New Innovations in Endoscopic Therapy

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The content of this work is dedicated to my wife Nikki – Her love and support has helped me to reach my goals and will continue to do so for the years ahead.

And for my son Joseph and daughter Eve

STATEMENT OF ORIGINALITY

I, Durayd Alzoubaidi, confirm that the work presented in this thesis is my own and any contribution made to the research by colleagues, with whom I have worked at UCL, UCLH and elsewhere during my fellowship at UCL, are fully acknowledged.

I declare that this is a true copy of my thesis, including any final revisions, as approved by my thesis committee and the graduate studies office, and that this thesis has not been submitted for a higher degree to any other university or institution.

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Special thanks to Dr Rehan Haidry for his guidance and generosity throughout this work and for introducing me to the world of therapeutic endoscopy. He will always be my role model.

Peer reviewed publications associated with this thesis

Barrett's oesophagus and cancer risk: how research advances can impact clinical practice.
di Pietro M, **Alzoubaidi D**, Fitzgerald RC.
Gut Liver. 2014 Jul;8(4):356-70.

Management of non-variceal upper gastrointestinal bleeding: where are we in 2018?
Alzoubaidi D, Lovat LB, Haidry R.
Frontline Gastroenterol. 2019 Jan;10(1):35-42.

Comparison of two multiband mucosectomy devices for endoscopic resection of Barrett's oesophagus-related neoplasia.
Alzoubaidi D, Graham D, Bassett P, Magee C, Everson M, Banks M, Novelli M, Jansen M, Lovat LB, Haidry R.
Surg Endosc. 2019 Nov;33(11):3665-3672.

Quality Indicators for Barrett's EndoTherapy (QBET): UK consensus statements for patients undergoing Endoscopic therapy for Barrett's neoplasia.
D Alzoubaidi, K Ragunath, S Wani, I Penman, N Trudgill, M Jansen, M Banks, P Bhandari, AJ Morris, R Willert, P Boger, HL Smart, N Ravi, J Dunn, C Gordon, J Mannath, I Mainie, M Di Pietro, A Veitch, S Thorpe, C Magee, M Everson, S Sami, P Bassett, D Graham, S Attwood, O Pech, P Sharma, LB Lovat, R Haidry.
Frontline Gastroenterology 2019;0:1–13.

Outcomes from an international multicenter registry of patients with acute gastrointestinal bleeding undergoing endoscopic treatment with Hemospray.
Alzoubaidi D, Hussein M, Rusu R, Napier D, Dixon S, Rey JW, Steinheber C, Jameie-Oskooei S, Dahan M, Hayee B, Gulati S, Despott E, Murino A, Subramaniam S, Moreea S, Boger P, Hu M, Duarte P, Dunn J, Mainie I, McGoran J, Graham D, Anderson J, Bhandari P, Goetz M, Kiesslich R, Coron E, Lovat L, Haidry R.
Dig Endosc. 2020 Jan;32(1):96-105.

Cryoballoon ablation for the treatment of patients with refractory oesophageal neoplasia after first line endoscopic eradication therapy
Durayd Alzoubaidi, Mohamed Hussein, Vinay Sehgal, Christwishes Makahamadze, Cormac G Magee, Martin Everson, David Graham, Rami Sweis, Matthew Banks,
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CHAPTERS

ABBREVIATIONS USED IN THIS THESIS

AA	Acetic Acid
ACG	American College of Gastroenterology
AFI	Autofluorescence Imaging
AOL	Aspergillus Oryzae Lectin
APC	Argon Plasma Coagulation
ASGE	American Society for Gastrointestinal Endoscopy
AUGIB	Acute Upper Gastrointestinal Bleed
BD	Twice Daily
BE	Barrett's Oesophagus
BET	Barrett's Endoscopic Therapy
BLI	Blue Laser Imaging
BP	Blood Pressure
BSG	British Society of Gastroenterology
CA	California
CESG	Clinical Effectiveness Steering Group
CI	Confidence Interval
CLE	Confocal Laser Endomicroscopy
CO_2	Carbon Dioxide
CR-D	Complete Resolution of Dysplasia
CR-IM	Complete Resolution of Intestinal Metaplasia
DEP	Doppler Endoscopic Probe
DNA	Deoxyribonucleic Acid
DOAC	Direct Oral Anticoagulants
ECT	Ecarin Clotting Time
ED	Emergency Department
EET	Endoscopic Eradication Therapy
EMR	Endoscopic Mucosal Resection
ER	Endoscopic Resection
ESD	Endoscopic Submucosal Dissection
ESGE	European Society for Gastrointestinal Endoscopy
ET	Endoscopic Therapy
EUS	Endoscopic Ultrasound
FISH	Fluorescent In-Situ Hybridization
GBS	Glasgow Blatchford Score
GI	Gastro Intestinal
GOJ	Gastro Oesophageal Junction
GORD	Gastro Oesophageal Reflux Disease
GWAS	Genome-Wide Association Studies
Hb	Haemoglobin

HD	High Definition
HGD	High Grade Dysplasia
IC	Image Cytometry
IC	Indigo Carmine
IHC	Immunohistochemistry
IM	Intestinal Metaplasia
IMC	Intra Mucosal Carcinoma
IPR	Inter-Percentile Range
IPRAS	Interpercentile Range Adjusted for Symmetry
IQR	Inter Quartile Range
IR	Intervention Radiology
LGD	Low Grade Dysplasia
LN	Lymph Node
lncRNA	Long non-coding RNA
LOH	Loss Of Heterozygosity
MAD-M	Mean Absolute Deviation from the Median
MB	Methylene Blue
MBM	Multiband Mucosectomy
MDT	Multi-Disciplinary Team
miRNA	Micro RNA
NBI	Narrow Band Imaging
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NFκB	Nuclear Factor kappa B
NICE	National Institute for Health and Clinical Excellence
NO	Nitric Oxide
NSAID	Non-Steroidal Anti Inflammatory Drug
NVUGIB	Non-Variceal Upper Gastrointestinal Bleed
OAC	Oesophageal Adenocarcinoma
OCT	Optical coherence tomography
OE	Optical Enhancement
OR	Odds Ratio
OTSC	Over-The-Scope Clip
PCC	Prothrombin Complex Concentrate
PDT	Photodynamic Therapy
PPI	Proton Pump Inhibitors
PSI	Per Square Inch
PUD	Peptic Ulcer Disease
QBET	Quality Indicators in Barrett's Endoscopic Therapy
QI	Quality Indicators
RCT	Randomised Controlled Trials
REC	Research Ethics Committee
RFA	Radiofrequency Ablation
RNA	Ribonucleic Acid

ROS	Reactive Oxygen Species
RR	Relative Risk
RS	Rockall Score
SCC	Squamous Cell Carcinoma
SCJ	Squamo-Columnar Junction
SD	Standard Deviation
SM	Submucosal
TDS	Three times daily
TT	Thrombin Time
UCL	University College London
UCLA	University of California, Los Angeles
UCLH	University College London Hospital
UGIB	Upper Gastrointestinal Bleeding
UGIT	Upper Gastrointestinal Tract
UK	United Kingdom
US	United States
USA	Unites States of America
VCE	Video Capsule Endoscopy
WLE	White Light Endoscopy

Abstract:

Barrett's oesophagus (BE) is the pre-cancerous condition that leads to oesophageal adenocarcinoma (OAC). The progression of BE from intestinal metaplasia (IM) to dysplasia and OAC occurs in only a few patients. Once dysplasia and intramucosal cancer (IMC) has developed, these patients carry a significant risk of developing OAC. Despite significant advances in treatment modalities in the past decade, there still remains a high mortality rate with only a small number of patients alive at five years from diagnosis. Successful intervention at an early stage of the disease has been shown to have desirable outcomes.

Historically, surgical intervention with oesophagectomy in patients with early disease has shown to achieve curative outcomes. Oesophagectomy by experienced surgeons in high volume tertiary referral centres still carries a significant mortality rate (2-3%).

The development of minimally invasive endoscopic therapeutic modalities such as radiofrequency ablation (RFA), endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have revolutionised the management of patient with early oesophageal neoplasia with great outcomes and acceptable complication rates. These modalities have now been endorsed by various international guidelines; however despite current treatment modalities there still exists a group of patients that do not respond adequately to available treatment modalities and therefore this thesis and the chapters that follow will examine the new treatment modalities for the management of patients with early oesophageal neoplasia and will test the hypothesis that patients with early oesophageal neoplasia can be successfully treated with minimally invasive endoscopic

therapy. This thesis will outline the use of a new endoscopic resection modality (EMR Captivator device) with a new ablative technique (Cryoablation) that utilises cold therapy rather than the conventional heat therapy (RFA). This thesis will also outline new quality indicators in endoscopic therapy of early oesophageal neoplasia, which was developed, in order to unify endoscopic therapy in the UK.

It is well known that endoscopic therapy can result into adverse events such as bleeding during or/and after the procedure. Currently haemostatic modalities exits but not always effective and limited by the site of the bleed and skills of the operator. Hemospray, is a new haemostatic powder that is increasingly used internationally. This thesis will outline the creation and development of the international Hemospray registry, and study Hemospray in various pathologies.

Impact Statement

Research at UCL has allowed the development of new resection and ablative modalities in Barrett's Oesophagus (BE) endoscopic therapy (Chapter 2 in this thesis). The new Endoscopic Mucosal Resection (EMR) Captivator device has been shown to be as effective as the previously established Duette device. The new device is also able to resect larger neoplastic specimens in the oesophagus in comparison to the older Duette device. This new modality is now part of the routine clinical practice in BE endoscopic therapy at University College London Hospital (UCLH). The outcome from this project has now been published in a peer reviewed journal.

In addition the new Cryoballoon ablation device has been studies at UCL and shown to be an alternative mode of therapy in patients with refractory BE neoplasia that have not responded to conventional therapy in the past (Chapter 3 in this thesis). This new modality is now part of the routine clinical practice in BE endoscopic therapy at UCLH. The international cryoablation registry is currently in development, which is a continuation of the work that was done at UCL. The outcome from this project has now been published in peer reviewed journal.

Furthermore, the Quality Indicators in BE Endoscopic Therapy (QBET) project has successfully developed QI in BE endoscopic therapy aiming at unifying clinical practice in the UK (Chapter 4 in this thesis). The outcome from this project was accepted for oral presentation at United European Gastroenterology (UEG) 2018 and won the prize for best oral presentation. The outcome from this project has now been published in a peer reviewed journal.

The international Hemospray registry is the result of cooperation amongst multiple international gastroenterology specialists that resulted in publication of one of the largest series in the use of Hemospray in GI bleeding (Chapter 5 in this thesis). The outcome from this project was accepted for oral presentation at Digestive Diseases Week (DDW) 2018. The expansion of this registry has provided further insight in the efficacy of this haemostatic agent in GI bleeding and further publications from this ongoing project is underway. The outcome from this project has now been published in a peer reviewed journal.

CHAPTER 1

Introduction Part 1

Barrett's Oesophagus

Publications from this chapter

- di Pietro M, **Alzoubaidi D**, Fitzgerald RC. Barrett's esophagus and cancer risk: how research advances can impact clinical practice. Gut Liver. 2014 Jul;8(4):356-70

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PART 1

PART 2

1.1 Natural History, Incidence and Prevalence of Barrett's Oesophagus

Barrett's oesophagus (BE) is an acquired condition in which a metaplastic columnar lining with intestinal differentiation replaces the stratified squamous epithelium in the distal oesophagus. The metaplastic epithelium comprises three different cell types: atrophic gastric-fundic-type epithelium containing parietal and chief cells; a transitional-type epithelium with cardiac mucous secreting glands; and specialized columnar epithelium with intestinal-type goblet cells (1). While American gastroenterological societies consider the specialized epithelium with goblet cells a requirement for the diagnosis of BE, British guidelines consider the possibility of including BE with gastric metaplasia only (2)(3).

The true prevalence of Barrett's oesophagus is still unclear. The Italian and Swedish researchers have been able to show a prevalence of 1.3 % and 1.6 % respectively, although in both studies a selection bias may have led to overestimating the outcomes (4)(5). More recently, a systematic review and meta-analysis by Qumseya et analysed 49 studies (307,273 individuals, 1948 with biopsy specimen-proven BE). Indications varied by study. The prevalence of BE for various populations was as follows: low-risk general population, 0.8% (95% CI, .6%-1.1%); gastro oesophageal reflux disease (GORD) 3% (95% CI, 2.3%-4%); GERD plus presence of any other risk factor, 12.2% (95% CI, 10.2%-14.6%); family history, 23.4% (95% CI, 13.7% -37.2%); age >50, 6.1% (95% CI, 4.6%-8.1%); obesity, 1.9% (95% CI, 1.2%-3%); and male sex, 6.8% (95% CI, 5.3%-8.6%). Prevalence of BE varies significantly

between Western and non-Western populations. There is a positive linear relationship between the number of risk factors and the prevalence of BE (6).

BE generally develops in the context of GORD and it is about ten times more frequent in individuals who complain of reflux symptoms (7)(8). BE is the only known precursor to oesophageal adenocarcinoma (OAC), with an annual conversion rate of approximately 0.3% (9)(10)(11).

In recent UK statistics, the oesophagus was rated as the 7th most common cancer site among males and 14th among females; however, oesophageal malignancy was the 4th most common cause of cancer-related death in men and 6th in women in this geographical area. Although these data related to both of the most common histologic types, adenocarcinoma and squamous cell carcinoma (SCC), it is known that the overall prognosis of these two types of cancer is similar (12).

The discrepancy between incidence and mortality rates stems from the fact that oesophageal cancer is aggressive in nature and relatively asymptomatic at early stages leading to a low overall 5-year survival rate (<15%) (13)(14).

There is a large geographical variation in the incidence of oesophageal cancer (Figure 1a), with a higher incidence of SCC in African and Asian Countries. Notably, the incidence of oesophageal adenocarcinoma has been worryingly increasing over the last 3-4 decades in the Western World (figure 1b) (15)(16), where it has become the most common oesophageal malignancy (17)(18). In keeping with this, GORD is also increasing in incidence in the Western population (19)(20) and has been found to be the most common GI diagnosis in an outpatient setting in the US (21). This epidemiological picture has led to the question of whether screening programs for BE are justified (22). Since the gold standard for a

diagnosis of BE is endoscopy with biopsies, this screening method would be too costly and invasive to be applied to the general population. All of the most recently published guidelines do not recommend screening of the unselected population, but do suggest targeting the population at higher risk of BE (3)(2).

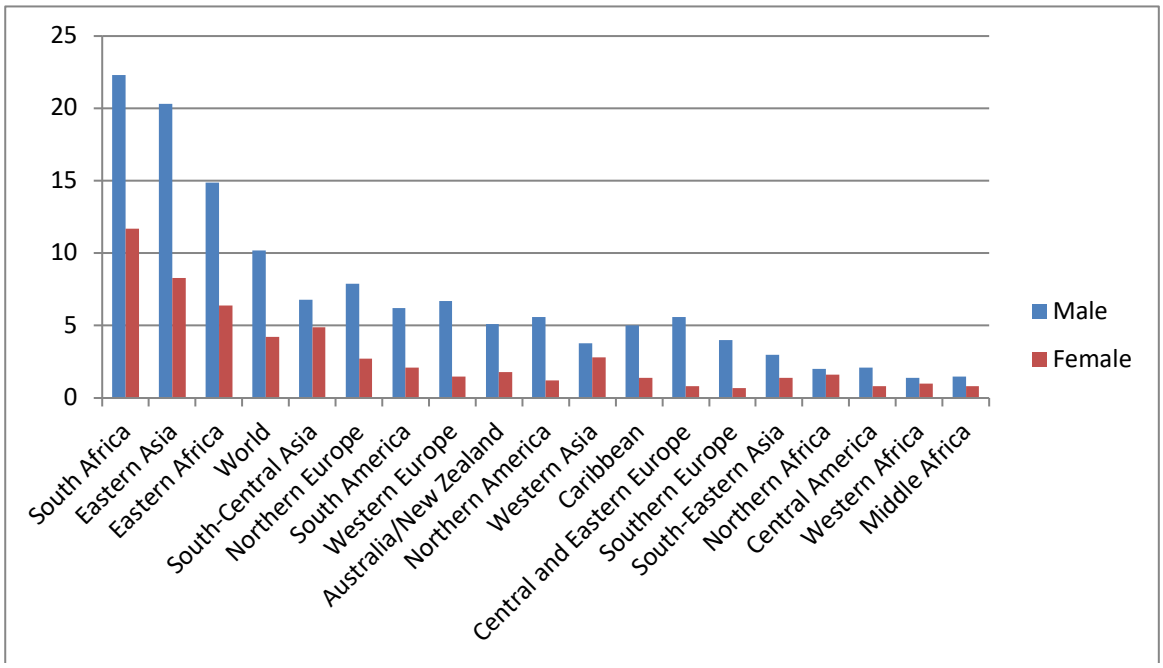


Figure 1a. World Age-Standardised Incidence Rates of oesophageal cancer per 100,000 Population. Estimates derived from Cancer Research UK statistics (Ferlay J)

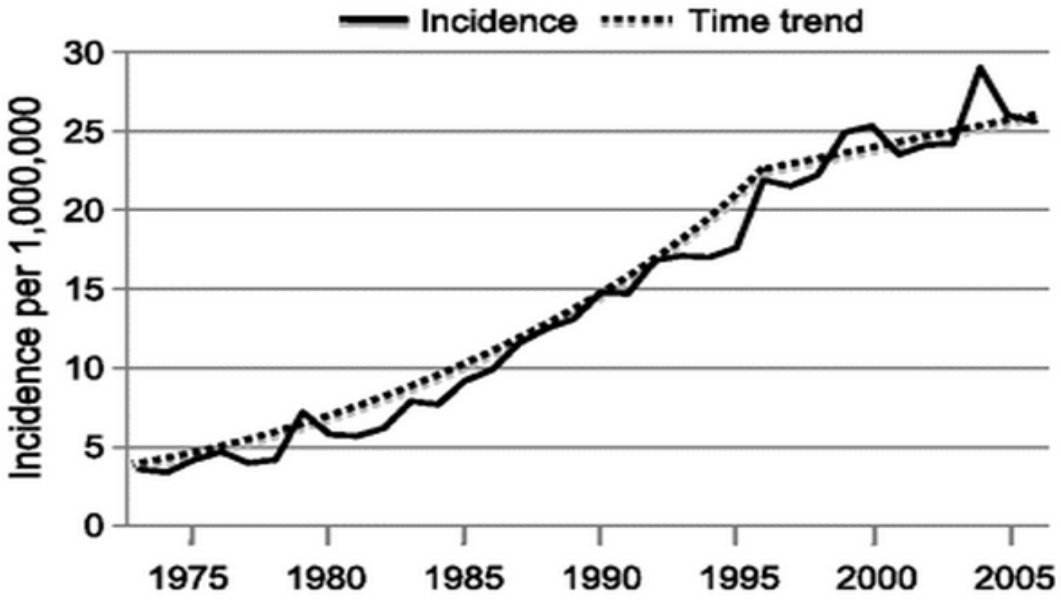


Figure 1b. Overall incidence trend in Oesophageal adenocarcinoma (1973-2006):

Pohl H, Sirovich B, Welch HG. Oesophageal adenocarcinoma incidence: are we reaching the peak? Cancer Epidemiol Biomarkers Prev. 2010 Jun;19(6):1468-70

1.2 Risk factors for Barrett's oesophagus

There are numerous risk factors for BE and they are generally shared with OAC. Gastro-oesophageal acid reflux is considered the most important factor. In a population-based case-control study, gastro-oesophageal reflux was associated with BE and OAC, with an odds ratio (OR) of 12.0 (95% CI 7.64-18.7) and 3.48 (95% CI 2.25-5.41), respectively (23). A recent meta-analysis showed that GORD symptoms increased the odds of long segment BE by fivefold (24). The prevalence of BE in patients with GORD varies between 3 and 15% amongst various studies (7)(8)(22)(23). This large range mostly relates to the stringency of criteria used for the selection of patients with reflux disease.

Obesity is the second strongest risk factor for the development of BE and OAC (4)(24). Obesity and GORD have synergistic effects according to a population-based case-control study, which demonstrated that obese individuals with symptoms of acid reflux had markedly higher risks of BE (OR, 34.4; 95% CI, 6.3-188) than people with reflux alone (OR, 9.3; 95% CI, 1.4-62.2) or obesity alone (OR, 0.7; 95% CI, 0.2-2.4) (25).

The distribution of fat also has a role in determining the risk in that large amount of visceral abdominal fat relative to subcutaneous fat is associated with a significant increase in the risk of BE (26)(27). Smokers and ex-smokers are also at increased risk of OAC (23). A meta-analysis demonstrated a strong association between cigarette smoking and OAC with a dose-response relation to disease outcome. In addition longer smoking cessation was associated with a decreased risk of adenocarcinoma (28); however, the association of smoking with BE remains controversial according to different studies (29)(30).

Other risk factors include male sex, white race, low vegetable intake and high red meat consumption, whereas data have showed an inverse correlation with Helicobacter Pylori infection (31)(32)(33)(34).

BE has also been shown to occur in familial clusters. Studies in different populations of patients with BE and OAC confirmed that about 7% of cases are familial (35)(36). Juhasz *et al,* studied 47 first degree relatives of patients with OAC and BE-related high-grade dysplasia from 23 families and confirmed BE in 13 relatives (27.7%) (37).

A genetic background to this disease is supported by genome-wide association studies (GWAS). A first GWAS report demonstrated that variants at two loci were associated with disease risk; chromosome 6p21, (OR=1.21, 95% CI 1.13-1.28), within the major histocompatibility complex locus, and chromosome 16q24, (OR=1.14, 95% CI 1.10-1.19), in close proximity to *FOXF1* gene, which is implicated in oesophageal development and structure (38).

In a second GWAS study Levine *et al,* compared OAC cases (n = 2,390) and individuals with BE (n = 3,175) with 10,120 controls. Three new association loci were identified; 19p13 within *CRTC1*, whose activation has been associated with oncogenic activity, 9q22 within *BARX1*, which encodes a transcription factor involved in oesophageal specification and 3p14 near the transcription factor *FOXP1*, which regulates oesophageal development (39). It is therefore justified to conclude that BE is a multifactorial disease with an interaction between environmental and genetic factors.

1.3 Molecular pathways related to BE development and progression to cancer

The cell of origin of BE within the oesophagus remains a controversial issue. Evidence in mice-models shows that BE may originate from progenitor cells present within the gastric cardia in close proximity with the gastro-oesophageal junction. Two models have been proposed to recapitulate the origin of BE. In *p63*-deficient mice, it was shown that the normal squamous re-epithelisation of the oesophagus during embryogenesis is impaired and this gives rise to upward migration of embryonic columnar remnant cells located at the level of the squamo-columnar junction (SCJ), generating a columnar epithelium reminiscent of BE (40).

Quante *et al*, showed that mice over-expressing interleukin-1β have an inflammatory response at the SCJ, which leads to a columnar lined oesophagus that is molecularly similar to BE (41). In these mice, increased oesophageal exposure to bile and acid triggered a sustained inflammatory response that reinforces Barrett's like carcinogenesis in a Notch-dependent fashion. Overall, these mouse models provide support to the theory that BE may originates from progenitor cells located at the SCJ and would explain why BE is generally in anatomical continuity with the cardia epithelium; however, the different anatomy of the murine oesophagus warrant further studies to translate these models into the human pathology. An alternative theory is that BE may originate through a process of trans-differentiation of squamous cells or reprogramming of oesophageal stem cell towards a different phenotype. This would likely involve epigenetic reprogramming of oesophageal

cells. In support of this theory is the evidence that genes normally involved in differentiation and gut axial specification are modulated in BE. Increased expression of the caudal-related gene CDX2 and CDX1, which are normally highly expressed in colon, has been shown in BE and related to the acquisition of the intestinal phenotype (42).

This gene regulation has been linked to change in the methylation status of the promoter (43) and associated to the acid/bile induced inflammation through the activation of nuclear factor kappa B (NFκB), a crucial transcription factor in the inflammatory response (44).

In addition, acquired deregulation of HOX genes during adulthood has been linked to carcinogenesis. Others have recently showed that three HOXB genes (*HOXB5*, *HOXB6*, and *HOXB7*) are activated in BE through an epigenetic mechanism involving histone post-translational modifications. Alterations to the HOX gene expression in oesophageal cells was associated with the induction of genes linked to an intestinal-phenotype (45).

The cell target of the epigenetic reprogramming of differentiation genes remain to be established, especially after lack of evidence of *bona fide* stem cells in the human oesophagus (46).

Chronic reflux of acid and bile into the oesophagus normally results in an acute and chronic inflammatory process. *In vivo* and *ex vivo* exposure of oesophageal cells to acid and bile salts can induce the production of reactive oxygen species (ROS) and nitric oxide (NO) (47)(48), which are related to oxidative DNA damage and double-strand breaks (49)(50). These events have been linked in general to carcinogenesis and metaplasia, dysplasia to cancer sequence in BE (49).

In addition, oxidative DNA damage in BE causes telomerase activation and telomere instability, which are known to result in mutation of cancer-related genes and promotion of cancer (51).

Inflammation is also related to recruitment of immune cells. Naive T cells , macrophages and dendritic cells are enriched in both non-dysplastic and dysplastic BE, as well as in OAC (52)(53)(54).

These cells could contribute to tumorigenesis through production of cytokines, chemokines and growth factors, which are released as part of the inflammatory response and can promote proliferation and angiogenesis (55).

Exposure to acid and bile salts has also been related to deregulation of microRNAs (miRNA), (56)(57) a class of short non-coding RNA involved in a variety of cellular processes. In particular miRNA-145 was linked to the activation of BMP4 pathway (58), which has been previously implicated in the development of BE through the activation of the Hedgehog pathway (59).

BE and OAC present a distinct miRNA expression profile (60)(61), which could be potentially useful for diagnostic purposes due to the fact that miRNAs are stable and detectable in blood (62).

Another class of non-coding RNA, long non-coding RNA (lncRNA), which have diverse cellular properties including gene regulation and control of cell growth and migration (63), has recently also been implicated in Barrett's carcinogenesis. Wu *et al,* showed that the lncRNA AFAP1-AS1 is hypomethylated and over-expressed in BE and OAC and its silencing in vitro, inhibited invasion and promoted apoptosis (64).

1.4 Clinical predictors of cancer risk

Until recently the only clinical factor with practical implications in the management of BE was the histological diagnosis of dysplasia. The two largest population studies in the N. Irish and Danish cohorts confirmed that the cancer risk in patients with low grade dysplasia (LGD) is approximately 5 times higher than non-dysplastic patients (9)(11).

It is standard practice to monitor patient with LGD at closer intervals. Unfortunately a histopathological diagnosis of dysplasia is often associated to a high degree of inter-observer variability even among expert GI pathologists, hence doubts have been shed on the exact clinical usefulness of this marker for patient stratification (65)(66).

There are additional clinical factors that have been shown to influence the risk of progression of BE to cancer. These clinical elements have the potential to inform the physician about the surveillance and management of patients with BE. Several studies have shown that increasing BE length is associated with higher risk of progression to high grade dysplasia (HGD) and malignancy (9)(10)(67)(68)(69).

The most common cut-off used in the literature for the definition of long segment of BE is 3 cm or more, however there is high variability in the literature in the cut-offs used. Overall it is justified to consider long segment of BE at higher risk. The 2013 British Society of Gastroenterology (BSG) guidelines for the management of BE recommend to tailor surveillance interval on basis of the length of the BE (2).

The North Irish population study has also found that the presence of intestinal metaplasia (IM) was associated with a hazard ratio for progression to cancer of 3.54 (95% CI 2.09-6.00)

(9); however, the issue of whether IM confers increased cancer risk conceptually applies only to countries, such as UK, where IM is not required for a diagnosis of BE (3)(2).

Visible endoscopic lesions including ulcers are also associated with a high risk HGD and early cancer and warrant close monitoring (70), but it must be recognized that the absence of dysplasia in the presence of visible lesions is often due to sampling error. Overall, it is clear that there is a paucity of clinical factors which can inform the physician about individual cancer risk and those that are currently used are affected by a significant degree of subjectivity either in the diagnosis, *i.e.* dysplasia, or in the definition, *i.e.* length. Hence there is the need for more objective risk stratification tools to inform patient management.

1.5 Molecular biomarkers

Molecular biomarkers have been investigated over the last decade in the field of BE with the aim of providing the physician with predictors of disease behaviour and hence aiding clinical management. The advantage of biomarkers over the current standard, i.e. dysplasia, relies on the possibility to provide an objective measure of the molecular changes in tissue, which are known to correlate with progression of disease. In addition, since molecular abnormalities can extend within the BE over larger epithelial surface than cellular dysplasia, they could be less subject to sampling error (71).

Gain or more rarely loss of individual chromosomes (aneuploidy) or duplication of the entire genome (tetraploidy) are common events in OAC and can precede the development of cancer or even dysplasia (Figure 2A) (72).

Gross abnormalities in the DNA content are tumorigenic since these can lead to altered expression of cancer-related genes. In particular loss of heterozygosity at tumour suppressor genes, such as p16 and p53, have been linked to acquisition of dysplasia in BE (73)(74).

Reid *et al*, have contributed significantly to the understanding of the timing and distribution of these molecular changes and have conducted large retrospective studies on prospectively collected samples to evaluate the usefulness of these biomarkers as cancer predictors. For example they have showed that among patients with non-dysplastic BE or at most LGD, those without aneuploidy had a 0% 5 year cumulative cancer incidence compared with 28% for those with aneuploidy (75).

In another study, the prevalence of 17p (p53) loss of heterozygosity (LOH) at baseline increased from 6% in non-dysplastic patients to 57% in patients with HGD. Using baseline 17p (p53) LOH as a predictor of progression in 325 patients with BE, those with this marker had increased risk of HGD and cancer with a relative risk (RR) of 3.6 (95% CI, 1.3 to 10) and 16 (95% CI, 6.2 to 39), respectively (76).

In a follow up study 3 biomarkers (abnormal DNA content, p53 LOH and p16 LOH) were evaluated as a panel in a cohort of 243 patients, and a step-wise increase in the cancer progression risk was found with increasing number of positive biomarkers. This showed a RR for cancer of 38.7 (95% CI 10.8-138.5) at 10 years of follow up when all three biomarkers were positive (77).

The main limitation of these studies was that assessment of aneuploidy was performed with a complex methodology involving flow-cytometric analysis on snap-frozen biopsies. However, it is now possible to assess aneuploidy with alternative techniques, which are potentially more applicable to clinical setting. One of them is image cytometry (IC), which can be performed on thick sections from paraffin embedded specimens. IC was showed to be comparable to flow-cytometry for the assessment of aneuploidy in BE tissue (78).

A retrospective case-control study confirmed that a panel consisting of LGD and two molecular biomarkers (aneuploidy by IC and immunohistochemistry (IHC) for Aspergillus oryzae lectin (AOL)) effectively separated progressors from non-progressors (79). Each individual positive marker was associated with an OR of 3.74 (95% CI 2.43-5.79) for progression to HGD/OAC. An alternative method for assessment of aneuploidy is fluorescent in-situ hybridization (FISH), which employs fluorescent probes to target specific DNA sequences. FISH has been studied in BE in combination with cytological brushings, which has the advantage over biopsies to sample larger epithelial areas. In particular it was found that

FISH for chromosome 7 and 17 was more accurate than IC for detection of aneuploidy on cytological preparations and could detect HGD/OAC with a sensitivity and a specificity of 85 and 84% respectively (80).

The same group used FISH to detect copy changes of cancer-related genes, such as *c-myc*, *EGFR* and 20q13 locus, which were found to be amplified in up to 14% and 50% of cases with HGD and OAC, respectively (81).

Similarly, a different group of authors found that FISH for 4 cancer-related loci (*c-myc*, *HER2*, 20q13 and *p16*) on brushing samples had better accuracy than conventional cytology or IC on brushings for the diagnosis of dysplasia (82).

Mutation in the tumour suppressor gene *p53* is the most recurrent genetic hit in OAC (83). P53 function is associated with G1 arrest during cell cycle and apoptosis; as a result, mutation of the *p53* gene will adversely affect control of cell proliferation and impair activation of apoptosis, promoting carcinogenesis (51)(84).

Mutation of *p53* leads to either stabilization of an inactive product or complete absence of the protein. Both events can be efficiently detected by IHC, which is a cost-effective test applicable to clinical setting (Figure 2B) (85).

A case-control study by Murray and co-workers found that abnormal p53 protein expression was associated with progression to OAC at follow up, with an OR of 11.7 (95% CI 1.93, 71.7) (86).

It was proposed that p53 expression can be used as biomarker of malignant expression in BE, however due to the low sensitivity it was also suggested that additional biomarkers would be needed as adjunct. These results have been confirmed in a larger case controlled study on 720 patients with BE, where p53 protein expression was associated with an

increased risk of neoplastic progression (RR 5.6, 95% CI 3.1-10.3) and proved to be a more powerful predictor of neoplastic progression than histological diagnosis of LGD (87).

P53 IHC has also been shown to be a useful adjunct to the histopathological diagnosis of dysplasia, assisting the pathologist in interpreting less straightforward pathological patterns (88).

In keeping with this, the 2013 BSG guidelines recommend the use of p53 IHC as adjunct to conventional histopathology (2).

Promoter hypermethylation can lead to silencing of gene expression and cancer and has been shown to be associated with widespread epigenetic changes involving global DNA hypomethylation and targeted hypermethylation of tumour suppressor genes (89).

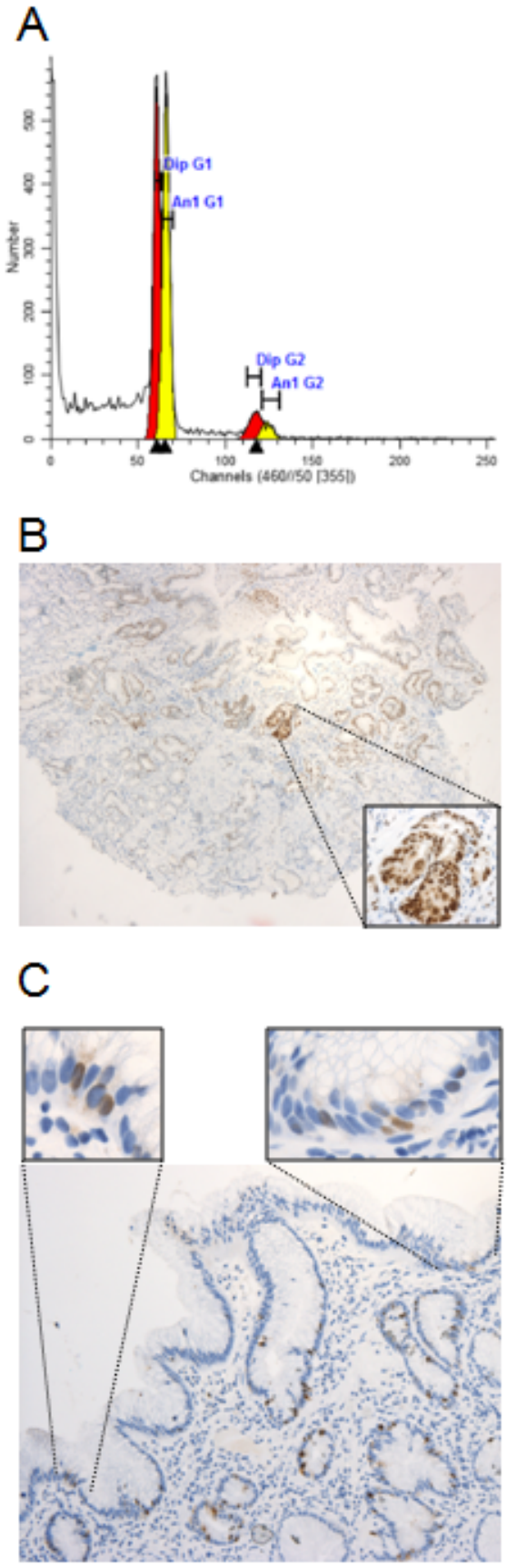
Kaz *et al*, used a microarray-based approach on 96 oesophageal samples to determine the methylation profiles of normal oesophagus, non-dysplastic BE, BE with HGD and OAC, and they found increasing methylation levels at gene promoters along the pathological progression (90). Hence, similarly to p53, methylation markers could represent a useful adjunct to histopathology. In a different study, a four-gene (SLC22A18, PIGR, GJA12, and RIN2) methylation panel was found to stratify patients with different stages of BE into three risk groups based on the number of genes methylated, with potential clinical utility (low risk: <2 genes, intermediate: 2, and high: >2) (91). Hypermethylation of p16 and APC was also found to be associated with dysplasia at a biopsy level and correlate with cancer risk at a patient level, with an OR for combined HGD/OAC of 14.97 (95% CI 1.7-inf) when both genes were methylated (92).

