acid achieved higher CR-D rates than Photofrin ($\chi 2=5.39$, $p=0.02$). It was also noted that strictures and skin photosensitivity were significantly more common after treatment with Photofrin (33% versus 9 % and 43% versus 6 %, respectively, $p<0.05$) (143). Although it was the first endoscopic ablative treatment which was proven to reduce cancer risk in dysplastic BO, PDT has fallen out of use due to its poor side effect profile and durability, coupled with the introduction of better endoscopic treatment modalities.

1.5.3 Endoscopic Mucosal Resection

Endoscopic Mucosal Resection (EMR) is used for the staging and treatment of superficial lesions and to confirm adequate resection margins. The technique was first described in Japan for oesophageal SCC tumours (144). The technique enables accurate histological assessment of the depth of invasion of early neoplastic lesions, thus being both a diagnostic and therapeutic intervention. Wani et al reported

that EMR upstaged the diagnosis in 10% of patients and down-graded the diagnosis in 21% (145). There are several techniques to perform EMR including cap assisted, ligation assisted (such as the multiband mucosectomy from Cook, United States) and injection assisted. A study comparing cap assisted and multiband mucoscectomy found the multiband ligator was cheaper and had fewer complications (146).

As a monotherapy, CR-D rates have been reported as 87%-96%. However, due to the often circumferential nature of BO, the resection margins can be extensive and circumferential resection can result in strictures rates of up to 88% (147,148). It should be noted that EMR of less than 50% of the circumference of the luminal wall is associated with far lower stricture rates of up to 12.5% 12.5%-88% (147,148). These results form the basis of current guidelines, that all visible lesions are first removed with EMR (due to the risk of buried dysplasia which can be diagnosed with an EMR sample histologically) and the residual Barrett's, whether dysplastic or only metaplastic is ablated (25).

1.5.4 Cryotherapy

Cryoablation utilises liquid nitrogen to form intracellular and extracellular ice that causes ischaemic necrosis on thawing and apoptosis of the treated cells. Limitations of cryotherapy include the large volume of gas that is produced during therapy, with an early study reporting a 94% eradication rate of HGD but complications including a gastric perforation (149). A new focal balloon device avoids this risk, as it is a self-contained unit that does not introduce gas into the stomach (Cryoballoon Focal Ablation System (CbFAS), C2Therapeutics, USA).

A 2015 single centre study reported on 64 patients with neoplastic Barett's, cryotherapy achieved complete resolutions of dysplasia (CR-D) in 100% of treatment naïve patients and 91% of those treated for rescue therapy, complete resolution of IM (CR-IM) rates were only 55% (150). The United Stated National Cryospray Registry reported on 96 patients with dysplastic Barrett's treated with cryotherapy (151). Patients with

LGD achieved a CR-D rate of 91% and a CR-IM of 61%, those with HGD had a CR-D of 81% and CR-IM of 65%. No perforations or deaths were reported and there was a single stricture which did not require dilatation (151).

1.5.5 Endoscopic Submucosal Dissection

In contrast to EMR, where large lesions may be removed piecemeal, endoscopic submucosal dissection (ESD) allows large lesions to be removed *en bloc*, as well as resection of tumours arising from the muscularis propria. ESD requires extensive training, longer procedure time and are associated with an increased risk of complications. In a randomised trial of 40 patients with early Barrett's neoplasia, ESD achieved a resection with margins free of disease more than EMR (10/17 vs 2/17, p=0.01), however, ESD resulted in 2 severe adverse events compared with none in the EMR group (p=0.49) (152). A 2009 meta-analysis reported higher curative resection rates with ESD versus EMR (OR 3.53, 95% CI 2.57-4.84) with lower recurrence in the ESD group (OR 0.09, 95% CI 0.040-0.18) (153). However, ESD was more time consuming and had higher rates of bleeding (OR 2.20, 95%CI 1.58-3.07) and perforation rates (OR 4.09, 95% CI 2.47-6.80) (153). Guo et al reported perforation rates of 4% with ESD compared with 1.34% with EMR (154). A further review also reported a higher stenosis rate with ESD compared with EMR (OR 7.3, 95%CI 3.8-10.8) (155).

A 2018 meta-analysis of ESD for Barrett's neoplasia included 11 studies. The lesions selected by these studies had a mean size of 27 mm and complete resection rates were 74.5% with a curative resection rate of 64.9%. Bleeding occurred in 1.7%, perforation in 1.5% and strictures in 11.6% (156).

The balance of evidence has resulted in the European Society of Gastrointestinal Endoscopy recommendation (157) that

"ESD may be considered in selected cases, such as lesions larger than 15mm, poorly lifting tumors, and lesions at risk for submucosal invasion."

1.5.6 Radiofrequency ablation

Radiofrequency ablation (RFA) (Covidien, Medtronic) is used to ablate the surface 500 μm of the gastrointestinal mucosa. It is primarily used in the treatment of Barrett's related neoplasia using a balloon (to provide a 360 degree ablation field) or a focal device, mounted over the endoscope (Figure 1.18). Several treatments are required to effectively treat Barrett's oesophagus and any associated neoplasia. The treatment has a high success rates and good durability data now exist (158). The next section addresses the evidence base in more detail. It should be noted that RFA is used a complimentary therapy to EMR. Visible lesions are first resected to ascertain an accurate histological diagnosis and confirm that there is unlikely to be nodal spread before the residual BO is ablated.

1.5.7 APC

APC uses argon gas to conduct electrical current to thermally ablate targeted tissue. A catheter is placed through the working channel of an endoscope. APC is often used an adjunct to alternative therapies as it is cheap and easy to treat small areas of residual disease and has been demonstrated to significantly increase recurrence-free survival for the patients undergoing ablation after EMR compared with those having EMR alone (3% versus 36.7%, p=0.005) (159). A feasibility study comparing APC with Radiofrequency Ablation (RFA), (Barrett's Randomised Intervention for Dysplasia by Endoscopy – BRIDE), recently reported preliminary findings that suggested that at 12 months there was no difference in CR-D rates (12.5% RFA versus 11.5% APC, OR 1.10, 95% CI 0.22-5.4) (160).

1.5.8 Monopolar Electrocoagulation (MPEC)

MPEC is performed through a catheter placed in the working channel of the endoscope, similarly to APC, and electrical current thermally ablates the target tissue. Dulai et al found no difference between MPEC and APC for the eradication of HGD (161), though the study only randomised 52 patients and did not report on any follow up period after successful eradication. It is a technique that is rarely used in the era of RFA and has a limited evidence base.

1.5.9 Laser

Neodymium-doped yttrium aluminium garnet (Nd:Yag) laser uses wavelengths of light to destroy tissue. Only small studies have been performed using laser therapy and in the era of RFA is seldom used. Sharma et al reported CR-D in 7/7 patients treated with laser and MPEC and RC-IM in 4/7 (162).

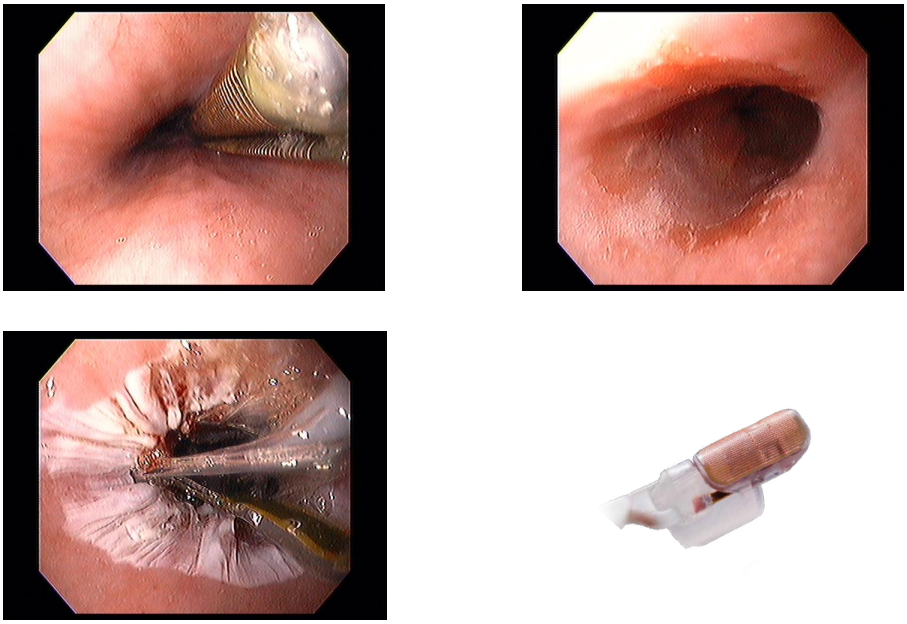


Figure 1.18: RFA of Barrett's Oesophagus. Circumferential Barrett's oesophagus prior to ablation (top left), placement of the 360 balloon catheter (top right) and following ablation (bottom left). Focal devices are also available (bottom right). (With kind permission of Medtronic)

1.6 Radiofrequency Ablation

1.6.1 Efficacy

Radiofrequency ablation (RFA) (Covidien, Medtronic) is used to ablate the surface 500 μm of the gastrointestinal mucosa by the direct application of the RFA device to the target tissue. It is primarily used in the treatment of Barrett's related neoplasia using a balloon (to provide a 360 degree ablation field) or a focal device, mounted over the endoscope (Figure 5). Several treatments are required to effectively treat Barrett's oesophagus and any associated neoplasia. The initial randomised controlled trial in 2009 required a mean of 3.5 treatments per patient and reported CR-D rates of 81% of patients with HGD with a 6% stricture rate

(163). RFA as a rescue therapy following PDT has been reported by our group to show CR-D rates of 86% (164).

RFA is not used for the ablation of visible lesions; these lesions are removed with EMR (and in some cases ESD) to allow accurate histological evaluation and staging before field ablation of the residual flat BO is performed. This combined approach of EMR and RFA has been reported by our group achieving CR-D rates of 86% and CR-IM rates of 62% (165). Recently, a multicentre European trial (EURO II) used a combined EMR and RFA approach but allowed visible Barrett's at the end of 12 months treatment to be retreated with either a further resection or APC treatment. This protocol achieved 92% CR-D and 87% CR-IM with only 4% of patients reporting recurrence at 36 months of follow up. Stricture rates were reported in 6% of patients (166). The SURF trial compared ablation with RFA versus surveillance alone in patients with LGD. Patients who received RFA had lower rates of progression to HGD or OAC (1.5% for ablation vs 26.5% for control; 95% CI 14.1%-35.9%; $p<0.001$). Treatment of patients with LGD had a high success rate with CR-D of 92.6% and CR-IM of 88.2% (167) and treatment of low grade dysplasia is now recommended by the BSG (25).

1.6.2 Safety

The safety profile of RFA has recently been assessed in a meta-analysis of 37 studies. Overall adverse events, defined as stricture formation, bleeding or perforation occurred in 8.8% of patients (95% CI 6.5%-11.9%). Strictures occurred in 5.6% (95% CI 4.2%-7.4%), bleeding in 1% (95% CI 0.8%-1.3%) and perforation in 0.6% (95% CI 0.4%-0.9%). The risk of adverse events was significantly higher in studies assessing EMR and RFA compared with RFA alone (RR 4.4) (168). The UK RFA registry reports a stenosis rate of 6.2% between 2011 and 2013 (158).

1.6.3 Recurrence

With all endoscopic therapies for Barrett's neoplasia, recurrence of disease following initially successful treatment remains a risk. RFA has been shown to be a durable treatment option for Barrett's associated neoplasia with a recent meta-analysis reported a pooled recurrence rate of 6.0% per patient year (95% Confidence Interval; 0.5%-11.6%) for dysplasia and 4.1% per patient year (95% CI 0 – 8.5) for HGD or OAC (169).

The BADCAT (BArrett's Dysplasia and CAncer Taskforce) consensus group advised that after eradication of HGD by endoscopic therapy or surgery, endoscopic follow-up is required(170). Recent work by our group with the United States RFA Registry has suggested follow up intervals can be stratified according to risk. Most HGD and early OAC/ Intramucosal cancers (IMC), should have endoscopic examinations of the treated oesophagus after 3 months, 9 months, 18 months and 30 months after treatment ends and should continue thereafter with yearly assessments (171). Few studies have reported follow up outcomes beyond 5 years and the risk of recurrence is thought to be low but remains unknown.

Several studies have addressed the issue of BE recurrence following successful treatment and several risk factors have been identified. Studies have reported varying IM recurrence rates, from 10% at 5 years (172) to 33% at 2 years (173). Risk factors of IM recurrence include advanced pre-treatment histology, increasing age, longer baseline BE segments and non-Caucasian patients (174). Fewer studies have purely addressed dysplasia recurrence, a recent meta-analysis of those treating only patients with dysplasia or IMC, reported a pooled recurrence rate of 6.0% per patient year (95% Confidence Interval; 0.5%-11.6%). The same systematic review reported increasing age (Odds Ratio =1.02; 95% CI, 1.01-1.03) and length of BO (Odds Ratio = 1.10; 95% CI, 1.05-1.15) as

risk factors for dysplasia recurrence (169). A subgroup analysis of all ablative studies found no difference in IM recurrence rates between studies that defined CR-IM as negative biopsies from a single endoscopy versus those that defined recurrence as after 2 successive endoscopies with negative biopsies. It should be noted that however, the analysis was limited by the fact that only 4 studies defined CR-IM as 2 successive endoscopies, of which only two directly reported outcomes on patients undergoing EMR and RFA treatment (169).

1.7 Current guidelines

Current guidelines for the management of dysplasia and IMC arising in Barrett's oesophagus recommend EMR of visible lesions and ablative therapy for flat dysplasia and residual BO after resection (175). The most common ablative technology used for this purpose is RFA. The rationale for treating the residual BO after resection is due to the risk of metachronous lesions (up to 30%) arising from the residual BO (176,177). This combined approach has been demonstrated to achieve complete resolution of dysplasia (CR-D) in 80-90% in clinical trials and 79% in real-life data published from the UK Registry (178) and complete resolution of intestinal metaplasia (CR-IM) in 54-62% (165,179,180).

1.7.1 Defining Treatment Success

The definition of complete resolution of BO after therapy in most published abstracts and studies involves a single endoscopy with random quadrantic biopsies taken every 1-2cm throughout the previously treated BO segment (175). The definition of CR-IM is generally accepted to be a single endoscopy, however, a single study defined treatment success as 2 negative endoscopies (181).

1.7.2 Current British Society of Gastroenterology guidelines

Current BSG guidelines recommendations regarding ablative therapy for flat HGD and more recently LGD after endoscopic resection are as follows (25):

> *"▸ In the presence of HGD or intramucosal cancer without visible lesions (flat HGD/intramucosal cancer), these should be managed with an endoscopic ablative technique.*
> *▸ There are few comparative data among ablative techniques, but RFA currently has a better safety and side-effect profile and comparable efficacy.*
> *▸ Eradication of residual Barrett's oesophagus after focal ER reduces the risk of metachronous neoplasia and is recommended.*
> *▸ Endoscopic follow-up is recommended after endoscopic therapy of Barrett's neoplasia, with biopsies taken from the GOJ and within the extent of the previous Barrett's oesophagus."*

1.8 Centralisation of Cancer Services

In 1995, the 'Calman-Hine' report, recommendations of an Expert Advisory Group on Cancer, advised that cancer surgery should be limited to high volume specialist centres with specialist multi-disciplinary teams in designated cancer centres (182). The commissioning guidance for upper gastrointestinal cancer services (which included oesophageal, gastric and pancreatic malignancies) suggested that specialist centres should each have a catchment area with a population of 1-2 million (183).

The rationale behind this decision can be traced back to a 1979 study that linked surgical volume and mortality outcomes for selected complex surgical procedures including vascular surgery, coronary bypass surgery, open heart surgery and transurethral resection of the prostate. Hospitals performing a higher volume of surgery had adjusted mortality rates 25-41% lower than those performing a low volume of surgery (184). A further retrospective cohort study on operative mortality from Begg et al (138) reported that higher volume surgical centres were linked with lower mortality across several operations. Subsequent studies looking at surgical volume and outcomes in cancer patients have reported similar findings in breast cancer (185), prostate cancer (186), colon cancer (187), lung cancer (188), thyroid cancer (189) and gynaecological malignancy (190).

It should be noted that this effect, of lower complications and improved outcomes, is also seen in specialist endoscopic procedures such as ERCP (191,192) and colonoscopy (193).

1.8.1 Improved outcomes in specialist centres for Upper GI Cancer

The original studies discussed above assessed surgical volume of a heterogeneous group of procedures. Begg et al found the largest difference in mortality was for oesophagectomy with mortality in low volume centres reported at 17.3% v compared with only 3.4% at high ($p<0.001$) (138).

Several further studies have reported improved outcomes in 3-month mortality following oesophagectomy at university centres compared with non-university teaching hospitals (2.5% vs 4.4%, $p< 0.05$) (194). Five year survival across hospital types also showed improved outcomes in specialist centres; 49.2% for university hospitals vs 32.6% for teaching non-university hospitals vs 27.3% for non-teaching hospitals ($P < 0.05$) (195).

A 2013 meta-analysis of 16 studies from 7 countries demonstrated improved long term survival after oesophagectomy for cancer in high volume centres and high volume surgeons. After adjustments for hospital volume, high volume surgeons still provided a survival benefit compared with low volume surgeons (HR=0.91, 95% CI 0.85 to 0.98) (196).

1.8.2 Measuring Changes in Procedural Outcomes

Cumulative sum (CUSUM) charts have been used since the 1950s to monitor automated processes, primarily in the industrial setting. The use of CUSUM methodology in medicine began with the monitoring of congenital malformations (197) and was then introduced to surgical outcomes, particularly for cardiac surgery (198). Outcomes measured must be binary and can include survival, success and even competence (such as in learning curve analysis). CUSUM charts monitor performance

over time in a sequential manner and allows almost real-time monitoring of performance (199).

The standard CUSUM chart assumes a constant risk of failure or death with every case or patient. With each case there is either a reward or punishment. To plot the chart, the horizontal axis represents the number of cases and the vertical axis the success compared with the expected success. If the risk of failure is 10% then for each success the line on the chart will increase by 0.1 but for each failure will decrease by 0.9. If after 10 cases there has been one failure, the plotted line will return to the baseline. If there is an improvement above the expected success rate then the line will trend upwards and conversely, if there are worse outcomes than expected the trend is downwards. This method allows real-time monitoring of outcomes to identify early trends in performance.

The calculations for CUSUM charts can also be reversed, such that the observed minus the expected mortality is plotted. These CUSUM charts demonstrate an improvement in outcome with a downward trend. An example of a standard CUSUM chart is seen below in Figure 1.19 where the procedure resulted in a large rate of complications initially (5 of the first 18 cases) before the slope of the curve moderates and by the end f the study there were only a total of 4 extra cases with complications than would be expected.

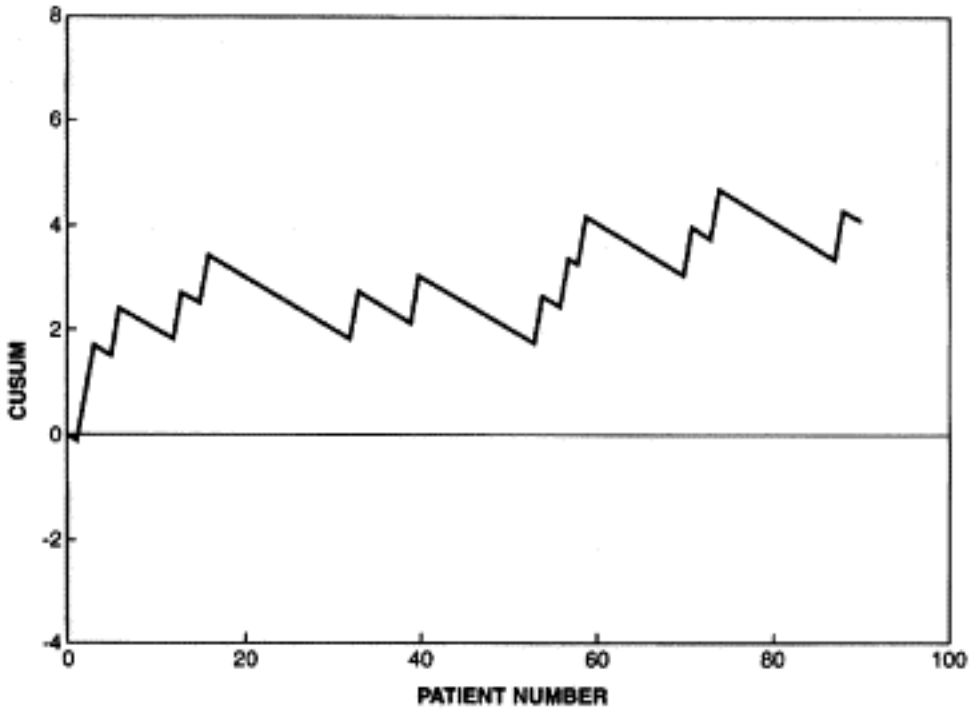


Figure 1.19: CUSUM analysis of clinical experience with telerobotic coronary artery bybass graft. *X axis* denotes consecutive patients. *Y axis* denotes the number of cumulative failures.

CUSUM methodology does not however account for the varying risk between patients for any given outcome, in that a frail 100 year old with multiple co-morbidities will not have the same mortality risk as a fit 40 year old. The CUSUM charts can be used once subgroups have been defined to provide a more accurate picture of expected and observed outcomes. The risk-adjusted CUSUM adjusts the risk based on each individuals risk prior to an intervention so that any changes in outcomes observed can be controlled for a change in the case group, such as more high risk patients resulting in a higher mortality rate following an intervention.

Steiner et al analysed outcomes of cardiac surgery using risk-adjusted and un-adjusted CUSUM charts (198). The risk-adjusted model used the first 2 years of outcomes to identify risk factors associated with poorer

outcomes through a logistic regression model. The comparison yielded significantly different findings between the two methods confirming that the patient mix can significantly alter outcomes and that risk-adjusted CUSUM charts are particularly useful where referral patterns may change over time (such as in referrals for LGD and HGD in Barrett's).