In a different study methylation of 10 genes (HPP1, RUNX3, RIZ1, CRBP1, 3-OST-2, APC, TIMP3, p16, MGMT, p14) were analysed in a large cohort of OAC cases (n=77), BE (n=93)

and normal oesophageal specimens (n=64). Three of them, p16, RUNX3 and HPP1, showed the most significant hypermethylation levels in cancer and in a case control cohort were associated with the risk of histological progression of BE to cancer at 2 year follow up with an OR of 1.74 (95% CI 1.33-2.2), 1.8 (95% CI 1.08-2.81) and 1.77 (95% CI 1.06-2.81), respectively (93).

Cyclin A is a protein that is involved in the regulation of progression through the cell cycle. In normal columnar gastrointestinal tissue, including non-dysplastic BE, the expression of cyclin A is confined to the base of the crypts. With increasing grades of dysplasia, the expression of cyclin A moves towards the upper third of the crypts and the surface epithelium (Figure 2C). In a study including 16 cases of BE that progressed to cancer and twice as many non-progressor controls, surface expression of cyclin A correlated with the risk of progression with an OR for cancer of 7.5 (95% CI 1.8-30.7) (94).

Despite the large number of molecular biomarkers studied, there is generally a lack of large prospective studies that have validated these and this has made introduction into clinical practice problematic. The biomarker with the largest data available is p53 IHC, which, due to the ample validation in independent cohorts and simplicity of the methodology, is currently in clinical application. Aneuploidy is also very promising, but validation with the use of cost-effective techniques is needed to make it compatible with a clinical setting.


A
Dip G1
An1 G1
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Number
Channels (460/50 [355])
B
C

Figure 2. Patient with Barrett's oesophagus with positivity at 3 different biomarkers. A Flow-cytometric analysis of nuclear DNA content. The aneuploidy peaks (AnG1 and AnG2) can be clearly identified separately from the normal G1 and G2 peaks. B. Over-expression of p53 detected by immunohistochemistry (10x magnification). C. Immunohistochemistry staining for cyclin A shows positive cells on the surface of the epithelium (inserts 40x). Positive cells in deep glands are considered within the normal limit

1.6 Guidelines

There are recent guidelines on screening and management of patients with BE; however, recent data have not provided strong evidence to support screening programmes. The American Society of Gastrointestinal Endoscopy (ASGE) guidelines concluded that endoscopic screening for BE is controversial due to lack of randomised controlled trials (RCT), hence it cannot be recommended (95).

On the other hand, the European Society of Gastrointestinal Endoscopy (ESGE) recommends endoscopic surveillance based on the length of the segment of BE, taking into account patient's age and co-morbidities. The ESGE does not recommend screening of the general population but screening can be considered in patients with long standing reflux symptoms (>5 years) and multiple risk factors (age ≥ 50 years, white race, male sex, obesity, first-degree relative with BE or OAC (96).

. This recommendation is in agreement with that issued by the BSG, which however is more practical with respect to the definition of the population at risk when considering multiple risk factors. These guidelines state that endoscopic screening should be taken into account in a selected population with gastro oesophageal reflux symptoms and multiple risk factors (at least three of age 50 years or older, white race, male sex, obesity) (2).

It is also advised that for individuals with a positive family history of BE and OAC the threshold for screening should be lowered. The issue of whether screening should focus on individuals with reflux symptoms remains unresolved. On the other hand, GORD is the strongest risk factor for BE and OAC, and included as generic risk factor among others, may

result in justifying screening in a large population of individual (e.g. every white male over 50 years of age), with significant burden on the health care system. Clearly there is a need to tailor recommendations for screening interventions in order to target the largest proportion of patients with prevalent disease, without exposing an unjustified number of individuals to procedures which may generate psychological morbidity, reduce the quality of life and increase insurance premiums in places where health provision is mainly insurance based. In addition, screening performed with conventional endoscopy and tissue biopsies is expensive and would have significant bearing on the health care budget. Hence there is a need for less invasive and cost-effective modalities for BE screening, ideally applicable to primary care. Non-endoscopic cell collection devices like the Cytosponge^{TM}, office-based transnasal oesophagoscopy and tethered or un-tethered capsule endoscopy are the most promising tools but more studies are required to make conclusions regarding their diagnostic accuracy and feasibility on a larger scale (22).

Surveillance in BE is also a controversial issue. While it is generally accepted that patients with BE should be monitored over time, definitive evidence that systematic endoscopic surveillance improves survival is still lacking. Several retrospective studies have showed that OAC and junctional adenocarcinomas diagnosed within a previous background of known BE have an earlier stage and improved survival compared to cancers presenting *de novo* (97)(98)(99); however, these studies are limited by lead time bias. By contrast, a case-control study from Corley *et al,* has suggested that previous endoscopic surveillance has no significant impact on mortality from OAC (100); however, the study found an unusually high prevalence of advanced stage cancers in patients undergoing surveillance, suggesting that in this cohort of patients endoscopic surveillance did not efficiently achieve the expected goal of detecting early disease. Also in this study, there was a higher proportion of dysplasia in

previous biopsies of cases that died of OAC compared to controls that did not die of this disease. Hence, there may be methodological problems with surveillance protocols in routine practice outside of specialist centres. Nevertheless the practice of surveillance is generally accepted and recommended by all gastroenterology societies.

The surveillance programmes recommended by the British Society of Gastroenterology (BSG), the American Society for Gastrointestinal Endoscopy (ASGE) and the European Society of Gastrointestinal Endoscopy (ESGE) are summarized in table 1. Overall, while we wait for convincing evidence that endoscopic surveillance is beneficial, in view of the well-established association between BE and OAC and the very poor outcomes from this cancer, it seems clinically sensible to survey BE patients over time.

One of the main implications of widespread surveillance is that the current gold standard is endoscopy with biopsies, which is invasive and expensive. Research is focusing currently on two directions to improve cost-effectiveness of surveillance. As discussed above, one is the development of biomarkers to risk stratify patients into low and high risk individuals. The rationale is to provide a more objective assessment of the individual cancer risk to overcome the shortfalls of a pathological assessment of dysplasia. This would allow stretching out intervals for surveillance in low risk patients with the potential to discharge them and on the other hand anticipate ablation treatment in high risk patients. The second research goal is to devise less invasive and more cost-effective technologies for surveillance. Differently from screening devices, those applicable to surveillance setting would need some form of tissue collection either for pathological analysis or biomarker assessment.

Currently little progress has been made with regards to chemoprevention, and this remains a key area for investigation. There are retrospective data that suggest that proton pump in-

hibitors (PPI) correlate with decreased risk of HGD and OAC (101), but definitive proof is lacking due to difficulties in designing RCTs with a placebo arm. The only drug that has made its way to an RCT is aspirin (AspECT study). Aspirin inhibits cyclooxygenase 1 and 2 (COX-1 and COX-2), regulator enzymes of prostaglandin E_2 production, which has been shown to be involved in angiogenesis and invasiveness in OAC and other GI malignancy (102)(103)(104). The study concluded that High-dose PPI and aspirin chemoprevention therapy, especially in combination, significantly and safely improved outcomes in patients with Barrett's oesophagus (105).

	BSG (2020)		ASGE (2018)	ESGE (2017)	
Non-dysplastic B0					
Length of BE taken into consideration	YES		NO	YES	
Gastric metaplasia compatible with BE diagnosis	YES		NO	YES	
Surveillance interval	BE < 3cm	BE> 3cm	Surveillance interval not stated	BE < 3cm	BE> 3cm
	3-5 years	2-3 years		5 years	3 years
HD WLE recommended	YES		YES	YES	
Indefinite for Dysplasia					
Acid suppression advised	YES		No recommendation made	YES	
Repeat OGD advised	YES in 6 months#			YES in 6 months#	
Low Grade Dysplasia					
Surveillance or EET	EET is recommended		EET is recommended	EET is recommended	
High Grade Dysplasia					
Surveillance or EET	MDT discussion with the view to perform EET		EET is recommended	EET is recommended	

Table 1. Comparison of surveillance recommendations in recently published guidelines.

if no definite dysplasia found in 6 month, patient should be regarded as non-dysplastic

BSG, British Society of Gastroenterology; ASGE, American Society for Gastrointestinal Endoscopy; ESGE, European Society of Gastrointestinal Endoscopy; BE, Barrett's oesophagus; OGD, Oesophagogastroduodenoscopy; MDT, Multi-Disciplinary Team; EET, Endoscopic Eradication Therapy.

1.7 Advanced endoscopic imaging to identify high risk patients

There has been a great deal of research in an attempt to develop novel endoscopic techniques to enhance detection of inconspicuous dysplasia (table 2). This would have the potential advantage of enabling biopsies to be targeted towards areas containing histological dysplasia and eliminate the need of multiple random sampling. The benefit would include, better cost-effectiveness due to shorter endoscopies and reduced work-load for the pathologist and Improved patient tolerance. Three main fields have been explored so far; i.e. dye chromoendoscopy, light filtering and electronic image reprocessing.

Chromoendoscopy is a technique by which a chemical agent is sprayed on the Barrett's mucosa in an attempt to enhance the detection of dysplasia. Several different agents have been studied including methylene blue (MB), Lugol's solution, indigo carmine (IC) and acetic acid (AA). MB is a vital agent that is avidly incorporated by cells with intestinal differentiation and has been the first dye investigated in the field of BE. There are conflicting results on the utility of MB in dysplasia detection. A meta-analysis by Ngamruengphong *et al* concluded that methylene blue does not provide a clinical advantage compared to the Seattle protocol (random quadrantic biopsies every 2 cm) (106).

IC is a contrast agent which helps highlight areas of subtle mucosal irregularity which are otherwise very difficult to identify on conventional white light endoscopy. IC has been studied by Kara and collaborators in a randomized crossover study, which compared high

resolution endoscopy (HRE), IC chromoendoscopy and NBI (107). In this study, HRE has equal yield of dysplasia compared to advanced imaging techniques.

Acetic acid (AA) at the concentration of 2-3% is an inexpensive and safe imaging adjunct that when in contact with surface epithelium causes protein denaturation and induces a typical whitening effect on BE mucosa. Increased vascularisation of areas of early neoplasia results in enhanced and rapid loss of aceto-whitening, which appears as area of redness on a white background. Despite two early randomized studies which failed to show increased detection rate of dysplasia by AA chromoendoscopy (108)(109), a more recent large single-centre retrospective study has found a higher histological yield in patients which received AA enhanced chromoendoscopy (110).

1.8 Imaging in BE endoscopy

Narrow band imaging (NBI) is based on optical filters controlled by a button switch, which allows one to isolate narrow wave-lengths corresponding to the green and blue spectra of light. In the blue-green range light has reduced penetration into tissues and therefore this helps visualization of superficial vessels and mucosal pits (111)(figure 3).

NBI can be less time consuming and easier to perform in comparison to white light endoscopy, but it is still subject to inter-observer variability. A prospective study with a tandem design, Wolfsen and collaborators showed that NBI was superior to standard-resolution white light endoscopy with random biopsies for the detection of higher grades of dysplasia (112).

A more recent multi-centre randomized cross-over study which compared NBI with high-resolution white light endoscopy only found a higher histological yield on the per-location analysis but not in the per-patient analysis, suggesting that the clinical overall value of NBI may be limited (113). NBI however required fewer biopsies per patient compared with the standard approach, which may lead to cost savings.

A meta-analysis by Mannath *et al* included 446 patients with 2194 lesions, reported that NBI with magnification shows high diagnostic precision in detecting high-grade dysplasia, with a sensitivity of 96% and specificity of 94% (114).

A B

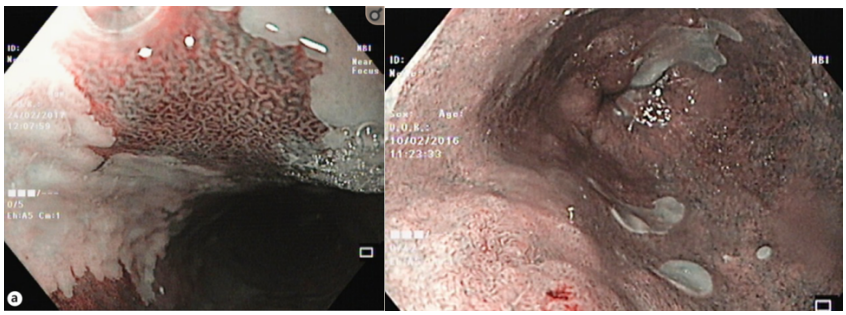

Figure 3. Narrow band imaging in A) Non-dysplastic BE and B) dysplastic BE

Autofluorescence imaging (AFI) utilizes high frequency blue light, which has the property to excite endogenous fluorophores to emit green fluorescence. In the presence of BE with early neoplasia, architectural and molecular changes in the columnar mucosa lead to reduction of green fluorescence. Dysplastic lesions therefore can be flagged-up as purple-red areas on a green background (figure 4). Despite early enthusiasm for the utility of AFI in dysplasia detection (115)(116), two cross-over studies and a recent analysis of available clinical trials have showed a very limited diagnostic value in this technology for BE endoscopic surveillance (117)(118). This is partly due to the high false positive rate of AFI, which in some studies has reached 80%. The significance of this false positivity is not yet clear. A multicentre European study by Boerwinkel *et al*, analysed biopsies directed by AFI for a large panel of molecular biomarkers and the outcome of the biomarker analysis was compared with that of the Seattle protocol. This study showed that AFI positivity correlated with molecular abnormalities of the BE tissue and even if that area was not dysplastic on a

focal biopsy there was a very high correlation between the molecular read-out from these areas and the overall dysplasia status of the patient (119). In the per-patient analysis, a small panel of 3 biomarkers (p53 IHC, cyclin A and aneuploidy) assessed on AFI positive areas had equal diagnostic accuracy to the Seattle protocol. AFI could therefore be a useful tool to direct biopsies for the detection of biomarkers and hence more objectively determine the risk status of the patient. In the future the combination of advanced imaging and molecular biomarkers could represent an improved strategy for improved stratification of BE patients (120).

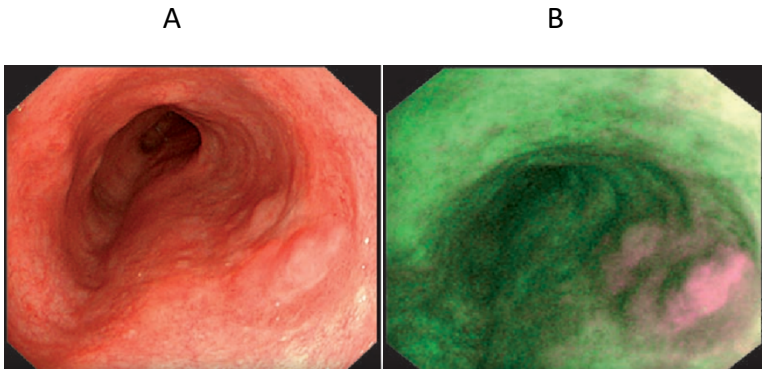

Figure 4. White light (A) and autofluorescence imaging (B) image of a neoplastic lesion in a Barrett's Oesophagus.

1.9 Other imaging technologies

Other imaging technologies include confocal laser endomicroscopy, optical coherence tomography, diffuse reflectance spectroscopy and light scattering spectroscopy.

Confocal laser endomicroscopy (CLE) allows for high resolution assessment of the mucosa using endoscopically delivered laser light with magnification beyond 1000× allowing for imaging of cellular and sub cellular structures and capillaries (121)(figure 5).

An international multicentre prospective randomized controlled trial by Sharma *et al* has shown that probe-based CLE used as part of a multi-modal imaging approach in combination with high-definition white-light endoscopy (HD-WLE) and NBI improves the sensitivity for dysplasia detection compared with HD-WLE alone (122). Another randomized controlled trial on 192 patients compared HD-WLE with Seattle protocol vs HD-WLE plus endoscope-integrated CLE (eCLE) and targeted biopsies (123). This study found that the addition of eCLE increased the diagnostic yield for neoplasia from 6 to 22%, with a 4.8 fold reduction in the number of total biopsies required; however, the main issue of CLE is the narrow field of view and the best flagging technique to direct the operator as to which regions to analyse with the CLE probe remains to be established.

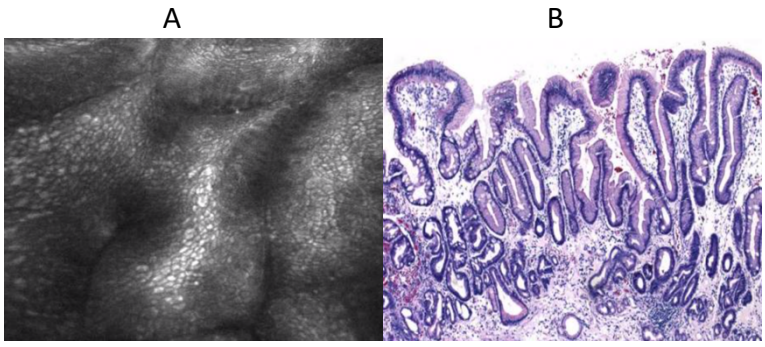

Figure 5. Confocal laser endomicroscopy showing regular shaped columnar lined epithelium with goblet cells (A) and histological image of BE with goblet cells (B).

Optical coherence tomography (OCT) relies on the backscattering of light to obtain cross-sectional images of the tissue. It enhances the endoscopic image of the superficial layers of the oesophagus. The technique is similar to endosonography, but the image formation in OCT depends on variations in the reflectance of light from different tissue layers (figure 6). OCT imaging has demonstrated anatomic structures such as crypts and glands that could potentially permit endoscopists to diagnose mucosal abnormalities such as BE, including dysplastic changes (124)(125).

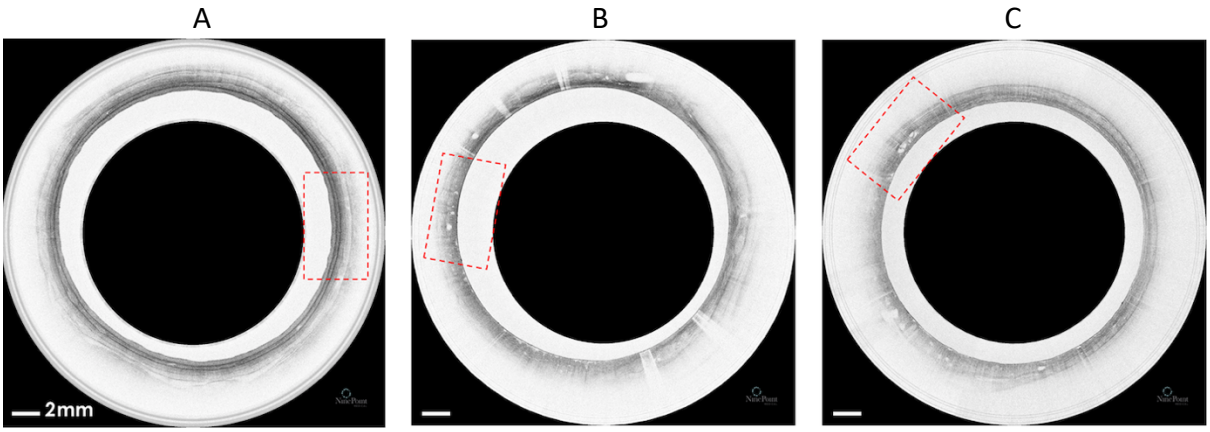

Figure 6. Optical coherence tomography (OCT) in normal oesophagus shows well defined layered structure (A), dysplastic BE shows loss of layering and irregular glands (B) and in oesophageal cancer with loss of layering (C)

Currently there is insufficient evidence to recommend advanced imaging modalities for routine Barrett's surveillance. High-resolution endoscopy should be the minimum standard and the addition of more complex imaging modalities should be reserved to tertiary referral centres with a high volume of dysplastic cases. In the future multi-modal imaging, in combination with molecular information has the potential to overcome many of the limitations of the current clinical standard.

Technique	Advantages	Disadvantages
Methylene blue chromoendoscopy	• Cheap • Widely available	• Conflicting data • Concerns about DNA toxicity
Indigo Carmine chromoendoscopy	• Cheap • Widely available	• Comparable to HRE
Acetic acid chromoendoscopy	• Cheap • Widely available	• Conflicting data • Validation required
Narrow Band Imaging	• Widely available • Endoscope integrated	• Conflicting data • Narrow field if combined to magnification
Autofluorescence Imaging	• Endoscope integrated • Easy read out • Wide field of view	• Conflicting data • High false positive rate • Not widely available
Confocal laser endomicroscopy	• Real time histology • Compatible with other red flag techniques	• Narrow field of view • Costs • Intravenous dye required
Optical coherence tomography	• Real time readout of histological patterns • Wide field of view	• Preliminary data only • Complex readout of imaging patterns • Costs

Table 2. Comparison of imaging techniques investigated to increase detection rate of dysplasia in Barrett's oesophagus

1.10 Endoscopic Treatment of BE

Endoscopic treatment for BE is dependent on the staging of the disease and is indicated for patients with BE LGD, HGD, mucosal OAC and 'low-risk' submucosal OAC (SM1 disease). Endoscopic therapy is the preferred treatment modality over surgery. The aim of endoscopic therapy is to resect all visible lesions followed by ablation of all remaining segments of BE (2)(96)(126). Ablation is not used as the primary treatment modality for early cancer in BE patients with endoscopically visible lesions due to the fact that post ablation, the treated mucosa will no longer be suitable for accurate staging, whereas in the absence of endoscopically visible lesions, ablative therapy is considered to be the appropriate treatment modality.

Endoscopic therapy for non-dysplastic BE is not recommended due to low risk of conversion to HGD and OAC but surveillance of non-dysplastic BE has been recommended by international guidelines.

1.10.1 Endoscopic Mucosal Resection (EMR)

Patients with BE lesion containing dysplasia and early OAC (SM1 disease) should receive EMR as the initial endoscopic therapy taking into account patient's wishes and co-morbidities. EMR will also allow accurate staging of disease. The tissue specimens will provide data on prognostic factors, such as grade of dysplasia, differentiation grade, infiltration depth, vascular invasion and completeness of the resection. EMR of all visible lesions has been shown to upgrade the pathological diagnosis in 39% of all patients. Most of

the change is associated with upgrading of grade of dysplasia and neoplasia. A study by Peters *et al* analysed 150 EMR specimens with dysplasia and early OAC. The study was able to show that Histology of EMR specimens led to a change in diagnosis in 49% of the focal lesions (in comparison to the original biopsies obtained by simple biopsy) and subsequently resulting in a change in treatment policy in 30% of patients (127).

Historically, the cap based system with snare (Olympus Ltd.), initially described in Japan by Inoue *et al*, (128) was used. It is an ER modality that uses a transparent cap placed distally at the tip of an endoscope. It allows the placement of a snare in the cap prior to resection. After submucosal injection for lifting, the mucosa is suctioned into the cap to create a pseudopolyp. The pseudopolyp is then resected by closing the snare at the base of the pseudopolyp and applying electrocautery. This technique is a rather complicated and results in prolonged procedure time in cases requiring multiple resections (129). Cap EMR has a role in select cases but has now been widely replaced by the custom made multiband mucosectomy (MBM) devices that utilises a transparent cap placed distally at the tip of an endoscope. The cap carries multiple pre-loaded rubber bands that are connected to a hand operated controller fixed at the proximal aspect of the accessory channel. The mucosa is suctioned into the transparent cap, followed by release of a band, resulting in creation of a pseudopolyp. The injection of the submucosal space is not routinely required. A snare is passed through the accessory channel of the endoscope and then is placed and closed at the base of the pseudopolyp, beneath the band. The pseudopolyp is then resected using electrocautery (130). This is a less complicated method as it combines the commonly known techniques of variceal band ligation and polypectomy (129).

The most commonly utilized MBM device is the Duette® Multi-Band Mucosectomy device (Cook Medical, Limerick, Ireland) (131). It is a modified version of the variceal band ligator that allows the passage of a snare into the working channel of the endoscope (Figure 7) (132).

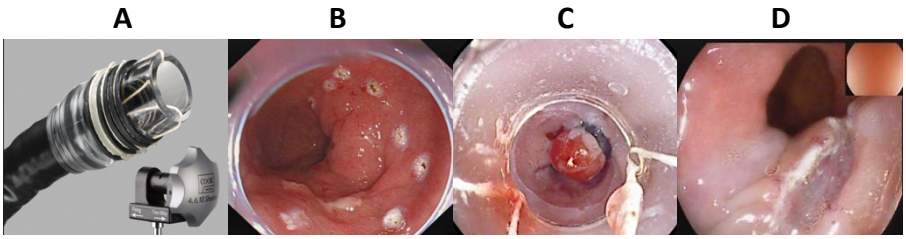

Figure 7: Duette EMR device: The single use Duette MBM device consists of a transparent cap with 6 rubber bands and a control handle (A). The transparent cap is mounted at the tip of the endoscope. With a trigger cord, the 6 rubber bands on the outside of the transparent cap are connected to the control handle at the proximal end of the accessory channel. Without prior submucosal injection for lifting, the neoplastic lesion is delineated with the tip of the hot snare (B) and suctioned into the cap until a complete red out occurred on the screen due to the entire cap being filled with mucosa and then a pseudopolyp is created by releasing a rubber band (C). The pseudopolyp is then resected (D) by placing and tightening the snare beneath the rubber band.

The Captivator MBM device (Captivator, Boston Scientific Ltd) consists of a cap placed at the distal end of an endoscope with a controller placed at the proximal aspect of the working channel. The cap carries 6 rubber bands that are placed at the proximal aspect of the cap allowing 360-degree peripheral viewing though the transparent cap (Figure 8).

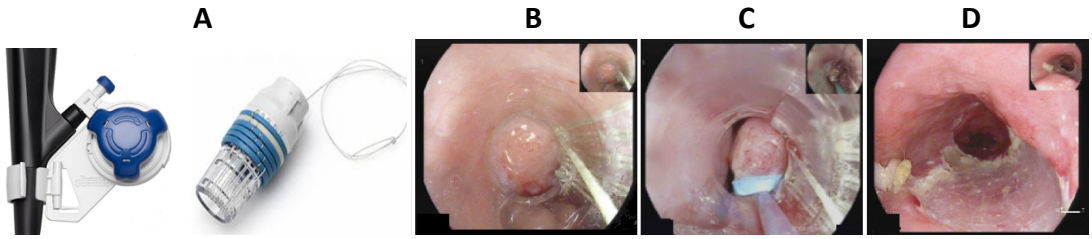

Figure 8: Captivator EMR device: The Captivator™ EMR device is a single use device. The device includes the Captivator™ EMR Band Ligator mounted at the proximal aspect of the accessory channel and a banding cap device placed at the distal end of the scope for creation of pseudopolyps (A). A pseudopolyp is created by suctioning the neoplastic mucosa into the cap (B) until a complete red out occurred on the screen due to the entire cap being filled with mucosa and then a band is deployed using a proximally attached band ligator (C). A snare is then passed through the accessory channel of the scope, placed over the pseudopolyp and then closed beneath the rubber band (C), the pseudopolyp is resected (D) in conjunction with coagulation current. The device can be used for up to 6 resections

Large number of studies have shown long-term complete remission rate of 85 to 96% with bleeding rates ranging from 0.7-7.9% and perforation rates ranging from 0.2-2.3% (133)(132)(134)(135). In a large prospective study of 1000 consecutive patients receiving endoscopic resection of mucosal adenocarcinoma, Pech *et al* were able to show a complete response to treatment in 96.3% of patients over a follow up period of 56.6 ± 33.4 months. Metachronous lesions or recurrence of cancer developed during the follow-up period in 14.5% of patients but endoscopic re-treatment was successful, resulting in a long-term complete remission rate of 93.8%. Major complications such as perforations were noted in 1.5% of patient but could be managed conservatively (136). Furthermore, the provision of EMR specimens to the pathology department results in an improvement in interobserver agreement among pathologists compared with biopsy specimens only (137)(138).

1.10.2 Endoscopic Submucosal Dissection (ESD)

Endoscopic submucosal dissection (ESD) is a more advanced endoscopic technique for removal of large mucosal lesions. In particular, it is performed on lesions which are scarred, or where there is concern of a risk of developing cancer or already harbouring some early cancer cells. ESD enables en bloc resection of lesions of any size that invade the mucosa and submucosa. Although ESD is safe and effective in experienced hands, it is technically demanding and requires intensive training.

Multiple studies have shown high en bloc resection rates ranging from 89-98.6% and R0 resection rates ranging from 72.4-87% with acceptable perforation (0-8.3%), bleeding (1.4-1.7%) and stricture rates (2.1-11.6%). When curative resections are achieved, good oncologic outcomes are likely in the management of early stage BE neoplasia by ESD (139)(140)(141)(142)(143). The ESGE recommendations (2015) state that EMR is acceptable for resecting lesions confined to the mucosa, regardless of the size, but ESD may be considered for lesions larger than 15 mm, poorly lifting tumours, and lesions at risk for SM invasion (144).

These data show that EMR and ESD are effective treatment modalities in the staging and treatment of early BE neoplasia with acceptable side effect profiles. It is however important to mention that operator skill and experience will have significant effect on patient outcome and therefore good training is paramount.

1.11 Endoscopic Ablation

1.11.1 Radiofrequency ablation

Radiofrequency ablation (RFA) has revolutionised the management of early BE neoplasia. In RFA, thermal ablation of the mucosa is performed using an electromagnetic current. The delivery devices can be focal or circumferential, resulting in delivery heat energy to a focal area or the whole circumference of a selected segment in the oesophagus respectively (figure 9). Complete ablation of the residual BE epithelium after endoscopic resection of

neoplastic lesions can significantly reduce recurrence rates (145). RFA of the residual BE epithelium is the current treatment standard and has been studies extensively. The multicentre EURO II study showed that RFA can achieve a CR-D and CR-IM rates of 92% and 87%, respectively (146), in patients with early BE neoplasia. A systematic review by Desai *et al* also showed that ET of BE neoplasia with resection of visible lesions followed by ablation of the remaining segment of BE can achieve a CR-D rate of 93.4% and CR-IM of 73.1% (134). The efficacy and safety profile of RFA suggests that it is an efficient modality (147) for patients with LGD and HGD without visible lesions.

A B

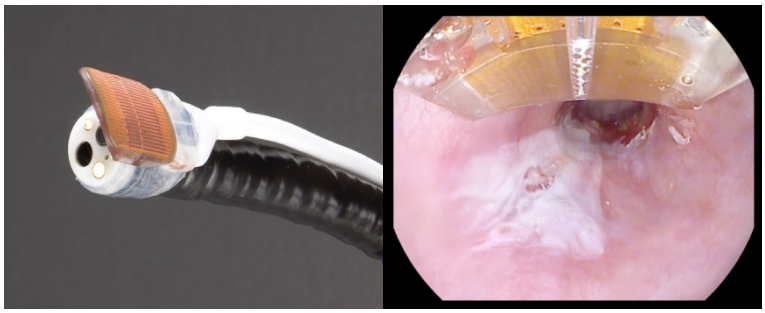

Figure 9: The focal RFA device attached at the distal aspect of a gastroscope (A). Post RFA ablation of the distal aspect of an oesophagus with the focal RFA device (B)

1.11.2 Cryoablation

Cryoablation is a new ablative technology for the treatment of patient with BE. Historically two approaches have been available. Endoscopic spray cryotherapy involves spraying either liquid nitrogen or rapidly expanding carbon dioxide gas over the BE segment; however, Cryoballoon ablation involves expanding a balloon at the level of the BE segment and then a focal spray ablation is performed. Both methods destroy the target mucosa by rapid freezing of the tissue (figure 9). Cryoablation with the Cryoballoon device (cryoballoon focal ablation system, Pentax Medical Inc) uses cycles of freezing (with nitrous oxide at -80 ^{0}C) and thawing to induce cell death by intra- and extracellular ice formation, leading to vascular injury, and ultimately apoptosis and cell death (148). The technique may ablate deeper than RFA whilst preserving the extracellular matrix (149) and therefore resulting into lower stricture rates and deeper tissue destruction (150). It is minimally destructive to the structural components of tissue, such as collagen, whereas heat-based ablation techniques irreversibly destroy proteins and therefore affecting the architecture of the collagen matrix (150). The effects of cryoablation are dose-dependent. The overlap of ice patches on adjacent treated sites, may result in higher application of cryogen and deeper injury and subsequent stricture development (figure 10)(151).

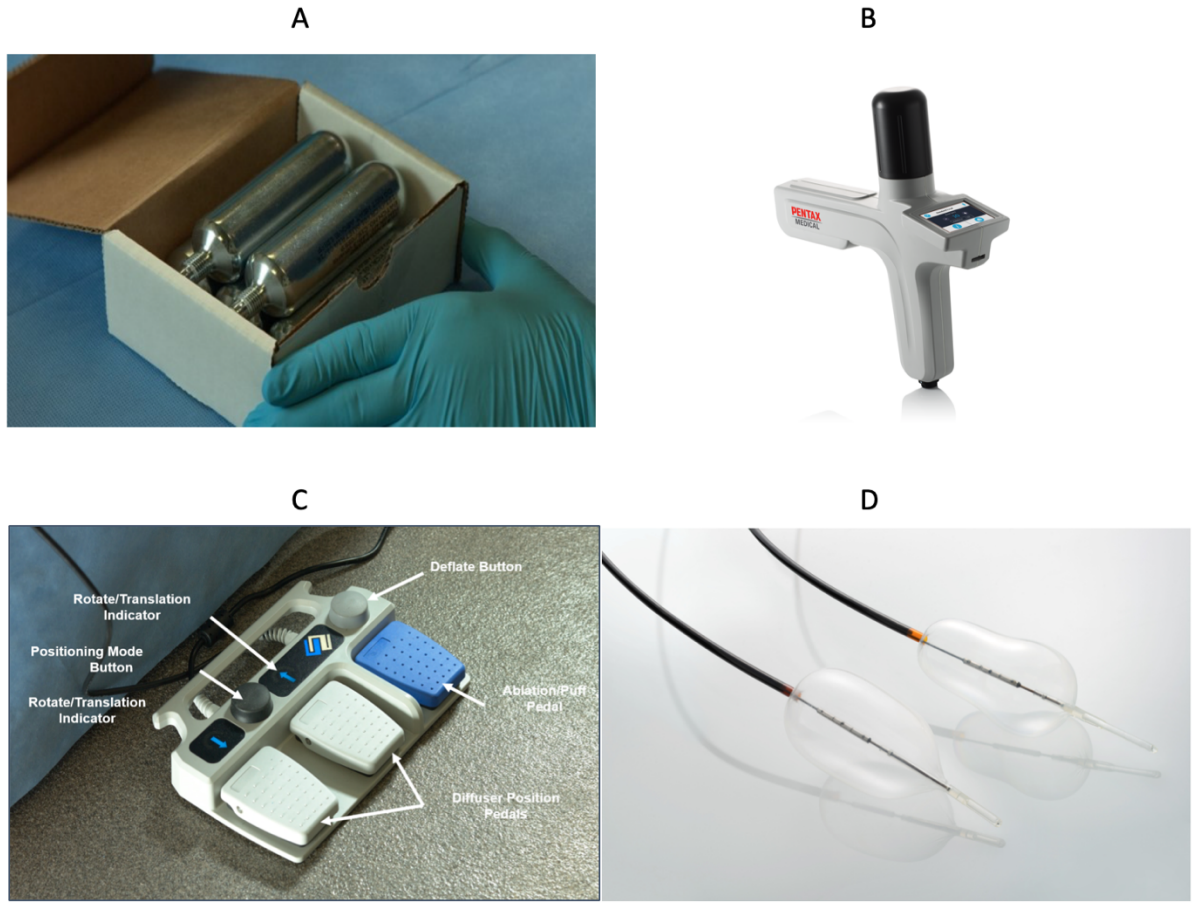

Figure 9: Cylinders containing nitrous oxide as the cryogenic agent (A). Hand-held controller device (B) and the foot pedal with cryoablation balloon catheters for the oesophagus and the GOJ junction.

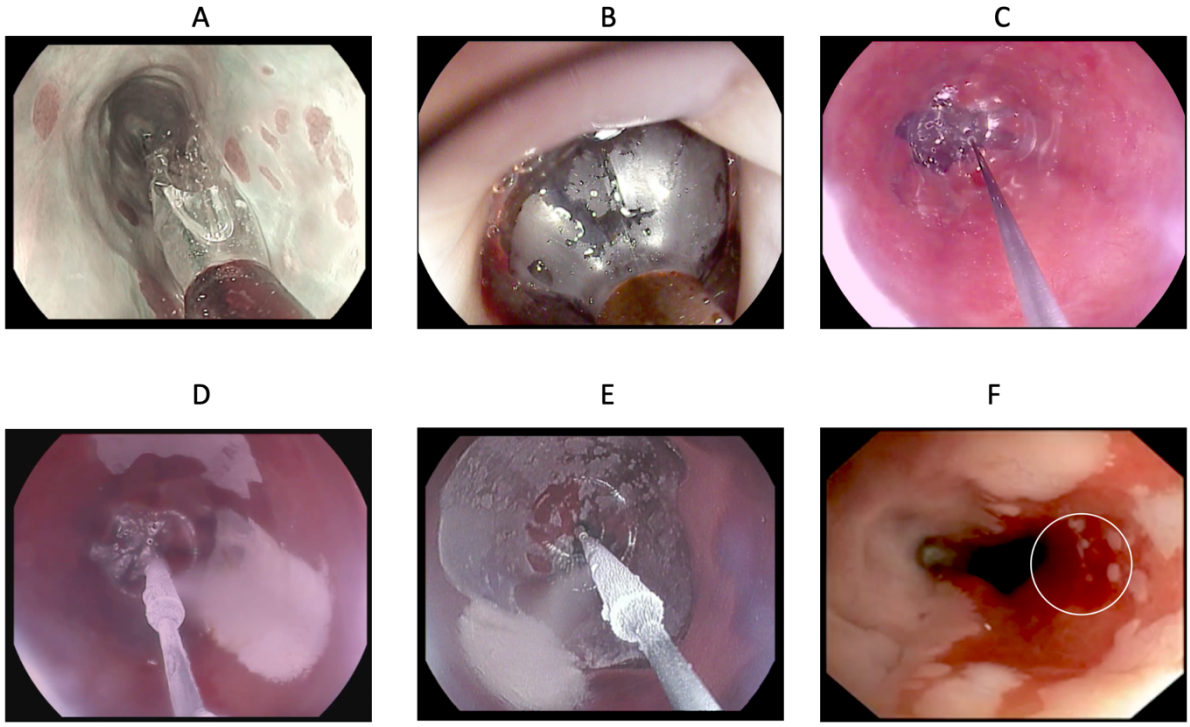

Figure 10: Cryoablation balloon in the oesophagus prior to insufflation (A). Balloon partially inflated (B), balloon fully inflated within the oesophagus (C), and Cryoablation of the left (D) and right (E) oesophageal wall. Post Cryoablation mucosal erythema as shown by the circled white line (F)

Recent studies have shown it to be better tolerated by patients and to be less painful (152)(153)(154); however, data regarding the treatment of dysplasia and EAC in patients with BE using cryoablation are limited. Previously publishes series have shown that cryoablation can achieve CR-D in 75-88% of patients with BE (155)(154)(156). A meta-analysis by Visrodia *et al,* analysed 11 studies with 148 patients with BE treated with cryotherapy for persistent dysplasia or IM after RFA. CR-D was achieved in 76.0% (95% CI, 57.7-88.0) and CR-IM in 45.9% (95% CI, 32.0-60.5) of patients (157). The efficacy if cryoablation balloon system in treatment-refractory patients with BE neoplasia will be presented later in this thesis.

1.11.3 Argon Plasma Coagulation

Argon plasma coagulation (APC), is one of the earliest thermal ablation techniques used for BE eradication, which relies on non-contact thermal energy to ablate tissue. It involves passing a high-frequency electric current through ionized argon gas applied to a lesion resulting in coagulation of tissue (figure 11).

A randomised long term follow up study of 63 patients with BE neoplasia (with previous curative resection of HGD or early OAC) analysed the effect of APC for complete BE ablation after a follow up period of 28.2±13.7 months (range 0-44). Mean number of 4±1.6 APC sessions were used. The study group concluded a 3% secondary lesion in the treatment

group with APC, in comparison to 36.7% in the surveillance group, leading to significantly higher recurrence-free survival for the patients undergoing ablation (158).

A major downside of APC is the operator dependency, the larger number of sessions that are needed to achieve complete eradication of the BE epithelium and the fairly high risk of residual islands of metaplasia. Nonetheless, APC is substantially less expensive than RFA and cryoablation.

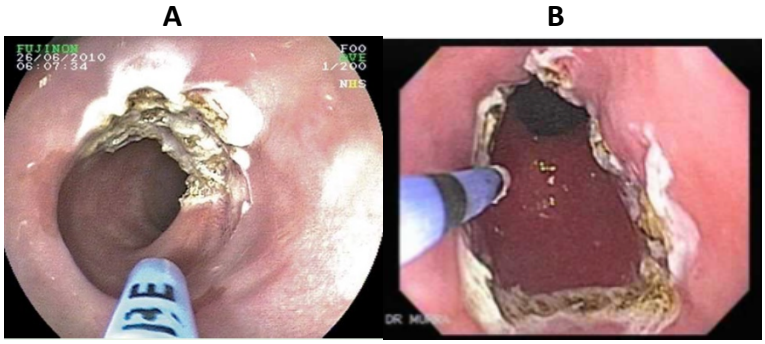

Figure 11: Focal (A) and Circumferential (B) ablation of dysplastic BE tissue with APC.

1.12 Summary

It is now clear that the endoscopic treatment of BE is effective, combining resection techniques with ablative therapy, in order to treat remaining segments of BE. This has now become the gold standard therapy focused mainly at tertiary high volume referral centres with surgery no longer the first treatment option in patient with BE dysplasia and early OAC. Patient's wishes for endoscopic treatment and the presence of co-morbidities are strong influential factors. In addition, endoscopic therapy continues to be part of a multidisciplinary approach that includes input from specialist surgeons and histopathologist that play a key role in the holistic management of patients with BE. The rapid development of imaging and therapeutic technologies by international industries, have allowed the endoscopic community to advance significantly in minimally invasive endoscopic therapy in the past decade. As the technology and skills develop further, we continue to see improvement and development of national and international guidelines that ensure clinical practice and healthcare systems are streamlined, efficient and high quality service is provided to all patients. Later in this thesis, new resection and ablative endoscopic modalities in BE neoplasia will be presented in detail.

The advancement of endoscopic intervention will inevitably see a arise in expected post endoscopic bleeding, which would certainly benefit from advancement in haemostatic modalities.

The second part of the Introduction chapter will focus on the management of upper gastrointestinal bleeding, outlining data on the current burden of upper GI bleeding and the development of new therapeutic modalities in recent decades.

Chapter 1

Introduction Part 2

Gastrointestinal Bleeding

Publications from this chapter

- **Alzoubaidi D**, Lovat LB, Haidry R. Management of non-variceal upper gastrointestinal bleeding: where are we in 2018? Frontline Gastroenterol. 2019 Jan;10(1):35-42

1.13 Non-Variceal Upper Gastrointestinal Bleeding

Upper Gastrointestinal bleeding (UGIB) is one of the most common acute GI emergencies. The associated mortality has remained unchanged for the past two decades, being higher among elderly patients with co-morbidities (159)(160). In the UK, GI bleeding is one of the most common medical emergencies with approximately 85,000 cases per year with 4000 deaths annually (160).

The majority of upper GI bleeds (80-90 %) are non-variceal. Patients often present with symptoms such as haematemesis, coffee-ground vomit, drop in haemoglobin, melaena and haematochezia, with or without haemodynamic instability (161). The presence of pre-existing co-morbidities is a significant contributor to mortality in elderly patients with UGIB (162).

Common aetiologies include: Peptic Ulcer Disease, Oesophagitis, Gastritis, Mallory-Weiss Tear, Dieulafoy Lesion, Gastroesophageal Varices, Cancer, and Haemobilia (163)(164)(165)(166)(167).

Despite advancements in therapeutic and interventional endoscopy, acute UGIB (AUGIB) remains a challenge for clinicians and endoscopists worldwide. The clinical community acknowledge that the management of these patients requires streamlining and improvement.

1.14 What is the problem?

The majority of the Non-Variceal Upper Gastrointestinal Bleed (NVUGIB) in the UK are caused by peptic ulcer disease. UGIB has an enormous burden on health care. In-patient bed stay, endoscopy provision and blood product transfusions are the main contributors to the overall cost of UGIB. The annual initial in-hospital treatment cost for all AUGIB cases in the UK was estimated to be £155.5 million with over £93 million (60%) of this cost due to in-hospital length of stay, £38.5 million (25%) to endoscopy and £12.6 million (8%) to blood transfusion (168).

UGIB have an associated mortality rate of 10% (159) (169) and endoscopic therapy remains the gold standard treatment. Early endoscopy (within 24 hours) is recommended for most patients with AUGIB, in order to achieve prompt diagnosis, provides risk stratification and haemostasis (170). The UK's National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report in 2015 concluded that only 44% of patients presenting with AUGIB received good care overall (159).

1.15 The Significance of Co-morbidities

Mortality in AUGIB is rarely related to the actual haemorrhage, but rather to co-existing co-morbidities. Recent studies have shown that about 18% of the total mortality is directly related to GI haemorrhage with the majority of deaths caused by concurrent co-morbidities. Pulmonary disease (24%), multi-organ failure (24%), and terminal malignancy (34%) are the most common co-morbidities (171).

1.16 Blood Product Transfusion before endoscopy

The United Kingdom Comparative Audit (2007) of UGIB and the Use of Blood has shown that AUGIB is a significant consumer of blood products in the UK. The study included 6750 patients from 208 hospitals across the UK, with 43% of patients needing at least one unit of blood transfusion (172). GI bleeding is the second commonest medical reason for transfusion in the UK after haematological malignancy, accounting for 14% of all blood transfusions (172). 15% of GI bleed patients receive 4 or more units of blood during their inpatient stay. Blood product use is inappropriate in 20% of cases (173).

Current evidence has shown favourable outcomes in patient's whose Hb transfusion commenced once haemoglobin (Hb) dropped below 70g/L (174). The European Society of

Gastrointestinal Endoscopy (ESGE) recommends a restrictive blood transfusion strategy that aims for a target Hb between 70g/L and 90g/L. A higher target Hb should be considered in patients with significant co-morbidity (e. g. ischaemic cardiovascular disease) (175). In addition at the time of discharge, a restrictive target of Hb 80-100 g/L has shown to have better outcomes in those presenting with AUGIB (176).

1.17 New Anti-Coagulant drugs

The emergence of the direct oral anticoagulants (DOACs: dabigatran, rivaroxaban, apixaban and edoxaban) has reduced regular serum monitoring that is required for patients on warfarin; however there is a 25-30% increased risk of GI bleeding with the use of DOAC when compared with warfarin (177)(178). The risk is mostly relevant in the elderly and those with hepatic disease, renal disease and patients on concomitant antiplatelet agents.

In the case of an AUGIB, reversal agents can be used; however different assays are needed to indirectly quantify DOAC level prior to reversal. These assays include the dilute Thrombin Time (TT) and Ecarin clotting time (ECT) for dabigatran and the drug-specific calibrated anti-Xa factor assay for rivaroxaban, edoxaban and apixaban (179). Reversal agents exist (prothrombin complex concentrate (PCC), activated PCC, Idaricizumab) with many others currently on clinical trials (178).

1.18 What are the commonly used risk stratification tools?

Early patient risk stratification will allow the planning and timing of life saving procedures such as endoscopic therapy with adequate and safe triage. The primary aim of the initial assessment is to determine whether endoscopy is required urgently or it can be delayed or even managed in the outpatient setting (160). At present 3 such scores exist and are in clinical practise.

1.18.1 Glasgow-Blatchford Score (GBS)

The Glasgow-Blatchford Score (GBS) utilises both clinical (Pulse, systolic BP, presence of melaena, presentation with syncope, presence of hepatic disease and heart failure) and serological parameters (Urea, Hb), that are easily available at initial assessment which allows the clinician to identify patients that would be suitable for management in the out-patient setting (Table 1) (180). The ESGE and NICE recommend the use of the GBS for pre-endoscopy risk stratification. Patients with the score of 0 or 1 do not require hospital admission and can be safely discharged and managed with outpatient endoscopy (175) (181).

Glasgow Blatchford Score (GBS) for Gastrointestinal bleeding:	
Blood urea (mmol/L)	**Score value**
6·5–7·9	2
8·0–9·9	3
10·0–25.0	4
>25·0	6
Haemoglobin for men (g/L)	
120–129	1
100–119	3
<100	6
Haemoglobin for women (g/L	
100–119	1
<100	6
Systolic blood pressure (mm Hg)	
100–109	1
90–99	2
<90	3
Other markers	
Pulse ≥100/min	1
Presentation with melaena	1
Presentation with syncope	2
Hepatic disease*	2
Cardiac failure†	2
*Known history, or clinical and laboratory evidence, of chronic or acute hepatic disease	
†Known history, or clinical and echocardiographic evidence, of cardiac failure	

Table 1: Glasgow Blatchford Score (GBS)

1.18.2 Rockall Score (RS)

In contrast, the Rockall score (RS) combines clinical parameters with endoscopic findings in order to predict the risk of mortality (Table 2). Lack of endoscopic findings in the initial assessment of a patient with AUGIB may deter the clinician from using the RS; however full post endoscopy RS remains an important tool in predicting mortality rate (182).

Rockall Score for Gastrointestinal bleeding:					
	0	**1**	**2**	**3**	
age	<60	60-79	>80		**initial score criteria**
shock	no shock	HR > 100	HR > 100, SBP < 100		
co-morbidity			cardiac failure, ischaemic heart disease	renal failure, liver failure, disseminated malignancy	
diagnosis	Mallory-Weiss, no lesion, no stigmata of recent haemorrhage	all other diagnoses	malignancy of upper gastrointestinal tract		**additional criteria for full score**
stigmata of recent haemorrhage	none or dark spot		fresh blood, adherent clot, visible or spirting vessel		
maximum additive score prior to diagnosis = 7					
maximum additive score after diagnosis = 11					

Table 2: Rockall Score

1.18.3 The AIMS65 score

The AIMS65 score is designed to predict in-hospital mortality, length of stay, and cost of GI bleeding (Table 3 & 4). In comparison to GBS and RS, it is superior in predicting in-patient mortality (183). AIMS65 score is inferior to GBS and RS in predicting re-bleeding. GBS, RS and AIMS 65 are similar in predicting length of hospital stay (183)(184). GBS is more accurate in terms of detecting transfusion need, re-bleeding rate and endoscopic intervention rate (183)(185).

AIMS 65 Score:	
	Score
age > 65	1
systolic BP < 90 mm Hg	1
altered mental status	1
INR > 1.5	1
albumin < 30 g/L	1

Table 3: AIMS 65 Score

In-Hospital mortality rate based on AIMS 65 Score:	
Total Score	**mortality rate**
0	0.30 %
1	1.20 %
2	5.30 %
3	10.30 %
4	16.50 %
5	24.50 %

Table 4: In-Hospital mortality rate based on AIMS 65 Score

1.19 What is the optimal timing of endoscopy?

The benefit of early endoscopy in the management of NVUGIB remains controversial (170); however, endoscopy has an important role in obtaining diagnosis with a sensitivity of 90-95% at locating the bleeding site (181).

Several studies have investigated the effect of endoscopy timing on clinical outcomes with varying results. In haemodynamically stable patients with ASA grade 1 or 2, early endoscopy within 12 hours of presentation, has no effect on mortality or recurrent bleeding (186)(187)(188); however, more high-risk endoscopic lesions are identified (189) in those receiving early endoscopy and these patients tend to have a shorter length of hospital stay. (190)(191)(192) Early endoscopy in haemodynamically stable patients with ASA grade 3 to 5 is associated with lower in-hospital mortality. In patients with hemodynamic instability, early endoscopy is associated with lower in-hospital mortality. (190) Although 2–10% of patients with AUGIB can die from their AUGIB, mortality in 80 % of these patients is due to other non-bleeding co-morbidities (193)(171)(181).

1.20 What are the common pharmacological therapies?

1.20.1 Proton Pump Inhibitors

Pharmacological agents such as Proton pump inhibitors (PPI) have significantly reduced the incidence of peptic ulcer disease (PUD) (194). Pre-endoscopic use of PPI reduces the detection rate of high-risk stigmata during endoscopy and the need for endoscopic therapy (160); however, there is no significant impact on the amount of blood transfusion, rebleeding rate, surgery, or death within 30 days (181)(195).

1.20.2 Prokinetic Drugs

The adminstration of prokinetic drugs such as metoclopramide and erythromycin has shown to improve endoscopic diagnostic yield in patients with AUGIB and reduced the need for repeat endoscopy (160). This is useful in cases where the upper GI tract is filled with large volume of blood; however there is lack of evidence in improving the duration of hospitalization, transfusion requirements, or surgery (196).

1.20.3 Tranexamic Acid

Tranexamic acid, a derivative of the amino acid lysine, has anti-fibrinolytic effect by preventing the degradation of fibrin networks (197). Studies have shown that it decreases re-bleeding and mortality in AUGIB, without increasing the thromboembolic adverse effects; however, it's routine use in clinical practice has not been recommended as further clinical trials are needed (198) (199).

1.21 The Forrest Classification

The endoscopic management of UGIB has evolved in recent decades as therapeutic modalities available to the endoscopist have evolved, driven by innovations in new techniques and accessories. Endoscopy in patients with AUGIB is effective in diagnosing and treating most causes of UGIB (160). The Forrest Classification (Figure 1) categorises the lesion morphology at the time of index endoscopy, allowing the endoscopist to decide when to intervene and prognosticate the risk of re-bleeding (200). This categorization has also been shown to correlate with the need for surgery and mortality (201); however, there is significant inter-observer disagreement in categorising the bleeding site, hence accurate photographic documentation is paramount (202).

Forrest Classification		
Stage	**Characteristics**	**Re-bleeding**
Ia	Spurting Bleed	60 - 100 %
Ib	Oozing Bleed	50%
IIa	Non-Bleeding Visible Vessel	40 - 50 %
IIb	Adherent Clot	20 - 30 %
IIc	Flat Spot in ulcer crater	7 - 10 %
III	Clean Base Ulcer	3 -5 %

Table 5: Forrest Classification

Ia	Ib	IIa	IIb	IIc	III
Spurting bleed	Oozing bleed	Non-bleeding visible vessel	Adherent clot	Flat spot in ulcer crater	Clean base ulcer

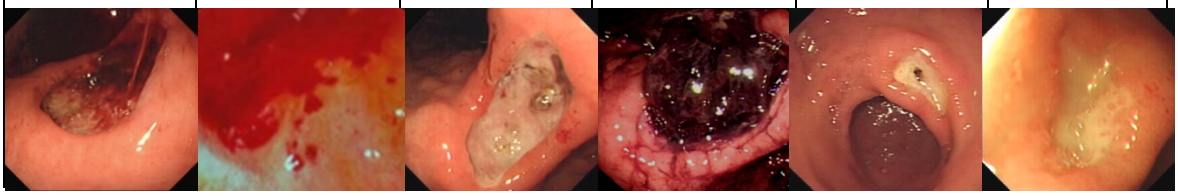

Figure 1: Showing different types of bleed based on the Forrest Classification:

1.22 What are the available endoscopic haemostatic techniques?

Several endoscopic treatment modalities have been developed, these include injection methods, heat cauterization, and mechanical therapy.

1.22.1 Adrenaline injection Therapy

This includes injection of dilute adrenaline (1:10,000) at the site of bleeding. It reduces blood flow by temporary creating local tamponade and vasoconstriction of blood vessels. Injection of large volume epinephrine (>13 ml) can reduce the rate of recurrent bleeding in patients with high-risk peptic ulcer and is superior to injection of lesser volumes (203) (204) (205).

1.22.2 Thermo-Coagulation

Thermo-coagulation uses direct contact with the bleeding site with thermal energy delivered via a variety of devices. Heater probe consists of a Teflon coated hollow aluminium cylinder with inner heating coil. It utilizes electrical current to generate heat.

The Gold Probe has a rounded gold distal tip with good conductivity and has irrigation and injection capability, in addition to delivering heat for thermo-coagulation (206).

Argon Plasma coagulation (APC) is a non-contact ablative modality that uses steam of ionized gas to conduct electricity for the coagulation of bleeding tissue (207).

1.22.3 Mechanical Therapy – Clips

Mechanical therapy is an attractive method for achieving endoscopic haemostasis. It has a significant impact on achieving haemostasis in difficult and challenging cases and a significant impact on outcomes (208).

Mechanical therapy with endoscopic clips has been shown to be effective by physically obstructing the blood flow in the vessel; however, this technique will require direct visualisation of the bleeding point and culprit vessel. Successful application of clip is better in achieving haemostasis when compared to injection therapy alone but similar to thermo-coagulation (209).

The over-the-scope clip (OTSC) has been reported to effectively achieve haemostasis and significantly reduces re-bleeding and re-bleeding associated mortality in NVUGIB. A recent multicentre study was able to show a haemostasis rate of 92.4 % with OTSC as a monotherapy in the treatment of acute NVUGIB with significant reduction in the occurrence of bleeding and mortality of re-bleeding (210).

1.23 Dual and triple therapy is better than monotherapy

Dual endoscopic therapy is superior to monotherapy with adrenaline injection alone in the management of patients with high risk bleeding peptic ulcer; Dual therapy reduces the risk of recurrent bleeding, the risk of emergency surgery (208) and mortality (211).

The possible adverse events from dual therapy include perforation and gastric wall necrosis, with very low occurrence rate. Dual therapy remain to be superior to monotherapy with adrenaline (212) (181).

1.24 The Doppler endoscopic probe (DEP)

Doppler probe through the accessory channel of a standard endoscope has been used to assess the blood flow in the superficial blood vessels at the site of bleeding peptic ulcer post endoscopic therapy. The audible signal generated by the probe is able to determine the type of blood flow (arterial or venous) and the location of the bleeding vessel (213)(214). Doppler signal from an ulcer, post endoscopic therapy has been associated with a higher risk of re-bleeding (214) (215); however, lack of audible signal post endoscopic therapy is not associated with improvement in re-bleeding rate (201).

1.25 Is intervention radiology suitable for GI bleeding?

Interventional radiology (IR) has shown to provide diagnostic imaging and endovascular therapeutic interventions that can localise the source of bleeding and provide endovascular embolization to achieve haemostasis successfully when conventional endoscopic haemostasis has been unsuccessful (216)(figure 2). A study by Kramer *et al,* was able to show that IR can control UGIB and achieve haemostasis with the use of minicoils for the embolisation of bleeding vessels with reduced risk of serious complications (217).

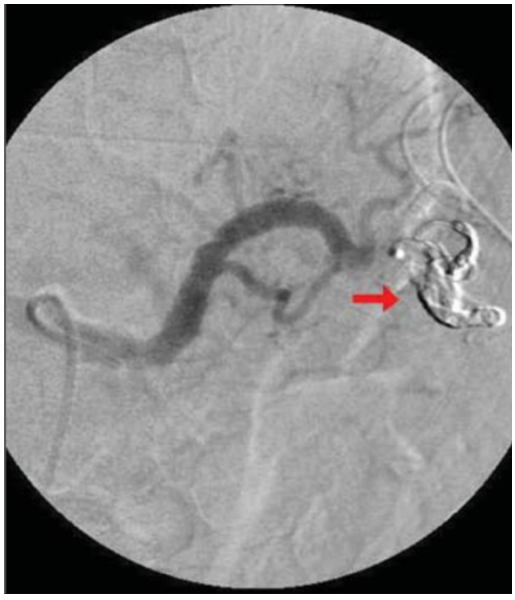

Figure 2: Post-short gastric arteries embolization angiographic follow-up (218)

1.26 What is the optimum post procedure management?

Post endoscopic treatment with high dose infusion of PPI (bolus of 80 mg followed by 8 mg per hour for 72 hours) in bleeding peptic ulcers, significantly reduces the risk of recurrent bleeding (219). Re-bleeding rate has also been shown to be associated with the Hb at the time of discharge. The re-bleeding rate in patients with a discharge Hb between 80 and 100 g/L is not significantly different when compared to patients with higher Hb at discharge (176). In addition, a discharge Hb between 80 and 100 g/L is associated with a lower consumption of Red Blood cells (176).

Re-bleeding is more common in patients with high stigmata lesions (Forrest Ia, Ib and IIa) at the time of endoscopy, hence repeat endoscopy and treatment should be considered in all high risk bleeds in particular, those with the need to recommence anti-coagulation and patients whom have had limited endoscopic therapy at the initial endoscopy. Surgery should be considered in those not responding to endoscopic therapy or radiological embolisation, taking into account, patient's status and co-morbidities (181).

1.27 What are the future developments?

The development of a risk stratification tool relevant to all GI bleeds should be an essential point of focus for all clinicians managing GI bleeding. Several novel modalities have been developed for the investigation and treatment of GI bleeding in recent years. These show promising results in achieving prompt diagnosis and haemostasis.

1.27.1 Video capsule endoscopy

The use of video capsule endoscopy (VCE) in the emergency department (ED) as a risk stratification tool for identifying high and low risk UGIB patients has been evaluated. It has shown potential to identify high and low-risk patients presenting with signs of AUGIB, helping to determine the need for intervention with significant reduction in the time to emergent endoscopic therapy (220). VCE in the ED is safe and effective in identifying AUGIB (221). A study by Meltzer *et al,* looked into the use of VCE in the ED performed by a gastroenterologist or a VCE trained clinician. The aim was to determine whether patients with signs and symptoms of upper GI bleeding can be discharged with outpatient follow up endoscopy. A total of 25 subjects were enrolled with excellent tolerance to the VCE. The study was able to show a sensitivity of 88 % with a specificity of 64 % for the detection of fresh blood in the upper GI tract (222). Similar studies have shown significant reduction in hospital admissions with no difference in the clinical outcome in terms of recurrent bleeding

and 30-day mortality in the VCE group and those receiving standard treatment (223). This is very exciting and further studies will be able to provide more data on this unique modality for the diagnosis of patients in the ED. This will potentially have a great impact on the number of hospital admissions (222).

1.27.2 EndoClot

The EndoClot (EndoClot Plus Inc., Santa Clara, CA, USA) is a polysaccharide haemostatic powder that can be delivered endoscopically to the site of bleeding in the GI tract without the need for direct mucosal contact. It is composed of absorbable polymer particles, that absorbs water from the blood on the surface of the bleeding site, hence increasing the concentration of platelets and clotting factors, resulting in haemostasis (224)(225).

An early clinical study on EndoClot in 21 patients with acute NVUGI bleeding have shown a 100% immediate haemostasis rates with a 30-day rebleed rate of 4.8% (95% confidence interval [95%CI] -4.34% to 3.94%), and a 30-day mortality rate of 19.0% (95%CI 2.29%-35.91%) (224).

Further prospective study by Prei et al, analysed 70 patients with acute GI bleeding with 83% (58/70) of the patients had upper and 17% (12/70) had lower GI bleeding. In the UGIT, haemostasis was achieved in 64% (30/47, 95% confidence interval, 50%-76%) after primary use and in 100% of patients, when EndoClot was used after conventional modalities had failed (95% confidence interval, 70%-100%). In lower GI bleeding haemostasis was achieved

in 83% of cases (10/12, 95% confidence interval 54%-97%). Rebleeding occurred in 11% (8/70) of the patients (226).

Kim *et al*, retrospectively studied 12 patients with UGIB secondary to gastric malignancy with a median tumour size of 40 mm (range, 15 - 100). Immediate haemostasis post EndoClot therapy was achieved in all patients. Rebleeding developed in 2 of 12 patients (16 %), 3 and 5 days after treatment. There were no significant EndoClot-related adverse events, with no documented mortality at 30 days post therapy (227).

EndoClot can be used safely and effectively in NVUG bleeding. It provides further therapeutic options in the management of GI bleeding. It can be used in sites with extensive bleeding such as diffuse malignancy in the stomach. It can also be used when access to the bleeding site is difficult. Further clinical trials are awaited.

1.27.3 Hemospray

Hemospray is a novel proprietary mineral blend that forms a mechanical barrier over the bleeding site when applied endoscopically. It gives the endoscopist the opportunity to apply therapy in challenging anatomies. Data on Hemospray has been shown to achieve good haemostasis rates with NVUGIB (228)(229)(230). The highly absorptive powder functions as a cohesive and an adhesive. Once in contact with blood in the GI tract, the powder absorbs water and forms a stable mechanical barrier which adheres to and covers the bleeding site. It promotes platelet aggregation and increases the concentration of clotting factors beneath it (231). There is no expected risk of toxicity as the powder is not absorbed by the GI mucosa

and the adherent layer is naturally eliminated from the GI tract within 24-72 hours (232)(233). Several studies have investigated the haemostatic ability of Hemospray in the management of bleeding peptic ulcers (232), malignancy (234), anticoagulated patients (235) and oesophago-gastric variceal bleed (236) with encouraging haemostasis rates (65-98%).

The multi centre European SEAL study, investigated 63 adult patients with NVUGIB needing endoscopic haemostasis that were treated with Hemospray. There were 30 patients with bleeding ulcers and 33 with other NVUGIB pathology. Fifty-five (87%) were treated with Hemospray as monotherapy; 47 (85%) of them achieved primary haemostasis and rebleeding rate at 7 days was 15%. Primary haemostasis rate for Hemospray in patients with peptic ulcer bleeds was 76%. Eight patients, who otherwise may have required either surgery or interventional radiology, were treated with Hemospray as second-line therapy after failure of other conventional endoscopic modalities, all of whom achieved haemostasis following the addition of Hemospray (229).

A systematic review and meta-analysis by Facciorusso *et al,* analysed 24 studies, of which 3 were RCT, with 1063 patients were included in the meta-analysis. Immediate haemostasis was achieved in 95.3% (93.3%-97.3%) of patients, with no significant difference based on treatment strategy, haemostatic agent used and bleeding aetiology. Haemostasis rate was lower in Forrest Ia bleed (91.9%). Hemospray showed similar efficacy as compared to conventional endoscopic therapy (odds ratio: 0.84, 0.06-11.47; $p = 0.9$). Thirty-day rebleeding rate was 16.9% (9.8%-24%) with no difference in comparison to other endoscopic treatments (odds ratio 1.59, 0.35-7.21; $p = 0.55$). All-cause and bleeding-related mortality rates were 7.6% (4%-10.8%) and 1.4% (0.5%-2.4%), respectively (237).

The French GRAPHE study analysed 202 patients with UGI bleeding of which 94/202 patients (46.5%) received Hemospray as monotherapy and 108/202 patients (53.5%) received Hemospray as salvage therapy once conventional modalities failed to achieve haemostasis. Overall, immediate haemostasis was achieved in 195/202 patients (96.5%), independently of whether Hemospray was used as first-line therapy (91/94; 96.8 %) or salvage therapy (104/108; 96.3 %).

The type of lesion did not influence immediate haemostasis rates, which was achieved in 96.0% (72/75) of ulcers, 95.1% (58/61) of malignant lesions, 97.1% (34/35) of post-endoscopic therapy bleedings, and 100% (31/31) of bleedings of other causes.

Recurrence of bleeding occurred in 26.7% (51/191) of the total patients at day 8. At day 30, the overall rebleeding rate was 33.5% (62/185). In the case of monotherapy with Hemospray, the overall rebleeding rates were 17.2% (15/87) at day 8 and 26.5% (22/83) at day 30. When Hemospray was used as salvage therapy, the overall rebleeding rate at day 8 was 34.6% (36/104) and at day 30, was 39.2% (40/102). Death directly related to bleeding occurred in 7 patients (230).

The current and on-going prospective International Multicentre Hemospray Registry (Alzoubaidi *et al*, UCL, London) has shown an overall haemostasis rate of 86%. Expansion of this study is currently in progress and shall provide further evidence on the use of Hemospray as monotherapy, dual therapy and rescue therapy in various pathologies (238). The initial published data from the International Multicentre Hemospray Registry will be presented in detail, later in this thesis.

1.28 Summary

GI bleeding remains to be a challenging clinical emergency with significant mortality and morbidity. The current treatment modalities (injection of adrenaline, heat coagulation therapy and mechanical clips) provide essential tools to endoscopists treating GI bleeding; however, certain skills are required in order to efficiently utilise these conventional modalities. There are cases that will not respond to conventional therapies and therefore 'easier-to-apply' modalities are required for those endoscopist with limited options either due to skill set or nature/site of bleed. In addition as the industry and technologies in endoscopic therapy progress further, in particular the management of early neoplasia in the upper gastrointestinal (GI) tract, we will therefore see more challenging and complicating GI bleeds due to endoscopic therapy.

This thesis will study the Hemospray technology that is increasing used internationally in the management of GI bleeding and bleeding secondary to endoscopic therapy. This thesis will also examine the efficacy of Hemospray in various other pathologies and will report success and failure rates in a heterogenous population.

Future studies should focus to explore which treatment modalities are more effective in specific pathologies, as currently no single modality is capable of treating all pathologies.

The focus of treatment should not only be the endoscopic therapy and a holistic approach is encouraged in order to optimise treatment by managing multi-organ failure and co-morbidities (171).