Risk-adjusted CUSUM charts have recently been used to identify significant change points in clinical outcomes for EMR during endoscopist proficiency gain using national data. The change point is defined as the point where there is a sustained improvement in the outcome, seen graphically as the downward deflection on the RA-CUSUM plot. The graphs in Figure 1.20 demonstrate significant change points after 1-4 cases for 30 and 90 day mortality, however, the need for elective re-intervention showed a longer proficiency gain with a change point at 43 cases. Once this point is defined, the outcomes of cases before and after can be compared using the $\chi 2$ test.

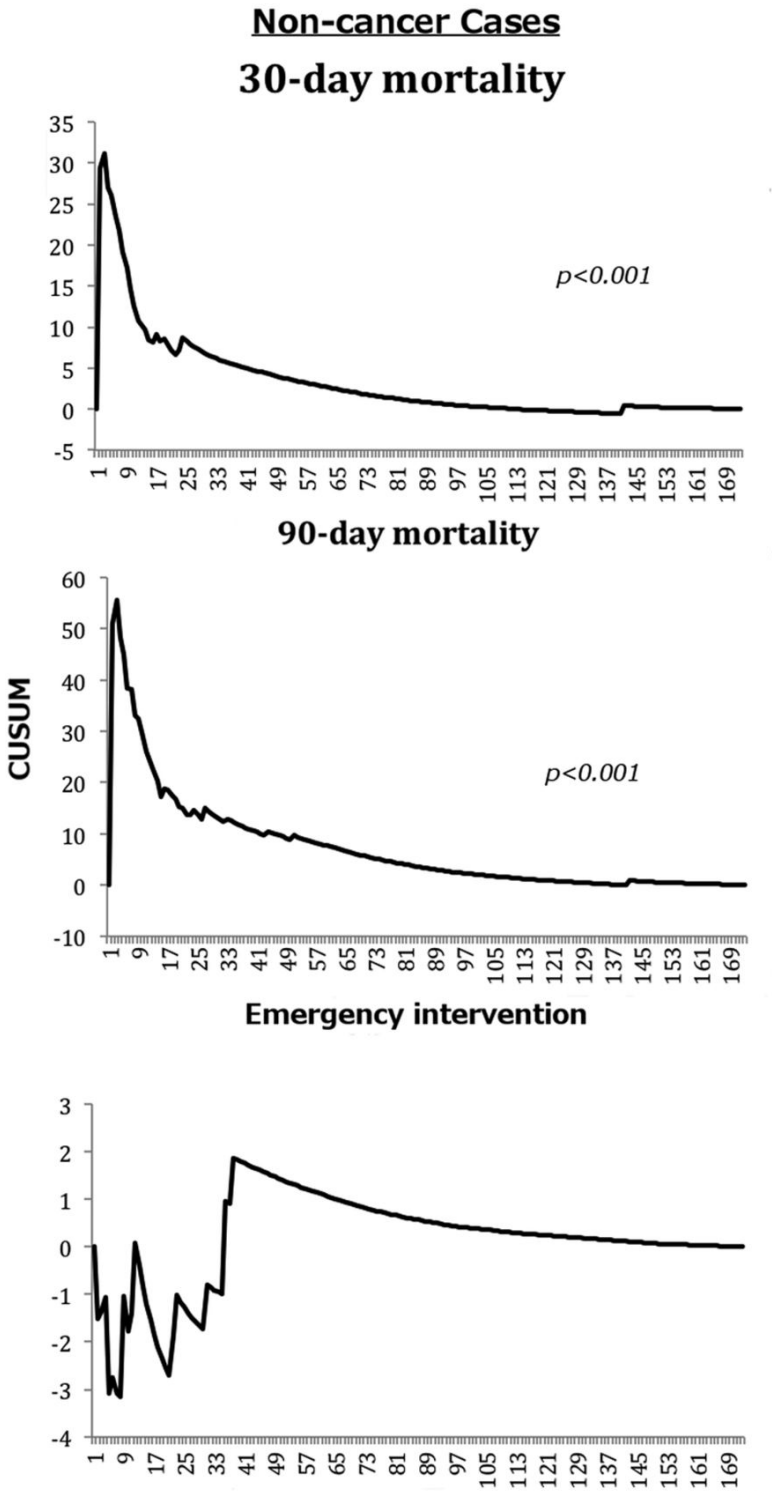


Figure 1.20: National risk-adjusted cumulative sum (RA-CUSUM) curves of non-cancer EMR cases showing significant change points in clinical outcomes for EMR during endoscopist proficiency gain. *X axis* number of cases, *Y axis* CUSUM (200)

1.8.3 BSG recommendations

As a technique, RFA requires specialist equipment. Specialist courses on the indications and use of RFA in BO are available for training specialists across the UK and Europe.
The BSG recommends that (25):

> *"‣ Endoscopic therapy of Barrett's neoplasia should be performed at centres where endoscopic and surgical options can be offered to patients.*
> *‣ A minimum of 30 supervised cases of ER and* ***30 cases of endoscopic ablation*** *should be performed to acquire competence in technical skills, management pathways and complications.*
> *‣ ER should be performed in high-volume tertiary referral centres. Radiofrequency ablation (RFA) should be performed in centres equipped with ER facilities and expertise."*

Reflecting the centralisation of upper GI surgical centres for cancer, the BSG also recommends the centralisation of endoscopic resection due to the low but significant risk of complications requiring surgical intervention. As most patients undergoing treatment for BO associated dysplasia require dual therapy with endoscopic mucosal resection and RFA, the BSG advises that RFA also be performed only in centres where endoscopic resection can be performed (25).

There are limited studies to guide requirements for RFA experience. Fudman et al (201) performed a retrospective analysis of 417 patients who had been treated by 7 endoscopists. RFA volume was correlated with CR-IM rates (rho = 0.85, p=0.014) and in multivariate analysis, higher RFA volume was associated with higher CR-IM rates. However,

no association was found between CR-IM rates and yearly endoscopic volume. Zemlyak et al retrospectively reviewed 70 consecutive patients treated at a single centre by a single endoscopist (202). Comparing the first 25% of those treated with the last 25%, there was no significant difference in length of procedure, procedures required to achieve CR-IM or complication rate.

A larger US registry based study by Pasricha et al reviewed 5521 patients across 148 institutions undergoing endoscopic therapy for Barrett's (51.7% for dysplasia) (203). Higher volume centres were associated with higher CR-IM rates ($P < 0.01$) but not CR-D rated ($P = 0.39$), however, the improvement in CR-IM was not significant after multivariate analysis.

1.9 The UK RFA Registry

The UK RFA Registry collects data from 28 sites in the UK and Ireland (Table 1.9 and Figure 1.21). Patient demographics and outcomes are collected on patients undergoing RFA for dysplasia arising in BO.

Figure 1.21: Map of Centres submitting data to the UK RFA Registry

Table 1.9: Centres submitting data to the UK RFA Registry

University College London Hospital	Royal Wolverhampton Hospitals NHS
St Mary's Hospital, London	Norfolk & Norwich University Hospital
Guy's & St Thomas' Hospital	Salford Royal NHS Foundation Trust
University Hospital Aintree	Nottingham University Hospital NHS Trust
Royal Bournemouth and Christchurch Hospital	County Durham & Darlington NHS Foundation Trust
Gloucestershire Royal Hospital	Watford Hospital
Manchester Royal Infirmary	Newcastle Hospitals
Queen Alexandra Hospital, Portsmouth	John Radcliffe Hospital, Oxford
Royal Liverpool University Hospital	Plymouth Hospital NHS Trust
Southampton University Hospital	Broomfield Hospital, Chelmsford
Bradford Teaching Hospital	Glasgow Royal Infirmary
Queen Elizabeth Hospital, Birmingham	Royal Infirmary Edinburgh
Addenbrookes Hospital (Cambridge)	St James, Dublin
Frimley Park Hospital	

1.9.1 Treatment Protocol for the UK RFA Registry

The treatment protocol for the UK RFA Registry can be seen in Figure 1.22:

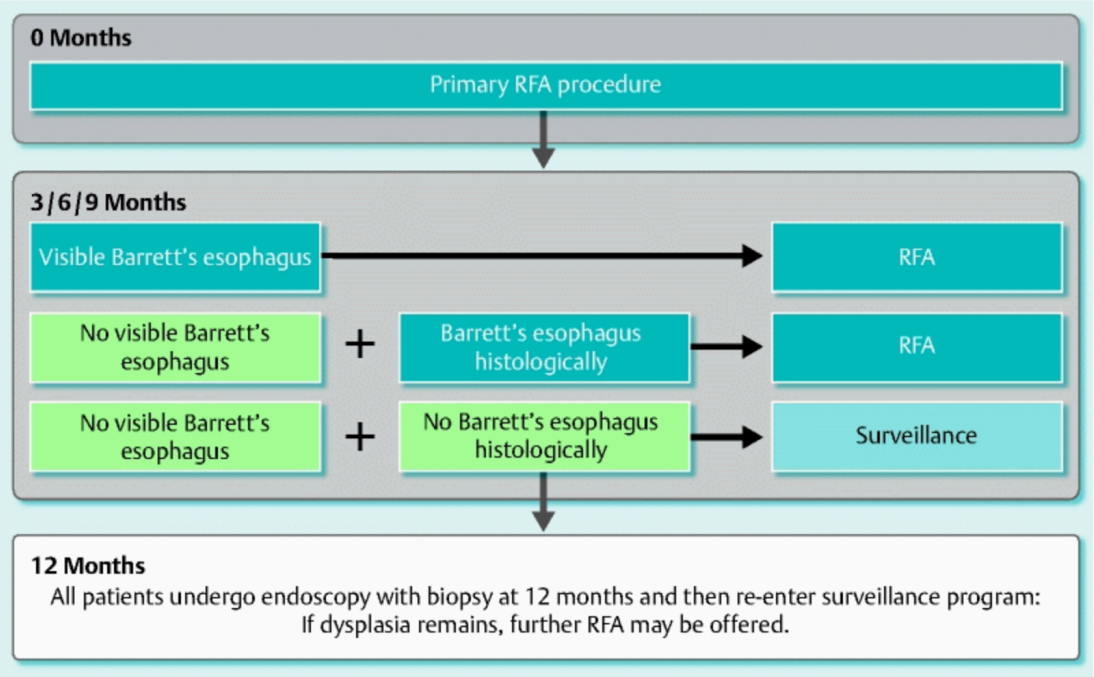


Figure 1.22: UK radiofrequency ablation (RFA) registry protocol. The treatment protocol starts following the first RFA treatment even in patients who had had prior RFA.

Following the completion of the RFA protocol, not all patients achieve CR-D and CR-IM. Patients who have successfully achieve CR-D but have residual BO (i.e. do not achieve CR-IM) continue to receive surveillance endoscopies without further treatment.

1.9.2 Outcomes from the UK RFA Registry

The UK RFA Registry outcomes have been published in several studies since 2013.

In 2013, the Registry reported on 335 patients who had completed the treatment protocol, with a CR-D of 81% and CR-IM of 62% after a mean

of 2.5 RFA procedures. EMR prior to RFA was not found to improve outcomes and strictures were reported in 17 patients (5.1%). CR-D was found to be 15% less likely for every 1 cm increment in BE length (odds ratio = 1.156; 95% confidence interval: 1.07–1.26; P < .001). At 19 months after the first RFA session, 94% remained clear of dysplasia (165).

In 2015, the Registry reported outcomes of the first 508 patients treated and compared those treated between 2008-2010 and 2011-2013. CR-D and CR-IM improved significantly with time (77% to 92% and 56% to 83%; p<0.0001) as did prior EMR rates (48% to 60%; p=0.013). Rescue EMR rates during RFA therapy fell (13% to 2%; p<0.0001) confirming the hypothesis that lesion recognition and resection are important prior to commencing RFA to improve CR-D outcomes (178).

A further study in 2015 found no difference in CR-D or CR-IM rates between those with HGD and those with IMC at the start of treatment. Unlike the 2013 outcomes, in the IMC cohort, RFA alone was associated with an increased risk of dysplasia recurrence compared with EMR followed by RFA (78% free of dysplasia vs. 94%; P=0.01 log rank test) (204).

1.9.3 Follow Up Protocol for the UK RFA Registry

The follow-up protocol for the UK RFA Registry was initially advised to be 3-monthly endoscopy for one year, 6 monthly for the next year and yearly thereafter. However, following our collaborative work with the USA RFA Registry where we modelled the risks of various follow up intervals, these have been amended to an endoscopy at 3, 9, 18 and 30 months after the end of treatment and yearly thereafter, as portrayed in Figure 1.23 (205).

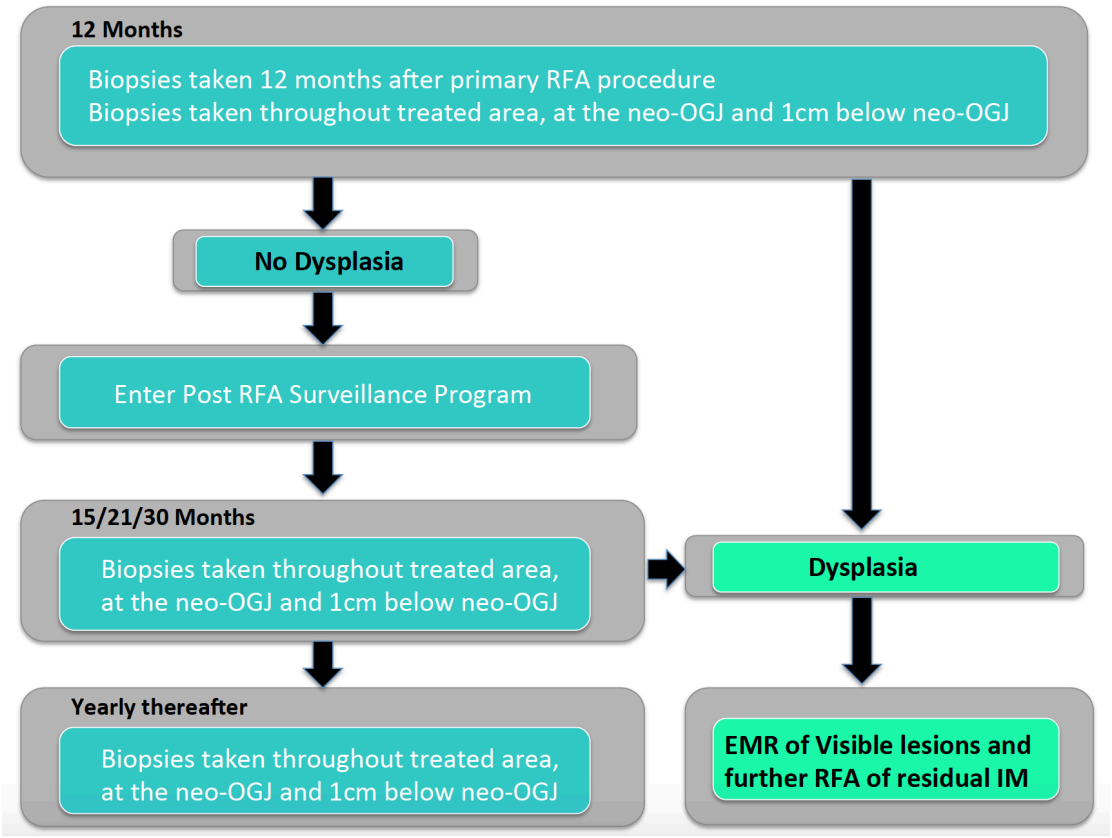


Figure 1.23: UK RFA registry follow up surveillance protocol following end of RFA treatment

1.9.4 Measuring quality in Barrett's Therapy

In 2017, the TREAT-BE (Treatment with Resection and Endoscopic Ablation Techniques for Barrett's Esophagus) Consortium published quality indicators for endoscopic eradication therapy in BO. Using the RAND/University of California, Los Angeles Appropriateness methodology, developed 14 formal validated quality metrics for patients undergoing endoscopic therapy (206). These indicators include a suggested median threshold of 80% of patients achieve CR-D and 70% achieve CR-IM within 18 months of treatment. There are plans to publish for a UK based quality framework in the future.

2 Aims

Aim 1

The early detection of dysplasia and cancer within a segment of Barrett's Oesophagus allows for endoscopic intervention. However, random biopsies sample <5% of the columnar lined epithelium at best. Targeted biopsies of abnormal areas may improve detection and real-time endoscopic assessment using acetic acid has already been demonstrated to improve detection. Novel imaging techniques have recently become available which include new virtual chromoendoscopy techniques.

Can we improve detection of dysplasia using novel imaging technology in combination with magnification endoscopy and virtual chromoendoscopy?

Aim 2

Treatment of Barrett's associated neoplasia is now performed in at least 27 centres in the UK and Ireland. Several of these centres are tertiary referral units with experience treating over 100 patients whilst others have treated less than 10 patients. Cancer services in the UK have been centralised to improve outcomes from surgery for cancer. Should Barrett's dysplasia and early oesophageal cancer follow this process?

Do high volume centres have better treatment outcomes than low volume centres?

Aim 3

After a year of treatment for Barrett's dysplasia, patients will either have residual disease and continue treatment or consider alternative treatment modalities. Altenatively, they may have complete resolution of their Barrett's and continue in regular follow up surveillance. There is, however, a third group with no residual dysplasia but with residual columnar lined epithelium. It is currently unknown whether these patients are at higher risk of recurrence and whether they should continue receiving further ablation therapy to the remaining Barrett's.

Does residual IM at the end of the treatment protocol confer a higher risk of relapse of dysplasia or progression to cancer?

3 Improving Dysplasia Detection in Barrett's Oesophagus

3.1 Introduction

Oesophageal adenocarcinoma (OAC) is the 6th commonest cause of cancer related death in the United Kingdom (207) and the majority of cases are diagnosed at an advanced stage. The only known precursor is Barrett's Oesophagus (BO), which carries an estimated annual risk of progression to OAC of 0.3% (33). Endoscopic surveillance to detect neoplasia at an early stage (175) permits successful minimally invasive endoscopic intervention (166,178,180).

The current gold standard for diagnosis remains histology. Guidelines recommend targeted biopsies of suspected areas followed by random sampling every 1-2cm throughout the BE segment ('Seattle protocol') (175,208). Dysplasia can be focal and easily missed since less than 5% of the BE is actually sampled by the random biopsy technique (68). Compliance with the Seattle protocol is poor and adherence worsens with longer BE segments (69). A further drawback is the cost of analysing the large number of biopsies generated with a relatively low yield for dysplasia.

To address these issues, enhanced endoscopic imaging seeks to identify dysplasia optically to allow targeted biopsy only. Enhanced imaging techniques include narrow band imaging (NBI) (Olympus Medical Systems, Tokyo, Japan), FICE (flexible spectral imaging color enhancement) (Fujinon In-telligent Chromo Endoscopy; Fujifilm, Tokyo, Japan), BLI (Blue Laser Imaging) (Lasereo; Fujifilm, Kanagwa, Japan), and *i*-Scan (Pentax, Tokyo, Japan). The most widely available is NBI. Several BE dysplasia classification systems have been suggested using NBI. All focus on 'flat' dysplasia, excluding nodular disease from analysis

due to the presumption of dysplasia in these lesions. Between 2006 and 2008, 3 systems were proposed (103–105). All describe changes in mucosal and vascular patterns following assessment of high quality still images. These basic principles of anomalies arising in vascular and mucosal micro structures in BE have formed the basis of all subsequent pieces of work creating and validating new classification systems with newer enhanced chromoendoscopy technologies. Several studies have validated these systems. Some focused specifically on the quality of the imaging rather than on the accuracy of detection of dysplasia (108,209,210). One study addressed classification systems using videos (211) but separated sensitivity and specificity for dysplastic and non-dysplastic lesions, so overall parameters are hard to determine. Nevertheless, sensitivity varied from 0.31-0.64 for non-dysplastic lesions amongst experts with a specificity of 0.50 – 0.76. For dysplastic lesions, these rose to 0.62-0.83 and 0.64-0.88 respectively. In a well-designed international randomised controlled trial of NBI compared to routine endoscopy, NBI detected dysplasia with an accuracy of 81% (102). This work was similar to work presented by our group in 2014 using *i*-Scan (115).

Recently, a consortium of NBI experts, the BING consortium, developed a simplified consensus driven NBI classification system of BE following a review of 60 NBI magnification images. The mucosa was classified as normal (circular, ridged or tubular pattern) or abnormal (absent or irregular patterns) and the vasculature was either normal (regular vessels with normal or long branching patterns) or abnormal (focally or diffusely distributed vessels following abnormal mucosal architecture). Lesions with abnormal mucosal pattern or vasculature pattern or both were classified as dysplastic. This reported an overall accuracy of 0.85, sensitivity 0.80%, specificity 0.88, positive predictive value (PPV) 0.81 and a negative predictive value (NPV) 0.88, with substantial overall inter-

observer agreement (κ =0.68). These high quality data have set a benchmark for other technologies to try and match or improve.

Some previous studies have used acetic acid in combination with virtual chromoendoscopy to generate classifications in BE. Chromoendoscopy with acetic acid results in an aceto-whitening reaction, highlighting the mucosal pattern and can potentially show the underlying vasculature in areas that have lost aceto-whitening. Dysplastic lesions lose aceto-whitening and appear red compared with non-dysplastic areas, permitting targeted assessment and sampling. A recent meta-analysis of 9 studies, calculated a pooled sensitivity of 92% and specificity of 96% for the diagnosis of high grade dysplasia or intramucosal cancer (212).

In light of emerging new technologies and the need to reduce unnecessary burden and cost on histopathology services, the Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) initiative of the American Society for Gastrointestinal Endoscopy (ASGE) has set thresholds that any new technology should meet for dysplasia detection in BE before the existing practice of random biopsies can be replaced (130). These thresholds have been set at a per patient sensitivity ≥90%, per patient NPV ≥98% and a specificity ≥80% (130).