CHAPTER 2

COMPARISON OF TWO MULTI BAND MUCOSECTOMY DEVICES FOR ENDOSCOPIC RESECTION OF BARRETT'S OESOPHAGUS RELATED NEOPLASIA

Publications from this chapter

- **Alzoubaidi** D, Graham D, Bassett P, Magee C, Everson M, Banks M, Novelli M, Jansen M, Lovat LB, Haidry R. Comparison of two multiband mucosectomy devices for endoscopic resection of Barrett's esophagus-related neoplasia. Surg Endosc. 2019 Nov;33(11):3665-3672

CHAPTER 2 CONTENTS

CHAPTER 2 FIGURES AND TABLES

2.1 Overview of Chapter 2

Background and Aim: Oesophageal adenocarcinoma carries a poor prognosis and therefore treatment of early neoplasia arising in the precursor condition Barrett's Oesophagus (BE) is desirable. Visible lesions arising in BE require endoscopic mucosal resection for accurate staging and removal. Resection of early neoplastic BE has become more common within the clinical community and endoscopists are now performing endoscopic resection on lesions that are more complicated and larger than those previously attempted.

Historically, the resection modalities included the cap based system with snare (now used less frequently) and now, newer custom made multiband mucosectomy (MBM) devices are available. The most commonly used MBM device is the Duette device by Cook Medical Ltd. Despite its good performance profile, there are limitations which include the small size of resection specimens and limited visibility through the cap.

A new MBM device has recently become available (Captivator, Boston Scientific Ltd), with larger resection specimens and better visibility through the cap, which will be **the focus of the second chapter in this thesis.**

This retrospective pilot study compares the efficacy, safety, specimen size and histology of EMR specimens resected with two MBM devices (Cook Duette and Boston Captivator) in treatment naive patients undergoing endoscopic resection for BE neoplasia.

Methods: Consecutive EMR procedures carried out by a single experienced endoscopist were analysed. All visible lesions were marked and resected using 1 of the 2 MBM devices. All resected specimens were analysed by the same two experienced pathologists. The

resected specimens in both groups were analysed for maximum diameter, minimum diameter, surface area and depth.

Results: Twenty consecutive patients were analysed (18M+2F; mean age 74) in the Duette group and 20 (17M+3F; mean age 72) in the captivator group. A total of 58 specimens resected in the Duette and 63 in the captivator group. Min diameter, Max diameter, Surface area and Depth of the ER specimens resected by the Captivator device were significantly larger than that by the Duette device [Min Diameter 9.89 mm vs 9.07 mm (p=0.019); Max Diameter: 13.54 mm vs 12.38 mm (p=0.024); Surface Area: 135.40 mm^2 vs 113.89 mm^2, (P=0.005); Depth 3.71 mm vs 2.89 (p=0.001)].

Conclusions: These two MBM devices showed equivalent efficacy and safety outcomes, but the EMR Captivator device resected specimens with a larger surface area in the oesophagus when compared with the Duette device. A possible advantage of this is in situations where en bloc resections with fewer EMRs are desirable for larger lesions.

2.2 Introduction

Barrett's oesophagus (BE) is a precancerous condition that predisposes to oesophageal adenocarcinoma (OAC) and is characterised by a change of normal squamous epithelium lining the oesophagus to metaplastic columnar epithelium due to chronic acid reflux (239). The incidence of OAC in Western countries has increased in recent years and despite advances in surgical and oncological interventions, long-term survival remains poor. Surgical management of early oesophageal neoplasia carries significant mortality rates (240) (241) (242). In recent years there have been significant developments in minimally invasive endoscopic eradication therapy (EET) of BE neoplasia with high eradication rates and a good safety profile; therefore, there has been more emphasis on targeting patients at an earlier stage which can be amenable to EET that can improve patient outcomes. Endoscopic therapy of dysplastic BE and adenocarcinoma has been recommended by various major societal guidelines (2) (96).

Current consensus is that visible lesions arising in BE are removed by endoscopic resection (ER) as they may harbour the most advanced histological stage. Accurate staging with endoscopic mucosal resection (EMR) is a key step in the treatment of early neoplasia as it allows accurate risk stratification of patients. Resection specimens provide information on depth of mucosal or submucosal invasion and presence or absence of lympho-vascular invasion, which subsequently would allow appropriate modalities of further treatment to be offered (243). Endoscopic resection is effective and safe in selected patients with early BE neoplasia with significantly high (up to 94%) long term complete remission rates and low

major complication rates (244) (136). The endoscopic management of early BE neoplasia is the preferred treatment modality as surgical options carry a much higher complication rate (240) (241) (245).

Historically, the cap based system with snare (Olympus Ltd.), initially described in Japan by Inoue *et al*, (128) was used. This is an ER modality that uses a transparent cap placed distally at the tip of the endoscope. The cap contains a distal internal ridge, allowing the placement of a snare in the cap prior to resection. The submucosal space is initially injected for lifting and subsequently the mucosa is suctioned into the cap in order to create a pseudopolyp. The pseudopolyp is then resected by closing the snare at the base of the pseudopolyp and applying electrocautery. This technique is a rather complicated process for the less experienced endoscopists, as it requires submucosal lifting and placing the snare at the distal ridge of the transparent cap prior to resection. This technique also results in prolonged procedure time in cases requiring multiple resections (129).

Cap EMR has a role in select cases but has now been widely replaced by the custom made multiband mucosectomy (MBM) devices that utilises a transparent cap placed distally at the tip of the endoscope. The cap carries multiple pre-loaded rubber bands that are connected to a hand operated controller fixed at the proximal aspect of the accessory channel. The neoplastic mucosa is suctioned into the transparent cap, followed by release of a band by the controller, resulting in the creation of a pseudopolyp. The contraction of the rubber band at the base of the pseudopolyp is only adequate to withhold the mucosa but not the underlying muscularis propria, hence the injection of the submucosal space is not routinely required. A snare is passed through the accessory channel of the endoscope and then is

placed and closed at the base of the pseudopolyp, beneath the band. The pseudopolyp is then resected using electrocautery (130). This is a an easier method and the learning curve for MBM is shorter compared with that of ER cap as it combines the commonly known techniques of variceal band ligation and polypectomy (129).

The most commonly utilized MBM device is the Duette® Multi-Band Mucosectomy device (Cook Medical, Limerick, Ireland) (131). It is a modified version of the variceal band ligator that allows the passage of a snare into the working channel of the endoscope (Figure 1) (132). A new MBM device has been launched (Captivator, Boston Scientific Ltd). This device also consists of a cap placed at the distal end of the scope with a controller placed at the proximal aspect of the working channel. The cap carries 6 rubber bands that are placed at the proximal aspect of the cap allowing 360-degree peripheral viewing though the transparent cap without obstructions by the ligator bands (Figure 2). An in vitro assessment of the performance of the new EMR Captivator device by Scholvinck *et al*, showed that the new MBM device potentially allows better visualisation through the cap and easier passage of accessories through the scope with significantly better suction power (246).

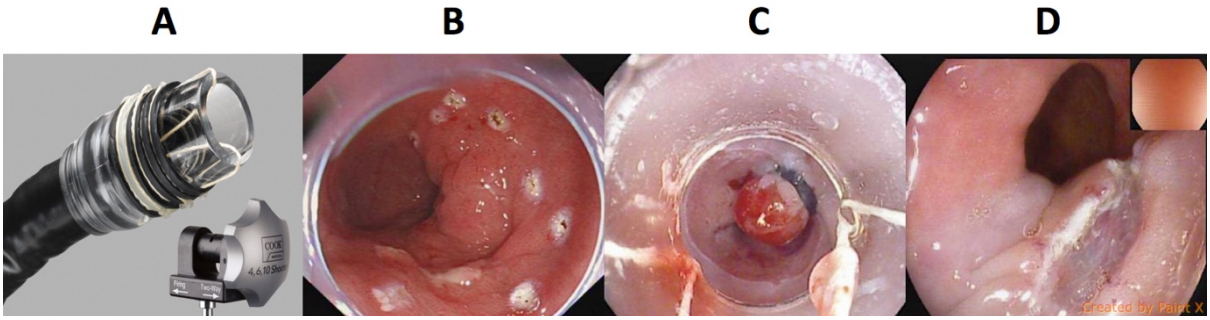

Figure 1: Duette EMR device: The single use Duette MBM device consists of a transparent cap with 6 rubber bands and a control handle (A). The transparent cap is mounted at the tip of the endoscope. With a trigger cord, the 6 rubber bands on the outside of the transparent cap are connected to the control handle at the proximal end of the accessory channel. Without prior submucosal injection for lifting, the neoplastic lesion is delineated with the tip of the hot snare (B) and suctioned into the cap until a complete red out occurred on the screen due to the entire cap being filled with mucosa and then a pseudopolyp is created by releasing a rubber band (C). The pseudopolyp is then resected (D) by placing and tightening the snare beneath the rubber band.

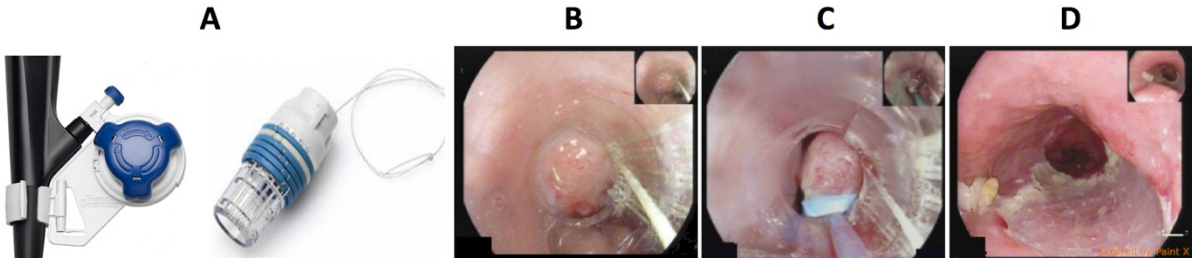

Figure 2: Captivator EMR device: The Captivator™ EMR device is a single use device. The device includes the Captivator™ EMR Band Ligator mounted at the proximal aspect of the accessory channel and a banding cap device placed at the distal end of the scope for creation of pseudopolyps (A). A pseudopolyp is created by suctioning the neoplastic mucosa into the cap (B) until a complete red out occurred on the screen due to the entire cap being filled with mucosa and then a band is deployed using a proximally attached band ligator (C). A snare is then passed through the accessory channel of the scope, placed over the pseudopolyp and then closed beneath the rubber band (C), the pseudopolyp is resected (D) in conjunction with coagulation current. The device can be used for up to 6 resections.

2.2.1 Objectives

The primary objectives of this study were to assess the efficacy (defined by successful resection of all the delineated areas in one single session) and safety of the two MBM devices (Cook Duette and Boston Captivator) in treatment naïve patients with BE neoplasia undergoing EMR.

Secondary objectives included retrospective comparison of the size of the resected EMR specimens by the 2 MBM devices in consecutive patients with BE neoplasia. Minimum diameter, maximum diameter, surface area and depth (defined as microscopically measured thickness) of the resected EMR specimens were compared to identify if either of the devices is capable of resecting larger EMR specimens. Final histology of EMR specimens obtained by the 2 MBM devices were also compared.

2.3 Materials and Methods

2.3.1 Patient selection and Inclusion Criteria

A retrospective study looking at treatment naive patients (defined as those with no prior endotherapy and radiotherapy) with BE neoplasia undergoing EMR from March 2015 to October 2017. Consecutive patients treated by the Cook Duette or the Boston Captivator device in a high volume tertiary referral centre were analysed. Patients aged 18-90 years with a visible lesion detected on white light endoscopy (WLE), narrow band imaging (NBI) or optical enhancement (OE), confirmed on recent endoscopy and deemed suitable for endoscopic resection were included. Written informed consent was obtained from all patients prior to the procedure.

2.3.2 Exclusion Criteria

Patients with previous oesophageal EET, including EMR / Endoscopic Submucosal Dissection, radio frequency ablation (RFA), cryoablative therapy, laser treatment, photodynamic therapy (PDT), argon plasma coagulation (APC) or radiotherapy were excluded from the study. In addition, patients with oesophageal stenosis (preventing the passage of a gastroscope), oesophageal varices, and coagulopathy were also excluded from this study.

IRB approval was not required as this project was a retrospective audit of routine clinical care and deemed exempt as per UK guidelines on clinical audit (247).

2.3.3 Endoscopic Procedure

All endoscopic resections were performed by a single experienced senior endoscopist with extensive experience in endoscopic mucosal resection in the oesophagus using both the Duette and the Captivator devices. The same PENTAX therapeutic gastroscope with a 3.2 mm working channel was used.

At the time of endoscopy, the distance of the visible lesions (cm) from the incisors was recorded in addition to the location and estimated size of the lesion (mm). Lesions were classified according to the Paris classification (248). The length of the BE segment was also defined as per Prague Classification (249). Visible lesions were delineated (figure 1) with the tip of the device snare (ERBE VIO 300D, Forced Coag, Effect 2, 40 W). After delineation, lesions were resected using one of the 2 MBM devices, Duette or Boston Captivator (Figure 1 and 2). The decision on which device was used was non-randomized and not controlled for in the study and device selection was done at the outset of each case at the endoscopist's discretion.

Immediately after the resection in both groups, the snare was retracted, the resected specimen was pushed into the stomach, and the resection base was inspected. Subsequent

resections were performed (if necessary) in the same way to cover all marked areas, with only a small overlap between adjacent resections to prevent residual tissue bridges. After completion of resection of the delineated area, the resection base was carefully re-inspected to ensure that all delineation markings have been removed.

Identical diathermy setting (ERBE VIO 300D, Forced Coag, Effect 2, 40 W) and suction pressures (100 kPa) were used in all resections. Submucosal injection and lifting of the mucosa was not used in any of the cases. All resected specimens were successfully retrieved from the stomach using a Roth Net ® (US endoscopy, a subsidiary of STERIS corporation). All specimens were pinned down to cork board (figure 3) by the same endoscopy nurses and preserved in identical volumes of formalin for histological evaluation by the same 2 experienced senior GI pathologists.

The endoscopist and the endoscopy nurses were not blinded to the type of device used but the GI pathologists (performing the measurements on the specimens) were not aware of the devices used for the mucosal resection.

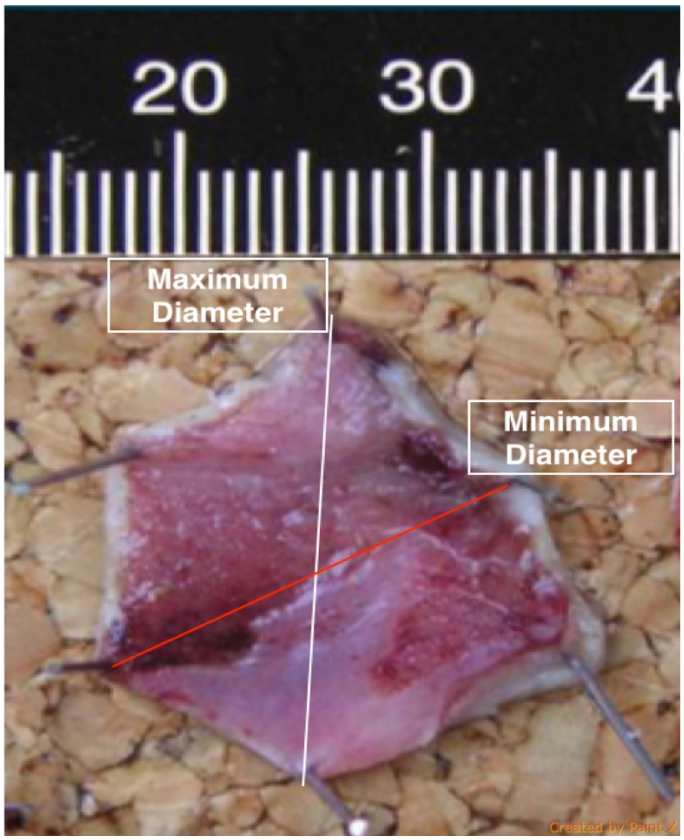

Figure 3: EMR specimen post resection

Pinned down on cork board, showing the Maximum Diameter and the Minimum Diameter.

These measurements were done macroscopically by the GI pathologist.

2.3.4 Preparation of Histological specimens

EMR specimens were placed in formalin after fixation to a non-absorbent cork board (figure 3), then sectioned in 2-mm slices, and embedded in paraffin, after which 4 µm thick slices were cut, placed on glass slides, and stained with haematoxylin and eosin. The dimensions of resected EMR specimens were measured macroscopically by the pathologist prior to sectioning. These included the maximum diameter and the minimum diameter (figure 3). The depth (defined as the microscopically measured thickness) of each EMR specimen including submucosal invasion was measured microscopically by the pathologist. These measurements were provided on the histology report. Grading of intraepithelial neoplasia was in concordance with the Vienna classification. (250) The surface area (mm^2) of each specimen was then approximated by multiplying the minimum diameter (mm) by the maximum diameter (mm) for each specimen.

2.3.5 Statistical Analysis

Statistical analysis was performed using the SPSS Statistics software (Version 25). Quantitative variables were expressed as means (±SD) and qualitative variables were presented as percentages. The mean value in the two groups (Duette and Captivator) was compared using Student t-test. Fisher's exact test used to compare R0 and R1 between the two groups.

2.4 Results

The study included 20 patients in each group (Duette: 18M+2F; mean age 74 years; Captivator: 17M+3F; mean age 72 years) with a mean length of BE of C4M6 in the Duette and C3M5 in the Captivator group, p=NS (Table 1). The endoscopically estimated mean lesion diameter was 12 mm in the Duette and 15 mm in the Captivator group (p=0.22). This estimate was carried out prior to resection by the endoscopist. Successful resection was achieved in 100% of the cases with a total of 58 specimens resected in the Duette and 63 in the captivator group. The mean number of EMRs performed per delineated lesion was 2.6 in the Duette and 2.8 in the Captivator group, p=0.67 (Table 2).

		Duette	Captivator	t-test
Number of patients		20 (18M + 2F)	20 (17M + 3F)	
Mean Age		**74**	**72**	**p=0.51**
SD		±9	±10	
95% CI		70-78	67-76	
Mean Prague Classification	**C**	**4**	**3**	**p=0.76**
	Range	0-15	0-13	
	M	**6**	**5**	**p=0.85**
	Range	1-15	1-15	

Table 1: Patient demographic and mean Prague classification for the Duette and the Captivator group. SD: Standard Deviation, 95% CI: 95% Confidence interval

	Duette	Captivator	t-test
Total Number of specimens	58	63	
Mean Endoscopically Estimated Lesion Diameter (mm)	**12**	**15**	**p=0.22**
SD	±9	±13	
95% CI	7-16	10-21	
Mean No. of EMR per lesion	**2.6**	**2.8**	**P=0.67**
SD	±1.6	±2.1	
95% CI	1.9-3.4	1.9-3.7	

Table 2: Total number of specimens, mean endoscopically estimated lesion diameter and mean number of EMR per lesion for the Duette and the Captivator group. SD: Standard Deviation, 95% CI: 95% Confidence interval

2.4.1 Histology

All lesions were described using the Paris classification prior to EMR. Paris IIa was the most common lesion seen (table 3) in both groups [80% (16/20) in the Captivator and 75% (15/20) in the Duette group; p=0.70]. Table 3 shows the Paris classification of all the lesions.

Paris Classification	Is	Ip	IIa	IIb	IIa/IIc
Captivator	2/20 (10%)	0	**16/20 (80%)**	1/20 (5%)	1/20 (5%)
Duette	0	1/20 (5%)	**15/20 (75%)**	2/20 (10%)	2/20 (10%)

Table 3: Comparison of Paris Classification of all the lesions in the Duette and the Captivator group (p=0.70)

Nineteen patients in the Captivator group had EMR specimens with clear deep margin in comparison to 17 in the Duette group, p=0.61 (Table 4). Fifteen of the patients in the Captivator group showed cancer on the EMR specimens in comparison to 12 in the Duette group (p=0.50). Of those with cancer on EMR specimens, 50% showed submucosal involvement in the Duette group and 20% in the Captivator group, p=0.13 (Table 5).

	R0	**R1**
Number of patients in the **Captivator** group	19/20 (95 %)	**1/20 (5 %)**
Number of patients in the **Duette** group	17/20 (85 %)	**3/20 (15 %)**
Fisher's exact test	P=0.61	

Table 4: Invasion of deep margin of EMR specimens with BE neoplasia in the Duette and the Captivator group

	CANCER	**Mucosal Cancer**	**Submucosal Cancer**
Number of patients in the **Captivator** group	**15/20 (75 %)**	12/15 (80 %)	**3/15 (20 %)**
Number of patients in the **Duette** group	**12/20 (60 %)**	6/12 (50 %)	**6 /12 (50 %)**
Fisher's exact test	**P=0.50**	P=0.13	

Table 5: Cancer cases with Submucosal invasion based on the EMR specimens in the Duette and the captivator group

2.4.2 EMR specimen size comparison

The mean Minimum diameter, Maximum diameter, Surface area and Depth of all resected specimens with the Captivator device was compared with that resected by the Duette device (Table 6). The data showed that the captivator EMR specimens to be significantly larger than similar specimens resected with the Duette device [Minimum diameter 9.89 mm vs 9.07 mm (p=0.019); Maximum diameter: 13.54 mm vs 12.38 mm (p=0.024); Surface area: 135.40 mm^2 vs 113.89 mm^2, (P=0.005); Depth 3.71 mm vs 2.89 (p=0.001)].

	Duette group	Captivator group	t-test
Number of specimens	58	61	
Mean Min Diameter (mm)	**9.07**	**9.89**	**p = 0.019**
SD	± 1.99	± 1.76	
Lower 95% CI of mean	8.55	9.45	
Upper 95% CI of mean	9.59	10.33	
Mean Max Diameter (mm)	**12.38**	**13.54**	**p = 0.024**
SD	± 2.63	± 2.89	
Lower 95% CI of mean	11.69	12.82	
Upper 95% CI of mean	13.06	14.26	
Mean Surface Area (mm2)	**113.89**	**135.40**	**p = 0.005**
SD	±38.75	± 42.68	
Lower 95% CI of mean	103.83	124.77	
Upper 95% CI of mean	123.95	146.02	
Mean Depth (mm)	**2.89**	**3.71**	**p = 0.001**
SD	± 1.19	± 1.53	
Lower 95% CI of mean	2.58	3.33	
Upper 95% CI of mean	3.20	4.09	

Table 6: Comparing Specimen Size between the Duette and the Captivator group. SD: Standard Deviation, CI: Confidence Interval

2.4.3 Complications

There were no reported perforations in either group. There was minor bleeding during the procedure that occurred in 2 (10%) patients in the Captivator group and 1 (5%) patient in the Duette group (p=NS). These were successfully treated with the tip of the hot snare and there were no reported re-bleeding or hospitalization. In our study re-bleeding was only considered a relevant complication if it led to unplanned admission, endoscopic re-intervention and the need for blood transfusion. There was 1 (5%) delayed bleed at 48 hours post Captivator EMR and 1 (5%) at 9 days post Duette EMR (p=NS). Both cases required conventional endoscopic therapy that was successful on first attempt. Both patients had an in-patient stay of 48 hours post endotherapy for routine observation only. First follow up endoscopy (3-months post EMR) showed 1 (5%) stricture in both groups (p=NS) requiring 1 endoscopic dilatation.

2.5 Discussion

ER for visible BE neoplasia can achieve successful outcomes if diagnosed at an early stage. (251) (134) (135) Minimally invasive EET has significantly developed in the past decade and has shown improved mortality and morbidity in comparison to surgical management of early BE neoplasia (240) (241).

MBM is a widely used technique for the endoscopic resection of neoplasia in the oesophagus. MBM is effective in selected groups of patients (136) and it allows safe piece-meal resections in patients with BE neoplasia. Time and costs are saved compared with the cap and snare technique (252).

This study showed that the EMR specimens resected with Captivator device appear to have a larger minimum diameter, maximum diameter, surface area and depth in the oesophagus when compared with the Duette device in similar treatment naive BE segments. Baseline lesion morphology and subsequent resection pathology were similar in both cohorts of examined patients. A possible clinical advantage of this is in situations where en bloc resection is wanted for larger or more extensive lesions (>10mm) with fewer resections per lesion. This may also have a positive impact on reducing procedure time as fewer resections may be needed for any given lesion size and shorter procedure time is known to reduce the total cost of treatment (129); however our study did not formally assess the procedure time between the 2 groups and we do not have data to support this notion in this study. In addition, fewer resections may reduce the number of complications such as bleeding and

perforation; however our study showed no significant difference between the two groups with regards to bleeding and there were no recorded perforations. This is a potential objective for future studies on the Captivator device. Successful resection was achieved in 100% of the cases which illustrates that both devices are very effective in this respect.

Complete resection of an extensively large lesion during the first endotherapy session is desirable as subsequent strictures and fibrosis may preclude further endotherapy and resection. Also resecting larger areas at baseline endoscopy may leave less residual BE reducing the number of sessions for further endotherapy with ablation and the potential need for rescue EMR (253). A large study by Pech *et al*, from 1000 consecutive patients with IMC suggested that complete removal of the whole neoplastic lesion in one session is favourable in order to reduce the risk of treatment failure (136). This further supports the use of the Captivator device in patients with large lesions requiring complete successful resection in one session.

A previous study by Matsuzaki *et al,* demonstrated that larger ER specimens result in deeper resections (254). Our study was able to show that the Captivator device resected specimens that had significantly larger microscopically measured depth in comparison to that with the Duette device; however, this did not result in higher perforation or bleeding rates, which were not significantly different, compared to that in the Duette group. The deep resection margins and radicality of neoplasia resection in our cohort of cases was not different in both the cancer and dysplasia cases. Deeper resection may be an important factor to consider in patients with suspicions of submucosal invasion at baseline. In these patients, for example those that have significant contraindications to surgery, EET with a device with the potential

of deeper resection capability may provide them with the best chance of curative endoscopic therapy. Larger and deeper EMR specimens also allow more precise evaluation of the depth of tumour penetration than any other available methods, which would allow differentiation of mucosal from submucosal tumours (253). Large EMR specimens may be able to identify patients with submucosal invasion suitable for escalation to surgical management and therefore excluded from endoscopic therapy that may result in a less favourable long term outcome.

In recent years, en bloc resection with Endoscopic Submucosal Dissection (ESD) in large lesions have become attractive in the management of patients with BE neoplasia (255) (256) (257). ESD is only available in expert centers with highly skilled operators. The use of the EMR Captivator device in BE neoplasia can potentially mimic this for larger lesions by acquiring larger tissue specimens and therefore in comparison to the Duette device, it may become the preferred tool for larger lesions.

Both MBM devices were shown to be equally safe and effective at resecting visible lesions in patients with BE neoplasia when performed by an experienced endoscopist in identical clinical environment. The intra-procedural acute minor bleeding episodes were considered clinically irrelevant because all were treated endoscopically during the same procedure by coagulation using the tip of the hot snare. The intra-procedural acute minor bleeding and delayed bleeding in both groups were not significantly different. The acute and delayed bleeding rates were better than that of recently published data (134) (135). There were no reported perforations. Sample size was not calculated and therefore the patient numbers in both groups may have been inadequate to show statistically significant difference in

complication rates between the Captivator and the Duette group. We emphasize that this was a clinical audit and feasibility analysis that may in due course support a large scale powered RCT. In addition, the stricture rates for both groups (Captivator 5%, Duette 5%; p=NS) were lower than that documented in major recent studies (10%-37%) (134) (135); however, one must take into account that all procedures were performed by the same senior endoscopist with extensive experience in endoscopic mucosal resection. Considering the total number of patients and resections performed in this study, it may be possible to see more accurate bleeding, perforation and stricture rates if the number of participants were to increase significantly and if endoscopists with variable range of experiences were to perform the procedure.

The visualisation through the Captivator cap is potentially better compared with the Duette cap. This is due to the position of the bands on the Captivator cap which are placed at the very proximal end of the cap, allowing a clear and unobstructed view through the transparent cap. This visualisation is further improved with each release of a rubber band. Improved view through the Captivator cap was based on the endoscopist's experience with the devices and not formally assessed in our study. A formal analysis of visualisation through the Captivator cap was analysed by Scholvinck *et al*, that showed significantly higher overall median score for the visualization with the Captivator cap (246). The endoscopist also noted that the passage of accessories through the working channel of the scope was better with the Captivator device; however, this was not formally assessed, but again previously confirmed by Scholvinck *et al*, that showed the passage of accessories to be significantly easier with the Captivator device (246).

There are several limitations to our retrospective study. First, retrospective collection of data may have resulted in information bias and may have underestimated adverse events. Secondly, this study was performed by an experienced endoscopist at a high volume tertiary referral centre with extensive experience in resection of large and complicated oesophageal neoplastic lesions, which may have influenced the results significantly and therefore we may have observed different results if the procedure were performed by endoscopists with less experience. Third, EMR specimens were placed in formalin, post resection and then sent to the pathology lab for measurement of their dimensions and histological analysis. Formalin may have affected the size of these specimens and therefore the measured dimensions may have been under or overestimated. The specimens were not measured directly after the resection. Fourth, in order to create a pseudopolyp, the EMR cap was angulated against the oesophageal wall and the mucosa was suctioned into the cap until a complete red out was visualized on the screen, prior to the deployment of the band. The quantity and volume of the suctioned mucosa into the cap is dependent on the angulation of the cap against the mucosa, where in the oesophagus the resection may be taking place and the elasticity of the tissue. The angulation of the cap against the mucosa was not controlled for in each group. In addition, tissue elasticity and fibrosis can affect the volume of mucosa suctioned into the cap. Variable prior exposure to acid reflux and scarring may have altered the tissue elasticity and fibrosis amongst some patients limiting the volume of tissue being suctioned and subsequently affecting the size of the resected specimens. Fifth, device selection was done at the outset of each case, which was non-randomized and not controlled for in the study and at the endoscopist's discretion. This introduces a selection bias. Finally, we measured the surface area of each EMR specimen by multiplying the minimum diameter by maximum

diameter of each specimen. These two dimensions are not independent of each other and therefore the calculated surface area may have created an artificial endpoint.

In conclusion, our data show that both the Captivator and the Duette MBM Devices demonstrate excellent safety and efficacy to successfully resect delineated oesophageal mucosal lesions in treatment naive patients with BE neoplasia. The Captivator device can resect larger specimens and therefore may be preferred for en bloc resections of larger complex oesophageal lesions. This may improve procedure time by reducing the number of overall resections which would contribute to a reduction of total procedure time for piecemeal endoscopic resection. Improved visualisation and passage of accessories through the working channel and comparable bleeding and perforation rates are features that are desirable by senior and trainee endoscopist. A large scale randomized controlled trial to compare the two endoscopic devices in order to define efficacy and safety in more detail would confirm these findings further.

CHAPTER 3

Cryoballoon ablation for the treatment of patients with refractory oesophageal neoplasia after first line endoscopic eradication therapy

Publication from this chapter

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3.1 Overview of Chapter 3:

Background and study aims: Endoscopic eradication therapy (EET) with endoscopic mucosal resection (EMR) for visible lesions followed by Radiofrequency ablation (RFA) for flat Barrett's Oesophagus (BE) is the accepted gold standard treatment for patients with early BE related neoplasia. In a minority of patients (up to 15%) first line EET is unsuccessful and alternative therapies are desirable to eradicate disease and avoid progression to cancer. Cryoablation with the Cryoballoon device is a novel ablative therapy that uses cycles of freezing and thawing to induce cell death. **This chapter of the thesis** presents a single centre prospective study that evaluated the feasibility of the new focal cryoablation device for the treatment of areas of refractory oesophageal neoplasia in patients who had undergone first line Endoscopic Eradication Therapy. Complete Remission of Dysplasia (CR-D) and Complete Remission of Intestinal Metaplasia (CR-IM) at first follow-up endoscopy, durability of disease reversal, rates of stenosis and adverse events were also studied.

Patients and methods: Eighteen cases treated. Baseline histology: 9 patients with Low Grade Dysplasia (LGD), 6 High grade Dysplasia (HGD) and 3 Intramucosal Carcinoma (IMC). Median length of dysplastic Barrett's Oesophagus (BE) treated was 3 centimetres. Median of 11 ablations applied per patient. Each selected area of visible dysplasia received 10 seconds of ablation. 1 session of cryoablation per patient. Biopsy taken at around 3-month post ablation.

Results: CR-D was achieved in 78% and CR-IM in 39% of all patient. There were no device malfunction or adverse events. Stenosis noted in 11% of cases. At a median follow up of 19-months, CR-D was maintained in 72% of patients and CR-IM in 33%.

Conclusions: Cryoablation appears to be a viable rescue strategy in patients with refractory neoplasia. It is well tolerated and successful in obtaining CR-D and CR-IM in "treatment-refractory" patients with BE. Further trials of dosimetry, efficacy and safety in "treatment-naive" patients are underway.

3.2 Introduction

Barrett's oesophagus (BE) is a pre-malignant condition with metaplastic cells that can progress to oesophageal adenocarcinoma (OAC). It is characterised by a change of normal squamous epithelial cells lining the oesophagus to metaplastic columnar cells (239). In most patients, BE only exists in the metaplastic stage without progression to dysplasia. Chronic exposure to acid reflux can result in epithelial cell inflammation and proliferation that can lead to the development of BE metaplasia and progression to low grade dysplasia (LGD), high grade dysplasia (HGD) and invasive oesophageal adenocarcinoma (OAC) (258). The incidence of OAC has increased in recent years and despite advances in medical and surgical interventions, long-term survival remains poor (259)(260) with only less than 20% of patients surviving at 5 years (31). Surgical management of early oesophageal neoplasia carries significant mortality rates (240)(241)(242). In recent years there have been significant developments in minimally invasive endoscopic eradication therapy (EET) of BE neoplasia with high eradication rates and a good safety profile.

The current endoscopic treatment of BE neoplasia consists of endoscopic resection (ER) of visible lesions for accurate staging and risk stratification of patients (243) followed by field ablation of remaining areas of flat BE to prevent the development of metachronous lesions (261). The most commonly used and studied ablative modality is radiofrequency ablation (RFA), that utilises pulsed radiofrequency energy to destroy superficial mucosal tissue with preservation of deeper tissue (262). This technique has been shown to be effective in achieving CR-D and CR-IM; however it can result into pain, bleeding and stricture in the

oesophagus (146)(134)(263). In a minority of patients, ablative therapy with RFA is ineffective and therefore alternative ablative techniques are warranted.

Recurrence of IM and dysplasia can occur after achieving CR-IM and therefore surveillance has been recommended. Data from the United States RFA registry noted a 20% recurrence of BE over a follow up period of 2.4 years and recurrence of dysplasia reported in 14% of those who had BE recurrence (264). A systematic review and meta-analysis by Krishnamoorthi *et al,* showed a recurrence rate for IM to be 7.1% per patient year, 1.3% for LGD and 0.8% for HGD/EAC (after first line EET) (265).

BE refractory to endoscopic therapy has been documented in various studies with overall rate ranging from 2% to 25% (146)(155).

The treatment of BE neoplasia by endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) have shown to be effective and less invasive than surgical oesophagectomy. Both techniques allow histological assessment of resected specimens that can be used to guide further therapy; however these techniques require advanced training in endoscopic therapy with noticeable adverse events such as bleeding (2.1%), perforation (2.5-5%) and stenosis (10%).

A new treatment for oesophageal neoplasia has been developed. Cryoablation with the Cryoballoon device (cryoballoon focal ablation system, Pentax Medical Inc) is a novel ablative therapy that uses cycles of freezing (with nitrous oxide at -80 ^{0}C) and thawing to induce cell death by intra- and extracellular ice formation, leading to vascular injury, and

ultimately apoptosis and cell death (148). The technique may ablate deeper than RFA whilst preserving the extracellular matrix (149) and therefore may result into lower stricture rates and deeper tissue destruction (150). In addition, recent studies have shown that cryoablation to be better tolerated by patients and to be less painful (152)(153)(154).

The aim of this study was to prospectively evaluate the feasibility of the focal cryoablation device for the treatment of areas of refractory oesophageal neoplasia in patients who had undergone first line EET in a single high volume tertiary referral centre.

3.3 Patients/Material and methods

Patients were treated by a single experienced endoscopist with several years' experience in advanced endoscopic management of oesophageal neoplasia including resection and ablative modalities.

Refractory oesophageal neoplasia was defined as:

- Failed 3 ablative procedures (APC or RFA) for patients with BE neoplasia
- Failed 2 ablative procedures (APC or RFA) with less than 50% reduction of BE after second ablation

  The reduction in the length of BE was determined by measuring the remaining length of BE using the Prague classification.

Primary objectives were: Complete resolution of dysplasia (CR-D) and Complete resolution of intestinal metaplasia (CR-IM) at 3 month follow up endoscopy. Secondary objectives included the rate of stenosis, adverse events and durability of disease reversal. Stenosis was defined as any stricture causing symptomatic dysphagia to solid and liquid and strictures preventing the passage of an adult gastroscope requiring endoscopic dilatation.

3.3.1 Inclusion Criteria

- All patients over the age of 18 years
- Previously received first line EET [ER and ablation (with RFA or APC for at least 3 sessions excluding cryoablation) for patient with BE neoplasia with biopsy proven residual disease
- Persistent flat areas of oesophageal neoplasia post first line EET confirmed by two expert pathologists
- Patients with IMC were included only if there was no evidence of poorly differentiated malignancy, involvement of deep resection margin (i.e. T1b deep) and lympho-vascular involvement on previous ER specimens

3.3.2 Exclusion Criteria

- The presence of oesophageal stricture preventing the passage of a therapeutic gastroscope and deployment of the cryoballoon ablation device
- Active GI bleeding or Perforations
- Active inflammation in the upper GI tract
- The presence of raised or high risk lesion requiring endoscopic resection

3.3.3 Baseline Histology

The baseline histology was persistent BE with Low Grade Dysplasia (LGD), High Grade Dysplasia (HGD) and Intramucosal cancer (IMC).

3.3.4 The Cryoablation Device and the endoscopic procedure

The cryoablation balloon system has two main components: The delivery catheter with a balloon probe (30mm in length) and a hand held controller device for the application of the cryogenic fluid with a small cylinder containing the nitrous oxide. The delivery catheter utilises one balloon probe for all sizes of oesophagi (Figure 1). The delivery catheter is introduced via the working channel of a therapeutic gastroscope (Pentax EG34-i10) and the balloon is inflated by the trigger on the foot pedal. The balloon is automatically inflated until it reaches the diameter of the treated oesophagus, hence preventing over inflation and trauma to the wall of the oesophagus. The inflated balloon is cooled by spraying nitrous oxide via the diffuser within the inflated balloon, which subsequently freezes the targeted mucosa to -80 ^{0}C. The cryogenic spray covers an area of about 2 cm^{2}. Rotation of the diffuser within the balloon (360 degree), is controlled by the foot pedal, which allows targeting of specific areas of the mucosa (Figure 2) (266). Following deflation of the balloon,

the gas is aspirated back automatically into the hand held controller and condensed. The treated mucosa becomes erythematous immediately after deflation of the balloon, allowing the endoscopist clear visualisation of the treated segment of the mucosa.

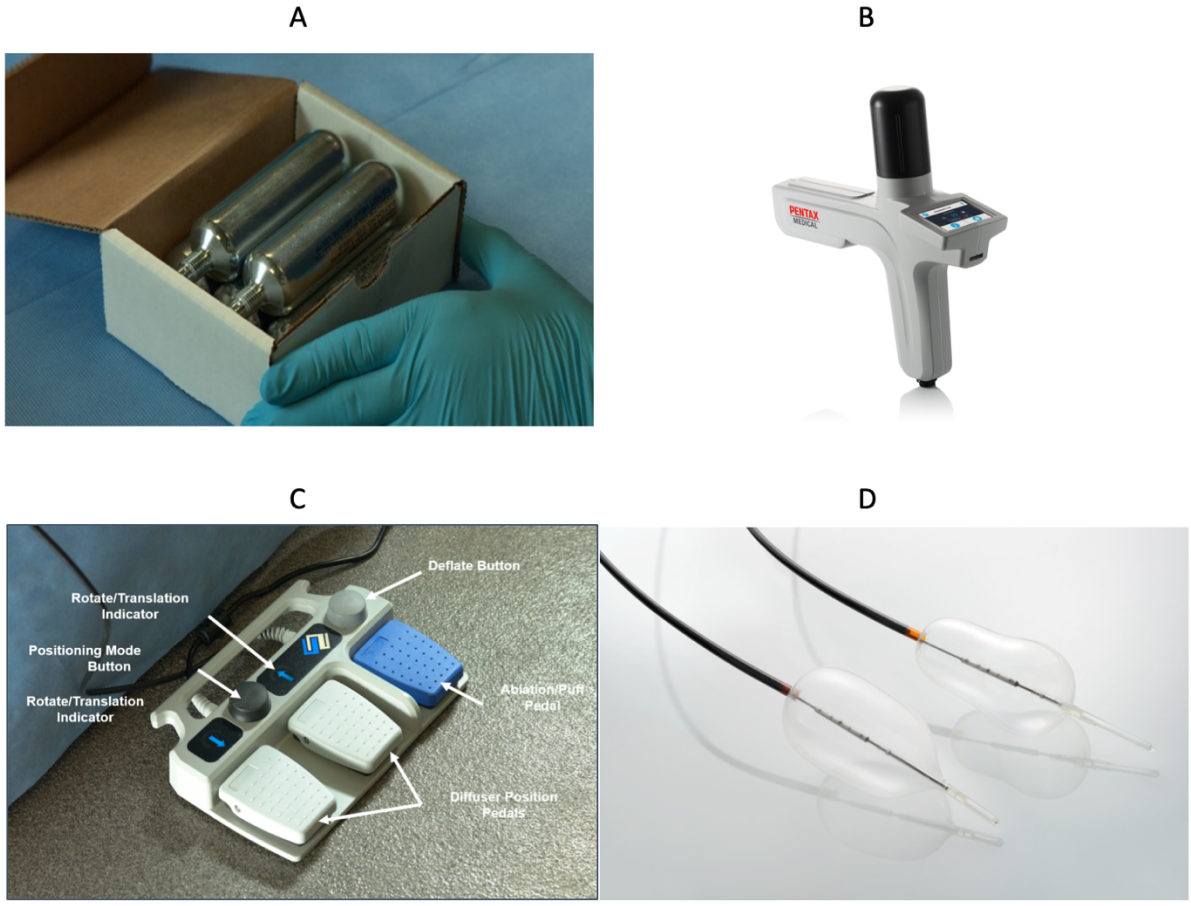

Figure 1: Cylinders containing nitrous oxide as the cryogenic agent (A). Hand-held controller device (B) and the foot pedal with cryoablation balloon catheters for the oesophagus and the GOJ junction.

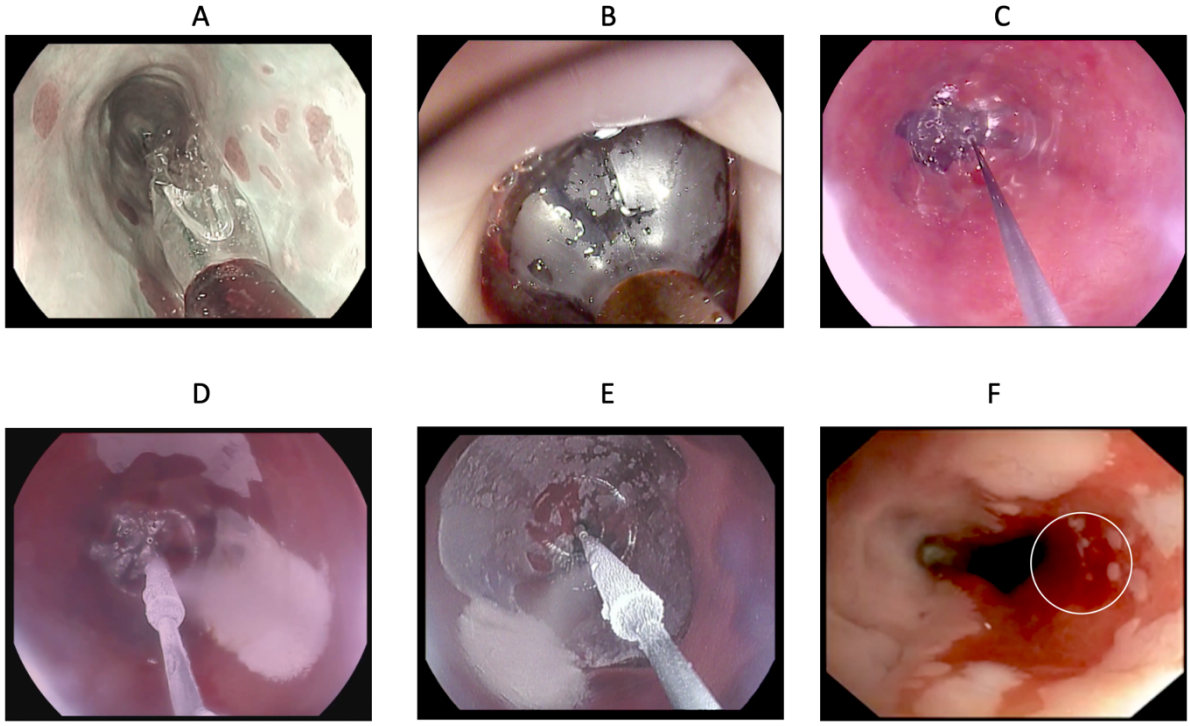

Figure 2: Cryoablation balloon in the oesophagus prior to insufflation (A). Balloon partially inflated (B), balloon fully inflated within the oesophagus (C), and Cryoablation of the left (D) and right (E) oesophageal wall. Post Cryoablation mucosal erythema as shown by the circled white line (F)

3.3.5 Endoscopic Therapy and Follow Up

The endoscopic procedure was performed under conscious sedation by the same GI endoscopist. The refractory areas of BE were measured as per the Prague C & M classification and careful inspection for any visible raised lesions was first carried out. The refractory areas of BE were ablated for 10 seconds by the cryoballoon device. After each ablation, the adjacent area was subsequently ablated until all areas of visible BE including the GOJ were treated. In patients with long segment of BE, there was a minimum overlapping area of cryoablation to ensure that all areas were treated adequately. Scraping of the ablated mucosa was not performed.

All patients received post ablative care, which included high dose acid suppressive medication (Omeprazole 40 mg bd, Ranitidine 300 mg nocte and Sucralfate liquid 2g TDS) and liquid diet for 24 hours followed by soft diet for 1 week. All patients received follow up endoscopy at about 3 months post cryoablation. At follow endoscopy, all treated area were inspected with white light endoscopy (WLE), virtual chromoendoscopy (NBI or OE) and chromoendoscopy (with acetic acid). All remaining areas of neoplasia were documented. In addition the presence of stenosis (if present) was also documented. Biopsies were then taken from 1 cm below the GOJ, the GOJ and the remaining segment of BE at 2 cm intervals, including target biopsies from any suspicious areas (Figure 1. Study Flow Chart).

3.3.6 Biopsy Specimen

All biopsies specimens were placed in formalin and fixed in paraffin and subsequently stained with haematoxylin and eosin. All our histological specimens were examined by the same 2 senior BE expert pathologist (MN, MJ) at University College London Hospital (UCLH).

3.3.7 Study Approval and Patient Consent

This project was presented to the local Clinical Effectiveness Steering Group (CESG) at UCLH for approval as a new procedure. The CESG committee gave their final approval in June 2016 and subsequently patient recruitment started. Written informed consent was taken from all participating patients prior to the endoscopic therapy with cryoablation.

3.3.8 Statistical Analysis

Statistical analysis was performed using the SPSS Statistics software (Version 25). Quantitative variables were expressed as median with range and qualitative variables were presented as percentages. This was a feasibility study and therefore sample size calculation was not performed. Kaplan–Meier analysis was used to determine the durability of CR-IM and CR-D post Cryoablation.

3.4 Results

A total of 18 patients with BE neoplasia (15 Male, 3 Female; median age 71.5, IQR 65-74), refractory to first line EET were treated with cryoablation from June 2016 to March 2018 (Table 1 and 2)(Figure 3).

		Baseline Histology prior to failed first line EET	Baseline Histology prior to Cryoballoon Therapy
BE neoplasia	Low Grade Dysplasia (LGD)	4 (22%)	9 (50%)
	High Grade Dysplasia (HGD)	6 (33%)	6 (33%)
	Intramucosal Carcinoma (IMC)	8 (44%)	3 (17%)

Table 1: Baseline histology

Patient No.	Pre EET Histology	Pre Cryoablation Histology	Post Cryoablation Histology
1	IMC	HGD	Normal Squamous Mucosa
2	HGD	HGD	Normal Squamous Mucosa
3	IMC	IMC	Normal Squamous Mucosa
4	IMC	HGD	Normal Squamous Mucosa
5	LGD	LGD	Normal Squamous Mucosa
6	LGD	LGD	Normal Squamous Mucosa
7	IMC	LGD	Normal Squamous Mucosa
8	LGD	LGD	IM only. No dysplasia
9	HGD	LGD	IM only, no dysplasia
10	HGD	HGD	IM only, no dysplasia
11	HGD	LGD	IM only, no dysplasia
12	LGD	LGD	IM only, no dysplasia
13	IMC	IMC	IM only. No dysplasia
14	HGD	LGD	IM only. No dysplasia
15	IMC	HGD	LGD
16	HGD	LGD	HGD
*17	IMC	HGD	HGD
18	IMC	IMC	IMC
Patient received inadequate ablation with the cryoballoon due to a tortuous and dilated oesophagus			

Table 2: Baseline histology with corresponding post cryoablation histology at 3 months follow up for all patients

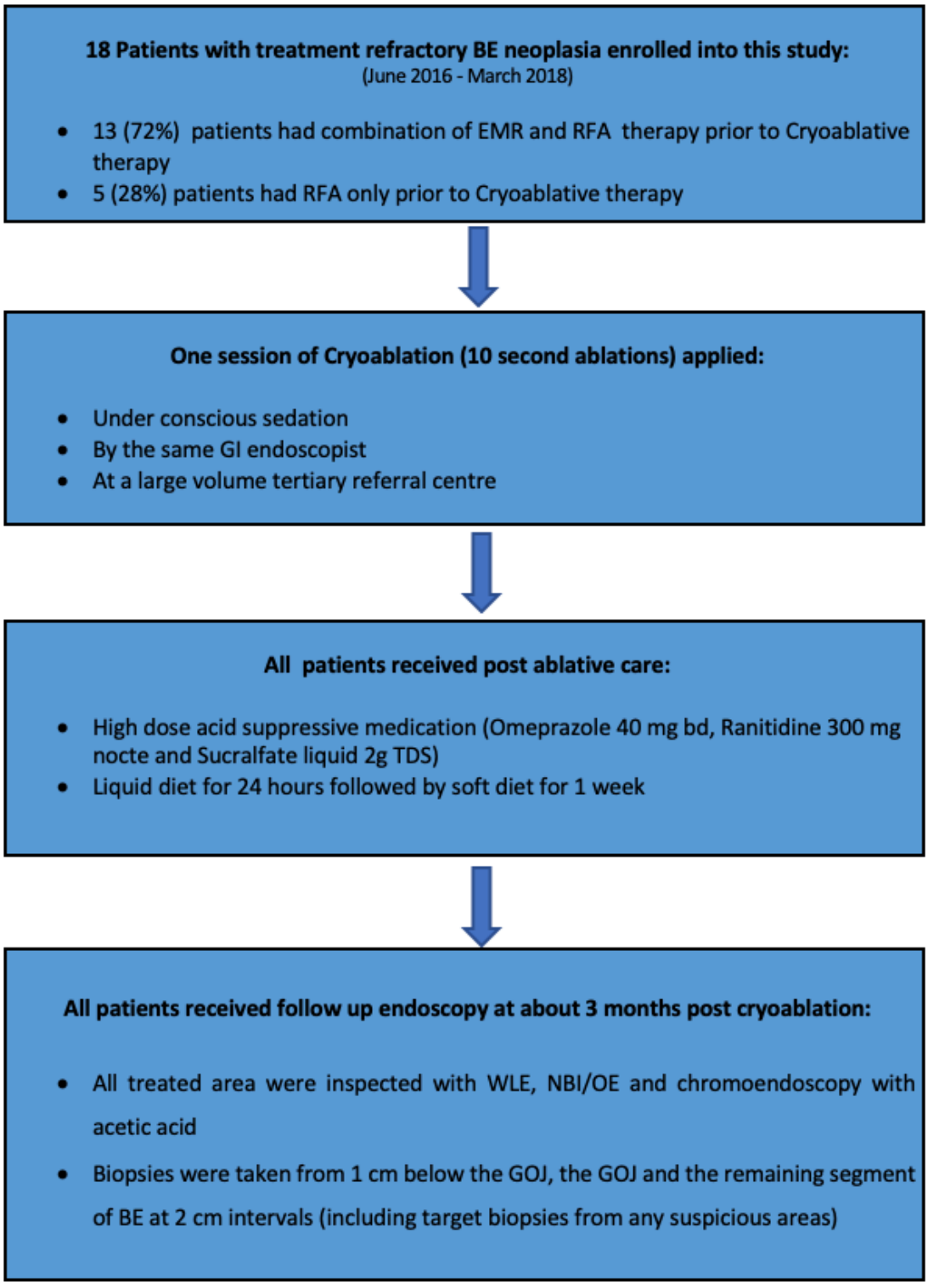

Figure 3: Study flow chart

The baseline sequential EET included a combination of EMR and RFA in 13 (72%) patients and RFA only in 5 (28%) patients with BE neoplasia with a median length of dysplastic BE treated was 3 cm (IQR 3-4.25)(Table 3).

No.	Gender	Age	Pre EET Length of BE	Pre Cryoablation Length of BE	Post Cryoablation Length of BE	No. of Cryoablation
1	F	71	C14M14	C1M3	4 small islands < 1cm	14
2	M	75	C6M7	COM1	All resolved	2
3	M	70	C1M4	C0M2	C0M1	9
4	M	83	C10M11	C0M2	All resolved	11
5	M	55	C8M9	C0M3	All resolved	12
6	F	70	C8M8	C0M3	1 small islands < 1cm	9
7	M	85	C2M2	C0M3	C0M2	11
8	M	63	C7M8	C0M3	C0M1	11
9	M	63	C1M10	C1M3	3 small islands < 1 cm	8
10	M	63	C2M3	C0M4	All resolved	6
11	F	73	C4M7	C0M3	All resolved	4
12	M	76	C14M14	COM10	C0M2	22
13	M	65	C9M15	C0M3	All resolved	9
14	M	70	C16M16	C6M8	C4M6	24
15	M	74	C2M4	C1M3	All resolved	10
16	M	74	C10M11	C6M6	C1M2	18
17	M	74	C7M8	C2M4	C1M2	15
18	M	72	C8M8	C1M5	C0M4	19

Table 3: Baseline length of BE with corresponding number of cryoablation for each patient

Successful ablation was achieved in 17 (94%) patients with only 1 (5.5%) patient receiving inadequate ablation with the cryoballoon due to a tortuous and dilated oesophagus, preventing adequate contact between the mucosa and the cryoballoon device.

Median of 11 (IQR 9-16) ablations applied per patient. Each patient received only 1 session of cryoablation (table 3). At follow up endoscopy 3 months after treatment with cryoablation, CR-D was achieved in 78% (14/18) of patients and CR-IM was achieved in 39% (7/18) of patients (table 4). Lack of response to Cryoablation was seen in 1 (5.5%) patient with IMC and disease progression from LGD to HGD was confirmed in 1 (5.5%) patient at 3 months follow up endoscopy (Table 4). All patients with remaining segment of BE (with IM or dysplasia) post cryoablation, received further endoscopic therapy with EMR, RFA or both, with the aim to achieve complete eradication of BE.

Technical difficulty due to Anatomy	5.5% (1/18) Tortuous and dilated oesophagus
Stenosis	11% (2/18)
No response	5.5% (1/18) 1 case with IMC
Progression	5.5% (1/18) Progressed from LGD to HGD
CR-D	78% (14/18)
CR-IM	39% (7/18)

Table 4: Summary of results

There were 2 (11%) reported oesophageal strictures post cryoablation, each requiring 1 successful endoscopic dilatation. There were no recorded complications or adverse events.

Durability of disease reversal:

The analysis of all patients post endoscopic therapy with cryoablation, showed that CR-D was maintained in 72% (13/18) and CR-IM in 33% (6/18) after a median follow up of 19 months (IQR 13-28) (figure 4).

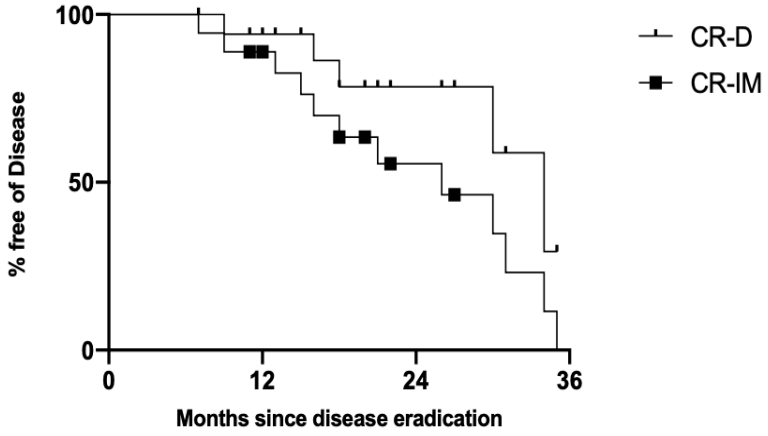

Figure 4: Kaplan Meier curve showing the durability of disease reversal in all patients with BE neoplasia, treated with cryoballoon therapy

3.5 Discussion

The endoscopic treatment of early oesophageal neoplasia has significantly developed in the past decade. The current consensus is to resect any visible lesions followed by ablative therapy using RFA or APC for BE neoplasia. Depressed lesions are associated with high risk submucosal invasion and would be undertreated by ablation.

RFA is safe and effective treatment modality (146)(267)(253) in BE neoplasia. ET is also more cost effective than surgery (268); however, the treatment can be painful and risk of stenosis post ET is not negligible (269), especially in those requiring circumferential ablation (270).

Recurrence of BE and BE neoplasia has been documented in various studies ranging from 5% to 40%. Long term surveillance are therefore needed in order to maintain remission and detect early recurrence of disease (271)(272)(273)(274). Non-compliance with endoscopic surveillance and failure to achieve complete remission at 12 months post ET are predictors of progression (275). In addition, a number of patients (2%-25%) (146)(155) will not respond to first line EET and therefore alternative rescue treatment modalities other than surgery are needed as some of these patient may not be suitable surgical candidates and surgery can be associated with a noticeable mortality and morbidity rates (134)(276)(277). Acid suppression is an important factor in the treatment of patients with BE and refractory disease. GORD is associated with BE and therefore controlling acid reflux is essential part of the treatment. Uncontrolled acid reflux is associated with persistent IM post RFA. Persistent acid reflux is also associated with higher mean number of RFA sessions needed to achieve CR-IM and recurrence of disease after EET (278)(279). Challenging anatomy due to dilated

and tortuous oesophagus and strictures post EET and the presence of submucosal carcinoma has been shown to limit efficacy of endoscopic therapy and subsequently resulting in treatment failure and relapse (146).

Cryoballoon therapy using nitrous oxide as the cryogenic agent is a novel new therapy for the management of early BE neoplasia that has been shown to be safe and effective with success rates that are comparable to that of RFA (153)(280). In this single centre prospective feasibility cohort study, Cryoablation with the cryoballoon device appears to be a viable treatment modality in patients with BE neoplasia refractory to sequential first line EET.

This study was able to achieve CR-D and CR-IM in patients that previously did not respond completely to standard first line EET. We were able to achieve these eradication rates (CR-D: 78% and CR-IM: 39% in patient with BE) with only one session of cryoablation in treatment-refractory patients with wide range of pre-cryoablation pathologies including LGD, HGD and IMC.

We were also able to demonstrate a durability of disease reversal with 72% (13/18) of patients with BE neoplasia maintained CR-D and 33% (6/18) maintained CR-IM after a median follow up of 19 months (IQR 13-28).

Our data is in line with previously publishes series (CR-D achieved in 75-88% of patients) (155)(154)(156). A recent meta-analysis by Visrodia *et al,* analysed 11 studies with 148 patients with BE treated with cryotherapy for persistent dysplasia or IM after RFA. CR-D was

achieved in 76.0% (95% CI, 57.7-88.0) and CR-IM in 45.9% (95% CI, 32.0-60.5) of patients (157).

We have also shown that cryoablation is a safe modality with acceptable stricture rate. The documented symptomatic stricture rate from several major studies on BE endotherapy range from 2.1-14% (134)(270)(141) requiring a median of 2-4 dilatations post endotherapy. Despite circumferential ablation of the GOJ in all patients and pre-ablation EMR rate of 71%, we were able to show a stricture rate of 11% that is comparable with that reported by similar studies (280)(151)(281).

The benefit of Cryoablative therapy over RFA is due to intrinsic and technical differences between the two modalities. The rapid freeze and thaw cycles delivered by cryotherapy achieves a greater depth of tissue penetration with relative preservation of tissue architecture (282). Cryotherapy is minimally destructive to the structural components of tissue, such as collagen, whereas heat-based ablation techniques like RFA, irreversibly destroy proteins and therefore affecting the architecture of the collagen matrix (150). The effects of cryoablation are dose-dependent. The overlap of ice patches on adjacent treated sites, may result in higher application of cryogen and deeper injury and subsequent stricture development (151). The cryoballoon pressure is regulated by the controller to 3.5 pound-force per square inch (psi), which is significantly lower that the dilating balloons that exert pressures of 44 to 147 psi (283). The procedure time for cryoballoon ablation are short and the portability and ease of use of the cryoballoon ablation device is appealing.

Our data suggest that cryoballoon ablation is a promising treatment modality for refractory BE neoplasia. Our study showed that this technique is relatively easy and quick without

serious adverse events. It allows the treatment of large circumferential areas in the oesophagus in addition to small islands. There is no significant published data showing how deep cryoablation can reach into the mucosa or submucosa. Several studies in BE neoplasia (154) and other fields of medicine have shown that cryoablation is less painful (284)(285). Pain perception was not formally assessed in this study, but previous studies have shown that the cooling process may have an anaesthetic effect (286) by reducing or blocking nerve conduction and therefore less postprocedural discomfort than that seen with RFA (284). In addition the vasoconstriction of blood vessels as the result of the cooling process may reduce the development of oedema and the release of painful inflammatory mediators (287).

There were some limitations to this study. First, there was a small sample size and patients were treated in a single high volume tertiary referral centre with no control group, which was due to only a small number of treatment refractory patients with residual disease in our hospital. An increase in the number of patients may alter the results achieved. In addition it may have been possible for patients with long segments of BE refractory to RFA sessions to achieved CR-IM if further RFA therapy session was utilised and therefore cryoablation may have never been required. The median segment of treated BE was 3 cm and the efficacy of cryoablation on long segments of BE refractory to EET is yet to be studied.

There was no formal assessment of pain perception and use of analgesia amongst patients participating in this study.

There was only a relatively short follow up period after treatment, which is important taking into account the late recurrence of disease reported in major studies. This has therefore

limited the conclusions regarding the risk of progression or recurrence in this high risk group of patients.

Side by side ablation for 10 seconds of a large segment of BE maybe time consuming. Our study did not formally assess the duration of the procedures.

Finally, analysis for determinants for successful ablation and for complications was not performed.

In conclusion, Cryoablation is a promising treatment modality for the treatment of patients with BE neoplasia refractory to first line EET. The achieved CR-D and CR-IM rates in this study with the encouraging safety profile, shows that it may be an alternative therapeutic modality for those that are not suitable for RFA or in cases where RFA was not successful.

Longer-term follow-up is needed to determine complete remission durability for cryoablation with application to larger/circumferential areas in order to determine efficacy and stricture rate. Further studies to illicit the effects of double or multiple session of cryoablation with randomised controlled trials and comparison with RFA are recommended.

CHAPTER 4

Quality Indicators for Barrett's EndoTherapy (QBET): UK consensus statements for patients undergoing Endoscopic therapy for Barrett's neoplasia

Publication from this chapter

- **D Alzoubaidi**, K Ragunath, S Wani, I Penman, N Trudgill, M Jansen, M Banks, P Bhandari, AJ Morris, R Willert, P Boger, HL Smart, N Ravi, J Dunn, C Gordon, J Mannath, I Mainie, M Di Pietro, A Veitch, S Thorpe, C Magee, M Everson, S Sami, P Bassett, D Graham, S Attwood, O Pech, P Sharma, LB Lovat, R Haidry. Quality indicators for Barrett's endotherapy (QBET): UK consensus statements for patients undergoing endoscopic therapy for Barrett's neoplasia. Frontline Gastroenterology. Aug 2019

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CHAPTER 4 FIGURES AND TABLES

4.1 Overview of Chapter 4

Background and study aim: Endoscopic therapy for the management of patients with BE neoplasia has significantly developed in the past decade. The previous chapters of this thesis have shown new developments in endoscopic eradication therapy (EET) in BE neoplasia; however, the clinical practice in the UK remains variable, with patients still on the surveillance program despite guidelines that recommend endoscopic therapy. **This chapter presents** the development of Quality Indicators for Barrett's Endoscopic Therapy using expert opinion combined with the best available evidence, aimed at unify clinical practice in BE endotherapy in the UK.

Method: The RAND/UCLA Appropriateness Method was utilised to combine the best available scientific evidence with the collective judgment of experts to develop QBET in 4 sub-groups: Pre-endoscopy, intra-procedure (resection & ablation) and post-endoscopy. International experts including gastroenterologists, surgeons, BE pathologist, clinical nurse specialist, and patient representative participated in a 3-round process to develop 15 QIs that fulfilled the RAND/UCLA definition of appropriateness.

Results: Seventeen experts participated in Round 1 and 20 in Round 2. Of the 24 proposed QIs in round 1, 20 were ranked as appropriate (put through to round 2) and 4 as uncertain (discarded). At the end of round 2 a final list of 15 QIs were scored as appropriate.

Conclusions: This UK national consensus project has successfully developed QIs for patients undergoing BET. These QIs can be used by service providers to ensure that all patients with BE neoplasia receive uniform and high quality care.

4.2 Introduction

The past decade has seen significant advancement in minimally invasive endoscopic treatment modalities for Barrett's oesophagus (BE) neoplasia. Short and long term data report high eradication rates, acceptable disease eradication durability and good safety profile that are comparable to the outcomes of surgical treatment (288). There has been great emphasis on targeting patients at earlier disease stages amenable to endoscopic eradication therapy (EET). EET for early neoplastic BE has been recommended by various major international guidelines (2)(96).

EET for BE neoplasia has revolutionised the management of patients with BE neoplasia and is increasingly used at high volume tertiary referral centres and smaller district general hospitals (289). Adherence to Quality Indicators (QIs) introduced by the American Gastroenterological Association for the endoscopic management of patients with BE has been shown to improve dysplasia detection rate (290). Despite various societal guidelines (2)(291)(126), there still exist a great variation in clinical practice that results in variable patient outcomes.

It is important to note that the management of patients with BE neoplasia is just not confined to the endoscopic procedure only. It requires case discussion in a dedicated Multidisciplinary team (MDT) meeting with careful explanations to patients of their disease status and available therapies prior to and after endotherapy.

The current endoscopic management of BE neoplasia consists of endoscopic resection (ER) of visible lesions for accurate staging and risk stratification of patients (243) followed by field ablation of remaining areas of flat BE to prevent the development of metachronous neoplasia (261). It is therefore important that cases are carefully selected for endoscopic therapy following discussion in MDTs with appropriate choice of therapy (after discussion with the patient) with strict follow up of these cases to ensure high quality service provision and better patient outcomes (292).

It is essential that medical resources are used appropriately and that health provision is shaped and maintained at the highest standard in order to ensure the best possible patient outcomes. Healthcare systems and providers will therefore need to be aligned to ensure a streamlined, efficient and high quality service provision to all patients. QI for Barrett's endotherapy (BET) in the United Kingdom (UK) and Europe are lacking and have led to variable outcomes in the past (253).

The aim of this project was to develop physician-lead Quality Indicators in BE Endotherapy (QBET) to define standardised clinical practice and achieve optimal clinical outcomes for all patients with BE neoplasia.

The aim from this project is not to replace existing guidelines but to create an adjunct so that clinicians can measure performance in a systematic way.

4.3 Method

4.3.1 The RAND/UCLA Appropriateness Method (RAM)

RAND/UCLA Appropriateness Method (RAM) was developed in the 1980s as part of the RAND Corporation/UCLA Health Services Utilisation Study. It is a tool used to measure the overuse and underuse of resources. In the RAM an appropriate measure refers to one in which the expected health benefit exceeds the expected negative consequences by a wide margin such that the procedure is worth performing without considering the cost (293). This methodology is used in situations where there is no adequate high quality research (e.g. randomised controlled trials) to guide clinical practice and therefore the best available evidence is combined with expert opinion, in order to develop quality indicators. RAM is a modified Delphi method that gives experts the opportunity to have a face to face discussion. RAM has been utilised in various clinical specialties including gastroenterology (292). This methodology was successfully utilised in establishing similar quality measures in EET in the US endorsed by the ASGE and ACG (292).

We utilised RAM to combine the best available scientific evidence with the collective judgment of experts to develop QBET in 4 sub-groups that are integral to patient selection, treatment and follow up in BET (Figure 1). The expert panel was selected based on membership in the UK RFA registry and publication history in the field of BE and BET. In addition, geographical variation was considered to ensure expert representation from all regions in the UK, which could be representative of the European variation in practice. The experts consisted of gastroenterologists and therapeutic endoscopists (n=20), including 2

surgeons performing surgery for advanced oesophageal adenocarcinoma (OAC) and providing BET and 1 BE expert pathologist. We also had participation from a BE clinical nurse specialist, a medical statistician and a patient representative. We developed QIs in 4 subgroups, as follows:

- Pre-endoscopy
- Intra-procedure (resection)
- Intra-procedure (ablation)
- Post endoscopy

Round Zero:

RAND/UCLA utilises 3 rounds as shown in figure 1. In round zero, experts were introduced to the project methodology and objectives (via teleconference on the 18th September 2017 by RJH, DA and KR) and familiarised with the RAM process. In addition, one expert was allocated as lead for each subgroup to facilitate the discussions during the face to face meeting (round 2). After round zero, the core group leading the project (RJH, DA, KR, PS, OP) met to collate a list of potential QI's. These were then reviewed with the project leads and the project leads (consisting of national and international experts) then proposed potential QIs for each of the 4 subgroups, which were put forward for ranking at round 1 (24 QIs in total).

Round One:

In round 1, 17 experts had the opportunity to rank each of the 24 QIs electronically in an independent fashion. This was done without interaction with other colleagues. The proposed QIs were sent to all the participating experts via a REDCap database.