A novel virtual chromoendoscopy technology, *i*-Scan (Pentax Hoya, Japan), utilises post-processing technology to provide surface and contrast enhancement in 3 modes (surface enhancement - mode 1, contrast enhancement - mode 2, combined surface and contrast enhancement - mode 3). A new Pentax EG-2990Zi MagniView endoscope permits magnification endoscopy of up to 136 times of the mucosa in all *i*-Scan modes to further characterise the mucosa and micro-vasculature in great detail.

3.2 Aims

- To validate a previously reported Narrow Band Imaging (NBI) classification system using mucosal and vascular structures with i-Scan magnification endoscopy and acetic acid chromoendoscopy.
- To evaluate whether a systematic assessment using acetic acid and magnification endoscopy improves the accuracy of dysplasia detection with this validated classification system in a routine clinical scenario.

3.3 Methods

3.3.1 Patients:

Patients were invited to enrol if they were undergoing surveillance of BE or endoscopic assessment prior to treatment of dysplasia between January 2013 and January 2015. The study had ethical approval and was registered with ISRCTN (Registration: 58235785). Exclusion criteria included pregnancy, symptomatic oesophageal strictures, erosive oesophagitis, varices and prior treatment to the oesophagus, including endoscopic mucosal resection, radiofrequency ablation or radiotherapy.

Following informed consent, patients underwent routine upper GI endoscopy with a high definition magnification endoscope (Pentax EG-2990Zi MagniView endoscope, *i*-Scan EPK-i7000 High-Definition Video Processor, Figure 3.1).

Figure 3.1: Pentax EG-2990Zi MagniView endoscope (Courtesy of Pentax)

The default setting is high definition white light endoscopy and I-Scan modes (1,2 and 3) can be turned on at the touch of a button on the endoscope hand piece.

Magnification is controlled on the hand piece of the endoscope allowing a variable degree of zoom. The optical magnification allows the operator to focus on an area of interest up to a 136x magnification. It is best performed with a cap on the tip of the endoscope to allow a minimal focal length and avoid blurring of images (Figure 3.2). Small movements by the operator of patient can result in loss of focus and therefore image quality relies on a comfortable patient and endoscopists experience.

Figure 3.2: Pentax OE-A58 Distal Rubber Tip for the Pentax MagniView endoscope

A detailed examination of the BE segment was performed using high definition white light endoscopy (HD-WLE) followed by all *i*-Scan modes. The oesophageal mucosa was washed with Simethicone and 2% N-Acetyl cysteine via a spray catheter. Excess gastric secretions and fluid were aspirated from the stomach. Initial examination was performed using HD-WLE, from the top of the gastric folds to the squamo-columnar junction and the entire oesophagus was imaged from the centre of the lumen, this was repeated in *i*-Scan modes 1,2 and 3 (surface enhancement, contrast enhancement and tone enhancement). Each *i*-scan mode delivers unique information about a lesion and therefore when used in combination can provide an overall assessment of a potentially abnormal area. Nodules ≥10 mm or ulcers were excluded, in keeping with similar studies (110). Areas of suspected dysplasia were then recorded with magnification endoscopy in white light and in all *i*-Scan modes. After all areas of interest had been examined, 2% acetic acid was administered and the process repeated. A corresponding biopsy or mucosal resection specimen was taken to confirm pathology from areas of interest and further random biopsies consistent with the Seattle Protocol were taken throughout the BE segment. The process is summarised in Figure 3.3.

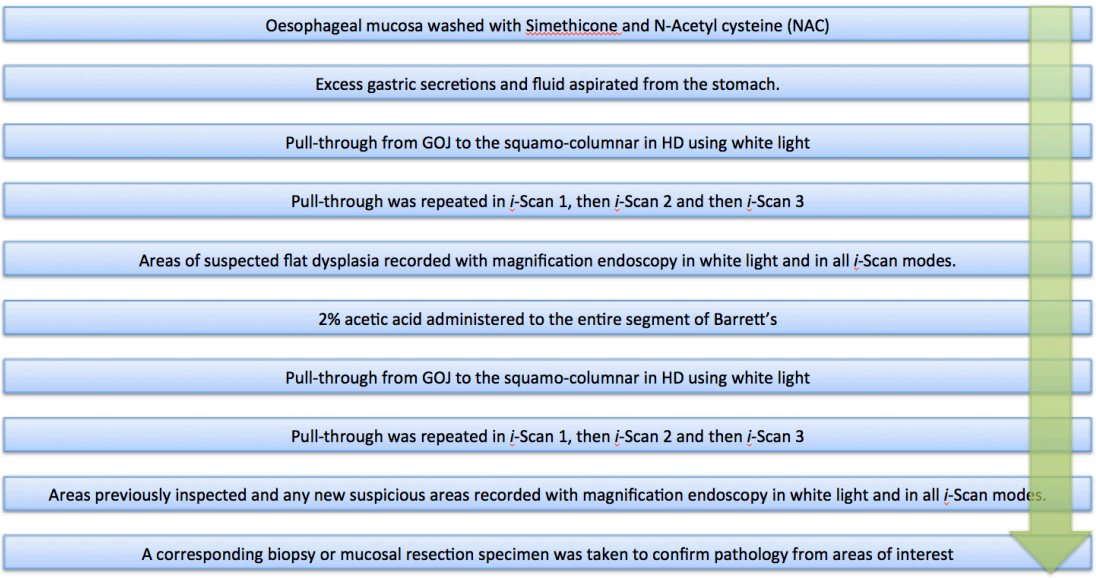


Figure 3.3: Process recorded at endoscopy

In our study, all modes were used in an inter-changeable manner for each video and experts were able to view all lesions allowing them to use the particular enhancement that best suited the lesion in question. Some lesions were only identified with mucosal abnormalities and therefore *i*-Scan 1 was preferred, whereas others had more pronounced vascular abnormalities and therefore *i*-scan 2 or 3 were better. Acetic acid is excellent at highlighting the mucosa though mucosal hyperemia and for identification of abnormal areas with loss of aceto-whitening. However, once an area has lost aceto-whitening, the vasculature remains visible and using *i*-Scan modes 2 and 3 can easily be assessed (as per the examples seen below in Figure 3.4 to Figure 3.11).

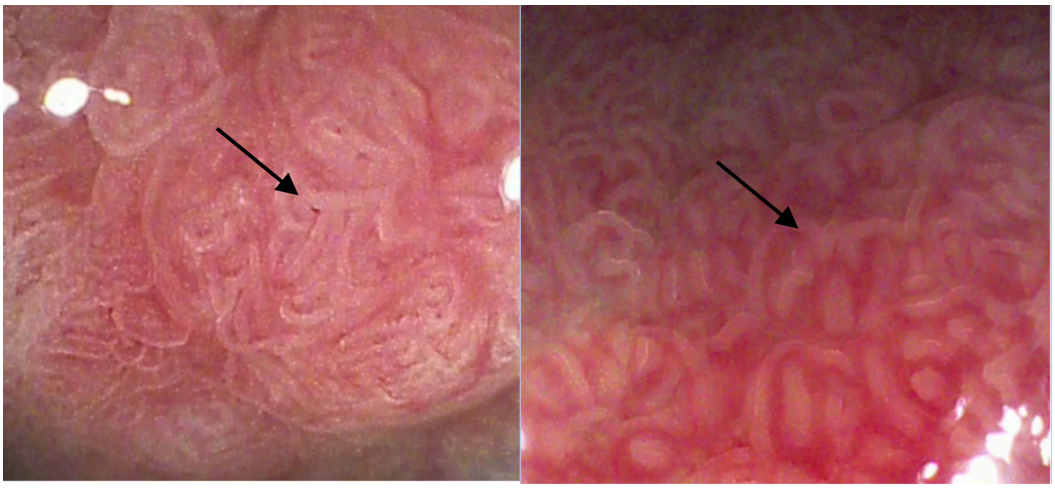


Figure 3.4: Normal micro-mucosa (M1) as seen with various i-scan modes without acetic acid (regular and uniform mucosal patterns – shown by arrows). (all images from edited video footage)

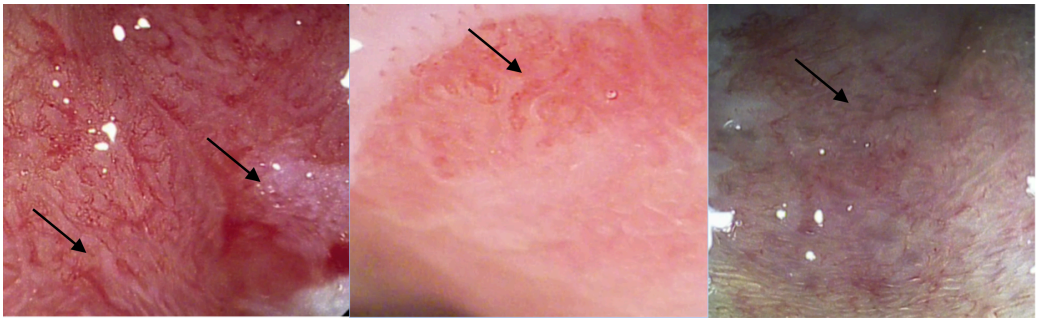


Figure 3.5: Abnormal micro-mucosa (M2) as seen with various i-scan modes without acetic acid (irregular, featureless and distorted mucosal patterns – shown by arrows). (all images from edited video footage)

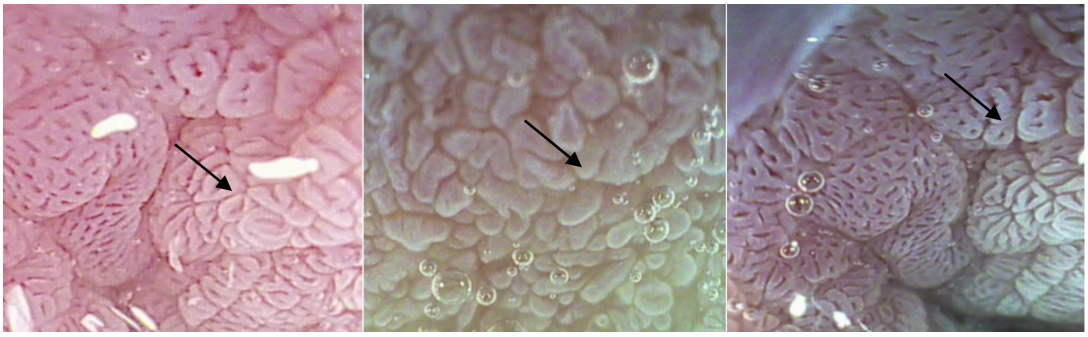


Figure 3.6: Normal micro-mucosa (M1) as seen with various i-scan modes with acetic acid (regular and uniform mucosal patterns – shown by arrows). (all images from edited video footage)

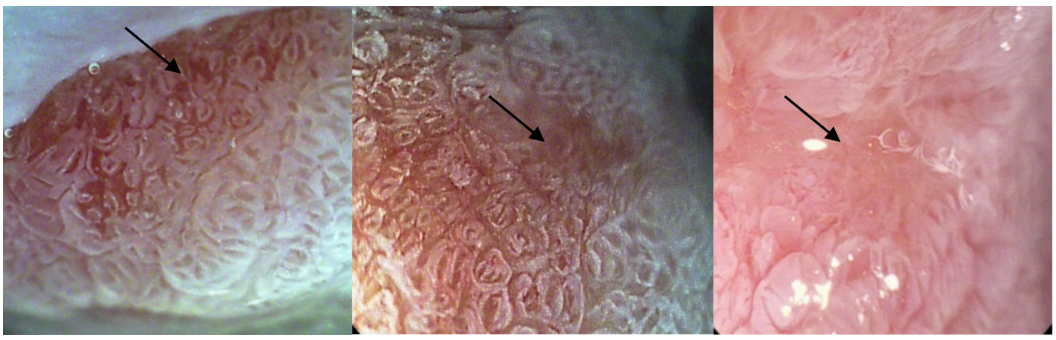


Figure 3.7: Abnormal micro-mucosa (M2) as seen with various i-scan modes with acetic acid (irregular, distorted and featureless mucosal patterns – shown by arrows). (all images from edited video footage)

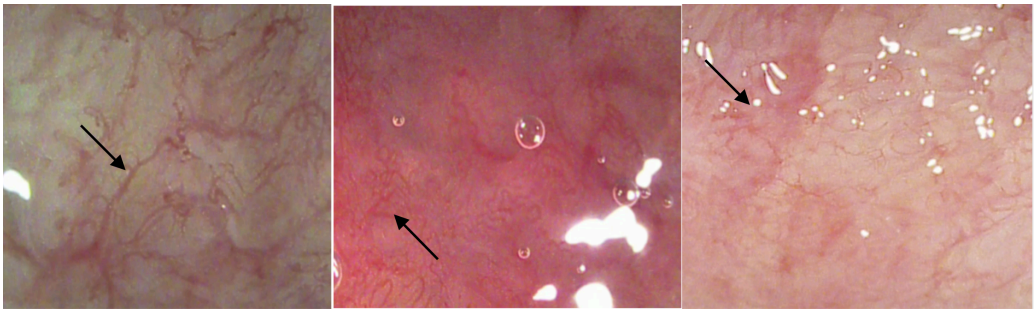


Figure 3.8: Normal micro-vasculature (V1) as seen with various i-scan modes without acetic acid (regular and uniform microvasculature – shown by arrows). (all images from edited video footage)

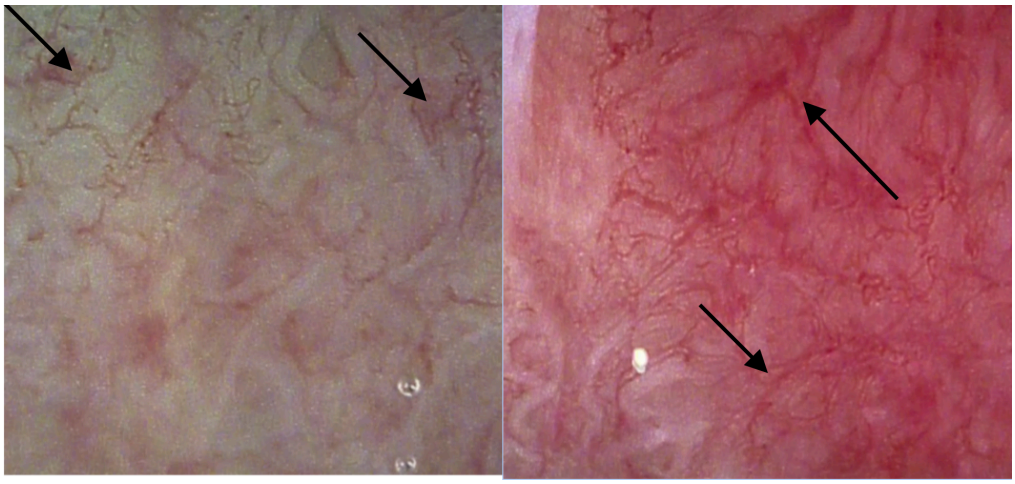


Figure 3.9: Normal micro-vasculature (V1) as seen with various i-scan modes after the addition of acetic acid (regular and uniform microvasculature – shown by arrows). Despite the hyperaemia caused by the addition of acetic acid one can still make out the underlying regular vessels. (all images from edited video footage)

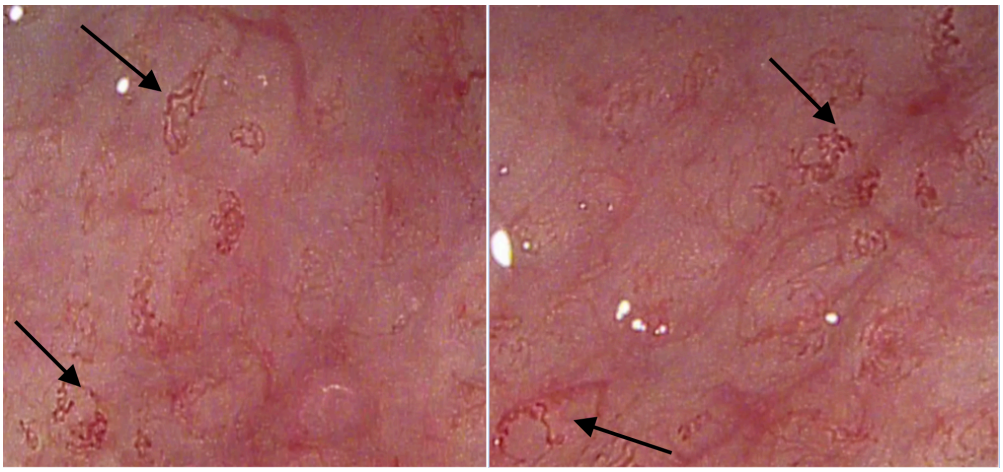


Figure 3.10: Abnormal micro-vasculature (V2) as seen with various i-scan modes without acetic acid (irregular, distorted and tortious microvasculature – shown by arrows). (all images from edited video footage)

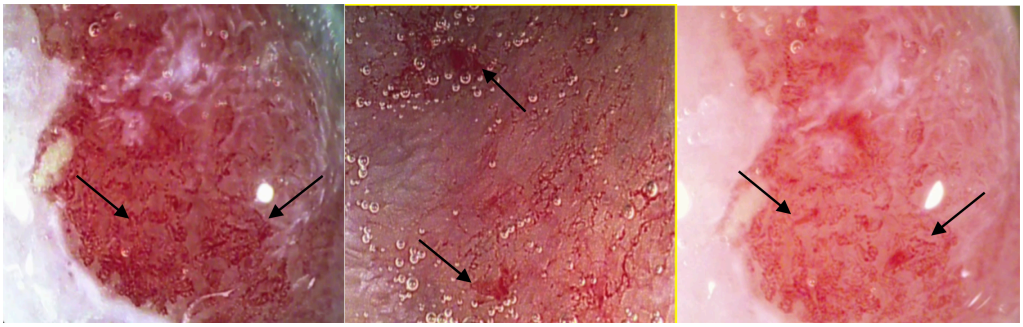


Figure 3.11: Abnormal micro-vasculature (V2) as seen with various i-scan modes after the addition of acetic acid (irregular, distorted, dilated and tortious microvasculature – shown by arrows). Despite the hyperaemia caused by the addition of acetic acid one can still make out the underlying irregular vessels. (all images from edited video footage)

3.3.2 Validation of the NBI Classification System Using *i*-Scan and Acetic Acid

Patients undergoing endoscopy at 3 tertiary referral centres (UCLH, Nottingham University Hospital and Universitaire Ziekenhuizen Leuven) were included. Videos were collected targeting individual areas both before and after acetic acid administration. Videos were converted to MP4 format using Brorsoft Video Converter and edited on an Apple Mac using iMovie software. Clips were exported as 1080p HD videos. Each procedure was edited to several short clips of magnification endoscopy with each clip containing footage of a single targeted area. Between 1 and 3 targeted areas were identified at each endoscopic procedure and each was recorded both before and after acetic acid. Each edited clip contained footage of a single lesion with magnification views in all I-Scan modes with an average length of 30 seconds. Only lesions recorded before and after acetic acid were included for analysis. A single editor (GL) edited all videos.

Videos were shared with 6 expert endoscopists in the field of magnification endoscopy in BO; RB (University Hospital Leuven, Leuven, Belgium), KR and JOFS (Nottingham University Hospital, Nottingham, UK), RH and RS (University College Hospital, London, UK) and JME (Hospital Clínico San Carlos, Madrid, Spain). Videos for the validation phase were provided on an encrypted memory stick for viewing at the experts' discretion.

Training on the classification system was performed via a PowerPoint slideshow, watched individually, highlighting examples of the classification system using stills from videos not included in the trial.

Two independent expert GI pathologists reported all biopsies. The consensus report was considered the gold standard. Specimens were graded as NDBE, indefinite for dysplasia (IND), low-grade dysplasia

(LGD), or HGD/OAC. Only specimens that confirmed NDBE, HGD or OAC were used to develop the classification system.

I edited all the videos. The six experts viewed videos on an HD screen in a randomly assigned order to ensure they were blinded to both diagnosis and pairing of lesions (before and after acetic acid). Using the previously reported BING criteria, lesions were scored for mucosal and vascular patterns: M1 regular oval or villous pits and M2 irregular or featureless mucosa; V1 regular vessels and V2 irregular (dilated or corkscrew) vessels (Table 3.1).

Table 3.1: I-Scan Magnification Classification System for the detection of dysplasia

Mucosa Pattern	M1	Regular circular or villous pits
	M2	Distorted or irregular pits OR Featureless mucosa
Vascular Pattern	V1	Regular and uniform vessels
	V2	Irregular, dilated corkscrew vessels

M1VI was classified as ND-BE and M1V2, M2V1 or M2V2 were all classified as D-BE. (Table 3.2)

Table 3.2: Interpretation of M and V scores

MV classification	Diagnosis
M1 V1	NO DYSPLASIA
M1 V2	DYSPLASIA
M2 V1	DYSPLASIA
M2 V2	DYSPLASIA

3.3.3 Modeling of Clinical Scenario

Further videos from 20 patients were collected from the three sites. This time, videos were created from the entire endoscopy rather than from assessments only of individual lesions. Each patient had at least one area identified for targeted magnification endoscopy with a biopsy or mucosal resection. For each patient 4 video clips were viewed in a blinded fashion, a 'pull-through' assessment of the entire BE segment before acetic acid, a second 'pull-through' after acetic acid, the lesion before acetic acid and the lesion after acetic acid. All experts met in February 2016 at a meeting which I coordinated and individually viewed the lesion videos on HD iPads at the same time in a random order. After this, the pull-through videos were also displayed in random order.

Lesions suspicious for dysplasia on 'pull-through' were recorded by experts with a time (seconds into the clip) and location on a clock face (anterior wall lesion = 12 o'clock, right wall = 3 o'clock etc). If no dysplasia was seen, the 'pull-through' was reported as normal.