Study data were collected and managed using REDCap electronic data capture tools hosted at University College London Hospital (294)(295). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Instructions were also sent to the panel indicating that each QI should be scored by each expert based on their current expertise and knowledge on the topic. The experts were advised to score each QI as it would be applied to an average patient presenting to an average medical facility and to an average physician without the consideration for cost or feasibility of applying the QI in clinical practice. Each QI was ranked from 1 to 9 as per RAM protocol.

- Score of 1,2,3 = Inappropriate QI
- Score of 4,5,6 = Uncertain QI
- Score of 7, 8, 9 = Appropriate QI

Following round 1 voting, all the scores were collected and analysed using 4 statistical methods by an expert statistician with knowledge of the RAM process.

In addition, an extensive literature search on PubMed on the topic of BE and BET was performed around the proposed QIs. The literature search was limited to publications from 1st January 1990 to 23rd January 2018.

Prior to the round 2 face to face interaction and voting, the following was sent to all the investigators:

- A summary copy of the literature search for each QI
- A document showing the distribution of all the responses from round 1, including the investigator's personal response.

Round Two:

Only QIs that were deemed appropriate at round 1 (based on round 1 voting and statistical analysis), were put forward for discussion at round 2. The round 2 meeting (face to face meeting) took place on the 14th of March 2018 in London. At this meeting 20 investigators were provided with individual iPads containing all the overall results of the round 1 voting, a summary of all the literature searches around the QI's, and full text copies of all manuscripts and references for reference and discussion. The lead for each subgroup led the discussion for each QI in that subgroup during this meeting. Each QI was discussed in detail taking into account the opinion from all those present and the available scientific literature. QIs were

reworded, deleted and new QIs were developed (where necessary) for each of the 4 sub-groups.

At the end of round 2 meeting, a set of 15 QIs were finalised and scored by each investigator [pre-endoscopy 2 QIs; intra-procedure (resection) 5 QIs; intra-procedure (ablation) 6 QIs; and post-procedure 2 QIs]. The experts also agreed on setting performance thresholds for each QI (if indicated) in order to set aspirational targets for all service providers. The median score (and range) of suggested performance thresholds are included with each QI. There were no set aspirational targets for QIs with pre-defined performance target in the text [e.g. Intra-procedural (ablation) QI number 4]. The expert panel recognised that some performance targets had to be set cautiously in order to avoid undermining established efficient practices and therefore aspirational targets were set to encourage centres to work towards enhancing their practice and performance.

There were no attempts to force the expert panel to reach a consensus and each expert had the opportunity to score the finalised QIs independently.

Figure 1: RAND/UCLA Appropriateness Method (RAM) – Summary

4.3.2 Statistical Method

Firstly, summaries of the number of responses in three categories were produced. Each response was categorised into one of the following categories:

- Inappropriate: Score 1-3
- Uncertain: Score 4-6
- Appropriate: Score 7-9

In addition to the categorisation, the median score for each QI was calculated and summarised.

Group	QI	Inappropriate n (%)	Uncertain n (%)	Appropriate n (%)	Median	Median interpretation
Pre-Endoscopy	1	0 (0%)	0 (0%)	20 (100%)	9	Appropriate
	2	0 (0%)	0 (0%)	20 (100%)	9	Appropriate
Intra-Procedure (EMR)	1	0 (0%)	0 (0%)	20 (100%)	9	Appropriate
	2	0 (0%)	0 (0%)	20 (100%)	9	Appropriate
	3	0 (0%)	0 (0%)	20 (100%)	9	Appropriate
	4	0 (0%)	0 (0%)	20 (100%)	8.5	Appropriate
	5	0 (0%)	0 (0%)	20 (100%)	8.5	Appropriate
Intra-Procedure (RFA)	1	0 (0%)	0 (0%)	20 (100%)	9	Appropriate
	2	0 (0%)	0 (0%)	20 (100%)	9	Appropriate
	3	0 (0%)	0 (0%)	20 (100%)	8	Appropriate
	4	0 (0%)	0 (0%)	20 (100%)	8	Appropriate
	5	0 (0%)	0 (0%)	20 (100%)	9	Appropriate
	6	0 (0%)	0 (0%)	20 (100%)	8	Appropriate
Post-Endoscopy	1	0 (0%)	0 (0%)	20 (100%)	9	Appropriate
	2	0 (0%)	0 (0%)	20 (100%)	8	Appropriate

Table 1: Summary of responses from round 2 to individual QI

The deviation in the responses between the panel members was assessed using a number of different methods. Firstly, deviation was assessed by the MAD-M statistics. This is the mean absolute deviation from the median. Higher values of MAD-M indicate more spread in responses between the panel. A second measure was based on the BIOMED Concerted Action on Appropriateness definition. This method calculates the number of raters outside of the response category (i.e. inappropriate uncertain, appropriate) containing the median response. Disagreement was assumed if the number of raters outside this category meets a pre-defined threshold. In the RAND/UCLA handbook guidance is given for panel sizes up to 16 raters, but none is provided for 20 raters, as per this panel. Although there were no set guidelines for this number of raters, the decision was based on the same criteria as for a 16 rater panel (agreement if ≤4 raters outside the category). The third measure used the RAND method that tests hypotheses about the distribution of ratings in a hypothetical population of repeated ratings. It is hypothesised that 90% of the hypothetical population of repeated ratings are within one of two extra wide regions (1-6 or 4-9). The binomial test was used to calculate the probability (p-value) that that 'true' value is below 90%. If the calculated probability is below the pre-determined level of 0.10, the conclusion will be reached that there is disagreement amongst raters. The final measure of deviation uses the IPRAS methods. This method is based on the inter-percentile range (IPR) between the 30th to 70th percentiles. The IPRAS is a statistic based on the IPR which is adjusted for symmetry. Disagreement was assumed if the IRPAS was larger than the IPR.

An additional set of analyses examined the threshold values for questions where these were appropriate. Median values and ranges were calculated for the thresholds.

The measures of spread included:

- The count of responses in each 3-point region (1,2,3 – 4,5,6 – 7,8,9)
- The mean absolute deviation from the median (MAD-M)

Appropriateness was measured using:

- Median rating
- BIOMED Concerted Action on Appropriateness definition
- P-value
- Interpercentile range adjusted for symmetry (IPRAS)

A QI was deemed appropriate if it met the definition of appropriateness, using ALL defined statistical methods.

4.4 Results

Summary of responses from round 2 for each individual QI are shown in table 1. At round 2, 20 investigators ranked 15 QIs that were all deemed appropriate and shown in tables 2 to 5 with corresponding aspirational performance target (if indicated) and evidence summary. During round 1, 17 investigators ranked 24 QIs of which 20 were deemed appropriate and 4 uncertain (Table 6).

4.4.1 Appropriate Pre-Procedure Quality Indicators

1. **BET should be performed in high volume centres within a local cancer network to meet efficacy and safety standards**

   Aspirational performance target: 100% (range: 90-100)

Evidence summary:

Endoscopic training should start with knowledge acquisition, followed by resection and ablation in animal models, before training in human subjects. Endoscopist proficiency increases with the numbers of treatment sessions performed (296). Adherence to BE surveillance biopsy protocol in non-tertiary centres are poor, resulting in reduced dysplasia detection rate. Adherence to this protocol is further reduced with an increasing length of BE

segment (297)(298). Advanced imaging with HD-WLE and NBI have been shown to improve the detection rate of early neoplasia in patients with BE (112)(107)(113). The majority of gastroenterologists from academic centres use HD-WLE to classify BE as per guidelines and perform significantly more EET procedures per month, in comparison to those in district general hospitals. These factors favour the referral of patients with BE neoplasia to dedicated high volume centres (299).

In addition, data from the UK RFA registry has shown that increasing experience in performing EET is associated with significantly improved Complete Remission of Dysplasia (CR-D) and Complete Remission of Intestinal Metaplasia (CR-IM) rates, less number of rescue EMRs and faster protocol completion. At the start of the registry and at a time when only less than 20 patients were enrolled, the documented CR-D and CR-IM after completing EET were 79.8% and 71.3% respectively; however with increasing experience (i.e. once > 40 patients enrolled), the study was able to show significantly better CR-D (91%) and CR-IM (83.9%) ($p<005$) (300). This data supports improvement in experience and outcomes with increase in the number of procedures performed. The expert panel has therefore suggested that endoscopic therapy should be performed in high volume referral centres to optimise outcomes. Hospitals performing > 40 EET cases per year, may therefore be suitable centres for performing BE endoscopic eradication therapy.

2. Patients considered for BET, should be discussed in an Oesophago-Gastric MDT

Aspirational performance target: 93% (range: 85-100)

Evidence summary:

The National Institute for Health and Clinical Excellence (NICE) (August 2010) guidelines on ablative therapy for the treatment of BE, recommends to discuss the MDT's views on the range of appropriate treatments with the patient. It also recommends giving patients verbal and written information about their diagnosis, available treatments, patient support groups, and the uncertainty of the long-term outcomes of ablative therapies (301). In addition the BSG recommends that the treatment of patients with BE neoplasia should be discussed in a dedicated GI specialist MDT taking into account patient comorbidities, nutritional status, patient preferences and staging (2). Patients should be provided with information on all treatment options and offered verbal and written information on support groups available to them (2) including clinical nurse specialists. Despite little evidence, the expert panel advocates a MDT approach (including an expert BE pathologist) for these patients in order to safeguard against incorrect use of BET in patients with more advanced disease and to ensure that the case management provided is directed to best patient interest.

Pre-endoscopy QIs	Median Score	MAD-M	BIOMED Analysis	P-Value	IPRAS Analysis	Performance Threshold Median % (Range)
BET should be performed in high volume centres within a local cancer network to meet efficacy and safety standards	9	0.2	No disagreement	1	No disagreement	100 (90, 100)
Patients considered for BET, should be discussed in an Oesophago-Gastric MDT	9	0.3	No disagreement	1	No disagreement	93 (85, 100)

Table 2: Appropriate Pre-endoscopy quality indicators after Round 2 voting with the median score, MAD-M, BIOMED Analysis, p-value, IPRAS analysis and the performance threshold

4.4.2 Appropriate Intra-Procedure (Resection) Quality Indictors

1. **Adherence to the Prague and Paris classification is mandatory**

   Aspirational performance target: 95% (range: 80-100)

Evidence summary:

Several studies have investigated the validity of the Prague circumferential and maximum length (C & M) classification showing high overall validity for the endoscopic assessment of visualised BE lengths amongst expert endoscopists (302)(303), community hospital endoscopists (303) and trainees (249). The BSG guidelines recommend endoscopic reporting be performed using the Prague criteria (2)(290)(304).

Description of lesion morphology using the Paris classification is based on the Japanese system used to classify early gastric cancer. This provides information on the likelihood of invasion of cancer and helps communication between endoscopists (305)(248). Description of lesion morphology using the Paris classification improves lesion recognition at the time of endoscopic therapy. It gives an indication of the likelihood of invasive cancer and aids communication between clinicians. The BSG recommends the use of Paris classification for all visible lesions (2)(306); therefore adherence to the Prague and Paris classification is recommended.

2. **All patients undergoing BET and follow up, should have assessment with High-definition white light (WL) endoscopy with (virtual) chromoendoscopy**

   Aspirational performance target: 93% (range: 80-100)

Evidence summary:

Endoscopy in BE patients should be performed with careful inspection of the columnar-lined oesophagus using HD-WLE, with biopsy of any suspicious areas followed by 4-quadrant biopsies of the BE metaplasia. The use of the HD-WLE is associated with improved detection of dysplasia during routine BE surveillance (307). In addition, chromoendoscopy allows for detailed imaging of the mucosal and vascular surface patterns in BE. Recent studies have shown that imaging techniques such as chromoendoscopy or virtual chromoendoscopy increase the diagnostic yield for identification of dysplasia or cancer in patients with BE; however the evidence for advanced endoscopy boosting dysplasia detection rate on a per-patient basis is slim (308).

The application of a dilute acetic acid (AA) solution to the BE mucosa results in mucosal colour change and highlights mucosal patterns more clearly, facilitating sensitive and specific identification of potentially neoplastic areas. Furthermore, the premature loss of aceto-whitening in areas of the mucosa and the speed at which it disappears is also associated with the presence of early neoplasia. The efficacy of AA chromoendoscopy has been demonstrated in few studies showing a sensitivity and specificity of up to 98% and 96%, respectively (309)(310).

Three main virtual chromoendoscopy modalities are currently available: narrow band imaging (NBI - Olympus), the i-Scan imaging system (Pentax), and blue laser imaging (BLI – Fujifilm). Recent studies have indicated the potential of NBI as a replacement for AA chromoendoscopy with an accuracy of 92%, and sensitivity and specificity of 91% and 93%, respectively, in the identification of early dysplastic lesions on still images (311). Other studies have also shown that i-Scan can improve neoplasia detection in patients with BE with an impressive accuracy and sensitivity, of up to 94% and 83%, respectively. The use of i-Scan in combination with zoom magnified endoscopy and the addition of AA can also provide further improvement in dysplasia detection rate (312). A recent study by Subramaniam *et al* validated a classification system for Blue laser imaging (BLI) which identifies dysplastic BE tissue with sensitivity and specificity of 96%, based on both increased pit pattern irregularity and the presence of disordered and dilated micro-vessels (313). Currently, only AA and NBI have reached the ASGE PIVI requirement.

The current data on advanced imaging modalities in improving dysplasia yield is encouraging, but the data does not provide evidence on how these modalities can impact EET. Most studies to date have either been performed using still images or have been limited to high volume BE referral centres. The expert panel has therefore suggested that all patients undergoing BET and follow up should have assessment with HD WLE with chromoendoscopy or virtual chromoendoscopy.

3. **All visible lesions should be entirely resected with EMR or ESD**

   Aspirational performance target: 93% (range: 80-100)

Evidence summary:

ER is the cornerstone of endoscopic therapy of early oesophageal neoplasia, which aims to provide accurate histological staging with therapeutic intent. ER of early BE neoplasia with Multiband Mucosectomy (MBM) is effective and safe. Large number of studies have shown long-term complete remission rate of 85 to 96% with bleeding rates ranging from 0.7-7.9% and perforation rates ranging from 0.2-2.3% (136)(133)(132)(134)(135). EMR of all visible lesions has been shown to upgrade the pathological diagnosis in 39% of all patients. Most of the change was associated with upgrading of grade of dysplasia and neoplasia. EMR for all visible lesions have been recommended by the ASGE (126). In addition the provision of EMR specimens to the pathology department results in an improvement in interobserver agreement among pathologists compared with biopsy specimens only (137)(138).

ESD for early stage BE neoplasia is also a feasible treatment option as it allows en-bloc resection and accurate histopathologic analysis of lateral resection margins in BE neoplasia. Multiple studies have shown high en bloc resection rates ranging from 89-98.6% and R0 resection rates ranging from 72.4-87% with acceptable perforation (0-8.3%), bleeding (1.4-1.7%) and stricture rates (2.1-11.6%). When curative resections are achieved, good oncologic outcomes are likely in the management of early stage BE neoplasia by ESD (139)(140)(141)(142)(143).

The ESGE recommendations (2015) state that EMR is acceptable for resecting lesions confined to the mucosa, regardless of the size, but ESD may be considered for lesions larger than 15 mm, poorly lifting tumours, and lesions at risk for SM invasion (144).

These data show that EMR and ESD are effective treatment modalities in the staging and treatment of early BE neoplasia with acceptable side effect profiles. It is however important to mention that operator skill and experience will have significant effect on patient outcome and therefore good training is paramount.

4. **The use of EUS is not routinely recommended for patients undergoing BET**

   Aspirational performance target: 90% (range: 70-100)

Evidence summary:

A systematic review and meta-analysis by Qumseya *et al* showed that EUS was able to detect only 14% of patients presenting with advanced disease and 4% in patients with advanced disease in the absence of nodules (314). A prospective study by May *et al* compared staging of early oesophageal neoplasia using HR endoscopy with staging using HR endosonography. The accuracy of the endoscopic and endosonographic staging were 83.4% and 79.6%, respectively. Sensitivity for mucosal tumours was more than 90% (EUS 91.2%, endoscopy 94.1%) while sensitivity for submucosal tumours was 48% for EUS and 56% for endoscopic staging. A combination of the two techniques increased the sensitivity for submucosal tumours to 60%. The overall diagnostic accuracy of both HR endoscopy and HR endosonography in early oesophageal cancer is approximately 80% with no significant differences between the two techniques (315). EUS can provide staging in patients with BE neoplasia, however there is a significant degree of over-staging and under-staging when compared with endoscopic resection (316)(317). The expert panel agreed that EUS is not recommended for the workup of patients with early oesophageal neoplasia, but only to exclude T2 disease or nodal involvement.

5. **Lesions with SM invasion are only to be considered for curative BET if deemed to present a low risk of metastasis**

   Aspirational performance target: 90% (range: 80-100)

Evidence summary:

Neoplastic lesions confined to the mucosa have a better prognosis when compared to those invading the submucosa. Lymph node metastasis and recurrence of the tumour correlates with the depth of invasion of the lesion into deeper tissue layers. Depth of tumour invasion, the grade of differentiation and lymphatic involvement are important decision making factors (318). Lesions confined to the mucosa and SM1 have a very low risk of lymphovascular invasion, however invasion beyond SM1 (>500μm measured from the deepest fibre of the muscularis mucosae) are at increased risk of developing recurrent disease within 5 years (319).

EET is used to treat superficial neoplasms in BE, but cannot cure cancers that have metastasized to lymph nodes (LN). The risk of occult LN metastases for patients with mucosal neoplasms in BE is in the range of 1% to 2% (276) . Oesophagectomy has a mortality rate that often exceeds 2% with substantial morbidity. Therefore, the risk of LN metastases alone does not warrant the choice of oesophagectomy over ET for HGD and IMC in BE (276). A study by Manner *et al* concluded that the rate of LN metastasis in pT1b SM1 early adenocarcinoma with histological low risk pattern was 2%, which was lower than the mortality rate of oesophagectomy (3%); high risk lesions, however, had a LN metastasis risk of 9%, suggesting that ET may be used as an alternative to surgery in low risk lesions only

(320)(321)(322). The expert panel has therefore recommended that only low risk lesions with SM invasion should be considered for curative BET and ALL patients with high risk SM lesions should be considered for surgery (unless not suitable due to comorbidities) following discussion at MDT and with the patient.

Intra-Procedure QIs (Resection)	Median Score	MAD-M	BIOMED Analysis	P-Value	IPRAS Analysis	Performance Threshold Median % (Range)
Adherence to the Prague and Paris classification is mandatory	9	0.1	No disagreement	1	No disagreement	95 (80, 100)
All patients undergoing BET and follow up, should have assessment with High-definition white light (WL) endoscopy with (virtual) chromoendoscopy	9	0.4	No disagreement	1	No disagreement	93 (80, 100)
All visible lesions should be entirely resected with EMR or ESD	9	0.3	No disagreement	1	No disagreement	93 (80, 100)
The use of EUS is not routinely recommended for patients undergoing BET	8.5	0.6	No disagreement	1	No disagreement	90 (70, 100)
Lesions with SM invasion are only to be considered for curative BET if deemed to present a low risk of metastasis	8.5	0.6	No disagreement	1	No disagreement	90 (80, 100)

Table 3: Appropriate Intra-procedure (Resection) quality indicators after Round 2 voting with the median score, MAD-M, BIOMED Analysis, p-value, IPRAS analysis and the performance threshold

4.4.3 Appropriate Intra-Procedure (Ablation) Quality Indictors

1. **Low and High grade dysplasia without visible lesions should undergo endoscopic ablation**

   Aspirational performance target: 95% (range: 80-100)

Evidence summary:

The multicentre EURO II study showed that RFA can achieve a CR-D and CR-IM rates of 92% and 87%, respectively (146), in patients with early BE neoplasia. A systematic review by Desai *et al* also showed that ET of BE neoplasia with resection of visible lesions followed by ablation of the remaining segment of BE can achieve a CR-D rate of 93.4% and CR-IM of 73.1% (134). ET for early BE neoplasia should therefore be offered after appropriate discussion with the patient as ET is associated with high rate of CR-D and CR-IM and reduction in disease progression and development of cancer (323). The efficacy and safety profile of RFA suggests that it is the best ablative modality currently available (147) for patients with LGD and HGD without visible lesions. The diagnosis of dysplasia should be reproduced and confirmed by expert BE pathologists prior to consideration for EET. Recent meta-analysis by Qumseya et al, studied the progression rates in LGD patients based on review by an expert GI pathologist. The group was able to show that the rate of progression from LGD to HGD/OAC was significantly higher among studies where expert GI pathologist

confirmed the diagnosis of LGD compared with studies that did not use a GI pathologist (126).

2. **Following endoscopic resection, patients undergo ablative therapy, every 2-4 months in order to achieve CR-IM**

   Aspirational performance target: 90% (range: 80-100)

Evidence summary:

The initial UK RFA registry of 335 patients with BE and neoplasia that received ER for visible lesion followed by RFA every 3 months until all areas of BE were ablated or cancer developed showed that by 12 months after initial RFA treatment CR-D was achieved in 81% and CR-IM in 62% of patients (324). The registry's later report in 2015 (consisting of 508 patients) showed a CR-D and CR-IM rates of 92% and 83%, respectively (253). There is increasing evidence to support the use of RFA (325) post-ER of any visible lesion in order to achieve CR-IM in the first 12-18 months post initial endoscopic ablation. Data is lacking on how often and at which interval RFA should be provided to these patients; however, our panel of experts suggest that an interval of 2-4 months would be acceptable practice.

3. **For patients undergoing RFA with a focal device, the dosimetry and treatment regimen is 12 J / cm^2 X 3, without interval cleaning and for patients undergoing RFA with a circumferential device the dosimetry and treatment regimen is 10J/cm^2, clean, 10J/cm^2**

   Aspirational performance target: N/A

Evidence summary:

Focal application of RFA without cleaning in between each ablation has been shown to be effective with 94% CR-D and 87% CR-IM with a stenosis rate of 11% (152). A multicentre randomised trial by Vilsteren *et al* showed that a simplified ablative regimen (3 X 15 J/cm2–no clean) is highly effective and can achieve higher complete remission of residual BE islands (73% vs 67%) than the standard method (2 X 15 J/cm2–clean–2 X 15 J/cm2) at 2 months (326). The same group was also able to show that the simplified regimen without cleaning was able to achieve higher BE surface regression (88% vs 83%) in comparison to the standard regimen in circumferential balloon based RFA with significantly shorter ablation time with the simplified technique ($P < 0.01$) (327). Furthermore, a multicentre RCT on focal RFA for dysplastic BE showed that the simplified RFA regimen (3×12 J/cm^2, without cleaning) is non-inferior to the standard regimen (2×15 J/cm^2, followed by cleaning, followed by 2×15 J/cm^2) and therefore is the preferred RFA regimen for the management of patients with BE dysplasia (328).

The volume of evidence supporting the use of the circumferential RFA device in published literature is increasing. Recent data have shown a regression of 78% of BE segment at 3 months post ablation with the circumferential device using a dose of 12J and 85% regression with 10J (329). Furthermore a randomised trial in the Netherlands assessed treatment regimens for the 360 Express RFA balloon catheter (360 Express) using standard (1x10J/cm^2-clean- 1x10J/cm^2), simple-double (2x10J/cm^2-no clean) and simple-single ablation regimen (1x10J/cm^2-no clean). The simple-double arm of the study was terminated early as the result of significant severe stenosis; however, the study was able to show higher median BE regression in the standard arm compared to the simple-single group: 85% (IQR 75-94), 95% CI:78-92% versus 73% (IQR 48-90), 95% CI:59-85%(p0.009) (329). It would therefore be appropriate to consider standard regimen (1x10J/cm^2-clean- 1x10J/cm^2) for the use of the circumferential RFA device.

4. **Centres undertaking BET should achieve CR-D ≥ 90 % and CR-IM ≥ 80 % within 18 months after the first treatment**

   Aspirational performance target: N/A

Evidence summary:

The Ablation of Intestinal Metaplasia Containing Dysplasia (AIM) trial included a 5-year follow up analysis of patients with BE and dysplasia managed by RFA in a randomized controlled trial. Data showed BE recurrence after CR-IM by RFA in almost one-third of patients with baseline dysplastic BE. Most recurrences occurred during the first year after CR-IM. However, patients that achieved CR-IM and remained BE free at 1 year after RFA had a low risk of BE recurrence (330). In addition, data from the UK RFA registry, the multicentre community practice registry, and the multicentre interventional EURO II study have all shown that ET is capable of achieving CR-D in 81-92% and CR-IM of 72-87% in patients with BE neoplasia at 12 months (253)(146)(324)(331). Recent systematic reviews and a meta-analysis have also shown that EMR followed by RFA in patients with early BE neoplasia can achieve CR-D of 91-93% and CR-IM of 73-78% with 5-10% stricture rate, 1% bleeding rate and 0.2% perforation rate (134)(271). Based on recent studies the expert panel suggests that centres undertaking BET should aim for CR-D > 90 % and CR-IM > 80 % at 18 months after the first treatment and end of treatment should be confirmed by 2 successive negative endoscopies after which patients should receive follow up endoscopies at appropriate intervals stratified according to risk of recurrence. The expert panel agreed that 18 months-

time point is appropriate as standard clinical practice cannot always ensure timely visits and a 12month time point would be too restrictive.

5. **Patients with residual dysplasia after 18 months, are to be re-discussed at a Oesophago-Gastric MDT**

   Aspirational performance target: 90% (range: 80-100)

Evidence summary:

The recurrence of neoplasia after ER can be significantly reduced if the residual BE is completely ablated (332). A prospective study by Pech *et al* showed a significant (96.6%) response to ET in patients with BE neoplasia. However, metachronous lesions in the BE segment developed in 21.5% of patients within 2 years. The risk factors most frequently associated with recurrence were piecemeal resection, long-segment BE, no ablative therapy of BE after complete response, time until complete response achieved >10 months, and multifocal neoplasia (273). It is therefore recommended that all patients with residual BE neoplasia after 18 months of endotherapy to be discussed in a dedicated OG neoplasia MDT and considered for further investigation and treatment.

6. **Post BET symptomatic stricture rate should not exceed 10-15 %**

   Aspirational performance target: N/A

Evidence summary:

The documented symptomatic stricture rate (SSR) from several major studies range from 2.1-14% (133)(134)(141)[90](270) requiring a median of 2-4 dilatations post therapy. These also include data from EURO II study (SSR=6%) (146), UK RFA Registry (SSR=6.2%) (253) and the meta-analysis by Yang *et al* (SSR=11.6%) (141) and Qumseya *et al* (SSR=5.6%) (333). EMR and ESD are increasingly used in the management of BE neoplasia and stricture rates are expected to rise accordingly. It is therefore reasonable to suggest that all centres undertaking BET should not have symptomatic stricture rate exceeding 10-15% post BET.

Intra-Procedure QIs (Ablation)	Median Score	MAD-M	BIOMED Analysis	P-Value	IPRAS Analysis	Performance Threshold Median % (Range)
Low and High grade dysplasia without visible lesions should undergo endoscopic ablation	9	0.4	No disagreement	1	No disagreement	95 (80, 100)
Following endoscopic resection, patients undergo ablative therapy, every 2-4 months in order to achieve CR-IM	9	0.3	No disagreement	1	No disagreement	90 (80, 100)
For patients undergoing RFA with a focal device, the dosimetry and treatment regimen is 12 J / cm^2 X 3, without interval cleaning and for patients undergoing RFA with a circumferential device the dosimetry and treatment regimen is 10J/cm^2, clean, 10J/cm^2	8	0.4	No disagreement	1	No disagreement	N/A
Centres undertaking BET should achieve CR-D ≥ 90 % and CR-IM ≥ 80 % within 18 months after the first treatment	8	0.4	No disagreement	1	No disagreement	N/A
Patients with residual dysplasia after 18 months, are to be re-discussed at a Oesophago-Gastric MDT	9	0.7	No disagreement	1	No disagreement	90 (80, 100)
Post BET symptomatic stricture rate should not exceed 10-15 %	8	0.5	No disagreement	1	No disagreement	N/A

Table 4: Appropriate Intra-procedure (Ablation) quality indicators after Round 2 voting with the median score, MAD-M, BIOMED Analysis, p-value, IPRAS analysis and the performance threshold

4.4.4 Appropriate Post-Procedure Quality Indictors

1. **Following successful BET, patients undergo follow up endoscopies at appropriate intervals stratified according to risk of recurrence**

   Aspirational performance target: 90% (range: 80-100)

Evidence summary:

ET does not eliminate the need for continued endoscopic surveillance or completely eliminate the risk of synchronous or metachronous disease. Particular concern remains over IM, which is buried under neo-squamous epithelium after ET (334)(335). This is a rare but recognized finding (336). The identification of these cases indicates the need for continued surveillance following RFA therapy, even after CR-IM (337). Increasing age and length of BE segment are associated with a longer time to achieve CR-IM. It is therefore essential to continue surveillance after RFA (272). By dividing patients into simple categories, clinicians may stratify risk to choose the appropriate surveillance regimen (338). A large prospective study by Shaheen *et al* has shown impressive CR-D and CR-IM rates at 2 years (CR-D 95% and CR-IM 93%) and 3 years (CR-D 98% and CR-IM 91%) post initial BET with an annual rate of neoplastic progression of 1.37% per patient-years (325). Phoa *et al* also showed a 90% remission at 5 years post BET (339). The UK RFA registry has demonstrated a risk of neoplasia recurrence of 19% at 5 years with the predicted risk of IM recurrence of 13% at 26 months with a 32% risk of IM recurrence at 5 years (253).

The literature supports an IM/neoplasia recurrence rate between 10-32% at 5 years. Therefore, follow up post endoscopic therapy of BE neoplasia is needed to exclude recurrence and to deliver further therapy as needed (2). A recent study by Cotton *et al* provided evidence-based surveillance intervals after completion of ET in patients with BE neoplasia. For patients with LGD the group proposed surveillance endoscopy at 1 and 3 years after achieving CR-IM with ET (340). For patients with HGD or IMC, the proposed surveillance endoscopy was at 3 months, 6 months and 1 year and then annually (for 5 years) after achieving CR-IM with ET (340). Based on recent evidence, our expert panel felt that it would be reasonable to consider endoscopic follow-up proposed by Cotton *et al* (340).

2. **At follow up endoscopy, biopsies should be taken from the Squamo-columnar junction and within the extent of the original BE length, for the first 2 years; thereafter biopsies should be taken from the Squamo-columnar junction and any visible lesion**

Aspirational performance target: 90% (range: 80-100)

Evidence summary:

Adherence to biopsy protocol will significantly increase the detection rate of dysplasia in patients with BE (304). IM can reoccur at the gastro-oesophageal junction in the absence of visible BE following the successful eradication of BE neoplasia. Recent studies have suggested evidence of buried glands post BET in 5.5-7% of patients, but the majority of these were not detectable at subsequent endoscopies (339)(341)(342). Our expert panel suggests that endoscopic follow-up should include biopsies at the GOJ and within the previous extent of the BE epithelium (2). This should include a high resolution gastroscope to assess the treated and remaining area of BE (292). In order to exclude synchronous neoplastic lesions, 4 quadrant biopsies should be performed at 1–2-cm intervals throughout the entire BE segment (292).

Post-Procedure QIs	Median Score	MAD-M	BIOMED Analysis	P-Value	IPRAS Analysis	Performance Threshold Median % (Range)
Following successful BET, patients undergo follow up endoscopies at appropriate intervals stratified according to risk of recurrence	9	0.6	No disagreement	1	No disagreement	90 (80, 100)
At follow up endoscopy, biopsies should be taken from the Squamo-columnar junction and within the extent of the original BE length, for the first 2 years; thereafter biopsies should be taken from the Squamo-columnar junction and any visible lesion	8	0.6	No disagreement	1	No disagreement	90 (80, 100)

Table 5: Appropriate Post-Procedure quality indicators after Round 2 voting with the median score, MAD-M, BIOMED Analysis, p-value, IPRAS analysis and the performance threshold

		Median Score	MAD-M	BIOMED Analysis	P-Value	IPRAS Analysis
Pre-Endoscopy	Before undertaking EET, endoscopists need to have attended BET academia platforms.	7	1.2	**Disagreement**	0.83	No disagreement
	It is recommended that prior to starting BET, a minimum of 30 supervised cases of endoscopic resection and 30 cases of endoscopic ablation should be performed to acquire competence in technical skills, management pathways and complications.	7	1.2	**Disagreement**	0.83	No disagreement
Intra-procedure (Ablation)	For patients undergoing RFA with a circumferential device, the recommended dose is 10 J / cm2 CLEAN 10J/cm2 (EXPRESS)	7	1.5	**Disagreement**	0.83	No disagreement
Post Procedure	Following successful eradication after BET, patients should undergo follow up surveillance endoscopies at 3, 6, 9, 21 months and then annually (if fit for endoscopy)	8	1.7	**Disagreement**	0.51	No disagreement

Table 6: Quality indicators ranked as uncertain after Round 1 voting with the median score, MAD-M, BIOMED Analysis, p-value, IPRAS analysis

4.5 Discussion

Endoscopic treatment for dysplastic BE and early OAC has been recommended by various major societal guidelines (2)(96); however QIs for the management of patients with BE neoplasia have been lacking. This piece of work delivers a UK-based collection of QIs that will allow streamlined and accountable delivery of best clinical practice to patients undergoing BET.

This nationwide project combined the best available evidence with the collective judgment of national and international experts in order to develop a set of formally validated QIs for the management of patient with BE neoplasia using a rigorous and validated methodology (RAM). The RAM, unlike the original Delphi, provides the expert panel with the opportunity to have a face-face discussion in round 2. Unlike guidelines which use a consensus methodology, the RAM reduces the possibility of results being influenced by the opinion of the most senior or most vocal member of the panel (343).

These UK-based QIs reflect those recently published QIs in BET in the United States (292); We were able to develop QIs for the intra-procedure component of patient care and for the management of patients at the pre-endoscopy and post endoscopy stage. In addition this UK-based project covered various aspects of patient care including the importance of formal training of endoscopists prior to service provision, the use of high quality endoscopic imaging modalities for lesion recognition in BE surveillance (112)(107)(344) and the need for individual patient discussion at dedicated MDTs.

Adherence to Prague classification is known to result in improved dysplasia detection in patient with BE. This may be influenced by data from tertiary centres where diagnosis was obtained by expert BE endoscopist that are more likely to adhere to Prague classification with access to better endoscopic equipment including high definition endoscopy and virtual chromoendoscopy.

Our expert panel acknowledged the importance of endoscopic resection modalities (EMR and ESD) for the management of visible lesions in BE neoplasia. ESD is a feasible treatment option that allows en-bloc resection for histological staging and treatment of patients with early BE neoplasia. ESD is likely to expand in the near future and these QIs may need to evolve in order to cater for that in due course (139)(140)(141)(142)(143).

It is important that the clinical community recognises the balance between performing BET and the rate of success and stenosis. Therefore the expert group emphasized the importance of minimising stricture rates (not exceeding 10-15%) post BET and the need for discussion of patients' care in MDTs prior to BET and when BET fails to achieve successful outcomes.

The current published evidence in BET (253)(267)(340) provides data that is confined to a limited time period (less than 10 years); however BET is expanding rapidly and therefore we need to continue long-term follow up in these patients and monitor outcomes, which will provide us with essential information that will shape our future practice.