A clinical scenario was then modeled to represent real time endoscopic assessment. Videos were interpreted as in clinical practice with 4 steps; step 1, a 'pull-through' with *i*-Scan assessment before application of acetic acid, step 2, focus on any abnormal areas, step 3, a repeat pull-through after application of acetic acid and step 4, a further assessment of any previously noted areas of interest and any new areas seen after acetic acid. On a per patient basis the sensitivity, specificity, PPV and NPV was calculated at each of these steps to determine the change in yield when acetic acid was combined with magnification endoscopy and *i*-Scan enhancement. If no abnormality was detected at step 1 then no detailed assessment of a lesion would occur and the result of step 2 would be ignored. If, however, a lesion was identified at step 1 then all further detailed assessments would be included. Similarly, if a suspicious lesion was noted at any subsequent step, then all further

steps would be assessed by the clinician. The process is summarised in Figure 3.12.

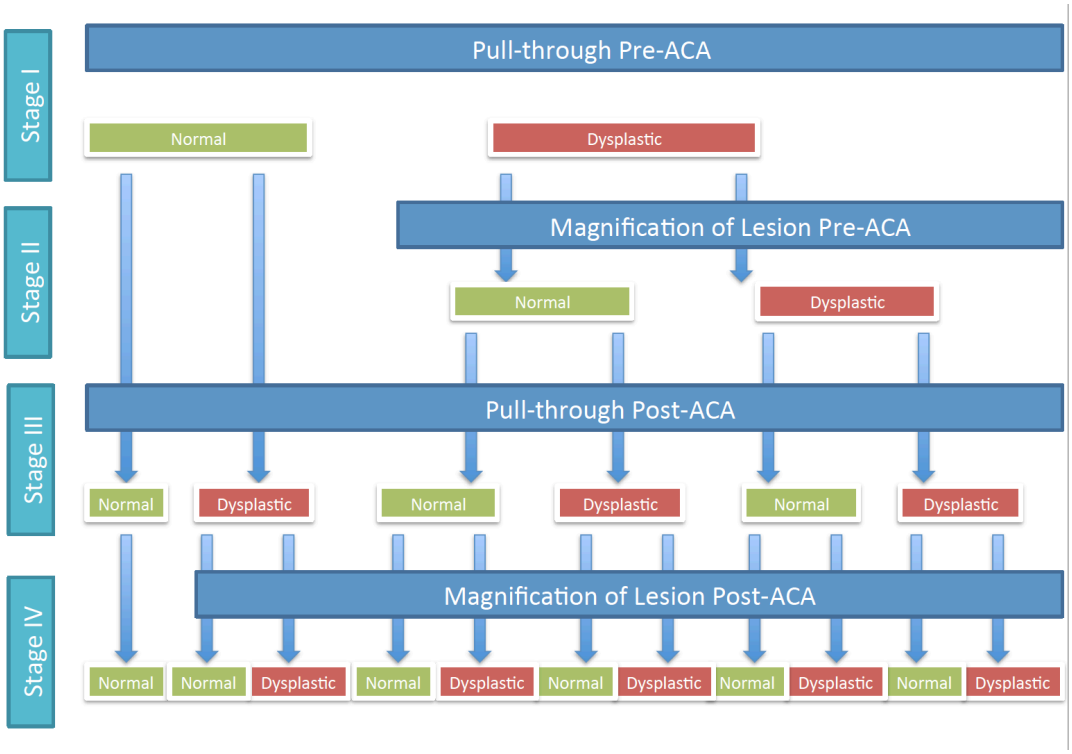


Figure 3.12: Interpretation of dysplasia detection in 4 stages of examination

3.3.4 Statistical Analysis

Normal distributions of data can be confirmed using Shapiro-Wilk's test ($p>0.05$) (213,214) with a visual inspection of histograms, normal Q-Q plots and box plots. However, using 6 scorers results in only 6 data points for each measure (sensitivity, specificity, accuracy, PPV and NPV). Therefore, the Levene's Test for Equality of Variances was used to ensure a normal distribution (215). The Levene's Test for Equality of Variances tests the null hypothesis that the population variances are equal. It is commonly used before comparing the means of two populations.

Inter-observer variability, calculated as a Kappa value, is the most commonly used in medical literature. This measure is based on the

difference between the observed agreement and the expected (by chance) agreement, where 1 is perfect and 0 is what would be expected by chance. Previous BO classification studies have reported inter-observer variability using kappa values (105,110). Kappa values can be calculated using a variety of calculations including Krippendorf's alpha, Fleiss' Kappa and Average Pairwise Cohen's Kappa. When analysing binary data the Average Pairwise Cohen's Kappa is most relevant, as has previously been used in similar studies (110).

Sensitivity, specificity, accuracy, PPV and NPV were calculated using the inter-observer data with Microsoft Excel using a 2 x 2 table. Paired t-test was used to determine significant difference between the groups. Statistical significance cut-off was taken as $p < 0.05$. Inter-observer agreement was calculated using k-statistics and a modified Likert scale developed by Landis and Koch (216) was used to interpret k values (poor <0.20; fair =0.21-0.40, moderate =0.41-0.60, substantial =0.61-0.80; very good =0.81-1.00). IBM SPSS was used for analyses. Cohen's kappa test and 95% C.I were calculated using the Kappa.test function in the FSMB library in R/Bioconductor version 3.3.3.

3.3.4.1 Power calculation

There are no prior studies of *i*-Scan to detect dysplasia in BE. However, earlier work by our group using *i*-Scan without acetic acid reported dysplasia was detected with an accuracy of 69% (Standard deviation 4%), sensitivity of 67% (Standard deviation 26%) and specificity of 69% (Standard deviation 15%) (115).

The BING group aimed for a 4% improvement in the accuracy of diagnosing dysplasia using the NBI classification system with a power of 80% and assumed a one sided α of 0.05. Using earlier work from our group, the mean accuracy of the *i*-Scan Classification System was 75% with a SD 0.14. A power calculation was performed to calculate the

number of videos required to demonstrate a 4% improvement in the accuracy of diagnosing dysplasia with a power of 90%. An improvement of 4% was chosen to mirror the improvement level set by the BING group who also assumed a one-sided significance level of 0.05 (110). A one-sample t test power calculation was performed using R/Bioconductor version 3.2.5 using the power.t.test function (217). Twenty-seven videos with 6 scorers would be required to determine if the mean accuracy could be improved by 4%, using acetic acid in the *i*-Scan Classification System.

3.4 Results

3.4.1 Validation of NBI Classification System Using *i*-Scan

For validating our *i*-scan classification against the previous NBI system, 27 lesions were recorded in 21 new patients undergoing assessment for BE dysplasia Table 3.3.

Table 3.3: Patient Characteristics

Number of Patients	21
Number of lesions recorded	27
Mean length of endoscopy recording (minutes:seconds)	22:09 SD 5:14
Mean Age (range)	70 (46-83)
Male	84%
Mean Barrett's Circumferential Length (cm, range and SD)	2.7 (0-12, SD 3.4)
Mean Barrett's Maximal Length (cm, range and SD)	5.0 (1-15, SD 3.6)

The mean length of recorded footage was 22 minutes 09 seconds (range 13 minutes 14 seconds – 26 minutes 15 seconds). Each procedure video was edited to several 30-second clips of different lesions. In total there

were 54 videos; 22 non-dysplastic (ND-BO) and 32 dysplastic (D-BO) (6 LGD, 26 HGD/IMC). There was no statistically significant difference between the mean length of ND-BO and D-BO videos, independent T-test *p*=0.22 (Table 3.4). The mean length of videos pre and post acetic acid was not statistically different (29.0 seconds, SD 6.1 vs 26.1 seconds, SD 7.6; *p*=0.09).

Table 3.4: Characteristics of the videos for non-dysplastic and dysplastic lesions

	Non-dysplastic BE	Dysplastic BE
Number of videos	22	32
Mean video length	28.4 seconds (SD 7.8 seconds)	26.9 seconds (SD 6.5 seconds)
Number of Pre acetic acid videos	11	16
Number of Post acetic acid videos	11	16

Of the 324 video evaluations (54 by each of 6 experts), classification was uncertain in only 4.6%. Reasons included lack of focus and uninterpretable mucosal or vascular pattern. Pathology was predicted as ND-BE or D-BE based on the experts' classification of mucosal and vascular patterns.

Acetic acid improved the experts' mean overall accuracy from 69% to 79% (p=0.01) for dysplasia detection. There was a trend following acetic acid of improved sensitivity (79% vs. 87%, p=0.08) and specificity (53% vs. 68%, p=0.07) of the classification system though neither reached statistical significance. Inter-observer agreement was fair (κ = 0.261) pre acetic acid and moderate (κ = 0.403) after acetic acid, 95% C.I 0.03 to 0.83 (Table 3.5).

Table 3.5: Validation of the Classification System

	Mean Pre Acetic acid	Mean Post Acetic acid	Paired t-test p value
Accuracy	69% (SD 13%)	79% (SD 11%)	0.012
Sensitivity	79% (SD 10%)	87 %(SD 14%)	0.081
Specificity	53% (SD 23%)	68% (SD 21%)	0.067
PPV	73% (SD 11%)	81% (SD 13%)	0.112
NPV	63% (SD 16%)	81% (SD 17%)	0.016
Cohen's κ	0.261	0.403	
95% C.I	-0.18 to 0.68	0.03 to 0.83	

Only 2 lesions with LGD were included in the validation phase of the study. All 6 experts scored one lesion abnormal and 5 of the 6 experts scored the second lesion abnormal, the remaining expert felt unable to interpret the clip.

3.4.2 Modeling of Clinical Scenario

In the modeling of a clinical scenario, the same experts from the working group reviewed 79 videos (40 clips of pull-throughs and 39 videos of lesions) from 20 patients not previously seen (13 from University College, 6 from University Hospital Leuven and 1 from Nottingham University Hospital). Experts' diagnosis of ND-BE or D-BE was recorded for each pull-through video and magnification video.

In total 40 pull-through clips (average length 65 seconds, range 12-139 seconds) and 39 lesions (average length 31 seconds, range 8-50 seconds) were scored (8 NB-BE and 12 D-BE). The length of videos, pre and post acetic acid, was not statistically different for lesions (31 vs 30 seconds, p=0.62) but was significantly longer for pull-throughs before acetic acid (74 vs 56 seconds, paired T-test p= 0.002). Median video

length was similar for non-dysplastic and dysplastic pull-throughs (72 seconds vs. 66 seconds, non-paired T-test p=0.26) and for non-dysplastic and dysplastic lesions (31 seconds vs. 32 seconds, non-paired T-test p=0.65) (Table 3.6).

Table 3.6: Characteristics of the videos for clinical scenario. The upper part of the table shows data on pull through videos. The lower part shows data on videos of individual lesions

	Non-dysplastic BE	Dyslastic BE	Significance (non-paired T test)
Mean Maximum BE length	5.6 cm (range 2-10 cm)	5.4 cm (range 1-12 cm)	p= 0.74
Pull-throughs before acetic acid	8	12	
Pull-throughs after acetic acid	8	12	
Mean pull-through video length (range)	72 seconds (24-139)	66 seconds (12-128)	p= 0.26
Lesions before acetic acid	8	12	
Lesions after acetic acid	8	11	
Mean lesion video length	31 seconds (range 16-50)	32 seconds (range 8-44)	p= 0.65

No uncertainty was reported in any of the 240 pull-through video evaluations (40 by each of 6 experts). Of the 234 lesion assessments (39 by each of 6 experts), 8.1% were felt to have an uncertain classification. Pathology was again predicted based on classification of mucosal and vascular patterns (Table 3.2). If a lesion was not classified, the result of the previous step was recorded.

Interpreting the clips as a clinical scenario, the addition of magnification endoscopy (Step 1 versus Step 2) or acetic acid (Step 1 versus Step 3 or Step 2 versus Step 4) alone did not significantly improve accuracy or sensitivity. However, the complete protocol of magnification endoscopy with the classification system followed by acetic acid did significantly improve the accuracy. Inter-observer agreement at step 4 of the process was substantial (κ =0.69), 95% CI: 0.36 to 1.01 (Table 3.7).

Table 3.7: Results for each step of the protocol as per the clinical modelling scenario (Step 1, a pull-through, Step 2, a focus on any abnormal area, Step 3, a pull-through after application of acetic acid and Step 4, a further assessment of any previously noted areas of interest and any new areas seen after acetic acid) in all patients.

	Step 1	Step 2	Step 3	Step 4	Paired t-test P value Step 1 vs. Step 4
Accuracy	76%	77%	75%	83%	0.047
Sensitivity	91%	81%	94%	85%	0.19
Specificity	57%	74%	52%	80%	0.0008
PPV	72%	77%	70%	84%	0.005
NPV	84%	78%	88%	81%	0.63
Cohen's κ	0.667	0.365	0.679	0.690	
95% C.I.	0.22-1.09	0.18-1.0	0.28-1.09	0.36-1.01	

Sub-group analysis comparing LGD (n=3) and non-dysplastic lesions (n=8) demonstrated similar results. The addition of magnification endoscopy and acetic acid significantly improved the accuracy and specificity of dysplasia detection and diagnosis (Table 3.8).

Table 3.8: Results for each step of the protocol as per the clinical modelling scenario (Step 1, a pull-through, Step 2, a focus on any abnormal area, Step 3, a pull-through after application of acetic acid and Step 4, a further assessment of any previously noted areas of interest and any new areas seen after acetic acid) comparing only patients and LGD with those who had no dysplasia.

	Step 1	Step 2	Step 3	Step 4	Paired t-test P value Step 1 vs. Step 4
Accuracy	64%	68%	63%	80%	<0.001
Sensitivity	78%	57%	94%	88%	0.17
Specificity	59%	71%	52%	78%	0.003
PPV	39%	36%	40%	56%	0.04
NPV	89%	85%	97%	95%	0.12
Cohen's κ	0.657	0.25	0.625	0.621	
95% CI	0.22 - 1.09	-0.35 - 0.85	0.15 - 1.09	0.22 - 1.09	

3.5 Discussion

Early identification of dysplasia through endoscopic surveillance of BE allows patients access to minimally-invasive endoscopic eradication therapy. There is however limited data to show that surveillance in patients with BE impacts significantly on overall survival. The ProBar group examined 783 patients in a multicentre prospective study to examine the clinical benefit of BE surveillance (70). They concluded OAC was diagnosed at an earlier stage during BE surveillance than in the general population ($p<0.001$) and carried a similarly good prognosis to non-surveillance patients diagnosed at the same stage of disease. These findings strengthen the case for routine endoscopic surveillance of BE.

With the on-going advancements in endoscopic imaging it is vital to utilise these tools in a structured manner to give the endoscopist every chance to diagnose dysplasia accurately. *i*-Scan post-processing endoscopic imaging has been shown superior to white light in the detection of IM in BE in previous studies (130). In this study, a combination of *i*-Scan enhancements coupled with magnification endoscopy and acetic acid allowed experts to identify Barrett's associated dysplasia through early changes in mucosal and vascular patterns using a simple classification system that has previously been validated using NBI (110). Following a systematic assessment of Barrett's Oesophagus using acetic acid and magnification results in an accuracy of 83%, with substantial inter-observer agreement (κ =0.69). These are on par with previous data for similar classification systems (Table 3.9).

Table 3.9: Magnification endoscopy with I-Scan imaging compared with the BING classification

	I-Scan Classification System	BING
Accuracy	0.83	0.85
Sensitivity	0.85	0.80
Specificity	0.80	0.88
PPV	0.84	0.81
NPV	0.81	0.88
K Value	0.69	0.681

Several NBI endoscopic classification systems that were developed to identify dysplasia have focused on the mucosal and vascular patterns (103–105). Evaluation and validation of these systems has relied on the use of selected still images (107,108). Two studies have, however, used videos to validate these classification systems, Baldaque-Silva et al evaluated NBI with optical magnification videos by 6 endoscopists with varying degrees of experience (109). Dysplasia detection varied from 62-90% with inter-observer agreement (κ) ranging 0.39-0.48. A further study using videos compared classification systems and reported accuracy of 'experts' for diagnosing dysplasia was 0.75-0.78 with no significant difference across the scoring systems. However, global κ agreement scores were moderate for the Kansas (0.44) and Amsterdam (0.47) systems and only fair for the Nottingham (0.34) classification system (106).

Recently, a consortium of NBI experts, the BING consortium, developed a simplified consensus driven NBI classification system of BE following a review of 60 NBI magnification images. This was validated with still images and following a web-based survey reported overall accuracy 0.85, sensitivity 0.80%, specificity 0.88, positive predictive value (PPV)

0.81 and a negative predictive value (NPV) 0.88, with substantial overall inter-observer agreement (κ =0.68). Of note, analysis was performed on a per-image rather than per-patient basis (110).

Ours is the first clinical study with endoscopic videos to validate this classification system using *i*-Scan technology and demonstrate a benefit in clinical practice through an improvised real time clinical scenario. The scenario was designed to reflect real-life endoscopic assessment of BE; a general view of the BE segment before focusing on areas of suspicion and repeating the process after application of acetic acid. Magnification endoscopy with *i*-Scan can identify the same mucosal and vascular features described with NBI. Our study validates the use of the NBI classification system with *i*-Scan technology using an international group of expert endoscopists viewing videos collected from several European centres. Addition of acetic acid significantly raised the accuracy of the classification system using *i*-Scan from 69% to 79% (p=0.012). Further, in our model of routine clinical practice, accuracy of dysplasia detection was significantly improved with magnification endoscopy and acetic acid compared to HD-WLE and *i*-Scan alone (83% vs. 76%, p=0.047). Inter-observer agreement of the classification system is moderate but when incorporated into a clinical decision making protocol, it improves to substantial (κ = 0.69). This later scenario mimics what happens in daily clinical practice and is therefore likely to be a reasonably accurate representation of real life endoscopy. Sub-group analysis of LGD lesions alone generates similar results, with an accuracy of 80% although these numbers are very small.

Previous studies have used acetic acid purely for the detection of suspicious lesions and not to diagnose them according to a standardised classification system using magnification endoscopy. This study reports the first use of acetic acid as an adjunct to magnification endoscopy and demonstrates that the use of acetic acid should not be limited to the

macroscopic assessment of BO. One reason for this may be that once the mucosa has lost aceto-whitening (noticeably in dysplastic lesions), the micro-vessels become visible under the lost or hyperaemic mucosa layer. This allows the endoscopist to focus on the vessels that that have become visible precisely because of the loss of aceto-whitening removing the mucosal barrier. To illustrate this, specific examples with arrows can be seen in Figure 3.11, using *i*-scan 2 and 3 (Tone and contrast enhancement) to illustrate the micro-vasculature with magnification after acetic acid.

The results of this study do not meet the current PIVI thresholds for adopting *i*-Scan magnification endoscopy with acetic acid instead of the current practice of random biopsies (Table 3.10). However, this may reflect the low number of lesions reviewed, the prevalence of dysplasia in our sample population and the use of videos rather than still images.

Table 3.10: Magnification endoscopy with I-Scan imaging compared with PIVI values

	I-Scan System	Classification	PIVI
Sensitivity	0.85		≥ 0.90
Specificity	0.80		≥ 0.80
NPV in study population	0.81		≥ 0.98

Following an improvised clinical scenario to replicate the real life diagnostic endoscopic approach and analysis on a per-patient basis, *i*-Scan magnification with acetic acid has a higher sensitivity than the BING study (85% vs. 80%) but a lower specificity (80% vs. 88%) and accuracy (83% vs. 85%), though has similar inter-observer agreement (0.69 vs. 0.68) (110). Direct comparisons are, however, difficult as the

BING study and most others of NBI were based on assessment of still images. It is reasonable to assume that the images chosen for analysis in all these studies would have been the best images available.

It should also be noted that the pull-through videos after acetic acid were significantly shorter than pre-acetic acid videos, although this may represent real life clinical practice that less time is spent looking following an initial evaluation.

Previous studies have identified nodules and ulcers in BE as high risk for dysplasia and neoplasia (218). This and similar studies excluded lesions >10 mm. However, advances in endoscopic technologies with optical magnification makes previously unrecognised small nodules and ulcers visible, which may bias experts to classify these lesions as dysplastic. The field continues to develop with increasingly good imaging techniques. Future studies should include assessment of small nodules and superficial ulcers to determine whether they improve dysplasia classification.

3.5.1 Limitations

There are several limitations to this study, particularly when working with videos and classification systems to interpret clinical findings.

Editing was performed by a trainee gastroenterologist with the aim of editing large quantities of video to 30-second clips. There was no quality control to ensure that the underlying impression of the endoscopists who performed the endoscopy was reflected in the final clips. Not all edited clips contained images from all *i-Scan* modes due to the quality of the initial recordings. Pull-through videos after acetic acid were significantly shorter than those pre acetic acid, though this may represent real life clinical practice that less time is spent looking after an initial evaluation.

Few studies have investigated dysplasia detection using videos, with most focusing on still images. Like videos, these carry a bias of using images that have been cherry picked to give an optimal view, which may not be achievable in clinical practice. Due to differences in study design, the use of videos rather than still images, it is difficult to directly compare data with NBI studies. The single reported study using video clips of the Kansas, Amsterdam and Nottingham classification systems reported expert accuracy between 0.53-0.57 and moderate to fair global κ agreement scores (Kansas 0.44, Amsterdam 0.47 and Nottingham 0.34) (106). The data presented here include an accuracy of 0.79 and a global κ agreement score of 0.403 for the validation phase. The NBI study authors attributed the modest sensitivities and specificities to the difficulty in scoring videos rather than still images and it should also be noted that the study utilised standard definition rather than high definition videos (106).

A further limitation is that the original recordings were each performed by one of the 6 scoring experts and despite the multicentre nature of the study design, one centre provided over half of all the videos. RH, who recorded the majority of the procedures used in this study, had the highest sensitivity and the 2nd highest accuracy amongst all the experts.

Classification systems are developed by experts to verbalise their thought processes in order that non-experts can reach similar conclusions to experts by following a simple algorithm. It would appear that all the classification systems for diagnosing D-BO have been simplified to abnormal mucosa and vascular patterns and thus the process of determining what is normal or abnormal boils down to pattern recognition and ultimately by the time the classification system is useful to non-experts, they have already become an expert in their field.

Imaging studies rarely reflect true clinical experience and although this study design has tried to imitate a protocol that can be followed in clinical practice, ultimately, endoscopists can choose to focus on areas of suspicion that may be visible after more than a minute of observation. Nevertheless, this study, based on assessment of videos, is likely to closer represent the real clinical scenario.

Previous studies have identified nodules and ulcers in BO as high risk for dysplasia and neoplasia (218). This study and similar studies have excluded lesions >10 mm from inclusion in imaging studies. However, advances in endoscopic technologies with optical magnification enables previously unrecognised small nodules and ulcers to be visible, which may bias scorers to classify these lesions as mucosal or vascular abnormalities.

Whilst the first phase of the study was powered to assess the impact of acetic acid, the second clinical modelling phase was not and numbers recruited were small. Whether these results are reproducible by non-expert endoscopists or those with limited training remains to be seen, particularly as previous work has shown a learning curve with the introduction of new magnification endoscopy (219).

During the first phase of the study, scorers viewed videos at their own discretion, there was no standardised viewing display and videos may have been watched on any device including smartphones, tablet devices, widescreen ultra-HD monitors. Scorers were not requested to view the videos at specific times of the day and all admitted to viewing videos at the end of a long day or on long haul flights. There is evidence in students that cognitive ability reduces as the day progresses (220) and professionals demonstrate decision fatigue and are more likely to default to a ‘safe’ option as the day progresses (221,222). This potential bias was removed for the second phase of the study, when all scorers viewed

videos on i-Pads in a darkened room at the same time, with no other distractions.

3.5.2 Future Work

Future work using the classification system should assess both still images and videos from the same cohort to quantify whether images are a valid reference tool, as most endoscopists rely on video footage rather than stills for diagnostic purposes. A study of still images using i-Scan technology rather than videos may result in a sensitivity, specificity and NPV of the Classification System to meet ASGE-PIVI thresholds, as the very highest quality still images are likely to be chosen for assessment. New *i-Scan* technology utilising light-filtering and post-processing technology with optical magnification may also improve the accuracy of dysplasia detection (223). A larger study using *i*-Scan technology may enable PIVI thresholds to be met, particularly if micro-nodularity and superficial ulceration are included in the assessment.

Following the work in this chapter, Everson *et al* assessed *i-Scan* OE for the detection of dysplasia in trainees and experts. Still images in HD-WLE (130 images) and *i-Scan* OE (132 images) were obtained from 41 patients undergoing assessment of BO. *i-Scan* OE improved the detection of dysplasia in trainees (76% vs 63%, OR, 2.00; 95% CI, 1.61 - 2.49; P<0.001) and experts (85% vs 77%, OR, 1.74; 95% CI, 1.34 - 2.25; p<0.001). Using the mucosal and vasculature classification in this chapter, the accuracy for diagnosing dysplasia was improved from 66.7% to 79.9% (p <0.001) for experts (224).

In summary, this study presents data validating the NBI classification system using *i*-Scan endoscopy with magnification endoscopy and acetic acid. This system has good sensitivity and specificity with fair inter-observer agreement using *i*-Scan. Combining *i*-Scan magnification endoscopy with acetic acid can be used in a step-wise manner resulting

in high accuracy, sensitivity and specificity with substantial inter-observer agreement. The proposed protocol may reduce the need for random biopsies for dysplasia detection.

4 Centre Caseloads and Outcomes in UK RFA Registry

4.1 Introduction

Data from the US RFA Registry has demonstrated that higher centre volume is associated with fewer procedures required to achieve CR-IM ($P < 0.001$). Furthermore, after an endoscopist has treated 30 cases they required 0.35 fewer endoscopies to achieve CR-IM compared with those who had completed 10 or fewer cases (203). This study appears to be the basis for the BSG recommendation for a minimum of 30 RFA cases performed with supervision to ensure competence in technical skills and managing complications (25). This chapter addresses outcomes from the UK RFA Registry based on centre volumes.

4.2 Aim

Upper GI surgery outcomes have been demonstrated to improve with operator experience (196). Data from the US RFA Registry also suggest that outcomes of treatment of RFA improve with endoscopists experience (201).

Treatment of BO related dysplasia is performed at a limited number of centres in the UK and Ireland, of which 27 have submitted data to the UK Registry. This section addresses the question of whether higher volume centres in the UK RFA Registry have better outcomes.

4.3 Methods

The UK registry collects data on patients referred with dysplastic BO undergoing endoscopic management at specialist centres. Entry criteria

for patients into the Registry have previously been described. Patients who had completed the treatment protocol with eradication of dysplasia between January 2008 and November 2015 were included in this analysis. Patients previously treated for Barrett's neoplasia with photodynamic therapy were excluded. All patients free of dysplasia at 12 months or end of protocol were entered into a post-RFA surveillance protocol.

Centres with at least one patient that had completed the treatment protocol (see Figure 1.22) were included in this analysis.

Centres were grouped by the total number of patients entered on the Registry, irrespective of whether they had completed the protocol yet. Since all centres in the Registry submitted all the procedures they had ever performed, centres were divided into low volume (<50 patients), medium volume (50-100 patients) and high volume (>100 patients) centres. Outcomes of patients that had completed the 12-month treatment protocol were analysed.

The primary outcomes for this study were CR-D, CR-IM and dysplasia recurrence (as defined by histological evidence of LGD, HGD or IMC on biopsies or EMR specimens).

Data were analysed using the SPSS version 23 (IBM Corp., Armonk, NY, USA). Comparisons between groups for available data were analysed using the χ^2 test for categorical variables. Non-continuous variables underwent a homogeneity test to ensure a normal distribution. Following this a one-way ANOVA was performed and any results that demonstrated a significance of <0.05 underwent a Tukey post-hoc test.

An Analysis of Variance (ANOVA) compares the variance of the means of three or more groups with the variance within those groups. By

dividing the variance between the groups by the variance within groups, an F-ratio is generated. A large F-ratio suggests a difference between the groups. If the significance of the F-value is less than the set threshold (0.05 for this study) there is a significant difference between the groups. However, to understand which group of the three is significantly different requires a post-hoc analysis, most commonly performed using a Tukey test, which utilizes a series of t-tests to determine which results are significant. Tukey's test can be applied as long as the data demonstrate normality, homogeneity and independence.

Log rank test was used to compare the difference in the rate of disease recurrence between the groups at latest follow-up.

4.4 Results

Centre Volumes

Twenty-seven centres entered data into the Registry until November 2015. Only 24 centres reported outcomes on patients who had completed the treatment protocol. Five centres were classed as high volume centres (total patients completing treatment n=418), 4 were medium volume centres (n=145) and 15 were low volume centres (n=115). Table 4.1 summarises the numbers of patients recruited and those who have completed treatment at each centre. The high-volume centres have treated 62% of all patients in the Registry. It should be noted that although each high volume centre has recruited over 100 patients each, only 418 in total have completed the treatment protocol, reflecting the low completion rate recorded in the registry.

Table 4.1: Patients recruited and completing treatment at each centre

Centre	Total Number of Patients Recruited	Number of Patients Completed Treatment	Percentage of Patients Completed Treatment
University College London Hospital	312	152	49%
St James, Dublin	196	71	36%
Addenbrookes Hospital, Cambridge	132	45	34%
Glasgow Royal Infirmary	132	74	56%
Royal Liverpool University Hospital	120	76	64%
Royal Infirmary Edinburgh	98	38	39%
Manchester Royal Infirmary	97	41	42%
Royal Bournemouth and Christchurch Hospital	90	32	36%
Southampton University Hospital	52	34	65%
Nottingham University Hospital NHS Trust	43	5	12%
Salford Royal NHS Foundation Trust	41	8	20%
Guy's & St Thomas' Hospital	35	10	29%
Gloucestershire Royal Hospital	32	10	31%
Queen Alexandra Hospital, Portsmouth	27	11	41%

St Mary's Hospital, London	24	17	71%
University Hospital Aintree	23	14	61%
Newcastle Hospitals	21	0	0%
John Radcliffe Hospital, Oxford	20	3	15%
Royal Wolverhampton Hospitals NHS	19	3	16%
Norfolk & Norwich University Hospital	19	7	37%
Watford Hospital	18	7	39%
Queen Elizabeth Hospital, Birmingham	17	3	18%
Frimley Park Hospital	17	9	53%
Bradford Teaching Hospital	14	7	50%
County Durham & Darlington NHS Foundation Trust	8	1	13%
Plymouth Hospital NHS Trust	1	0	0%
Broomfield Hospital, Chelmsford	0	0	0%

4.4.1 Demographic data

681 patients completed treatment between 2008 and November 2011 (median follow up 26 months). The baseline characteristics of all patients completing treatment can be seen in Table 4.2. Over 90% had a diagnosis of HGD or IMC and 53% have had a previous EMR before RFA treatment.

Table 4.2: Table of Baseline Characteristics of Patients who have completed treatment with RFA in the UK RFA Registry

Total number of patients competed treatment	678
Sex (M)	82.2%
Median Age (Range)	68 (39-91)
Median Initial Length (Range)	5 cm (1-20 cm)
Prior EMR	53.0%
Rescue EMR	5.1%
Entry Histology	
- IMC	24.4%
- High Grade Dysplasia	69.5%
- Low Grade Dysplasia	6.0%
Mean number of RFA Treatments (Range)	2.5 (1-7)
Median time to protocol completion (months)	11.5
CR-IM	76.7%
CR-D	85.3%
Dysplasia recurrence	12.7%
Median time in follow up (months)	13.3

4.4.2 Outcomes

Baseline characteristics across the three groups of centre volumes can be seen in Table 4.3. Patients were marginally older in low volume centres compared with high volume centres ($p<0.05$).

Neither 12 month CR-D nor CR-IM rates were any different between the groups (CR-D 86.4-89.5%, CR-IM 73.7-81.1%). Dysplasia recurrence was significantly lower in high volume centres compared with low volume centres (Log Rank p=0.001) (Table 4.3).

Interestingly, rescue EMR during RFA treatment was performed less frequently in medium volume centres (0% versus high 5.3% and low volume 10%, p=0.001), although with no clear effect on CR-D or recurrence rates. There was a trend for the high-volume centres to perform more RFA sessions per patient but this was not reflected in the median time taken to complete the protocol.

Table 4.3: Table of Efficacy of RFA on the Basis of Centre Experience

	Low Volume n=115	Medium Volume n=145	High Volume n=418	Significance
Sex (M)	88.1%	80.4%	81.4%	0.188
Age	69.7	68.4	67.3	0.056
Initial Length (M)	5.1	5.2	5.7	0.380
Prior EMR	57.6%	56.6%	50%	0.197
Rescue EMR	10.1%	0%	5.3%	**Low vs Medium 0.001** Low vs High 0.205 Medium vs High 0.112
Entry Histology				0.402
- IMC	27.1%	23.8%	23.7%	
- HGD	69.5%	67.1%	70.2%	
- LGD	3.4%	9.1%	6.1%	
Median number of RFA Treatments	2.1	2.4	2.7	**Low vs Medium 0.038 Low vs High <0.001 Medium vs High 0.048**
Median time to protocol completion (months)	11.4	11.7	12.1	0.578
CR-IM	73.7%	81.1%	74.9%	0.263
CR-D	86.4%	89.5%	87.0%	0.687
Dysplasia recurrence	19.1%	13.3%	14.0%	Log Rank Medium vs High p=0.237

	Low vs High **p=0.001** Low vs Medium P=0.066

4.5 Discussion

Studies assessing complex surgical procedures repeatedly demonstrate improved survival outcomes in specialist centres (138,184–190). The BSG recommend a minimum of 30 supervised RFA procedures before competency is attained (25), though this is based on limited evidence.

There have been several reasons postulated for the improved outcomes seen in surgical studies to date. Better infrastructure, staffing levels, resources and wider specialist and technology services have all been mooted as reasons (225).

The data presented above suggest that centre volume is not a significant factor in determining successful initial outcomes for the treatment of BO dysplasia with RFA, namely CR-D (86.4% versus 87.0% versus 89.5%) and CR-IM (73.7% versus 74.9% versus 81.1%). However, dysplasia recurrence is significantly higher in low volume centres (Log rank 0.001), though these numbers are small (22 cases in the small volume centres and 58 in the high volume centres).

Data from the UK Registry does not demonstrate improved outcomes at higher volume centres. One reason may be that the learning curve for RFA and management of these patients is very low, thus endoscopists with even minimal experience can achieve excellent outcomes.

Interestingly, medium volume centres had a significantly lower Rescue EMR rate compared with both the high and low volume centres. The

significance of this finding is unclear and could be interpreted as either, medium volume centres successfully clear all visible dysplasia prior to commencing RFA, or, that they are missing residual disease. Neither explanation explains why ultimately the CR-D and recurrence rates are not significantly different for the medium volume centres, though a combination of both the above listed reasons may even out the long-term outcomes.

4.6 Centre Experience

Although the data presented in the previous section suggests lower dysplasia recurrence rates at high volume centres, overall CR-D and CR-IM do not appear to be affected by the volume of work a centre performs. Previous work published by our group has demonstrated improvements over time (178). Patients treated between 2011 and 2013 compared with those treated between 2008 and 2010 have significantly improved CR-D rates (92% versus 77%; $p<0.0001$), CR-IM rates (83% versus 57%, $p<0.0001$) and increased EMR rates prior to commencing RFA ($p=0.016$).

4.7 Aim

This section aims to identify whether a learning curve exists for the treatment of BO dysplasia with RFA and if there is a learning curve, what is the number needed to obtain proficiency.

4.8 Methods

The same cohort of patients from the UK RFA Registry as described in the previous section were analysed according the order treated at each centre. The first group included the first 20 patients treated in all centres, the second group included patients 21-40 at each centre and the third group all patients from 41 onwards. The primary outcomes for this study were CR-D, CR-IM and dysplasia recurrence and statistical methods have been previously described.

Previously multivariate analysis of the UK RFA cohort reported increasing age (OR 1.316), prior EMR (OR 1.358) and shorter lengths of BE at baseline (OR 1.103) were more likely to achieve CR-D whereas

rescue EMR (OR 0.426) reduced the chance of achieving CR-D (178). These were the factors used to risk adjust for the RA-CUSUM analysis.

4.8.1 Risk-Adjusted Cumulative Sum curve analysis

To identify the existence and length of a proficiency-gain curve for HALO a combination of Risk-Adjusted Cumulative Sum (RA-CUSUM) and change-point analysis was performed in collaboration with Dr Sheraz Markar.

RA-CUSUM curves were plotted for the cumulative difference between the observed and the expected outcome against hospital case number; using the CUSUM equation $Si=Si-1+(\Sigma i- \Sigma R)$; $S0=0$: Si is the cumulative sum, Σ i the sum of events at procedure number i, and ΣR the sum of expected events at procedure number i. Therefore at each case number the curve goes upwards if the outcome is worse than expected and down if better than expected. According to the unique anonymised hospital codes within the dataset; the first case in each hospital case series was assigned case one and subsequent case numbers assigned according to ascending date order. The expected outcomes were derived from logistic regression models for each binary outcome; these provided the predicted probability of each outcome in each case.

Potential confounding factors (from previous multivariate analysis of the sample population), which were risk adjusted for, in the models were age, entry histology, length of Barrett's oesophagus, rescue endoscopic mucosal resection (EMR) and previous EMR.

An inverse relationship was expected between experience and adverse outcomes and the length of the proficiency-gain curve was defined as the number of cases for a sustained improvement in outcome. This was represented graphically on the CUSUM curve as the maximal positive

deflection; the point at which outcomes changed from worse than expected to better than expected. The clinical significance of this change point was determined by comparing outcomes before and after. These binary outcomes were compared using Chi-Square and a threshold of significance was set at a p value of less than 0·05.

4.9 Results

4.9.1 Demographic data

Experience treating patients with Barrett's associated dysplasia and neoplasia results in fewer rescue EMRs (p=0.016), faster time to completion of the treatment protocol and higher CR-D and CR-IM rates (Table 4.4). There is no difference in CR-D or CR-IM rates between the second 20 cases and those performed after 40 cases (p=0.869 and p= 0.398 respectively).

Table 4.4: Table of Efficacy of RFA on the Experience (0-20, 21-40, >40) – entry criteria and outcomes

	Cases 1-20 n=316	**Cases 21-40 n=164**	**Cases >40 n=198**	**Significance**
Sex (M)	84.5%	77.6%	82.4%	0.164
Age	68.4	66.7	67.8	0.173
Initial Length (M)	5.5	5.4	4.7	0.068
Prior EMR	55.2%	50.3%	51.8%	0.542
Rescue EMR	7.3%	5.5%	1.5%	**0.016**
Entry Histology				**0.023**
- IMC	27.2%	23.2%	21.1%	
- HGD	69.9%	66.5%	71.4%	
- LGD	2.8%	10.4%	7.5%	
Median no. of RFA Treatments	2.5	2.6	2.5	0.411
Median time to completion of protocol (months)	12.1	12.9	10.9	1^{st} 20 vs 2^{nd} 20 0.345 **1^{st} 20 vs 3^{rd} 20 0.045** **2^{nd} 20 vs 3^{rd} 20 0.003**
CR-IM	71.3%	78.2%	83.9%	**0.004** **Tukey** 1^{st} 20 vs 2^{nd} 20 0.203 **1^{st} 20 vs 3^{rd} 20 0.003** 2^{nd} 20 vs 3^{rd} 20 0.398
CR-D	79.8%	89.1%	91.0%	**0.001**

				Tukey **1st 20 vs 2nd 20** **0.017** **1st 20 vs 3rd 20** **0.001** 2nd 20 vs 3rd 20 0.869
Dysplasia recurrence	15%	12.8%	11.6%	Log rank = 0.259

4.9.2 Hospital RA-CUSUM curve analysis

Analysis of the RA-CUSUM curve for incomplete resolution of dysplasia (Figure 4.1) showed a significant change-point at 12 cases, with a significant reduction from 24.5% to 10.4%; P<0.001 (Table 4.5). A longer RA-CUSUM curve was seen for incomplete resolution of Barrett's oesophagus (Figure 4.2) with a significant change-point at 18 cases, and a significant reduction from 30.7% to 18.6%; P<0.001.

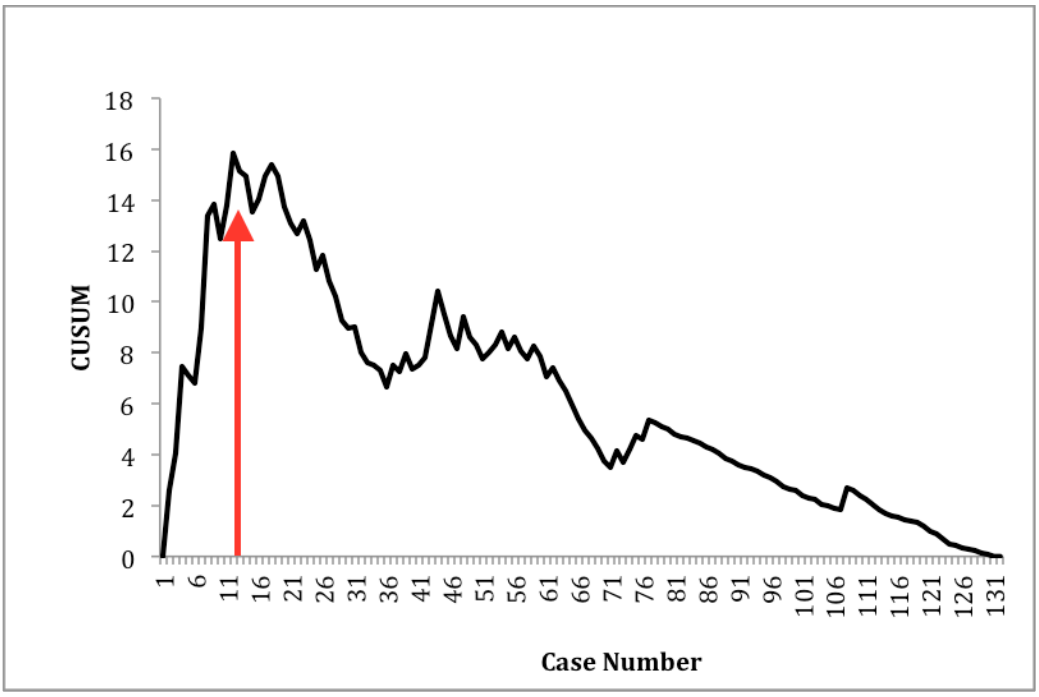


Figure 4.1: RA-CUSUM curve for CR-D following HALO, showing a s significant change-point at 12 cases, and reduction from 24.5% to 10.5%; P<0.001

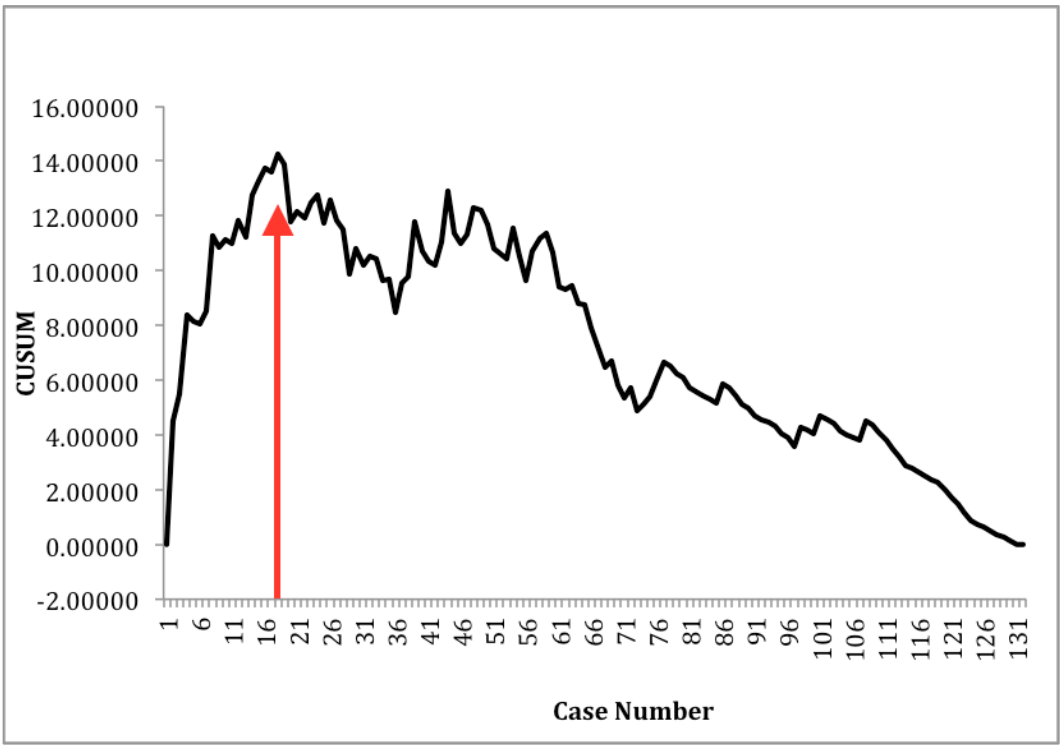


Figure 4.2: RA-CUSUM curve for CR-IM following HALO, showing a significant change-point at 18 cases, and reduction from 30.7% to 18.6%; P<0.001

Table 4.5: Analysis of outcomes before and after change-points in RA-CUSUM curves.