In this project we were also able to set aspirational performance thresholds to ensure that patient care is of highest standard. Regulatory and accrediting agencies as well as hospitals and clinicians may use these QIs to measure performance and highlight areas for improvement. The regular audit of outcomes and adverse events will ensure the efficacy and safety of endoscopic therapy for patients with early BE neoplasia (345). Auditing results may be used to implement changes in routine practice nationally, allowing comparison of local practices to national standards. These QIs may also be used for teaching, service development and standardisation of care at all hospitals preforming BET. Future studies will need to investigate the positive and the negative impact of these QI on patient outcomes.

There were some limitations to this study. First, high-quality evidence such as randomised controlled trials (RCTs) in the literature was not available for some QIs; however, this situation is common in many aspects of health care, and it was the very reason that the expert panel methodology such as RAM was developed (293). Second, some health care centres in the country may not be equipped with high quality endoscopic modalities and therefore these QIs may have a negative impact on their practice. Third, there was lack of validation of these QIs by an external committee and our expert panel voted on QIs that they developed themselves hence all the QIs in round 2 voting performed very well. Finally, the expert panel failed to determine the number of procedure needed to be performed by a centre to qualify as high volume centre and also failed to determine the adequate number of procedures needed by an endoscopist prior to performing independent BET.

In conclusion, this is the first UK national consensus project that has utilised a validated methodology to successfully develop process-based QIs for patients undergoing endoscopic

treatment for early BE neoplasia. These indicators identify meaningful and important steps for providing a unified high quality care based on the best available evidence and expert opinion. These QIs may also be used for the training of the new generation of advanced endoscopists and adherence to these measures would ultimately result in improving patient outcomes.

CHAPTER 5

Outcomes from an International Multicentre Registry of patients with acute gastrointestinal bleeding undergoing endoscopic treatment with Hemospray

Publication from this chapter

- **Alzoubaidi D**, Hussein M, Rusu R, Napier D, Dixon S, Rey JW, Steinheber C, Jameie-Oskooei S, Dahan M, Hayee B, Gulati S, Despott E, Murino A, Subramaniam S, Moreea S, Boger P, Hu M, Duarte P, Dunn J, Mainie I, McGoran J, Graham D, Anderson J, Bhandari P, Goetz M, Kiesslich R, Coron E, Lovat L, Haidry R. Outcomes from an international multicenter registry of patients with acute gastrointestinal bleeding undergoing endoscopic treatment with Hemospray. Dig Endosc. 2020 Jan;32(1):96-105.

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5.1 Overview of Chapter 5

Background and study aim: Acute Gastrointestinal bleeding carries poor outcomes unless prompt endoscopic haemostasis is achieved. Mortality in these patients remains significant. The rapid development of endoscopic therapy (including resection and ablation technology) in recent decade has provided new challenges to the clinical community that is battling gastrointestinal bleeding secondary to endoscopic therapy. Conventional haemostatic modalities (adrenaline injection, heat coagulation and mechanical clips) may not be adequate in challenging cases either due to the nature and site of bleeding or the limited skills of the endoscopist. Hemospray is a novel intervention that creates a mechanical barrier over bleeding sites. It can be used at sites that may not be directly accessible by conventional modalities and requires little expertise for its usage in the GI tract. **This chapter of the thesis** reports the largest dataset of patient outcomes after treatment with Hemospray from an international multicentre registry in a heterogenous population with various pathologies.

Patients and Methods: Prospective data (Jan 2016 – May 2018) from 12 centres across Europe were collected. Immediate haemostasis was defined as endoscopic cessation of bleeding within 5 minutes after application of Hemospray. Re-bleeding was defined as subsequent drop in haemoglobin, haematemesis, persistent melaena with haemodynamic compromise post therapy.

Results: 314 cases have been recruited worldwide (231M & 83F). Median pre-treatment Blatchford score was 11 (IQR: 8-14) and median Complete Rockall score was 7 (IQR: 6-8) for all patients. Peptic ulcer disease was the most common pathology (167/314 = 53%) and Forrest Ib the most common bleed type in PUD (**100/167 = 60%)**. 281 patients (89.5%) achieved immediate haemostasis after successful endoscopic therapy with Hemospray. Re-bleeding occurred in 29 (10.3%) of the 281 patients who achieved immediate haemostasis. 7-day and 30-day all-cause mortality were 11.5% (36/314) and 20% (63/314) respectively (lower than the predicted rates as per the RS). Similar haemostasis rates were noted in the Hemospray monotherapy (**92.4%**), combination therapy (**88.7%**) and rescue therapy (**85.5%**) group.

Conclusions: This data shows high rates of immediate haemostasis overall and in all subgroups. Re-bleeding and mortality rates were in keeping/lower than the predicted rates.

5.2 Introduction

Upper gastrointestinal bleeding (UGIB) is one of the most common acute gastrointestinal (GI) emergencies. Worldwide annual incidence of about 37 to 172 per 100000 (166) with significant mortality rate (3-14%) (166)(346)(172). Endoscopic therapy remains the gold standard treatment. Several endoscopic hemostatic techniques have been developed (160). Various guidelines recommend the use of at least dual therapy in the management of NVUGIB (181) (175) and there remains variation in their application in routine clinical use (159). A UK audit has shown that 22% of endoscopists still use monotherapy for the management of NVUGIB (159). Limited operator skill and higher cost of other modalities are contributing factors (347).

Despite the current haemostatic modalities, the endoscopic management of NVUGIB carries failure rate of 8-15% and re-bleeding rate of 10-25% in some series with subsequent effects on mortality and morbidity (348).

We have seen the emergence of topically applied powders in the endoscopic management of acute UGIB. Hemospray (TC-325; Cook Medical, Winston Salem, North Carolina, USA) is a novel agent. A proprietary mineral powder that is CE-marked and FDA approved for use in the endoscopic treatment of NVUGIB.

Data on Hemospray has been shown to achieve good haemostasis rates with NVUGIB (228)(229)(230). The highly absorptive powder functions as a cohesive and an adhesive. Once in contact with blood in the GI tract, the powder absorbs water and forms a stable

mechanical barrier which adheres to and covers the bleeding site. It promotes platelet aggregation and increases the concentration of clotting factors beneath it (231) (Figure 1). There is no expected risk of toxicity as the powder is not absorbed by the GI mucosa and the adherent layer is naturally eliminated from the GI tract within 24-72 hours (232)(233).

A B C

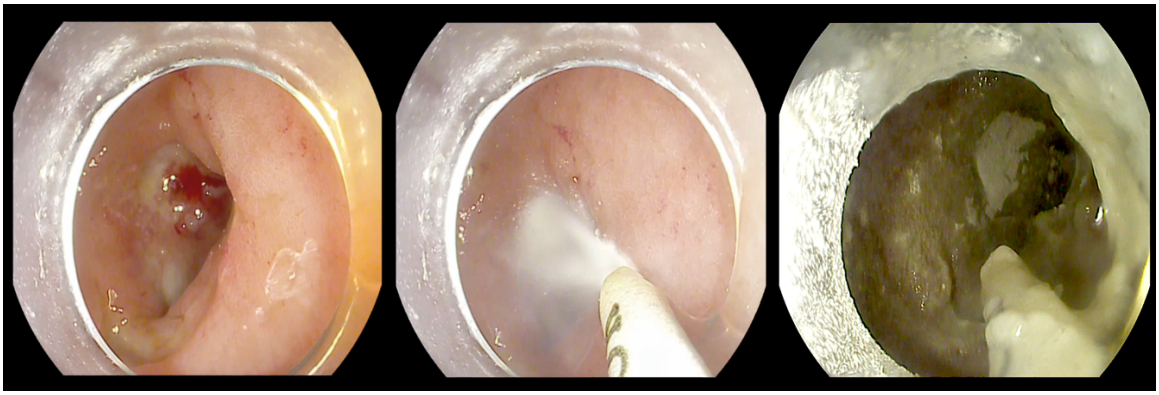

Figure 1: A) oozing duodenal ulcer (Forrest Ib), B) application of Hemospray on the bleeding lesion, C) haemostasis achieved after application of Hemospray

5.3 Patient/Material and Methods

5.3.1 Patient Recruitment

Patients (over 18 years of age) presenting with signs of acute UGIB (hematemesis, melaena, acute drop in haemoglobin and hemodynamic instability) and with post endotherapy bleeding (post EMR, ESD and Ablation) were recruited prospectively from January 2016 to May 2018. 12 centres participated (8 centres in England, 1 in Northern Ireland, 2 in Germany and 1 in France). The decision to use Hemospray was at the endoscopist's discretion at the time of endoscopy. All participating clinicians had training in Hemospray use. Patients were consented using the endoscopy consent forms as hemospray was performed as part of routine clinical practice.

5.3.2 Data Collection

A custom made on line electronic database (https://secure.amplitude-registry.com) was created for prospective collection of patient's data that was maintained anonymized. Data was collected on:

- Baseline patient characteristics
- Initial clinical assessment

- Endoscopic findings
- Biochemical parameters
- Comorbidities
- Mode of Hemospray use (monotherapy, combination therapy or rescue therapy)
- Device performance
- Site of bleeding lesion
- Blatchford (BS) and full Rockall scores (RS)
- Forrest classification (in peptic ulcer bleed)
- Use of anticoagulants
- Success of primary haemostasis
- Re-bleed
- All-cause mortality
- Complications

5.3.3 Device, Procedure and Follow up

Hemospray device consists of a syringe containing hemostatic powder that is propelled through a 7 or 10 Fr catheter using a built-in pressurized CO_2 canister. Hemospray is sprayed under direct vision until complete coating of the lesion with the hemostatic material is achieved (349). The site was then observed for 5 minutes to ensure complete haemostasis was achieved.

Patients that failed to achieve immediate haemostasis (treatment failure) were subsequently managed with either surgery, radiological embolization or conservative.

Patients were followed up for 30 days from the initial date of endotherapy with Hemospray. Data was collected at day 0, 1, 3, 7, 14 and 30 days post endotherapy with Hemospray. Patient follow up was achieved by direct patient review on the ward, in clinics and by telephone interviews and included review of all patient paper and electronic records.

5.3.4 Risk Stratification

The risk stratification of patients at initial clinical assessment allows the planning of endoscopic therapy and can predict re-bleeding and mortality rates. It can also determine whether endoscopy is required urgently (160). Our study looked at the Blatchford score and the complete Rockall score (172)(164)(182).

5.3.5 Outcomes

The primary outcome of our study was:

- The immediate endoscopic haemostasis (observed cessation of bleeding within 5 minutes after endoscopic application of hemospray) of GIB when Hemospray is used on its own as Monotherapy, as Dual therapy and as Rescue therapy in UGIB, irrespective of the severity of bleed.

  [Monotherapy is defined as the use of Hemospray on its own. Combination therapy referred to the use of Hemospray with conventional modalities (adrenaline injection,

thermocoagulation and mechanical clips) as an adjunct therapy to a single modality to help achieve haemostasis or as an adjunct with two other modalities after successful haemostasis. Rescue therapy is the use of Hemospray when all other conventional modalities failed to achieve haemostasis on the same endoscopic session].

Secondary outcomes were:

- Re-bleeding less than 24 hours post initial endoscopy, at 24-72 hours, 4-7 days,

  7-14 days and more than 14 days after initial endoscopic therapy with Hemospray.

  (Re-bleeding was defined as a subsequent and sustained drop in Hb (>2g/l), haematemesis, haematochezia and persistent melaena with ongoing haemodynamic compromise post endoscopic therapy) (350)
- 7-day and 30-day all-cause mortality
- Baseline pathology and disease specific outcomes (PUD, post endotherapy and malignancy)
- Adverse events

There was no scheduled second-look endoscopy unless clinical signs of re-bleeding. In the event of re-bleeding, patients were referred for further endoscopic therapy with conventional modalities or other therapeutic approaches such radiological embolisation, surgery or conservative management.

5.3.6 Research Ethics Committee (REC) Approval

This study was presented to the local research ethics committee (London - South East REC). REC concluded that the study should be classified and managed as service evaluation and development project in England. Centres in other participating countries also obtained approval from their local authorities.

5.3.7 Statistical Analysis

Statistical analysis was performed using the Stata 15.1 software (StataCorp LP, College Station, Texas, USA). Data are presented as median with inter-quartile range and frequency (percentage of the total study population). The separate association between each patient factor and the outcome was examined separately. Odds ratios (OR) were computed. The factors were then considered jointly in a single multivariable analysis using logistic regression. A P value < 0.05 was considered statistically significant.

5.4 Results

314 patients were enrolled to the registry from January 2016 to May 2018. The most common pathology was peptic ulcer, 167/314 (53%) [oesophageal ulcers 24% (41/167), gastric ulcers 22% (36/167) and duodenal ulcers 54% (90/167)]. Other pathologies included malignancy 50/314 (16%), bleeding post endoscopic procedure 49/314 (16%), bleeding from severe inflammation (oesophagitis, gastritis, duodenitis) 35/314 (11%), oesophageal variceal bleed 8/314 (2.5%) and cases with no obvious source found despite stigmata of UGI bleeding 5/314 (1.6%) (Table 1).

	Overall	PUD	Malignancy	Post-Endotherapy	Severe bleeding inflammation	Other
Age, median (IQR), years	71(60-80)	73 (61-82)	71 (78-67)	72 (67-79)	69 (56-78)	59 (29-90)
Male, n (%)	231 (74%)	121 (72%)	35 (70%)	33 (67%)	26 (74%)	10 (77%)
Female, n (%)	83 (26%)	46 (28%)	15 (30%)	16 (33%)	9 (26%)	3 (23%)
Initial hypotension, n (%)	105 (33%)	76 (46%)	16 (32%)	0	9 (26%)	6 (46%)
Antiplatelets, n (%)	55 (18%)	40 (24%)	3 (6%)	6 (12%)	5 (14%)	1 (8%)
Anticoagulants, n (%)	40 (13%)	23 (14%)	6 (12%)	5 (10%)	6 (17%)	0
Patients on combination of anti-thrombotic drugs	12 (4%)	7 (4%)	2 (4%)	0	2 (6%)	1 (8%)

Table 1: Baseline characteristics of patients

The median baseline BS and RS for all patients was 11 (IQR: 8–14) and 7 (IQR: 6 - 8) respectively. **Immediate haemostasis following endoscopic application of Hemospray was achieved in 281 (89.5%) patients.** 33 did not achieve immediate haemostasis [10.5% (33/314)] (Table 2). Multivariate analysis showed that only BS was significantly associated with treatment failure. A higher BS was associated with a higher risk of treatment failure. A one-unit increase in the score was associated with a 21% increase in the odds of not achieving haemostasis [OR:1.21(1.10-1.34);P<0.001].

	Treatment Success achieved immediate haemostasis	Treatment Failure Did not achieve immediate haemostasis	
No. Patients	89.5% (281/314)	10.5% (33/314)	
Median Rockall Score	7 (IQR: 6-8)	8 (IQR: 7-9)	p=0.12
Median Blatchford Score	11 (IQR: 7-14)	14 (IQR: 11-16)	p<0.001

Table 2: Treatment Success and Failure post endoscopic therapy with Hemospray for all patients (n=314)

5.4.1 Re-bleeding

Re-bleeding occurred in 29/281 patients who achieved immediate haemostasis (10.3%). The median re-bleed time was 24-72 hours. Multivariate analysis showed that only BS was associated with increased re-bleeding risk. Re-bleeding significantly increased with higher Blatchford scores. A one-unit increase in the score was associated with a 13% increase in the odds of re-bleeding [OR:1.13(1.03,1.25);P=0.01].

5.4.2 All-cause mortality

The 7-day and 30-day all-cause mortality were 11.5% and 20.1% respectively (Table 3 & 4). 78% of those who died had achieved immediate endoscopic haemostasis with Hemospray and cause of death was due to progression of other co-morbidities.

In the monotherapy group (118 patients), there was a total of 30 deaths (25.4%) of which 24 patients (80%) achieved immediate haemostasis with Hemospray and the cause of death was due to progression of other co-morbidities and only 6 patients (20%) did not achieve haemostasis with Hemospray.

Multivariate analysis of data showed that only BS was associated with an increased risk of dying. A higher BS was associated with a higher risk of dying. A one-unit increase in the BS was associated with a 38% increase in the odds of 7-day mortality [OR: 1.38 (1.22, 1.56); P<0.001] and a 29% increase in the odds of 30-day mortality [OR: 1.29 (1.18, 1.41); P< 0.001].

	Treatment Success (achieved immediate haemostasis)	Re-bleed		7-day all-cause mortality	30-day all-cause mortality	
No. patients	89.5% 281 / 314	10.3% 29 / 281		11.5% 36 / 314	20.1% 63 / 314	
Median Rockall Score	7 IQR: 6-8	8 IQR: 7-9	*Rockall 8 Predicted Re-bleed rate 25-40%*	8 IQR: 6.25-9	8 IQR: 7-9	*Rockall 8 Predicted Mortality rate 40-45%*
Median Blatchford Score	11 IQR: 7-14	13 IQR: 11-15		15 IQR: 13-16	14 IQR: 12-16	

Table 3: Re-bleed following successful endoscopic therapy with Hemospray and all-cause Mortality for all patients (n=314)

	Mono-Therapy (n=118)	Combination Therapy (n=141)	Rescue Therapy (n=55)	P-Value
Achieved Immediate Haemostasis	92.4% 109/118	88.7% 125/141	85.5% 47/55	p=0.35
Median Blatchford Score	10 IQR: 8-14	11 IQR: 8-14	11 IQR: 6-14	p=0.94
Median Rockall Score	8 IQR: 7-9	7 IQR: 6-8	7 IQR: 6-8	p=0.004
Rockall Score 7 & 8 Predicted Re-bleeding rate: 25-40%				
Re-bleeding	7.3% 8/109	9.6% 12/125	19.1% 9/47	p=0.08
Rockall Score 7 Predicted Mortality rate:20-30% *Rockall Score 8 Predicted Mortality rate:40-45%*				
7-day mortality	11.9% 14/118	9.9% 14/141	14.5% 8/55	p=0.66
30-day mortality	25.4% 30/118	14.9% 21/141	21.8% 12/55	p=0.04
Monotherapy is defined as the use of Hemospray on its own in the endoscopic management of GIB. Combination therapy referred to the use of Hemospray with conventional modalities . Rescue therapy is the use of Hemospray when all other conventional modalities (injection therapy, thermocoagulation and mechanical clips) failed to achieve haemostasis on the same endoscopic session. In the combination therapy and rescue therapy groups, Hemospray was the last modality used in the management of GI bleeding.				

Table 4: Subgroup Analysis [Mono-Therapy (n=118), Combination therapy (n=141) and Rescue therapy group (n=55)] post endoscopic therapy with Hemospray

5.4.3 Subgroup Analysis (Monotherapy, Combination therapy and Rescue therapy group)

There was no significant difference in immediate haemostasis amongst the 3 groups (monotherapy = 92.4%, combination therapy = 88.7% and rescue therapy 85.5%, p=0.35). Higher re-bleeding rate of 19.1% was noted in the Rescue therapy group (p=0.08).

Higher 30-day all-cause mortality rates were seen in the Monotherapy (25.4%) compared to the other groups (p=0.04).

In the combination therapy group, the use of Hemospray with injection therapy (adrenaline) was the most common mode of therapy, with a haemostasis rate of 89% (Table 5).

Combination therapy (n=141)					
Combination Modality	No. Patients	Achieved Haemostasis	Re-bleed	7-day all-cause mortality	30-day all-cause mortality
Injection + Hemospray	44/141 = 31%	39/44 = 89%	3/39 = 8%	3/44 = 7%	6/44 = 14%
Thermal + Hemospray	8/141 = 6%	8/8 = 100%	0	0	0
Mechanical + Hemospray	20/141 = 14%	15/20 = 75%	1/15 = 7%	3/20 = 15%	3/20 = 15%
Injection + Thermal + Hemospray	19/141 = 13.5%	16/19 = 84%	1/16 = 6%	2/19 = 11%	2/19 = 11%
Injection + mechanical + Hemospray	37/141 = 26%	35/37 = 95%	5/35 = 14%	3/37 = 8%	5/37 = 14%
Mechanical + Thermal + Hemospray	13/141 = 9%	12/13 = 92%	2/12 = 17%	1/13 = 8%	3/13 = 23%
In this group, Hemospray was used when bleeding had persisted after therapy by a single or dual standard modalities. Hemospray was the last modality for therapy in all cases.					

Table 5: Subgroup Analysis – Outcomes for the Combination Therapy of Hemospray with conventional modalities (n=141)

5.4.4 Subgroup Analysis - Peptic Ulcer Disease outcomes (n=167)

There were 167 Patients in the PUD group [oesophageal ulcers 24% (41/167), gastric ulcers 22% (36/167)and duodenal ulcers 54% (90/167)]. The most common type of bleeding lesion was Forrest Ib. The overall haemostasis rate was 86%. Combination therapy was the most common mode of therapy with a haemostasis rate of 87%. High median BS and RS was noted in the PUD group at baseline (13 and 7 respectively) with an overall re-bleeding rate of 12.7%. All-cause 7 and 30 day mortality rates in this group were 16.2% and 24.6% respectively (Table 6 & 7). 41% of the patients in the oesophageal ulcer group were on anticoagulants, antiplatelets or a combination of both in comparison to 47% in the gastric ulcer group and 62% in the duodenal ulcer group.

	No. Patients	Monotherapy	Combination therapy	Rescue therapy	Median Blatchford Score	Median Rockall Score	Re-bleeding	7-day all-cause mortality	30-day all-cause mortality
PUD	n = 167	44/167 = 26%	87/167 = 52%	36/167 = 22%	13 IQR: 10-15	7 IQR: 6-8	18/142 = 12.7%	27/167 = 16.2%	41/167 = 24.6%
	Achieved Haemostasis	38/44 = 86%	76/87 = 87%	29/36 = 81%					
Post Endotherapy	n = 49	14/49 = 29%	28/49 = 57%	7/49 = 14%	n/a	6 IQR: 5-6	0	0	0
	Achieved Haemostasis	14/14 = 100%	27/28 = 96%	7/7 = 100%					
Malignancy	n = 50	33/50 = 66%	13/50 = 26%	4/50 = 8%	10 IQR: 7-12	9 IQR: 9-10	7/47 = 14%	1/50 = 2%	11/50 = 22%
	Achieved Haemostasis	33/33 = 100%	11/13 = 85%	3/4 = 75%					
Anti-Thrombotic Therapy	n = 107	31/107 = 29%	54/107 = 50%	22/107 = 21%	12 IQR: 8-14	8 IQR: 7-8	10/95 = 11%	11/107 = 10%	21/107 = 19.6%
	Achieved Haemostasis	28/31 = 90%	48/54 = 89%	19/22 = 86%					
Bleeding severe inflammation	n = 35	22/35 = 63%	10/35 = 29%	3/35 = 9%	10 IQR: 8-14	7 IQR: 6-8	3/32 = 9.4%	5/35 = 14%	8/35 = 23%
	Achieved Haemostasis	19/22 = 86%	10/10 = 100%	3/3 = 100%					

Rockall 7 Predicted Re-bleeding rate: 25-40% Rockall 7 Predicted Mortality: 20-30%
Rockall 8 Predicted Re-bleeding rate: 25-40% Rockall 8 Predicted Mortality rate: 40-45%
Rockall 9 Predicted Re-bleeding rate > 40% Rockall 9 Predicted Mortality rate > 40%

Table 6: Outcomes for all treated pathology subgroups

5.4.5 Subgroup Analysis - Post Endotherapy outcomes (n=49)

An overall haemostasis rate of 98% was achieved in the post endotherapy group. Combination therapy was the most common mode of therapy (28/49 = 57%) with a haemostasis rate of 96%. There was no re-bleeding or mortality (Table 6).

5.4.6 Subgroup Analysis - Malignancy outcomes (n=50)

There were 50 documented patients with malignancy [oesophageal 17 (34%), gastric 30 (60%) and duodenal 3 (6%)]. Overall immediate haemostasis was achieved in 47 (94%) patients with symptomatic bleeding secondary to UGI malignancy. Monotherapy was the most common mode of therapy (33/50 = 66%) with a haemostasis rate of 100%. Re-bleeding occurred in 2 patients at 24-72 hours, 2 patients at 4-7 days, 1 patient at 7-14 days and 2 patients > 14 days after achieving the initial endoscopic haemostasis with Hemospray. The 7-day and 30-day all-cause mortality rates were 2% and 22% respectively (Table 6). In the 3 cases with treatment failure, 1 was maintained with supportive care, 1 had surgery and the other died. The overall documented mortality rate in this group was due to progression of disease rather than treatment failure.

Forrest Classification		Achieved Haemostasis	Median BS	Median RS	Re-bleed	7-day all-cause mortality	30-day all-cause mortality
Ia	29/167 = 17%	24/29 = 83%	13 IQR = 10-15	8 IQR = 6-8	6/24 = 25%	6/29 = 21%	8/29 = 27.5%
Ib	100/167 = 60%	82/100 = 82%	13 IQR = 10-15	7 IQR = 6-8	7/82 = 8.5%	16/100 = 16%	25/100 = 25%
IIa	14/167 = 8%	14/14 = 100%	12 IQR = 9-15	7 IQR = 6-8	1/14 = 7%	1/14 = 7%	2/14 = 14%
IIb	16/167 = 10%	15/16 = 94%	12 IQR = 9-15	7 IQR = 6-8	3/15 = 20%	3/16 = 19%	4/16 = 25%
III	8/167 = 5%	7/8 = 88%	14 IQR = 8-15	7 IQR = 6-8	1/7 = 14%	1/8 = 13%	2/8 = 25%

- *Rockall 7 Predicted Re-bleeding rate = 25-40% and Predicted Mortality rate = 20-30%.*
- *Rockall 8: Predicted Re-bleeding rate = 25-40% and Predicted Mortality rate = 40-45%.*

Table 7: Outcomes of patients with Peptic Ulcer Disease post therapy with Hemospray as per Forrest Classification (n=167)

5.5 Discussion

Data on Hemospray show it to be a successful agent as a result of its ability to form a barrier over the bleeding lesion (231). The endoscopic application of Hemospray is simple (230). It may therefore be a more desirable modality for the less experienced endoscopist. Several studies have investigated the haemostatic ability of Hemospray in the management of bleeding peptic ulcers (232), malignancy (234), anticoagulated patients (235) and oesophagogastric variceal bleed (236) with encouraging haemostasis rates (65-98%). Other endoscopic haemostatic powders are available. EndoClot (EndoClot Plus, Santa Clara, CA, USA) is a polysaccharide haemostatic that can be delivered endoscopically to the site of bleeding in the GI tract without the need for direct mucosal contact. It is composed of absorbable polymer particles that absorb water from the blood on the surface of the bleeding site, hence increasing the concentration of platelets and clotting factors, resulting in haemostasis; however strong data on its efficacy is limited and further clinical trials are awaited (224)(225).

Our data demonstrated the use of Hemospray in diverse, heterogeneous and high-risk populations based on the varied baseline pathologies and median BS (=11) and complete RS (=7). Hemospray was effective in achieving primary haemostasis with an overall haemostasis rate of 89.5%. High haemostasis rates were achieved when Hemospray was used on its own (92.4%), in combination with other modalities (88.7%) and as a rescue therapy (85.5%). These results reflect those of recently published studies (346)(229)(230)(351).

In comparison to major recent studies (346)(230)(351)(352), we were able to show lower re-

bleeding rates overall and in all subgroups despite our high risk population.

Published data have shown that dual endoscopic therapy for GIB is superior to monotherapy with adrenaline injection alone (181)(175); Dual therapy reduces the risk of re-bleeding, the risk of emergency surgery (208) and mortality (211). Our study was able to show that Hemospray in combination with conventional modalities had lower re-bleed rate and all-cause mortality rate than monotherapy and rescue therapy. Data have suggested that using a combination of conventional modalities in the UGIT, may have a potential risk of perforation and gastric wall necrosis (212); however our study did not show any adverse events.

A recent study by Barkun *et al*, showed that the use of Hemospray in combination with conventional modalities, was cost effective (353). Our study did not formally investigate the cost of treatment; however the outcomes in this study support the use of Hemospray in combination with other modalities.

A UK audit on the management of UGI bleeding (354) showed that 38% of patients presenting with acute UGIB received dual endoscopic therapy despite various guidelines (181)(175). Endoscopist's limited experience or challenging anatomy could have been a contributing factor. Hemospray may be able to resolve these issues as it does not require highly experienced hands and the application of the hemostatic powder does not rely on direct contact with the bleeding lesion (229).

PUD was the most common pathology in our study. Despite high baseline BS and RS, the PUD group was able to achieve an overall haemostasis rate of 86%, compatible with previously published data (346)(229)(230) with overall re-bleeding and all-cause mortality rates in keeping with the predicted values. Hemospray in combination with other modalities

was the most common mode of therapy in bleeding PUD lesions (Table 5). In this subgroup, haemostasis was achieved in 87% of cases. This data supports the use of Hemospray in combination therapy with conventional modalities. Based on the rapid elimination of the powder from the GI tract, and the observed mortality rates, Hemospray as monotherapy should be used with caution in bleeding PUD. Further analysis of our data showed high haemostasis rates in all Forrest groups (82-100%) with re-bleeding rates (7-25%) that were in keeping or lower than that in major recent studies (346)(229)(230)(355).

The management of UGIB secondary to malignancy can be very challenging due to the limited response to conventional therapies as a result of fragile nature of malignant tissue and lesion size. Our study included 50 patients with UGI malignancy that as expected had high BS and RS. Overall haemostasis was achieved in 94% and Hemospray as a monotherapy was the most common mode of therapy. The monotherapy subgroup achieved immediate haemostasis in 100% of cases. This is significantly higher than recently published data (351)(356). We also observed an overall re-bleeding rate of 14% and a 7-day and 30-day all-cause mortality of 2% and 22% respectively, which were lower than the predicted rates as per the RS (=9). Our results suggest that Hemospray may provide a solution to challenging UGI malignant lesions as first line therapy and may become the treatment of choice in this group of patients.

The rapid development of endoscopic therapy in the past decade has had significant impact on patient outcomes (357); however endotherapy can result in re-bleeding. Excellent haemostasis rates were achieved (98%) in this group and there was no re-bleeding or mortality. Hemospray has the potential to become the treatment of choice in post endotherapy bleeds as conventional therapies can damage the fragile submucosa. There

were no documented adverse events, allergic reaction or systemic toxicity.

Patients on anti-thrombotic therapy are a difficult group to treat in GI bleeding. The haemostasis rates achieved in the mono, combination and rescue therapy groups are not widely different (90%, 89% and 86% respectively) and the combination therapy was used in 50% of patients with UGIB while on anti-thrombotic therapy. This data favours the use of Hemospray in patients with UGIB on anti-thrombotic therapy.

Limitation to our study include the lack of control group and randomization. The inclusion of patients was non-consecutive and at the discretion of the endoscopist at the time of endoscopy with possible non-intentional selection bias, reflected by relatively more UGIB cases secondary to malignancy than previous studies as it seems that Hemospray was selected more frequently for the treatment of bleeding tumours which are difficult to treat by other conventional modalities, and conversely, the PUD with Forrest Ia, which may have been avoided; Furthermore selection bias may have contributed to the fact that RS was not found to be significantly associated with treatment success and failure whereas there was a significant association between BS and treatment success and failure (Table 2). Due to this possible selection bias, our study cannot suggest which of the 2 scores (BS and RS) is better for risk prediction and stratification; however, our study compared its outcomes rates with the predicted rates as per the RS. This study remains to be valuable for real-world data. No consensus was decided on criteria for when to apply Hemospray and therefore there could be variation as to when Hemospray is applied.

Registered PU were variable with respect to their locations and aetiologies including use of anticoagulants, antiplatelets and NSAIDs. Detection of Helicobacter pylori was not documented in this database, which is considered a limitation.

The documented malignancies were confined to bleeding lesions in the oesophagus, stomach and the duodenum; however gross macroscopic features of these lesions and exact histological diagnosis was not documented in the database.

Severe bleeding inflammation group consisted of oesophagitis, gastritis and duodenitis with bleeding mucosa; however gross macroscopic features, exact location and cause of inflammation was not documented.

The exact cause of death and list of co-morbidities were not documented but only the all-cause mortality was noted in the registry. Due to this, we cannot comment on the exact nature of death in various groups, but the majority of deaths occurred due to progression of co-morbidities.

Finally ulcers may have been wrongly classified as noted in Table 7, that 7 of 8 Forrest III ulcers achieved immediate haemostasis. Forrest III ulcers are defined as those with a clean base and no active bleeding.

Conclusion:

This multicentre international registry was able to investigate the efficacy and safety of Hemospray. In addition, we were able to investigate the efficacy of Hemospray as monotherapy, in combination therapy and as a rescue therapy. Despite having a high-risk population, our registry was able to show high haemostasis rates. Hemospray is a safe novel agent that is easy to use, and our study supports its use in routine and emergency cases.

This study further supported the results of previous studies on Hemospray (346)(229)(230), supporting a recommendation of its use regardless of the endoscopists' skill or bleeding source. Larger studies with randomisation and controlled groups will be needed to further support the use of Hemospray in GI bleeding.

CHAPTER 6

CONCLUSION

CHAPTER 6 CONTENTS

6.1 The Burden of BE disease

The prevalence and incidence of BE in the western world is low but not insignificant. It is now increasingly clear that BE is a multifactorial disease, where a genetic predisposition interacts with the environment. Since the initial description of BE in 1950, significant progress has been made in understanding of BE pathogenesis and extensive research has yielded improvements in endoscopic diagnosis and management of BE and the identification of dysplasia; however, many challenges in clinical practice and research still remain.

In the absence of practical ways to identify individuals at high risk based on their genetic profile, for the time being it seems logical to look for clinical risk factors, such as reflux symptoms, age >50 years, white race, male sex and obesity. These are the key elements that trigger referral for endoscopic screening.

The advancement in medical technologies and improvement in health care systems have improved access to early diagnostic procedures. The rate of oesophageal cancer on a background of BE has significantly increased in the past two decades in western civilisations with no significant change in survival rates. Survival of patients with oesophageal cancer remain to be low and only a small number of patients have potentially curable disease at presentation.

The current surveillance algorithm heavily relies on the histological assessment of dysplasia based on random biopsies. It is still debated whether endoscopic surveillance is an effective

measure to improve survival in patients with BE. Dysplasia is difficult to detect endoscopically, as well as the fact that endoscopists adhere poorly to recommended protocols and pathologists struggle to agree on the diagnosis of dysplasia (297). There is uncertainty over the most appropriate surveillance strategy which is reflected by the various published international guidelines, hence earlier in this thesis the QBET project aimed at identifying quality indicators in order to unifying clinical practice in BE endotherapy in the UK.

The surveillance interval for patients with BE and BE neoplasia will remain a subject for debate amongst the clinical community, but it is important to mention that current diagnostic modalities have certainly aided early diagnosis resulting in provision of endoscopic therapy in early BE neoplasia. The advancement in endoscopic therapy as seen earlier in this thesis, have also provided additional treatment modalities to patients that did not respond well to conventional therapies

It is important that future research is focused on identifying a minimally invasive screening test, with low cost and wide applicability to both primary and secondary care.

6.2 Therapeutic endoscopy

6.2.1 Endoscopic resection

The endoscopic eradication therapy of BE neoplasia has significantly advanced in recent years as shown earlier in this thesis. Endoscopic eradication therapy for early BE neoplasia have now replaced surgical oesophagectomy that once was deemed the treatment of choice, despite its limitations and adverse events. As mentioned earlier in this thesis, the standard of care in the endoscopic management of early BE neoplasia is mucosal resection of visible lesions (with EMR or ESD), followed by ablation of the flat mucosa (with RFA, APC or Cryoablation), with the aim of achieving complete eradication of intestinal metaplasia (358)(70). A key part of treatment is maximal acid suppression. After eradication is confirmed, continued surveillance is necessary.