Outcome	All patients	Change-point (CP)	CR-D Failure rate before CP	CR-D Failure rate after CP	P value
Unable to achieve CR-D	100/678	12 cases	24.5%	10.4%	<0.001
Unable to achieve CR-IM	159/678	18 cases	30.7%	18.6%	<0.001

RA-CUSUM plots were attempted to identify a minimum number of RFA patients that need to be treated at each centre each year to maintain the standard of outcomes achieved after 12-18 patients. However, due to low numbers performed per year at most centres, no significant findings could be reported.

4.10 Discussion

Previous analysis of the UK RFA registry has demonstrated improved outcomes with time (178) and this data demonstrates a similar effect, that the more cases a centre performs the better the outcome. After treating 40 patients with a combined EMR and RFA approach, outcomes

are significantly better than for the first 20 patients treated in the same centre (CR-D 91% versus 79.8. %; p=0.001, CR-IM 83.9% versus 71.3% p=0.004). The subsequent RA-CUSUM plots demonstrate a learning curve for the management of these patients with a change point at 12 and 18 cases for CR-D and CR-IM respectively (p<0.001).

There is currently limited data to guide requirements for RFA experience before independent practice. Fudman et al performed a retrospective analysis of 417 patients who had been treated by 7 endoscopists with a median RFA volume of 62 patients (range 20–188) (201). The study was performed at 3 teaching centres and endoscopists who had treated less than 10 patients were excluded from the analysis. RFA volume (both number of patients treated and number of RFA procedures) correlated with CR-IM rates (rho = 0.85, p=0.014) and in multivariate analysis, higher RFA volume was associated with higher CR-IM rates. However, no association was found between CR-IM rates and yearly endoscopic volume. No data on CR-D rates were reported in this study and the authors raised concerns about using CR-IM as an appropriate quality metric for RFA therapy. Further imitations of the study include the small number of endoscopists and lack of a common treatment protocol.

Zemlyak et al retrospectively reviewed 70 consecutive patients treated at a single centre by a single endoscopist (202). Comparing the first 25% of those treated with the last 25%, there was no significant difference in length of procedure, procedures required to achieve CR-IM or complication rate. They concluded that *“By measure of treatment time, complication rate, and efficacy of therapy, there is minimal or no “learning curve” for experienced endoscopists.”* However, only 74% of these patients had dysplasia and no strictures were reported (one patient complained of dysphagia). However, the overall rate of complications was very low (one case of dysphagia, one case of transient chest pain

and one case of abdominal pain) compared with similar studies (165,202) and only 74% had dysplasia (11.4% HGD and 62.9% LGD).

A larger US registry based study by Pasricha et al reviewed 5521 patients across 148 institutions undergoing endoscopic therapy for Barrett's (51.7% for dysplasia) (203). Higher volume centres were associated with higher CR-IM rates ($P < 0.01$) but not CR-D rated ($P = 0.39$), however, the improvement in CR-IM was not significant after multivariate analysis. Centre volume was associated with fewer procedures required to achieve CR-IM ($P <0.001$) and after an endoscopist had treated 30 cases they required 0.35 fewer endoscopies to achieve CR-IM compared with those who had completed 10 or fewer cases. The US Registry data includes almost 50% of non-dysplastic Barrett's patients which may have a significant impact on the learning curve of US operators and make the data difficult to extrapolate to a UK population for whom RFA is only indicated in the presence of dysplasia.

A recent paper assessing EMR proficiency in the UK using data from a UK Hospital Episode Statistic (HES) database reported a lower 30-day mortality with high volume endoscopists with a change point of 4 cases seen when comparing 30-day mortality in cancer patients (200). This data assessed EMR data alone with mortality and complications (including repeat surgery) as outcomes. The study did not address treatment outcomes or assess those disease-free after intervention. It is however, a useful aid understanding the results of the UK RFA Registry and that the learning curve of 12-18 cases required for RFA and EMR is only partly accounted for by dual therapy with EMR.

It is important to note that the association between surgical volume and improved outcome has not been consistently agreed. In contrast to the above studies, a UK based study on individual surgeon volume and lung cancer outcomes did not demonstrate an association between individual

surgeon volume and in-hospital mortality (226). This same study highlighted the need to assess the best 'patient centred outcome measures', as mortality in lung cancer patients following surgery is a rare event. Extrapolating this to the cohort of Barrett's therapy, perhaps a more holistic view of endoscopic treatment for Barrett's should address the future burden of endoscopic surveillance and impact on the quality of life rather than solely on CR-D and CR-IM rates.

4.10.1 Strengths

This study has several strengths; it is the largest study outside of the US, assessing 24 centres in the UK and Ireland, covering the majority of endoscopic therapy that occurs in the UK for patients with dysplastic BE. The RA-CUSUM plots removes the grouping of centres with similar volumes (such as high, medium or low volume centres) but assesses each centre on the number of patients and the risk adjusted profile of each patient treated to demonstrate a learning curve in the effectiveness of endoscopic therapy for dysplastic BE.

4.10.2 Limitations

As with any registry study, although a treatment protocol is advised it may not always be adhered to. Multiple sites across the UK and Ireland enter data from the Registry. Clinical pressures result in significant variation in RFA treatment intervals and sessions within 12 months, although in this analysis no difference in RFA sessions was identified between cohorts. Furthermore, as a retrospective analysis, the fields captured in the database may not capture previously unrecognised confounding variables such as body mass index (BMI), tobacco history or a full medication history (13,19,66).

Cases performed prior to sites enrolling in the registry may not be included, however, sites were able to retrospectively enter data ensuring adequate capture of all cases treated. The UK registry does not require central pathology review of biopsies and EMR samples that may be important as variation amongst pathologist has been well documented (227,228), a similar drawback exists with the US RFA Registry (203).

The UK RFA Registry has been collecting data since 2008. During this time, the management of dysplasia arising in BO has changed; there is a greater focus on lesion detection and resection before RFA treatment begins and there have been advancements in lesion detection, recognition and interpretation due to higher quality imaging. More recently, low-grade dysplasia is now treated with RFA whereas previously it would have been monitored and most importantly, treatment success has improved with time (178).

4.10.3 Protocol Completion

As mentioned in the previous section, a large proportion of patients that enter a treatment program do not complete the protocol. Much of the protocol relies on support staff to ensure timings are met and patients can be seen despite competing waiting list targets. This may be more important when assessing how many patients who enter the treatment protocol, actually complete a year of treatment.

What is clear from this Registry data is that significant numbers of patients have not completed the 12-month protocol, either as they are still currently receiving treatment, or have been lost to follow-up during the course of treatment. The outcomes of these patients is unknown and understanding what proportion of patients who start treatment but fail to complete therapy is an important metric of how successful a centre is at treating dysplastic BE. Only 7 centres (4 low volume, 1 medium volume and 2 high volume centres) have completed treatment outcomes on at

least 50% of the patients they have recruited to the Registry. Future work to address whether these patients are lost to follow-up due to patient factors or hospital specific factors is needed.

In contrast to the US RFA Registry findings, we demonstrate that there is a learning curve with a significant change point after 12 and 18 cases for CR-D and CR-IM respectively. The UK Registry collects data only on patients undergoing treatment for dysplasia and neoplasia arising in BE and does not include patients treated for non-dysplastic BE, for which the BSG does not recommend endoscopic therapy. This removes the bias of endoscopists who may have treated large numbers of patients with non-dysplastic Barrett's prior to those with dysplasia.

Previous meta-analysis suggested surgical volume rather than centre volume is the most important factor for outcomes in upper GI surgery (229). The Registry does not allow sufficient breakdown of the data as to who performed each RFA session. Outcomes recorded are per centre and therefore unable to distinguish if the endoscopy unit (with nursing and administrative staff and the management system) or the individual endoscopists ability that we are measuring. However, it should be noted that most small centres have a single endoscopist and only the larger centres may have more than one endoscopist. For example, UCH, the largest centre in the registry has up to 4 endoscopists performing specialist upper GI endoscopic therapy, with no guarantee that the same endoscopists will treat the same patient at each of their endoscopies.

Currently, there are no overall performance assessment tools for EMR or RFA and a recent systematic review of measures of trainee performance in advanced endoscopy (230) recommended mean endoscopies required to achieve CR-IM as a potential performance measure based on the data from the US RFA Registry (203). The large Pasricha analysis (203) prompted the BSG to recommend a minimum of 30 RFA cases are

performed with supervision to ensure competence in technical skills and managing complications (25).

Previous studies in this field have focused on either EMR as a stand-alone procedure or RFA in isolation (200,202). This analysis does not differentiate between the two procedures but assesses outcomes of all patients treated for dysplasia. The learning curves described in this study are a composite of both EMR and RFA treatment. This approach is endorsed in BSG guidance (175) and is considered the best current treatment for dysplasia arising in Barrett's. Using previous work on EMR outcomes, our data suggests that much of the learning curve is due to the RFA component of treatment but it is a true reflection of everyday clinical practice.

4.10.4 Conclusion

In conclusion, this study has addressed the key outcomes of CR-IM and CR-D to clearly demonstrate a learning curve that suggests a minimum of 12-18 cases are required before outcomes improve. There is however, a word of warning, although outcomes improve with experience with a demonstrable learning curve, a lesson learnt from studies about patient preferences is the importance of distance required to travel in the decision making process (231,232). Likewise, with upper GI services, the difference in outcomes between a high volume and low volume centre does not support further centralisation of services to only high volume centres.

The findings in this chapter may guide the development of quality indicators of Barrett's endoscopic therapy and provide a barometer for the expected outcomes for each centre. Based on the data, it would appear reasonable that the BSG recommendation of 30 supervised cases of endoscopic ablation can be lowered to 20 cases to achieve the required competencies as demonstrated by the point change on the

graphs (Figure 4.1, Figure 4.2) and the lack or improvement in CR-D and CR-IM rates comparing cases 20-40 and >40 cases.

5 Residual Intestinal Metaplasia Following Radiofrequency Ablation for Barrett's Oesophagus Related Dysplasia and the Risk of Dysplasia Recurrence

5.1 Does Residual IM at the end of the treatment protocol confer an increased risk of dysplasia recurrence?

5.1.1 Aim

Large datasets from the US have reported varying IM recurrence rates, from 10% at 5 years (172) to 33% at 2 years (173). Risk factors of IM recurrence include advanced pre-treatment histology, increasing age, longer baseline BE segments and non-Caucasian patients (174). Fewer studies have purely addressed dysplasia recurrence as discussed in the introduction. A recent systematic review and pooled analysis compared several outcomes including recurrence rates between focal EMR followed by RFA and complete or stepwise EMR alone. The was no significant difference in recurrence of OAC, dysplasia or IM between the methods and the pooled estimates of recurrence for those undergoing EMR followed by RFA was 1.4% for OAC (95% CI, 0.2%-2.7%), 2.6% for dysplasia (95% CI, 0.5%-4.7%; I^2, 35.3%) and 16.1% for IM (95% CI, 7%-25.8%) (233). It should be noted that the median follow-up period ranged from 12-61 months but only 3 studies had a median follow-up more than 36 months.

The gastric mucosa closest to the OGJ is the cardiac mucosa and is lined with mucus-secreting glands. The presence of IM at the cardia in the general population has been estimated between 5-18% of normal

patients (234–236). However, the presence of IM is thought to be a normal variant. A 2017 study reported recurrence of IM was more common in the oesophagus of 260 patients followed-up after successful treatment; however, dysplasia recurrence was more common in the gastric cardia (17 cases) compared with the oesophagus (10 cases). The authors noted that IM isolated to the cardia was not considered recurrence and was reported in 42 (21.5%) of patients (237).

There is an increased risk of metachronous lesions arising in residual BO after endoscopic resection. Therefore, residual BO at end of treatment may also be associated with an increased risk of developing recurrent dysplasia following completion of treatment. This study aims to assess whether residual IM at the end of the treatment protocol confers an increased risk of dysplasia recurrence by analysing the current status of all patients who achieved CR-D in the UK RFA Registry.

5.1.2 Methods

5.1.2.1 Inclusion criteria

The UK registry collects data on patients referred with dysplastic Barrett's oesophagus undergoing endoscopic management at specialist centres. Cases of Barrett's neoplasia are discussed in a specialist multidisciplinary meeting before endoscopic treatment is commenced as recommended by British Society of Gastroenterology (BSG) guidelines (175). Patients who had completed the treatment protocol with eradication of dysplasia between January 2008 and November 2015 were included in this analysis. Patients previously treated for Barrett's neoplasia with photodynamic therapy were excluded.

All patients gave written informed consent to attend at regular intervals for treatment and subsequent surveillance procedures. Ethical approval was granted by the Joint UCL/UCLH Committee on the Ethics of Human

Research (REC REF 08/H0714/27). The UK registry is registered at http://www.controlled-trials.com, number ISRCTN93069556.

5.1.2.2 Pretreatment staging

All patients underwent high definition endoscopy with enhanced imaging and chromoendoscopy to assess their Barrett's segment. Barrett's length was measured according to the Prague classification (26) and mapping biopsies taken in keeping with the Seattle 4 quadrant biopsy protocol (238)(239). Nodules or visible lesions were resected before RFA performed. Entry histology was determined as the most advanced pre-RFA histological diagnosis based on biopsies or EMR specimens. Two expert gastrointestinal histopathologists reviewed all samples using the modified Vienna classification (32) to ensure accurate histological staging of disease.

All patients had LGD, HGD or IMC on at least two endoscopies prior to commencing treatment with RFA. Once treatment with RFA had begun, EMR could be carried out at any time.

5.1.2.3 Registry RFA treatment protocol

The first RFA treatment was recorded as time point zero, whether or not a previous EMR had been performed, as described in previous publications (180). The first ablation procedure was performed with either a circumferential device (HALO 360; Covidien, Sunnyvale, California, USA) or a focal device (HALO 90, HALO 60, HALO ULTRA, Channel HALO device). RFA treatment was repeated every 3 months until 12 months (recommended end of protocol) (Figure 1.1).

End of protocol mapping biopsies (following the Seattle 4 quadrant protocol of the treated segment and below the neo-OGJ) were taken to ascertain clearance of intestinal metaplasia and dysplasia. If clearance was achieved earlier than 12 months, the endpoint was the first

endoscopy with no visible Barrett's segment and no intestinal metaplasia or dysplasia on biopsies.

All new, visible lesions identified during the treatment protocol were treated with rescue EMR.

5.1.2.4 Follow-up program

All patients free of dysplasia at 12 months or end of protocol were entered into a post-RFA surveillance protocol. Follow-up took place at three to six month intervals for the first year, at 6 monthly intervals in the following year and annually thereafter.

Surveillance was recommended with high definition endoscopy with enhanced imaging. At every post treatment surveillance endoscopy biopsies were taken following the Seattle 4 quadrant protocol of the treated segment and further quadrantic biopsies were taken at the neo-Z line and 1cm below the neo-Z line as per BADCAT recommendations for follow-up post treatment (240). Recurrence or invasive disease was discussed at a specialist multidisciplinary meeting before appropriate management implemented, be that further endoscopic treatment, surgery or chemo-radiotherapy.

Residual IM was defined as a visible segment of columnar lined epithelium (CLE) proximal to the neo-oesophagogastric junction (neo-OGJ) with biopsies showing glandular IM. Neither visible CLE without IM in the oesophagus or IM of the gastric cardia were regarded as residual BE. Biopsies demonstrating IM of the cardia were not deemed residual IM, as these finding can be present in the normal population (235). This definition of residual IM is similar to previous studies that regarded recurrence as biopsy proven IM 3-10mm above the neo-squamocolumnar junction at the gastro-oesophageal junction (241)(172).

Patients with follow-up data up to November 2015 were included in the analysis. Focal IM distal to the neo-OGJ junction and from the gastric cardia was not deemed to be true recurrence or criteria for retreatment.

5.1.2.5 Clinical end points

The primary outcome for this study is dysplasia recurrence as defined by histological evidence of LGD, HGD or IMC on biopsies or EMR specimens. Two expert gastrointestinal histopathologists confirmed disease recurrence. Only patients who continue with endoscopic surveillance post treatment were included in this analysis.

Demographics, treatment characteristics and patient outcomes were analysed and compared between those with and without recurrence.

5.1.2.6 Statistical analysis

Data were analysed using SPSS version 23 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 6.0 (GraphPad Software, Inc., La Jolla, California, USA). Comparisons between groups for available data were analysed using the χ^2 test for categorical variables or Independent T Test for non-parametric variables. Univariate Cox Regression was used to identify differences in dysplasia recurrence (survival). Multivariate Cox Regression was then run. Kaplan–Meier (KM) survival curves were used to compare length of time to recurrence and Log rank test was used to compare the difference in the rate of disease recurrence between the groups at latest follow-up.

5.1.3 Results

5.1.3.1 Demographic data

From January 2008 to November 2015, 613 patients with mucosal neoplasia achieved CR-D at the end of protocol and remain in active

surveillance. Of these, 30 patients (4.9%) developed recurrent dysplasia at their most recent endoscopic assessment. On comparing those with recurrence and those without, there was no significant difference in age, sex, baseline BE length, prior EMR rates, number of RFA treatments required or median time to follow up between the cohorts. There was a significant difference between the cohorts in entry histology (with a greater proportion of IMC in those with no recurrence, p=0.025), time to completion of protocol (p=0.035) and residual IM at the end of protocol (p=0.001) (Table 5.1).

Table 5.1: Comparing those with and without dysplasia recurrence after successful eradication of dysplasia

	No Recurrence (N=583)	Recurrence (N=30)	P value
Mean Age (Range)	68 (39-91)	67 (50-83)	0.61
Male	99.3%	80%	0.76
Baseline Histology - LGD - HGD - IMC	 6.3% 69.0% 24.7%	 10% 86.7% 3.3%	**0.025**
Baseline BE length at start of RFA (max extent, cm)	4.9(0-20)	6.1(0-14)	0.051
EMR prior to RFA	52.3%	40.0%	0.19
Rescue EMR during RFA treatment	4.6%	3.3%	0.74
Median time to end of protocol (months)	13.9	11.2	**0.035**
Number of RFA Sessions	2.55	2.66	0.58
Residual IM at end of Protocol	14.6%	36.7%	**0.001**
Median time to most recent biopsy from first treatment for those still in follow-up (months)	26 (21-36)	28 (17-43)	0.75

5.1.3.2 Residual IM

Of the 583 patients who achieved CR-D, 517 achieved CR-IM and 96 had residual IM (but achieved CR-D) at the end of protocol. On comparing these groups there was no difference in sex, baseline histology, EMR rates prior to RFA, rescue EMR rates, RFA treatments required or time to completion of protocol. The CR-IM group were significantly younger (67 vs 70, p=0.019), had shorter baseline BE segments (4.7 vs 6.2cm, p<0.001) and were more likely to be free of dysplasia at their most recent follow up (96.3% vs 88.5%, p=0.001) (Table 5.2).

Table 5.2: Table comparing outcomes of those with and without residual IM at end of treatment protocol

	No Residual IM (N=517)	Residual IM (N=96)	P value
Mean Age (Range)	67 (39-91)	70 (47-84)	**0.019**
Male	83.9%	81.3%	0.61
Baseline Histology - LGD - HGD - IMC	 6.8% 70.6% 22.6%	 5.2% 65.6% 29.2%	0.36
Baseline BE length at start of RFA (max extent, cm)	4.7(0-20)	6.2(0-16)	**<0.001**
EMR prior to RFA	51.3%	54.2%	0.60
Rescue EMR during RFA treatment	22 (4.3%)	6 (6.3%)	0.39
Median time to end of protocol (months)	11.8	12.4	0.33
Number of RFA Sessions	2.58	2.42	0.203
Progression to cancer	0.6%	2.1%	0.13
Median time to most recent biopsy from first treatment for those still in follow-up (months)	31 (2-94)	33 (2-93)	0.38
% Free of dysplasia at most recent follow-up	96.3%	88.5%	**0.001**

5.1.3.3 Univariable and Multivariate cox regression

The odds ratio of dysplasia recurrence in the presence of residual IM at the end of protocol was 2.809 (95% CI 1.324-5.959, *p*=0.007) (Table 5.3).

Table 5.3: Table showing Odds Ratio (OR) comparing those with and without residual IM at end of treatment protocol, Age and Length of Original BE, using univariable cox regression model

	OR	95 % CI	*P*-value
With Residual IM	2.809	1.324 - 5.959	0.007
Age	0.996	0.959 - 1.034	0.828
Length of Original BE	1.077	0.974 - 1.190	0.149

To investigate the effect of baseline imbalance between the two groups (CR-IM vs CR-D only), multivariate cox regression was run using Age and the initial Length of Barrett's as covariates.

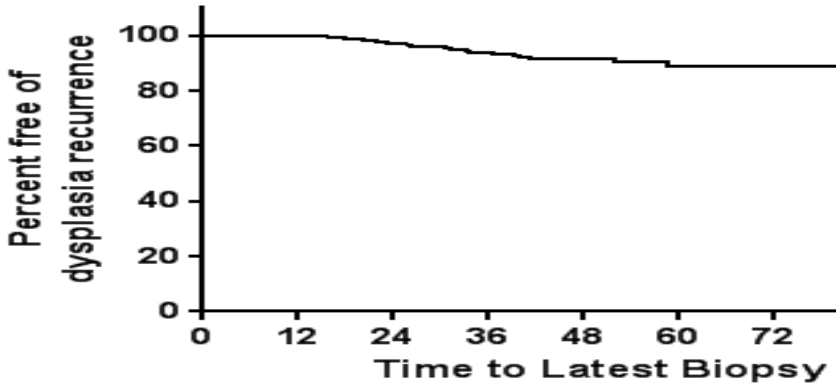
After adjusting for these potentially confounding factors, the OR comparing those with residual IM to those with CR-IM was 2.621 (95% CI 1.212-5.666, *p*=0.014) and the other factors are not significant (Table 5.4).

Table 5.4: Table showing Odds Ratio (OR) comparing those with and without residual IM at end of treatment protocol using multivariable cox regression model

	OR	95 % CI	*P*-value
Without Residual IM	1		
With Residual IM	2.621	1.212 – 5.666	0.014
Age	0.994	0.958 – 1.032	0.761
Length of Original BE	1.051	0.947 – 1.165	0.350

5.1.3.4 Dysplasia free survival

Figure 5.1 demonstrates the long-term durability of all patients who achieved CR-D at the end of RFA treatment and remain in follow up. KM analysis predicts a 91% likelihood of remaining free of dysplasia at 5 years in those who successfully clear dysplasia at end of treatment protocol.



Time to latest biopsy	0	12	24	36	48	60
Number of patients	613	523	360	215	117	60

Figure 5.1: Kaplan-Meier of the long-term durability of all patients who achieved CR-D (time zero = the start of the RFA treatment)

KM analysis predicts an 82% likelihood of remaining free of dysplasia in those who achieved only CR-D at the end of protocol compared with 90% in those who achieved CR-IM; log rank 0=0.005 (Figure 5.2). The majority of recurrences occur within the first 3 years after completion of treatment.

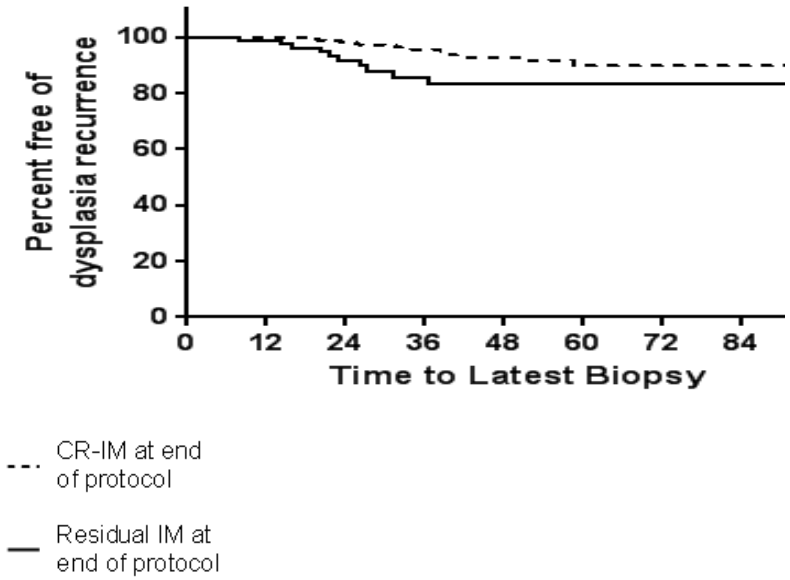


Figure 5.2: Kaplan-Meier of Dysplasia Recurrence in those with and without Residual IM at end of Treatment Protocol (time zero = the start of the RFA treatment). Log-rank (Mantel-Cox) test *P*= 0.0051

5.1.4 Discussion

Risk factors for dysplasia within BO include increasing age (Odds Ratio =1.02; 95% CI, 1.01-1.03) and initial length of BO (Odds Ratio = 1.10; 95% CI, 1.05-1.15) as risk factors for dysplasia recurrence (169). A meta-analysis of studies treating BO associated dysplasia and IMC reported a pooled recurrence rate of 6.0% per patient year (95% Confidence Interval; 0.5%-11.6%) (169). The risk posed by residual IM at the end of treatment has previously been reported by Small et al in follow-up of 135 patients treated for HGD and 111 patients treated for IMC. There was no significant increased risk of recurrence if there was residual IM in either the HGD (9% vs 8%; p=0.56) or IMC (7.4% vs 9.5%; p=054) groups (242).

The UK Registry data however, challenges this finding and reports that residual IM at the end of the treatment protocol confers an odds ratio of 2.6 (95% CI 1.212-5.666, *p*=0.017) of developing recurrent dysplasia

compared with those who achieve CR-IM at the end of the protocol. The implications of this are two-fold.

- Firstly, should we take a more aggressive stance to eradication of BO and change our end-point of treatment from a defined 12-month protocol to an end-point of CR-IM no matter how many RFA sessions are required?
- Secondly, should post-treatment surveillance interval be adjusted for this group who have a higher risk of recurrence?

It is also important to note that although residual IM at the cardia may well be a normal finding in 21.5% of patients, most dysplasia recurrence occurs at this very point (237) and adequate ablation of the cardia is an important step in the treatment of Barrett's dysplasia. There is a fine balance, between overtreatment (of potentially normal gastric cardia) with the risks of RFA and under treatment of persistent IM that may harbor dysplasia.

The data presented in this analysis report 30 recurrences (a rate 4.9%) to November 2015. Previous publications from the UK Registry have reported the risk of recurrence at 26 months as 7% (178), though without reporting exact numbers. This data is correct as of 2013 and although outcomes have improved with time there appears to be a low recurrence rate in this study. This highlights a major limitation; only those with a current diagnosis of dysplasia following successful eradication have been identified, patients who had undergone successful treatment for recurrence and were now disease free were not classified as recurrence and were instead grouped as disease free. Whilst this is reassuring for their clinical outcome, it may have significantly weight to bias the findings. Further work identifying these patients may be necessary.

5.2 Residual IM at the end of the treatment and dysplasia recurrence

5.2.1 Aim

The previous section presented evidence contrary to previously published work on residual IM and the risk of dysplasia recurrence. A limitation of the work is that the UK RFA Registry has not until now accurately identified patients who had dysplasia recurrence but were then treated again. Whilst the majority of recurrences are successfully treated endoscopically, this discrepancy results in an under-reporting of dysplasia recurrence. This analysis includes all recurrences after end of treatment in which CR-D was achieved to assess whether residual IM at end of protocol confers an increase risk of dysplasia recurrence.

5.2.2 Methods

A manual search of all patients registered on the online database was performed. Twenty-eight sites enter data for the Registry and significant differences were noted across sites defining 'end of protocol'. This was standardised during the search of the registry and all cases of dysplasia recurrence were recorded and censored at the date of the recurrence.

Data were analysed using the SPSS version 23 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 6.0 (GraphPad Software, Inc., La Jolla, California, USA). Comparisons between groups for available data were analysed using the χ^2 test for categorical variables or Independent T Test for non-parametric variables. Univariate Cox Regression was used to identify differences in dysplasia recurrence (survival). Multivariate Cox Regression was then run. Kaplan–Meier (KM) survival curves were used to analyse rates of recurrence and Log rank test was

used to compare the difference in the rate of disease recurrence between the groups at latest follow-up.

5.2.3 Results

5.2.3.1 Demographic data

Between January 2008 and November 2015, 580 patients with mucosal neoplasia achieved CR-D at the end of protocol remain in active surveillance. Of these, 59 patients (10.2%) developed recurrent dysplasia ranging from 8 months to 71 months after follow up. On comparing those with recurrence and those without, there was no significant difference in age, sex, baseline BE length, prior EMR rates, number of RFA treatments required or median time to follow up between the cohorts. As in the first results, there was a significant difference between the cohorts in entry histology (p=0.011), rescue EMR rates (p=0.001) and residual IM at the end of protocol (p=0.01) (Table 5.5).

Table 5.5: Table comparing those with and without recurrence after successful eradication of dysplasia with all known recurrences at any time point

	No Recurrence (N=521)	Recurrence (N=59)	P value
Mean Age (Range)	67.6	67.4	0.845
Male	82.3%	79.7%	0.259
Baseline Histology - LGD - HGD - IMC	 6.9% 67.2% 25.9%	 6.8% 84.7% 8.5%	**0.011**
Baseline BE length at start of RFA (max extent, cm)	4.9	5.5	0.292
EMR prior to RFA	278	29	0.54
Rescue EMR during RFA treatment	2.9%	11.9%	**0.001**
Median time to end of protocol (months)	11.8	12.7	0.235
Number of RFA Sessions	2.5	2.8	0.07
Residual IM at end of Protocol	13.1%	25.4%	**0.01**
Median time to most recent biopsy from end of treatment for those still in follow-up (months)	17.4	16.1	0.544

5.2.3.2 Residual IM

Of the 580 patients who achieved CR-D, 497 achieved CR-IM and 83 achieved CR-D only with residual IM. The mean length of residual IM was 2cm (range 0.5cm-10cm). On comparing these groups there was no difference in sex, baseline histology, EMR rates prior to RFA, rescue EMR rates, RFA treatments required or time to completion of protocol. The CR-IM group were significantly younger (67 vs 70, p=0.010), had shorter baseline BE segments (4.8 vs 6.3cm, p=0.001) and were more likely to be free of dysplasia at their most recent follow up (91.1% vs 81.9%, p=0.001) (Table 5.6).

Table 5.6: Table comparing outcomes of those with and without residual IM at end of treatment protocol

	No Residual IM (N=497)	Residual IM (N=83)	P value
Mean Age (Range)	67.2	70.1	**0.010**
Male	82.3%	80.7%	0.730
Baseline Histology - LGD - HGD - IMC	 7.0% 70.0% 22.9%	 6.0% 62.7% 31.3%	0.254
Baseline BE length at start of RFA (max extent, cm)	4.8	6.3	**0.001**
EMR prior to RFA	51.9%	59.0%	0.229
Rescue EMR during RFA treatment	3.6%	4.8%	0.597
Median time to end of protocol (months)	11.8	12.3	0.505
Number of RFA Sessions	2.6	2.4	0.177
Median time to most recent biopsy from end of treatment for those still in follow-up (months)	17.4	16.4	0.569
% Free of dysplasia at most recent follow-up	91.1%	81.9%	**0.010**

5.2.3.3 Univariable and Multivariate cox regression

The odds ratio of dysplasia recurrence in the presence of residual IM at the end of protocol was 2.765 (95% CI 1.489-5. 341, *p*=0.001) (Table 5.7).

Table 5.7: Table showing Odds Ratio (OR) comparing those with and without residual IM at end of treatment protocol using univariable cox regression model

	OR	95 % CI	*P*-value
Residual IM	2.765	1.489 – 5.134	0.001
Age	1.005	0.978 – 1.032	0.736
Length of Original BE	1.001	0.933 – 1.074	0.986

To investigate the effect of baseline imbalance between the two groups (CR-IM vs CR-D only), multivariate cox regression was run with the Age and the initial Length of Barrett's as covariates.

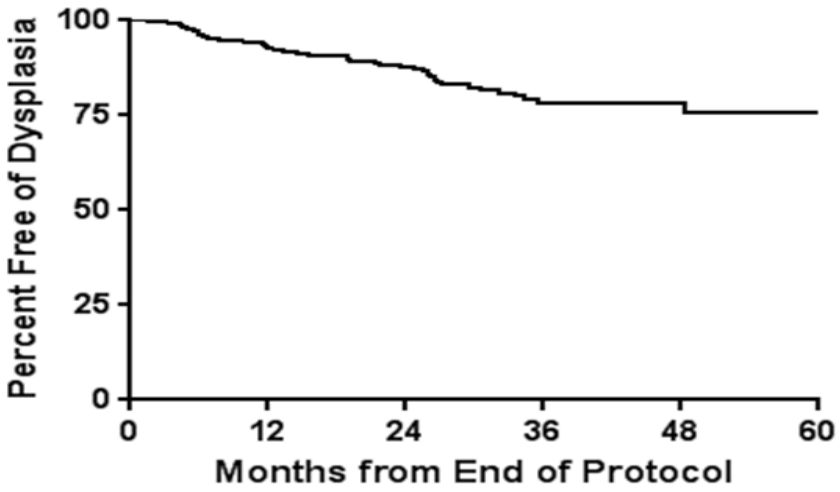
After adjusting for potentially these confounding factors, the OR comparing those with residual IM to those with CR-IM was 2.852 (95% CI 1.508-5.393, *p*=0.001) (Table 5.8).

Table 5.8: Table showing Odds Ratio (OR) comparing those with and without residual IM at end of treatment protocol using multivariable cox regression model

	OR	95 % CI	*P*-value
Without Residual IM	1		
With Residual IM	2.852	1.508 – 5.393	0.001
Age	1.001	0.975 – 1.028	0.930
Initial length	0.981	0.911 - 1.057	0.622

5.2.3.4 Dysplasia free survival

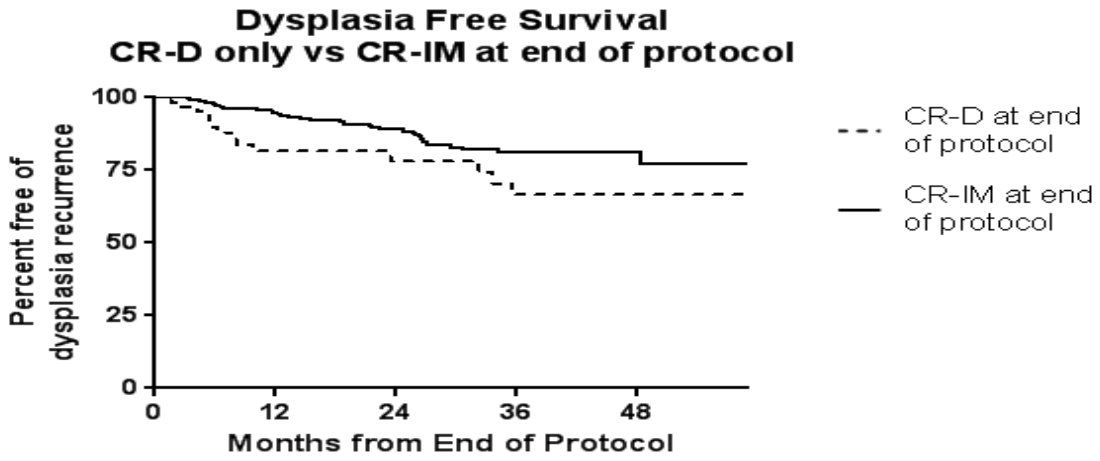
Figure 5.3 demonstrates the long-term durability of all patients who achieved CR-D at the end of RFA treatment and remain in follow up. KM analysis predicts a 77% 5-year dysplasia free survival in those who achieve CR-D at the end of treatment.



Months from end of protocol	0	12	24	36	48	60
Number of Patients	580	310	179	82	32	8

Figure 5.3: Kaplan-Meier of the long-term durability of all patients who achieved CR-D (time zero = end of treatment)

KM analysis predicts a 66% likelihood of remaining free of dysplasia at 4 years in those who achieved CR-D only at the end of protocol compared with 79% in those who achieved CR-IM; log rank 0=0.005 (Figure 5.4). The majority of recurrences occur within the first 3 years after completion of treatment.



Time to Latest Biopsy	0	12	24	36	48
Number of CR-D only Patients	83	32	23	16	7
Number of CR-IM only Patients	497	278	156	66	25

Figure 5.4: Kaplan Meier of Dysplasia Recurrence in those with and without Residual IM at end of Treatment Protocol (time zero = end of treatment). Log-rank (Mantel-Cox) test *P*= 0.005

5.2.4 Discussion

As previously discussed, risk factors for dysplasia within BO include increasing age and initial length of BO (169). Although previously outcomes by Small et al have suggested there is no increased risk posed by residual IM at the end of treatment (242), the risk of metachronous lesions arising in the residual BO after EMR or PDT for dysplasia is up to 30% (176)(177).

Residual IM at the end of the treatment protocol confers an odds ratio of 2.1 (95% CI 1.1-3.8, *p*=0.017) of developing recurrent dysplasia

compared with those who achieve CR-IM at the end of the protocol. Our data support the hypothesis that the remaining BO has an innately higher risk of dysplasia developing as evidenced by an increased risk of dysplasia recurrence in unsuccessfully treated BO.

Patients who have previously undergone treatment and achieved CR-D but not CR-IM may require more intensive follow-up surveillance to assess for recurrence. As a higher risk group, endoscopists should be aware of their risk. However, it remains unclear where disease recurrence was noted. The UK Registry does not collect data on the location of dysplasia and although it could be speculated that dysplasia recurrence occurs in the visible CLE, it may not be the case. Further work assessing this may improve detection or dysplasia recurrence and further improve longer-term outcomes.

The implication of the findings also suggest that treatment for BO with RFA should continue until all visible CLE in the tubular oesophagus has been removed. The recent EURO II study protocol allows for rescue RFA or EMR at the end of the 12-month protocol. This approach in a clinical trial reports 4% dysplasia recurrence after a median follow-up of 27 months after end of treatment (166).

One of the limitations of this study is the reliance of reporting by individual centres in the Registry. After each endoscopy, the registry is updated with the latest histology and the Prague classification. For the analysis, residual IM was defined as histologically confirmed IM with visible CLE, however, several cases were noted were the histological diagnosis was recorded as ‘non-dysplastic Barrett’s’ but the Prague classification was entered as C0M0. This may represent the fact that islands of CLE have not been accurately recorded, or, that histology of IM is in fact IM of the cardia rather than the tubular oesophagus.

To ensure the validity of these findings, all patients with 'non-dysplastic Barrett's' on completion biopsies would need to be verified that residual CLE that was visible at endoscopy.

5.3 Residual IM with visible CLE and risk of dysplasia recurrence

5.3.1 Aim

Reporting of residual IM across sites in the Registry was reviewed. Of the 83 patients with 'non-dysplastic Barrett's' on completion biopsies, 30 had a Prague classification of C0M0 recorded. A limited review of University College Hospital patients it was clear that these patients represented a heterogeneous group with some data entered in error, others with islands of CLE that had not been recorded and others with no visible CLE.

After confirming that all cases of reported CLE with histological evidence of IM at the end of treatment endoscopy the question of whether residual IM at end of protocol confers an increase risk of dysplasia recurrence was assessed.

5.3.2 Methods

Each centre in the registry was contacted and the endoscopy and histology reports from the completion endoscopy of the 30 patients recorded as having C0M0 but non-dysplastic BO histologically were reviewed to ensure the presence of visible CLE in the tubular oesophagus and IM in biopsies taken from the tubular oesophagus. Biopsies confirming IM in the cardia only were not included as residual IM. Analysis was repeated to identify whether residual IM confers a higher risk of recurrence.

Data were analysed using the SPSS version 23 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 6.0 (GraphPad Software, Inc., La Jolla, California, USA). Comparisons between groups for available data were analysed using the χ^2 test for categorical variables or Independent T Test for non-parametric variables. Univariate Cox Regression was used to identify differences in dysplasia recurrence (survival). Multivariate Cox Regression was then run. Kaplan–Meier (KM) survival curves were used to analyse rates of recurrence and Log rank test was used to compare the difference in the rate of disease recurrence between the groups at latest follow-up.

5.3.3 Results

30 cases recorded as 'non-dysplastic BE' with C0M0 at the end of protocol endoscopy were identified. Following review; 17 cases had no visible CLE at endoscopy, 1 had visible CLE but no IM in biopsies from the tubular oesophagus, 3 records were unavailable for review and were excluded and the remaining 9 patients had IM and visible CLE.

5.3.3.1 Demographic data

577 patients with mucosal neoplasia achieved CR-D at the end of protocol and remain in active surveillance. 59 patients (10.2%) developed recurrent dysplasia ranging from 8 months to 71 months after follow up. No new differences were identified between those with recurrence and those without that have not been described previously (Table 5.9).

Table 5.9: Table comparing those with and without recurrence after CR-D

	No Recurrence (N=518)	Recurrence (N=59)	P value
Mean Age (Range)	67.6	67.4	0.86
Male	82%	79.6%	0.63
Baseline Histology - LGD - HGD - IMC	 6.9% 67.2% 25.9%	 6.8% 84.7% 8.5%	**0.011**
Mean baseline BE length at start of RFA (max extent, cm)	4.9	5.5	0.28
EMR prior to RFA	53.5%	49.2%	0.53
Rescue EMR during RFA treatment	2.9%	11.9%	**0.001**
Median time to end of protocol (months)	11.8	12.7	0.25
Number of RFA Sessions	2.5	2.8	0.076
Residual IM at end of Protocol	12.5%	25.4%	**0.007**
Mean Residual length (cm)	-	2.0	-
Median time to most recent biopsy from end of treatment for those still in follow-up (months)	17.5	16.1	0.53

5.3.3.2 Residual IM

Of the 577 patients who achieved CR-D, 513 achieved CR-IM and 63 achieved CR-D only with residual IM. The mean length of residual IM was 2cm (range 0.5cm-10cm). The CR-IM group were significantly younger (67 vs 70, p=0.032), had shorter baseline BE segments (4.8 vs 6.2cm, p=0.005) and were more likely to be free of dysplasia at their most recent follow up (91.1% vs 79.4%, p=0.007) (Table 5.10).

Table 5.10: Table comparing outcomes of those with and without residual IM at end of treatment protocol

	No Residual IM (N=514)	Residual IM (N=63)	P value
Mean Age (Range)	67.3	70.0	**0.032**
Male	82.5%	77.8%	0.358
Baseline Histology - LGD - HGD - IMC	 6.8% 70.2% 23.0%	 7.9% 58.7% 33.3%	 0.158
Mean baseline BE length at start of RFA (max extent, cm)	4.8	6.2	**0.005**
EMR prior to RFA	52.5%	57.1%	0.489
Rescue EMR during RFA treatment	3.5%	6.3%	0.265
Median time to end of protocol (months)	11.8	12.4	0.485
Number of RFA Sessions	2.6	2.4	0.191
Median time to most recent biopsy from end of treatment for those still in follow-up (months)	17.3	17.6	0.874
% Free of dysplasia at most recent follow-up	91.1%	79.4%	**0.007**

5.3.3.3 Univariate and Multivariate cox regression

The odds ratio of dysplasia recurrence in the presence of residual IM at the end of protocol was 2.143 (95% CI 1.155-3.976, *p*=0.016) (Table 5.11).

Table 5.11: Table showing Odds Ratio (OR) comparing those with and without residual IM at end of treatment protocol using univariable cox regression model

	OR	95 % CI	*P*-value
Without Residual IM	1		
With Residual IM	2.143	1.155 – 3.976	0.016
Age	1.005	0.978 - 1.032	0.732
Initial length	1.001	0.933 - 1.074	0.986

To investigate the effect of baseline imbalance between the two groups (CR-IM vs CR-D only), multivariate cox regression was run with the Age and the initial Length of Barrett's as covariates.

After adjusting for potentially these confounding factors, the OR comparing those with residual IM to those with CR-IM was 2.184 (95% CI 1.160-4.112, *p*=0.016) (Table 5.12).

Table 5.12: Table showing Odds Ratio (OR) of those with and without residual IM at end of treatment protocol using multivariable cox regression model

	OR	95 % CI	*P*-value
Without Residual IM	1		
With Residual IM	2.184	1.160 - 4.112	0.016
Age	1.003	0.976 - 1.030	0.855
Initial length	0.986	0.916 - 1.062	0.718

5.3.3.4 Dysplasia free survival

KM analysis predicts a 66% likelihood of remaining free of dysplasia at 4 years in those who achieved CR-D only at the end of protocol compared with 79% in those who achieved CR-IM; log rank 0=0.005 (Figure 5.5).

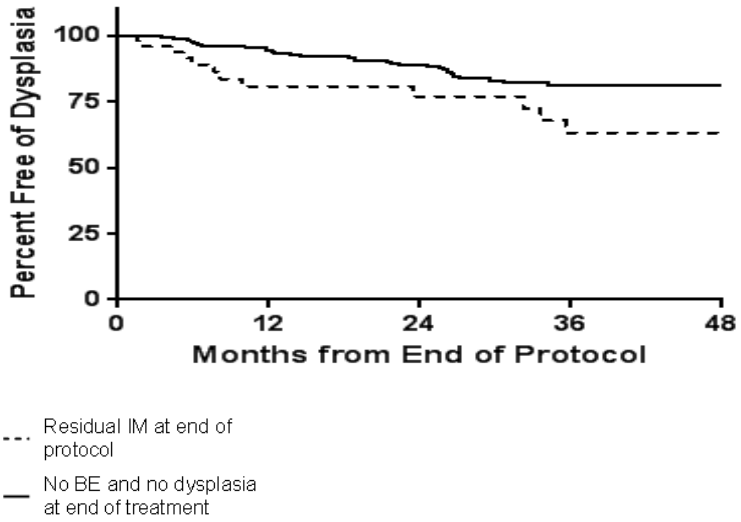


Figure 5.5: Kaplan Meier of Dysplasia Recurrence in those with and without Residual IM at end of Treatment Protocol (time zero = end of treatment). Log-rank (Mantel-Cox) test *P*= 0.005

5.3.4 Discussion

Increasing age and initial length of BO are known risk factors for dysplasia recurrence after successful CR-D (169). Previous work suggested residual IM posed no increased risk of recurrence (242), however the risk of metachronous lesions arising in the residual BO after EMR or PDT for dysplasia is up to 30% (176)(177). The UK RFA data reports an odds ratio of 2.3 (95% CI 1.2-4.4, p=0.01) of developing recurrent dysplasia in those with residual IM (and visible CLE) compared with those who achieve CR-IM at the end of the protocol. A reason for the discrepancy between previous work (242) may be the inclusion of patients with LGD in the UK outcomes or the larger numbers reported (577 compared with 246).

It remains unclear where the risk of recurrence within these patients is greatest. The Registry does not capture the location of dysplasia and it remains unclear if the risk is highest with the visible CLE or these patients with residual IM harbour an increased risk of buried glands and dysplasia developing beneath the re-epithelialised squamous mucosa.

It could be postulated that treatment for BO with RFA should continue until all visible CLE in the tubular oesophagus has been removed. The recent EURO II study protocol allows for rescue RFA or EMR at the end of the 12 month protocol. This approach in a clinical trial reports 4% dysplasia recurrence after a median follow-up of 27 months after end of treatment (166).

Follow-up surveillance strategies for those with residual IM may require shorter intervals between surveillance endoscopies and greater vigilance on the part of the endoscopist. However, it should be noted that most recurrence occurs within 3 years, particularly within the first 12 months in the residual IM group. This may represent the fact that residual IM only raises the risk of early recurrence or that the findings of dysplasia within

the first 12 months after treatment are not early recurrence but is residual disease that has been missed due to sampling error of random biopsies. To investigate whether there is a longer-term risk of residual IM at the end of treatment, only those with follow-up for more than 12 months could be analysed.

5.4 Residual IM at end of protocol and late dysplasia recurrence

5.4.1 Aim

Although there appears to be a significant difference in recurrence risk between those with and without residual IM at the end of treatment (in those that achieve CR-D), most recurrences, particularly in the residual IM group occur within 12 months. Therefore the increased risk conferred by residual IM may be limited to early recurrence. This analysis addresses whether residual IM at end of protocol confers an increase risk of late dysplasia recurrence, one year after completion of treatment.

5.4.2 Methods

Patients in surveillance for more than 12 months after the end of protocol and in on-going surveillance were included in the analysis. Residual IM was confirmed with histology and visible CLE at endoscopy. Statistical analysis was performed as has been previously described.

5.4.3 Results

5.4.3.1 Demographic data

310 patients with mucosal neoplasia achieved CR-D at the end of protocol and remain in active surveillance for more than one year. Of these, 30 patients (9.7%) developed recurrent dysplasia. On comparing those with recurrence and those without, there was no significant difference in age, baseline BE length, prior EMR rates, number of RFA treatments required or median time to follow up between the cohorts. There was no significant difference between the cohorts in entry histology, rescue EMR rates or residual IM at the end of protocol (p=0.085). There were a higher proportion of males in the recurrence group (p=0.045) (Table 5.13).

Table 5.13: Table comparing those with and without recurrence after CR-D and surveillance for more than 12 months

	No Recurrence (N=280)	Recurrence (N=30)	P value
Mean Age (Range)	66.9	66.5	0.836
Male	82.5%	96.7%	**0.045**
Baseline Histology			0.373
- LGD	5.0%	6.7%	
- HGD	70.4%	80.0%	
- IMC	24.6%	13.3%	
Mean baseline BE length at start of RFA (max extent, cm)	5.1	5.9	0.232
EMR prior to RFA	54.3%	43.3%	0.253
Rescue EMR during RFA treatment	3.2%	10.0%	0.067
Median time to end of protocol (months)	11.5	12.4	0.375
Number of RFA Sessions	2.7	2.8	0.530
Residual IM at end of Protocol	7.5%	16.7%	0.085
Median time to most recent biopsy from end of treatment for those still in follow-up (months)	29.4	25.3	0.059

5.4.3.2 Dysplasia free survival

KM analysis demonstrates no significant difference in the likelihood of remaining free of dysplasia at 4 years in those who achieved CR-D only at the end of protocol compared with those who achieved CR-IM; log rank 0=0.44 (Figure 5.6).

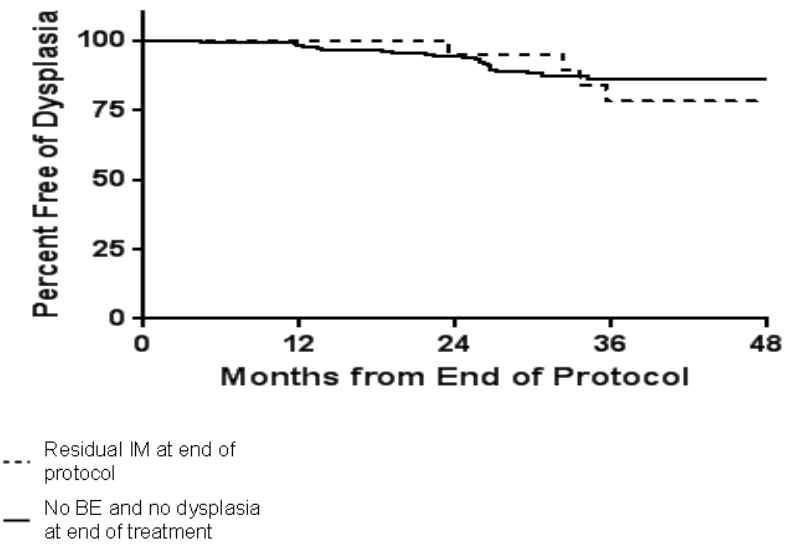


Figure 5.6: Kaplan Meier of Dysplasia Recurrence in those with and without Residual IM at end of Treatment Protocol (time zero = end of treatment). Log-rank (Mantel-Cox) test *P*= 0.44

5.4.4 Discussion

Previous studies have reported age and length of BO as risk factors for dysplasia recurrence (169). Data from the UK Registry reports residual IM confers increase risk (OR of 2.3) of dysplasia recurrence but most recurrence occurs early in the follow-up period. The recurrence rate in patients in surveillance for more than 12 months is 9.7% with a median follow-up of 29 months.

The analysis of patients with more than 12months follow-up presented here do not identify age or increasing BO length as risk factors, as has

previously been described. This may be due to the low numbers in surveillance for more than 12 months or that these factors are also associated with early recurrence.

Residual IM does not increase risk of dysplasia recurrence 12 months after completion of treatment. It may be that residual IM only raises the risk of early recurrence or that the findings of dysplasia within the first 12 months after treatment are not early recurrence but is residual disease that has been missed due to sampling error of random biopsies. To investigate this further and account for sampling error at surveillance endoscopies, 2 consecutive endoscopies with negative random biopsies may be required to confirm eradication of dysplasia. Therefore, repeating the analysis using patients with more than one negative biopsy should address whether residual IM confers an increased risk of early (within 12 months) dysplasia recurrence or is residual disease that has been missed on sampling.

5.5 Residual IM at the end of treatment and risk of early dysplasia recurrence

5.5.1 Aim

In patients who achieve CR-D at the end of treatment, those with residual IM appear to have an increased risk of early dysplasia recurrence. This increased risk compared to those who achieve CR-IM, does not appear to continue beyond 12 months. Perhaps this difference is not due to early recurrence but rather missed dysplasia and merely represents residual dysplasia? This analysis addresses the question of whether with a new, more robust definition of CR-D (2 consecutive endoscopies with negative biopsies rather than the previous single endoscopy with negative biopsies), does residual IM at the end of treatment confer an increased risk of dysplasia recurrence?

5.5.2 Method

Patients with follow-up data to May 2016 were included in the analysis. Only patients who completed treatment followed by at least 2 endoscopies with random biopsies were included in the analysis. Patients lost to follow-up were excluded. CR-D was defined as 2 consecutive endoscopies with normal biopsies. Residual IM and dysplasia recurrence was defined as previously described. Statistical analysis was performed as has been previously described.

5.5.3 Results

5.5.3.1 Demographic data

419 patients with mucosal neoplasia achieved CR-D (as defined by at least 2 consecutive endoscopies with normal biopsies) at the end of protocol and remain in active surveillance. Of these, 24 patients (5.7%) developed recurrent dysplasia. On comparing those with recurrence and

those without, there was no significant difference between the cohorts in residual IM at the end of protocol (No recurrence 7.8% vs Recurrence 12.5%, *p*=0.418).

5.5.3.2 Dysplasia free survival

KM analysis demonstrates no significant difference in the likelihood of remaining free of dysplasia at 5 years in those who achieved CR-D only at the end of protocol compared with those who achieved CR-IM; log rank 0=0.439 (Figure 5.7).

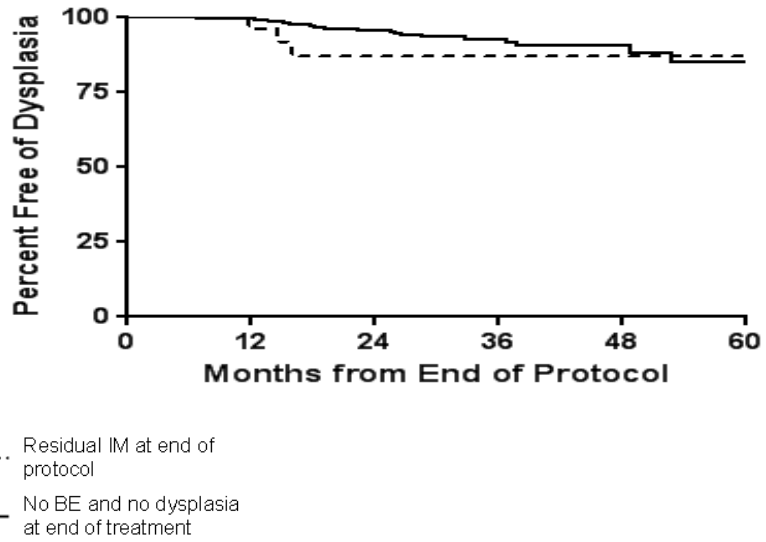


Figure 5.7: Kaplan Meier of Dysplasia Recurrence in those with and without Residual IM at end of Treatment Protocol (time zero = end of treatment). Log-rank (Mantel-Cox) test *P*= 0.44

5.5.4 Discussion

Risk factors for dysplasia recurrence include increasing age (Odds Ratio =1.02; 95% CI, 1.01-1.03) and length of BO (Odds Ratio = 1.10; 95% CI, 1.05-1.15) (169). Following successful CR-D, patients remain in a surveillance program to identify early recurrence that can continue to be treated with endoscopic therapies. Stratification of these patients is

increasingly important (171) and identifying further risk factors has clinical significance.

After several RFA treatments within a 12-month period, residual islands and / or tongues of visible CLE at the end of this period are not associated with dysplasia recurrence. This is despite previous studies suggesting a metachronous lesion rate of up to 30% in patients only treated with EMR or PDT (176)(177).

Interestingly, although initial analysis suggested residual IM confers an increased risk of dysplasia recurrence, after attempting to exclude cases of residual disease by changing the definition of CR-D to two successive endoscopies with negative random biopsies, this finding does not appear to be the case.

The new finding is in keeping with a single previous study of 135 patients with HGD and 111 with IMC who achieved CR-D at the end of RFA treatment. Recurrence of dysplasia was no different between those that achieved CR-IM and those with residual IM, whether they entered treatment with HGD (9% vs 8%; p=0.56) or IMC (7.4% vs 9.5%; p=054) (242).

5.5.5 Limitations

This study has several limitations. As a retrospective analysis, the fields captured in the database may not capture previously unrecognised confounding variables such as body mass index (BMI), tobacco history or a full medication history.

Multiple sites across the UK and Ireland enter data from the Registry. Clinical pressures result in significant variation in RFA treatment intervals and session within 12 months, although in this analysis no difference in RFA sessions was identified between cohorts.

The data entry site is an online portal and users do not always complete the fields correctly; as demonstrated by the 30 patients entered as C0M0 with biopsies confirming IM but only 9 of these patients truly had IM on histology and visible CLE. A further issue with online data capture, is the field for latest histology, which does not capture data on IM of the cardia. This may have been entered as IM of the tubular oesophagus in error, which could influence the analysis.

The Registry has been collecting data since 2008. During this time, the management of dysplasia arising in BO has changed; there is a greater focus on lesion detection and resection before RFA treatment begins, more recently low-grade dysplasia is treated with RFA whereas previously it would have been monitored and treatment success has improved with time (178).

The outcome of this study should not be dismissed because of the limitations described. Data from the UK RFA Registry reports on unselected patients; this represents the 'real world' clinical scenario that should and does influence our clinical practice. Although the initial question regarding residual IM post-protocol has been addressed, the analysis poses a far greater question. Do we need 2 consecutive endoscopies with normal biopsies to ensure we have confidently cleared dysplasia and IM? Future work to address this question could use the UK RFA Registry to assess treatment success (CR-D and CR-IM rates) and treatment durability (dysplasia recurrence) comparing the existing CR-D definition with the new suggested definition.

In summary, residual IM in visible CLE at the end of treatment for D-BE is not associated with dysplasia recurrence. The way we define CR-D may, however, influence outcomes from the UK RFA Registry and requires further investigation.

6 Summary and Proposals for Further Work

Oesophageal cancer is the eighth most common cancer worldwide (1) and carries a poor prognosis. Early detection is the key to early and successful treatment. Barrett's oesophagus is the only known precursor to oesophageal adenocarcinoma and can be detected with endoscopic assessment of the upper gastrointestinal tract.

Early identification of dysplasia through endoscopic surveillance of BE allows patients access to minimally-invasive endoscopic eradication therapy.

A simple classification system for detecting dysplasia has previously been validated using NBI (110) and the same classification system has been demonstrated to be effective with the use of *i*-Scan enhancements coupled with magnification endoscopy and acetic acid. This study is the first clinical study with endoscopic videos to validate this classification system using *i*-Scan technology and demonstrate a benefit in clinical practice through an improvised real time clinical scenario. The scenario was designed to reflect real-life endoscopic assessment of BE; a general view of the BE segment before focusing on areas of suspicion and repeating the process after application of acetic acid. Inter-observer agreement of the classification system was substantial when incorporated into a clinical decision-making protocol and mimics daily clinical practice. This study reports the first use of acetic acid as an adjunct to magnification endoscopy and demonstrates that the use of acetic acid should not be limited to the macroscopic assessment of BO. However, the results of this study do not meet the current PIVI thresholds for adopting *i*-Scan magnification endoscopy with acetic acid instead of the current practice of random biopsies and may reflect the low number of lesions reviewed, the prevalence of dysplasia in our sample population and the use of videos rather than still images.

Future work using the classification system should assess both still images and videos from the same cohort to quantify whether images are a valid reference tool, as most endoscopists rely on video footage rather than stills for diagnostic purposes. A study of still images using i-Scan technology rather than videos may result in a sensitivity, specificity and NPV of the Classification System to meet ASGE-PIVI thresholds, as the very highest quality still images are likely to be chosen for assessment. New *i-Scan* technology utilising light-filtering and post-processing technology with optical magnification may also improve the accuracy of dysplasia detection (223) and a larger study using *i*-Scan technology may enable PIVI thresholds to be met, particularly if micro-nodularity and superficial ulceration are included in the assessment.

Following the detection of dysplasia or early neoplasia within BO current guidelines recommending treatment have suggested competency requires specialists to perform a minimum of 30 EMR procedures. Centres within the UK RFA registry have varying degrees of experience treating patients and although outcomes improve with experience, the difference in outcomes between a high volume and low volume centre does not support further centralisation of services to only high volume centres. Previous analysis of the UK RFA registry has demonstrated improved outcomes with time (178) and data presented in this thesis demonstrates a similar effect, that the more cases a centre performs the better the outcome. After treating 40 patients with a combined EMR and RFA approach, outcomes are significantly better than for the first 20 patients treated in the same centre. Previous studies in this field have focused on either EMR as a stand-alone procedure or RFA in isolation (200,202). This analysis does not differentiate between the two procedures but assesses outcomes of all patients treated for dysplasia. The learning curves described in this study are a composite of both EMR and RFA treatment, an approach endorsed by the BSG (175). Based on the data, it would appear reasonable that the BSG recommendation of 30

supervised cases of endoscopic ablation can be lowered to 20 cases to achieve the required competencies.

A large proportion of patients that enter a treatment program do not complete the protocol, however, it is unclear whether they are still currently receiving treatment, or have been lost to follow-up during the course of treatment. Understanding what proportion of patients who start treatment but fail to complete therapy is an important metric of how successful a centre is at treating dysplastic BO. Future work to address the cause of why patients do not complete the treatment protocol is required and may influence future patent selection for treatment.

Following the completion of the treatment protocol, increasing age and length of initial BO are risk factors for dysplasia recurrence. As such patients continue to receive regular endoscopic surveillance. The data presented in this thesis demonstrates that residual IM at the end of a year-long treatment protocol is not a risk factor for dysplasia recurrence. Although these findings are reassuring for clinical practice the analysis poses a far greater question. How do we define treatment success and therefore dysplasia recurrence? Do we need 2 consecutive endoscopies with normal biopsies to ensure we have confidently cleared dysplasia and IM? Future work to address this question could use the UK RFA Registry to assess treatment success (CR-D and CR-IM rates) and treatment durability (dysplasia recurrence) comparing the existing CR-D definition with the new suggested definition.

I believe this thesis has addressed each of the aims that it set out to do.

Detection of dysplasia can be improved using novel *i*-Scan imaging with magnification endoscopy and chromoendoscopy in conjunction with a simple classification system. The use of technology in the clinical setting may improve detection and with further work may meet the PIVI criteria

to reduce the use of random biopsies.

Although cancer services have been centralized to improve outcomes, there data suggest that there is no difference in outcomes between larger and smaller volume centres treating Barrett's associated dysplasia and neoplasia. However, the BSG recommendation of 30 supervised cases of endoscopic ablation could be lowered to 20 cases to achieve the required competencies.

The focus of treating Barrett's associated dysplasia and neoplasia should not focus on treating all visible residual IM at the end of the treatment protocol to improve durability of therapy. However, the definition of treatment success or CR-D may require re-examination.

7 References

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