Endoscopic resection of early BE neoplasia has certainly evolved from the cap based system with snare (Olympus Ltd.), initially described in Japan by Inoue *et al*, (128) to the current multiband mucosectomy (MBM) devices (129).

Earlier in this thesis, it was shown that the EMR Captivator device, a new innovation in endoscopic therapy, offers an alternative modality in the management of BE neoplasia but also it provides larger ER specimens with deeper resections. Complete resection of an extensively large lesion during the first endotherapy session is desirable as subsequent strictures and fibrosis may prevent further resections. Resection of larger areas at baseline endoscopy can result in less residual BE, reducing the number of sessions for further therapy with ablation and the potential need for rescue EMR (253). Published data from

large series have shown that removal of the whole neoplastic lesion in one session is favourable in order to reduce the risk of treatment failure (136). This further supports the use of the Captivator device in patients with large lesions requiring complete successful resection in one session, in particular, those with significant co-morbidities that may not be fit for repeated sessions of endoscopic resection.

A previous study by Scholvinck *et al*, has shown that the new EMR captivator device, provides improved endoscopic visibility, smoother passage of accessories, and higher suction power in the management of early oesophageal neoplasia (246). Furthermore, randomised study by Belghazi *et al*, have shown that the EMR captivator device is capable of resecting specimens in the oesophagus as efficiently as the more commonly used Duette device (359). Future large randomised studies will be able to provide further insight into the efficacy and performance of the EMR captivator device.

6.2.2 Endoscopic ablation

Radiofrequency ablation (RFA) for BE neoplasia is a well-established therapeutic modality with strong published data in the past decades; however there still remains a group of patients that do not fully respond to RFA and therefore alternative ablative modalities have been studied.

Cryoablation with the Cryoballoon device is a novel ablative therapy that uses cycles of freezing and thawing to induce cell death with comparable safety and efficacy profile to RFA.

Earlier in this thesis, data was presented on the efficacy of Cryoablation in treatment refractory patients with BE neoplasia (CR-D = 78% and CR-IM = 39%) with good safety profile.

There are emerging data on the use of Cryoablation, but currently published data are based on small studies. A comparative study by Van Munster *et al,* analysed BE regression in patients with BE neoplasia undergoing ablative therapy with RFA and cryoablation. The group was able to show that BE regression post ablative therapy was comparable (cryoablation 88% vs RFA 90%, P=0.62) (154). Further systematic review and meta-analysis by Westerveld *et al,* studied 258 patients with BE neoplasia (HGD = 131, LGD = 75 and IMC = 52). The reported pooled rates of CR-IM and CR-D were 85.8 % and 93.8 %, respectively with an overall stricture rate of 5.8 % (360).

There is now evidence to suggest that Cryoablation is a safe and effective new innovation in ablative therapy for the treatment of BE neoplasia; however, further studies are needed to analyse efficacy and safety profile in large randomised controlled trials.

The above mentioned treatment modalities have shown that the battle against BE neoplasia is heading the right direction and have provided alternative treatment options that can be used in a heterogenous patient group.

6.2.3 Gastrointestinal bleed

All endoscopic therapies present a risk of bleeding. The advancement in endoscopic therapy means that we will see more complicated post endotherapy bleeds that may not respond adequately to conventional therapy, hence the need for new modalities that are easy to use even by those with limited endoscopic skills.

Historically the management of GI bleeding relied on the injection of diluted adrenaline, heat coagulation and mechanical clips. Recent decade has seen the emergence of adhesive powders which can be applied endoscopically and require little expertise in advanced endoscopic therapy. Hemospray is an effective treatment modality in the management of GI bleeding and several large prospective studies including the International Multicentre Registry that was presented earlier in this thesis have shown the effect of Hemospray therapy in various pathologies when used as a single modality or as an adjunct with conventional methods (229)(230)(361).

There is certainly a hesitation amongst some endoscopists to use Hemospray. This may be related to lack of experience in the use of Hemospray, but also the cost of the product which fortunately is currently significantly lower in the UK and EU when compared to that in the USA. The fast emerging data on Hemospray with the rapid expansion of the international Hemospray registry will provide further understanding of this haemostatic powder not only in uncomplicated bleeding scenarios, but also in refractory bleeding lesions, not responsive to conventional therapies and in those with bleeding post endoscopic therapy.

6.3 The Future

Despite recent advancement in interventional endoscopy, there are still several knowledge and skill gaps which would require further development.

There is limited data on the extent of training required to perform independent endoscopic therapy. Formalisation of training is needed in order to achieve competency in endoscopic therapy (362)(363)(364).

In the future, it is possible to envisage a scenario where inexpensive and minimally invasive screening techniques will help diagnose a large proportion of unknown BE. Coupled with the objective assessment of an individual's risk for cancer, this will allow tailoring patient management with choosing between early intervention in high risk BE and prolonged

endoscopic surveillance intervals or monitoring with minimally invasive devices in patients with low risk BE .

Further studies are currently under way to advance the work done in this thesis. Large prospective studies analysing cryoablation in treatment naïve patients with BE neoplasia are being developed. Furthermore, the expansion of the international Hemospray registry in particular in the USA and Australia will provide better understanding of the haemostatic agent in large heterogenous populations with various pathologies.

There is still room for further development in advanced endoscopy; however the current direction of travel is indeed on the right path.

References

1. Andrew Paull, Jerry Trier, David Dalton, Roger Camp, Peter Loeb RG. The histologic spectrum of Barrett's esophagus. The New England Journal of Medecine. 1986;314(3):144–9.
2. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson , et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014;63:7–42.
3. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American gastroenterological association technical review on the management of Barrett's esophagus. Gastroenterology. 2011;140(3):18–52.
4. Zagari RM, Fuccio L, Wallander MA, Johansson S, Fiocca R, Casanova S, et al. Gastro-oesophageal reflux symptoms, oesophagitis and barrett's oesophagus in the general population: The Loiano-Monghidoro study. Gut. 2008;57(10):1354–9.
5. Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, et al. Prevalence of Barrett's esophagus in the general population: An endoscopic study. Gastroenterology. 2005;129(6):1825–31.
6. Qumseya BJ, Bukannan A, Gendy S, Ahemd Y, Sultan S, Bain P, et al. Systematic review and meta-analysis of prevalence and risk factors for Barrett's esophagus. Gastrointestinal Endoscopy. 2019;90:707–17.
7. Connor M, Weston A, Mayo M SP. The prevalence of Barrett's esophagus and erosive esophagitis in patients undergoing upper endoscopy for dyspepsia in a VA population. Digestive Diseases and Sciences. 2004;49(6):920-4.

8. Charles Winters Jr, Timothy J.Spurling, Sarkis J.Chobanian, David J.Curtis, Regina L.Esposito, Joseph F.Hacker, David A.Johnson, David F.Cruess, J.D.Cotelingam, Michael S.Gurney ELCJ. Barrett's esophagus. A prevalent, occult complication of gastroesophageal reflux disease. Gastroenterology. 1987;92:118–24.

9. Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. Journal of the National Cancer Institute. 2011/06/16. 2011 Jul 6;103(13):1049–57.

10. Tusar Desai NS. The incidence of esophageal adenocarcinoma among patients with nondysplastic Barrett's esophagus has been overestimated. Clinical Gastroenterology and Hepatology. 2011;9:363–4.

11. Hvid-Jensen F1, Pedersen L, Munk EM, Drewes AM F-JP. Long-term complications to reflux disease in community practice. A 17-year cohort study of 4706 patients. Scandinavian Journal of Gastroenterology. 2011;46:1179–86.

12. Sundelöf M, Ye W, Dickman PW, Lagergren J. Improved survival in both histologic types of oesophageal cancer in Sweden. International Journal of Cancer. 2002;99(5):751–4.

13. Http://www.cancerresearchuk.org/cancerinfo/cancerstats/types/oesophagus/?script=true. Cancer Research UK. 2012. Accessed 23/09/2019

14. Eloubeidi MA, Mason AC, Desmond RA E-SH. Temporal trends (1973-1997) in survival of patients with esophageal adenocarcinoma in the United States: a glimmer of hope? American Journal of Gastroenterology. 2003;98:1627–33.

15. Pohl H, Sirovich B WH. Esophageal adenocarcinoma incidence: are we reaching the

peak? Cancer Epidemiol Biomarkers Prev. 2010;19(6):1468–70.

16. Thrift AP, Whiteman DC. The incidence of esophageal adenocarcinoma continues to rise: Analysis of period and birth cohort effects on recent trends. Annals of Oncology. 2012;23(12):3155–62.

17. Millikan KW, Silverstein J, Hart V, Blair K, Bines S, Roberts J DA. A 15-year review of esophagectomy for carcinoma of the esophagus and cardia. Archives of Surgery. 1995;130:617–24.

18. Rice TW, Zuccaro G, Adelstein DJ, Rybicki LA, Blackstone EH, Goldblum JR. Esophageal carcinoma: Depth of tumor invasion is predictive of regional lymph node status. Annals of Thoracic Surgery. 1998;65(3):787–92.

19. Kennedy T, Jones R. The prevalence of gastro-oesophageal reflux symptoms in a UK population and the consultation behaviour of patients with these symptoms. Alimentary Pharmacology and Therapeutics. 2000;14(12):1589–94.

20. Locke GR, Talley NJ, Fett SL, Zinsmeister AR ML. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology. 1997;112:1448–56.

21. Anne F. Peery, Evan S. Dellon, Jennifer Lund, Seth D. Crockett, Christopher E. McGowan, William J Bulsiewicz, Lisa M. Gangarosa, Michelle T. Thiny, Karyn Stizenberg, Douglas R. Morgan , Yehuda Ringel, Hannah P Kim, Marco daCosta DiBonaventura, Charlotte F. Burden of Gastrointestinal Disease in the United States: 2012 Update. Gastroenterology. 2012;143(5):1179–87.

22. Di Pietro M, Fitzgerald RC. Screening and Risk Stratification for Barrett's Esophagus. How to Limit the Clinical Impact of the Increasing Incidence of Esophageal Adenocarcinoma. Gastroenterology Clinics of North America. 2013;42(1):155–73.

23. Anderson LA, Watson RGP, Murphy SJ, Johnston BT, Comber H, McGuigan J, et al. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: Results from the FINBAR study. World Journal of Gastroenterology. 2007;13(10):1585–94.

24. Taylor JB, Rubenstein JH. Meta-analyses of the effect of symptoms of gastroesophageal reflux on the risk of Barrett's esophagus. The American journal of gastroenterology. 2010;105(8):1729, 1730–7

25. Smith KJ, O'Brien SM, Smithers BM, Gotley DC, Webb PM, Green AC WD. Interactions between smoking, obesity and symptoms of acid reflux in Barrett's esophagus. Cancer Epidemiol Biomarkers Prev. 2005;14:2481–6.

26. Akiyama T, Yoneda M, Inamori M, Iida H, Endo H, Hosono K, et al. Visceral obesity and the risk of Barrett's esophagus in Japanese patients with non-alcoholic fatty liver disease. BMC Gastroenterology. 2009;9:1–7.

27. Hashem B. El-Serag, Ali Hashmi, Jose Garcia, Peter Richardson, Abeer Alsarraj, Stephanie Fitzgerald, Marcelo Vela, Yasser Shaib, Neena S. Abraham, Maria Velez, Rhonda Cole, Margot B. Rodriguez, Bhupinderjit Anand, David Y. Graham JRK. Visceral abdominal obesity measured by CT scan is associated with an increased risk of Barrett's oesophagus: a case-control study. Gut. 2014;63(2):220–9.

28. Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: A pooled analysis from the International BEACON Consortium. Journal of the National Cancer Institute. 2010;102(17):1344–53.

29. Cook MB, Shaheen NJ, Anderson LA, Giffen C, Chow WH, Vaughan TL, et al. Cigarette smoking increases risk of Barrett's esophagus: An analysis of the barrett's and esophageal adenocarcinoma consortium. Gastroenterology. 2012;142(4):744–53.

30. Thrift AP, Kramer JR, Richardson PA, El-Serag HB. No significant effects of smoking or alcohol consumption on risk of Barrett's esophagus. Digestive Diseases and Sciences. 2014;59(1):108–16.

31. Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of Adenocarcinoma among Patients with Barrett's Esophagus. The New England Journal of Medicine. 2009;365(15):2301–3.

32. Farhad Islami FK. Helicobacter pylori and Esophageal Cancer Risk -- A Meta-Analysis. cancer prev Res. 2008;5:329–38.

33. Kubo A, Corley DA, Jensen CD, Kaur R. Dietary factors and the risks of oesophageal adenocarcinoma and Barrett's oesophagus. Nutrition Research Reviews. 2010;23(2):230–46.

34. Rex DK, Cummings OW, Shaw M, Cumings MD, Wong RKH, Vasudeva RS, et al. Screening for Barrett's Esophagus in Colonoscopy Patients with and without Heartburn. Gastroenterology. 2003;125(6):1670–7.

35. Verbeek RE, Spittuler LF, Peute A, van Oijen MG, Ten Kate FJ, Vermeijden JR, Oberndorff A, van Baal JW SP. Familial clustering of Barrett's esophagus and esophageal adenocarcinoma in a European cohort. Clinical Gastroenterology and Hepatology. 2014;12:1656–63.

36. Chak A, Ochs-Balcom H, Falk G, Grady WM, Kinnard M, Willis JE, et al. Familiality in Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastroesophageal junction. Cancer Epidemiology Biomarkers and Prevention. 2006;15(9):1668–73.

37. Juhasz A, Mittal SK, Lee TH, Deng C, Chak A, Lynch HT. Prevalence of Barrett esophagus in first-degree relatives of patients with esophageal adenocarcinoma.

Journal of Clinical Gastroenterology. 2011;45(10):867–71.

38. The Esophageal Adenocarcinoma Genetics Consortium and the Wellcome Trust Case Control Consortium. Common variants at the MHC locus and at chromosome 16q24.1 predispose to Barrett's esophagus. Nature Genetics. 2012;44(10):1131–6.

39. Levine DM, Ek WE, Zhang R, Liu X, Onstad L, Sather C, et al. A genome-wide association study identifies new susceptibility loci for esophageal adenocarcinoma and Barrett's esophagus. Nature Genetics. 2013;45(12):1487–93.

40. Wang X, Ouyang H, Yamamoto Y, Kumar PA, Wei TS, Dagher R, et al. Residual embryonic cells as precursors of a Barrett's-like metaplasia. Cell. 2011;145(7):1023–35.

41. Quante M, Bhagat G, Abrams JA, Marache F, Good P, Lee MD, et al. Bile acid and inflammation activate gastric cardia stem cells in a mouse model of barrett-like metaplasia. Cancer Cell. 2012;21(1):36–51.

42. Souza RF, Krishnan K, Spechler SJ. Acid, Bile, and CDX: The ABCs of making Barrett's metaplasia. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2008;295(2):211–8.

43. Liu T, Zhang X, So CK, Wang S, Wang P, Yan L, et al. Regulation of Cdx2 expression by promoter methylation, and effects of Cdx2 transfection on morphology and gene expression of human esophageal epithelial cells. Carcinogenesis. 2007;28(2):488–96.

44. Colleypriest BJ, Palmer RM, Ward SG, Tosh D. Cdx genes, inflammation and the pathogenesis of Barrett's metaplasia. Trends in Molecular Medicine. 2009;15(7):313–22.

45. Di Pietro M, Lao-Sirieix P, Boyle S, Cassidy A, Castillo D, Saadi A, et al. Evidence for a functional role of epigenetically regulated midcluster HOXB genes in the development

of Barrett esophagus. Proceedings of the National Academy of Sciences of the United States of America. 2012;109(23):9077–82.

46. Barbera M, Pietro MD, Walker E, Brierley C, MacRae S, Simons BD, et al. The human squamous oesophagus has widespread capacity for clonal expansion from cells at diverse stages of differentiation. Gut. 2015;64(1):11–9.

47. Dvorak K, Payne CM, Chavarria M, Ramsey L, Dvorakova B, Bernstein H, et al. Bile acids in combination with low pH induce oxidative stress and oxidative DNA damage: relevance to the pathogenesis of Barrett's oesophagus. Gut. 2006/12/04. 2007 Jun;56(6):763–71.

48. Vaninetti NM, Geldenhuys L, Porter GA et al. Inducible nitric oxide synthase, nitrotyrosine and p53 mutations in the molecular pathogenesis of Barrett's esophagus and esophageal adenocarcinoma. Molecular Carcinogenesis. 2008;47:275–85.

49. Sihvo EIT, Salminen JT, Rantanen TK, Rämö OJ, Ahotupa M, Färkkilä M, et al. Oxidative stress has a role in malignant transformation in Barrett's oesophagus. International Journal of Cancer. 2002 Dec 20;102(6):551–5.

50. Clemons NJ, McColl KEL, Fitzgerald RC. Nitric Oxide and Acid Induce Double-Strand DNA Breaks in Barrett's Esophagus Carcinogenesis via Distinct Mechanisms. Gastroenterology. 2007;133(4):1198–209.

51. Cardin R, Piciocchi M, Tieppo C, Maddalo G, Zaninotto G, Mescoli C, et al. Oxidative DNA Damage in Barrett Mucosa: Correlation with Telomeric Dysfunction and p53 Mutation. Annals of Surgical Oncology. 2013;20(3):583–9.

52. Berndt U, Philipsen L, Bartsch S, Hu Y, Röcken C, Bertram W, et al. Comparative Multi-Epitope-Ligand-Cartography reveals essential immunological alterations in Barrett's

metaplasia and esophageal adenocarcinoma. Molecular Cancer. 2010;9(1):177.

53. Salmela MT, Karjalainen-Lindsberg ML, Puolakkainen P, Saarialho-Kere U. Upregulation and differential expression of matrilysin (MMP-7) and metalloelastase (MMP-12) and their inhibitors TIMP-1 and TIMP-3 in Barrett's oesophageal adenocarcinoma. British journal of cancer. 2001 Aug 3;85(3):383–92.

54. Bobryshev Y V, Tran D, Killingsworth MC, Buckland M, Lord RVN. Dendritic Cell-Associated Immune Inflammation of Cardiac Mucosa: A Possible Factor in the Formation of Barrett's Esophagus. Journal of Gastrointestinal Surgery. 2009;13(3):442–50.

55. Picardo SL, Maher SG, O'Sullivan JN, Reynolds J V. Barrett's to Oesophageal Cancer Sequence: A Model of Inflammatory-Driven Upper Gastrointestinal Cancer. Digestive Surgery. 2012;29(3):251–60.

56. Matsuzaki J, Suzuki H, Tsugawa H, Watanabe M, Hossain S, Arai E, et al. Bile Acids Increase Levels of MicroRNAs 221 and 222, Leading to Degradation of CDX2 During Esophageal Carcinogenesis. Gastroenterology. 2013;145(6):1300–11.

57. Bus P, Siersema PD, Verbeek RE, van Baal JWPM. Upregulation of miRna-143, -145, -192, and -194 in esophageal epithelial cells upon acidic bile salt stimulation. Diseases of the Esophagus. 2014 Aug 1;27(6):591–600.

58. van Baal JWPM, Verbeek RE, Bus P, Fassan M, Souza RF, Rugge M, et al. microRNA-145 in Barrett's oesophagus: regulating BMP4 signalling via GATA6. Gut. 2013 May 1;62(5):664 LP – 675.

59. Wang DH, Clemons NJ, Miyashita T, Dupuy AJ, Zhang W, Szczepny A, et al. Aberrant epithelial-mesenchymal Hedgehog signaling characterizes Barrett's metaplasia. Gastroenterology. 2010/02/04. 2010 May;138(5):1810–22.

60. Bansal A, Lee I-H, Hong X, Mathur SC, Tawfik O, Rastogi A, et al. Discovery and validation of Barrett's esophagus microRNA transcriptome by next generation sequencing. PloS one. 2013/01/23. 2013;8(1):e54240–e54240.

61. Saad R, Chen Z, Zhu S, Jia P, Zhao Z, Washington MK, et al. Deciphering the unique microRNA signature in human esophageal adenocarcinoma. PloS one. 2013 May 28;8(5):e64463–e64463.

62. Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, et al. Circulating microRNAs as stable blood-based markers for cancer detection. Proceedings of the National Academy of Sciences of the United States of America. 2008/07/28. 2008 Jul 29;105(30):10513–8.

63. Qiu M-T, Hu J-W, Yin R, Xu L. Long noncoding RNA: an emerging paradigm of cancer research. Tumor Biology. 2013;34(2):613–20.

64. Wu W, Bhagat TD, Yang X, Song JH, Cheng Y, Agarwal R, et al. Hypomethylation of noncoding DNA regions and overexpression of the long noncoding RNA, AFAP1-AS1, in Barrett's esophagus and esophageal adenocarcinoma. Gastroenterology. 2013/01/16. 2013 May;144(5):956-966.e4.

65. Curvers WL, ten Kate FJ, Krishnadath KK, Visser M, Elzer B, Baak LC, et al. Low-Grade Dysplasia in Barrett's Esophagus: Overdiagnosed and Underestimated. American Journal of Gastroenterology. 2010;105(7). 1-8

66. Wani S, Falk GW, Post J, Yerian L, Hall M, Wang A, et al. Risk Factors for Progression of Low-Grade Dysplasia in Patients With Barrett's Esophagus. Gastroenterology. 2011;141(4):1179-1186.e1.

67. Sikkema M, Looman CWN, Steyerberg EW, Kerkhof M, Kastelein F, van Dekken H, et al. Predictors for Neoplastic Progression in Patients With Barrett's Esophagus: A

Prospective Cohort Study. American Journal of Gastroenterology. 2011;106(7). 1231-8

68. Wani S, Falk G, Hall M, Gaddam S, Wang A, Gupta N, et al. Patients With Nondysplastic Barrett's Esophagus Have Low Risks for Developing Dysplasia or Esophageal Adenocarcinoma. Clinical Gastroenterology and Hepatology. 2011;9(3):220-227.e1.

69. Weston, Allan P. M.D; Sharma, Prateek M.D; Mathur, Sharad M.D; Banerjee, Sushanta Ph.D; Jafri, A. Khatib M.D; Cherian, Rachel M.D; McGregor, Douglas M.D; Hassanein, Ruth S. Ph.D; Hall MP. Risk Stratification of Barrett's Esophagus: Updated Prospective Multivariate Analysis. American Journal of Gastroenterology. 2004;99(9):1657–66.

70. Bennett C, Vakil N, Bergman J, Harrison R, Odze R, Vieth M, Sanders S, Gay L, Pech O, Longcroft-Wheaton G, Romero Y, Inadomi J, Tack J, Corley DA, Manner H, Green S, Al Dulaimi D, Ali H, Allum B, Anderson M, Curtis H, Falk G, Fennerty MB, Fullarton G, Kri JJ. Consensus Statements for Management of Barrett's Dysplasia and Early-Stage Esophageal Adenocarcinoma, Based on a Delphi Process. 2016;36(5):1011–4.

71. Galipeau PC, Prevo LJ, Sanchez CA, Longton GM, Reid BJ. Clonal expansion and loss of heterozygosity at chromosomes 9p and 17p in premalignant esophageal (Barrett's) tissue. Journal of the National Cancer Institute. 1999 Dec 15;91(24):2087–95.

72. Merlo LMF, Wang L, Pepper JW, Rabinovitch PS, Maley CC. Polyploidy, Aneuploidy and the Evolution of Cancer BT - Polyploidization and Cancer. In: Poon RYC, editor. New York, NY: Springer New York; 2010. p. 1–13.

73. Lai LA, Paulson TG, Li X, Sanchez CA, Maley C, Odze RD, et al. Increasing genomic instability during premalignant neoplastic progression revealed through high resolution array-CGH. Genes, Chromosomes and Cancer. 2007 Jun 1;46(6):532–42.

74. Paulson TG, Galipeau PC, Xu L, Kissel HD, Li X, Blount PL, et al. p16 mutation spectrum in the premalignant condition Barrett's esophagus. PloS one. 2008/11/27. 2008;3(11):e3809–e3809.

75. Reid BJ, Levine DS, Longton G, Blount PL, Rabinovitch PS. Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low- and high-risk patient subsets. The American journal of gastroenterology. 2000 Jul;95(7):1669–76.

76. Reid BJ, Prevo LJ, Galipeau PC, Sanchez CA, Longton G, Levine DS, et al. Predictors of progression in Barrett's esophagus II: baseline 17p (p53) loss of heterozygosity identifies a patient subset at increased risk for neoplastic progression. The American journal of gastroenterology. 2001 Oct;96(10):2839–48.

77. Galipeau PC, Li X, Blount PL, Maley CC, Sanchez CA, Odze RD, et al. NSAIDs modulate CDKN2A, TP53, and DNA content risk for progression to esophageal adenocarcinoma. PLoS medicine. 2007 Feb;4(2):e67–e67.

78. Dunn JM, Mackenzie GD, Oukrif D, Mosse CA, Banks MR, Thorpe S, et al. Image cytometry accurately detects DNA ploidy abnormalities and predicts late relapse to high-grade dysplasia and adenocarcinoma in Barrett's oesophagus following photodynamic therapy. British journal of cancer. 2010/05/11. 2010 May 25;102(11):1608–17.

79. Bird–Lieberman EL, Dunn JM, Coleman HG, Lao–Sirieix P, Oukrif D, Moore CE, et al. Population-Based Study Reveals New Risk-Stratification Biomarker Panel for Barrett's Esophagus. Gastroenterology. 2012;143(4):927-935.e3.

80. Rygiel AM, Milano F, ten Kate FJ, de Groot JG, Peppelenbosch MP, Bergman JJGHM, et al. Assessment of chromosomal gains as compared to DNA content changes is

more useful to detect dysplasia in Barrett's esophagus brush cytology specimens. Genes, Chromosomes and Cancer. 2008 May 1;47(5):396–404.

81. Rygiel AM, Milano F, ten Kate FJ, Schaap A, Wang KK, Peppelenbosch MP, et al. Gains and Amplifications of c-myc, EGFR and 20.q13 Loci in the No Dysplasia–Dysplasia–Adenocarcinoma Sequence of Barrett's Esophagus. Cancer Epidemiology Biomarkers & Prevention. 2008 Jun 1;17(6):1380 LP – 1385.

82. Fritcher EGB, Brankley SM, Kipp BR, Voss JS, Campion MB, Morrison LE, et al. A comparison of conventional cytology, DNA ploidy analysis, and fluorescence in situ hybridization for the detection of dysplasia and adenocarcinoma in patients with Barrett's esophagus. Human pathology. 2008/07/07. 2008 Aug;39(8):1128–35.

83. Dulak AM, Stojanov P, Peng S, Lawrence MS, Fox C, Stewart C, et al. Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. Nature genetics. 2013/03/24. 2013 May;45(5):478–86.

84. Nakashima S, Natsugoe S, Matsumoto M, Kijima F, Takebayashi Y, Okumura H, Shimada M, Nakano S, Kusano C, Baba M, Takao S AT. Expression of p53 and p21 is useful for the prediction of preoperative chemotherapeutic effects in esophageal carcinoma. Anticancer Research. 2000;20(3):1933–7.

85. Kaye P V, Haider SA, James PD, Soomro I, Catton J, Parsons SL, et al. Novel staining pattern of p53 in Barrett's dysplasia – the absent pattern. Histopathology. 2010 Dec 1;57(6):933–5.

86. Murray L, Sedo A, Scott M, McManus D, Sloan JM, Hardie LJ, et al. TP53 and progression from Barrett's metaplasia to oesophageal adenocarcinoma in a UK population cohort. Gut. 2006/05/08. 2006 Oct;55(10):1390–7.

87. Kastelein F, Biermann K, Steyerberg EW, Verheij J, Kalisvaart M, Looijenga LHJ, et al. Aberrant p53 protein expression is associated with an increased risk of neoplastic progression in patients with Barrett's oesophagus. Gut. 2013 Dec 1;62(12):1676 LP – 1683.

88. Kaye P V, Haider SA, Ilyas M, James PD, Soomro I, Faisal W, et al. Barrett's dysplasia and the Vienna classification: reproducibility, prediction of progression and impact of consensus reporting and p53 immunohistochemistry. Histopathology. 2009 May 1;54(6):699–712.

89. Esteller M. Cancer epigenomics: DNA methylomes and histone-modification maps. Nature Reviews Genetics. 2007;8(4):286–98.

90. Kaz AM, Wong C-J, Luo Y, Virgin JB, Washington MK, Willis JE, et al. DNA methylation profiling in Barrett's esophagus and esophageal adenocarcinoma reveals unique methylation signatures and molecular subclasses. Epigenetics. 2011 Dec;6(12):1403–12.

91. Alvi MA, Liu X, O'Donovan M, Newton R, Wernisch L, Shannon NB, et al. DNA methylation as an adjunct to histopathology to detect prevalent, inconspicuous dysplasia and early-stage neoplasia in Barrett's esophagus. Clinical cancer research : an official journal of the American Association for Cancer Research. 2012/12/14. 2013 Feb 15;19(4):878–88.

92. Wang JS, Guo M, Montgomery EA, Thompson RE, Cosby H, Hicks L, et al. DNA promoter hypermethylation of p16 and APC predicts neoplastic progression in Barrett's esophagus. The American journal of gastroenterology. 2009/07/07. 2009 Sep;104(9):2153–60.

93. Schulmann K, Sterian A, Berki A, Yin J, Sato F, Xu Y, et al. Inactivation of p16, RUNX3,

and HPP1 occurs early in Barrett's-associated neoplastic progression and predicts progression risk. Oncogene. 2005;24(25):4138–48.

94. Lao-Sirieix P, Lovat L, Fitzgerald RC. Cyclin A Immunocytology as a Risk Stratification Tool for Barrett's Esophagus Surveillance. Clinical Cancer Research. 2007 Jan 15;13(2):659 LP – 665.

95. Evans JA, Early DS, Fukami N, Ben-Menachem T, Chandrasekhara V, Chathadi K V., et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. Gastrointestinal Endoscopy. 2012;76(6):1087–94.

96. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau J-M, Esteban J-M, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2017;49:1–8.

97. Cooper GS, Kou TD CA. Receipt of previous diagnoses and endoscopy and outcome from esophageal adenocarcinoma: a population-based study with temporal trends. American Journal of Gastroenterology. 2009;104(6):1356–62.

98. Fountoulakis A, Zafirellis KD, Dolan K, Dexter SPL, Martin IG, Sue-Ling HM. Effect of surveillance of Barrett's oesophagus on the clinical outcome of oesophageal cancer. BJS (British Journal of Surgery). 2004 Aug 1;91(8):997–1003.

99. Rubenstein JH, Sonnenberg A, Davis J, McMahon L, Inadomi JM. Effect of a prior endoscopy on outcomes of esophageal adenocarcinoma among United States veterans. Gastrointestinal endoscopy. 2008/06/11. 2008 Nov;68(5):849–55.

100. Corley DA, Mehtani K, Quesenberry C, Zhao W, de Boer J, Weiss NS. Impact of endoscopic surveillance on mortality from Barrett's esophagus-associated esophageal adenocarcinomas. Gastroenterology. 2013/05/11. 2013 Aug;145(2):312-9.e1.

101. Singh S, Garg SK, Singh PP, Iyer PG, El-Serag HB. Acid-suppressive medications and risk

of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. Gut. 2013/11/12. 2014 Aug;63(8):1229–37.

102. Buttar NS, Wang KK, Anderson MA, Dierkhising RA, Pacifico RJ, Krishnadath KK, et al. The Effect of Selective Cyclooxygenase-2 Inhibition in Barrett's Esophagus Epithelium: An In Vitro Study. JNCI: Journal of the National Cancer Institute. 2002 Mar 20;94(6):422–9.

103. Vaughan TL, Dong LM, Blount PL, Ayub K, Odze RD, Sanchez CA, et al. Non-steroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's oesophagus: a prospective study. The Lancet Oncology. 2005;6(12):945–52.

104. Falk GW, Buttar NS, Foster NR, Ziegler KLA, Demars CJ, Romero Y, et al. A combination of esomeprazole and aspirin reduces tissue concentrations of prostaglandin E(2) in patients with Barrett's esophagus. Gastroenterology. 2012/07/11. 2012 Oct;143(4):917-26.e1.

105. Jankowski JAZ, de Caestecker J, Love SB, Reilly G, Watson P, Sanders S, et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. Lancet (London, England). 2018/07/26. 2018 Aug 4;392(10145):400–8.

106. Ngamruengphong S, Sharma VK, Das A. Diagnostic yield of methylene blue chromoendoscopy for detecting specialized intestinal metaplasia and dysplasia in Barrett's esophagus: a meta-analysis. Gastrointestinal Endoscopy. 2009;69(6):1021–8.

107. Kara M, Peters F, Rosmolen W, Krishnadath K, ten Kate F, Fockens P, et al. High−Resolution Endoscopy Plus Chromoendoscopy or Narrow−Band Imaging in Barrett's Esophagus: a Prospective Randomized Crossover Study. Endoscopy. 2005;37:929–36.

108. Ferguson DD, DeVault KR, Krishna M, Loeb DS, Wolfsen HC WM. Enhanced

Magnification-Directed Biopsies Do Not Increase the Detection of Intestinal Metaplasia in Patients with GERD. American Journal of Gastroenterology. 2006;101(7):1611–6.

109. Hoffman A, Kiesslich R, Bender A, Neurath MF, Nafe B, Herrmann G, et al. Acetic acid–guided biopsies after magnifying endoscopy compared with random biopsies in the detection of Barrett's esophagus: a prospective randomized trial with crossover design. Gastrointestinal Endoscopy. 2006;64(1):1–8.

110. Longcroft–Wheaton G, Duku M, Mead R, Poller D, Bhandari P. Acetic Acid Spray Is an Effective Tool for the Endoscopic Detection of Neoplasia in Patients With Barrett's Esophagus. Clinical Gastroenterology and Hepatology. 2010;8(10):843–7.

111. Muto M, Katada C, Sano Y, Yoshida S. Narrow Band Imaging: A New Diagnostic Approach to Visualize Angiogenesis in Superficial Neoplasia. Clinical Gastroenterology and Hepatology. 2005;3(7, Supplement 1):S16–20.

112. Wolfsen HC, Crook JE, Krishna M, Achem SR, Devault KR, Bouras EP, et al. Prospective, Controlled Tandem Endoscopy Study of Narrow Band Imaging for Dysplasia Detection in Barrett's Esophagus. Gastroenterology. 2008;135(1):24–31.

113. Sharma P, Hawes RH, Bansal A, Gupta N, Curvers W, Rastogi A, et al. Standard endoscopy with random biopsies versus narrow band imaging targeted biopsies in Barrett's oesophagus: a prospective, international, randomised controlled trial. Gut. 2013;62(1):15–21.

114. Mannath J, Subramanian V, Hawkey CJ, Ragunath K. Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in Barretts esophagus: A meta-analysis. Endoscopy. 2010;42(5):351–9.

115. Kara MA, Peters FP, Fockens P, ten Kate FJW, Bergman JJGHM. Endoscopic video-

autofluorescence imaging followed by narrow band imaging for detecting early neoplasia in Barrett's esophagus. Gastrointestinal Endoscopy. 2006;64(2):176–85.

116. Curvers WL, Singh R, Song LMWK, Wolfsen HC, Ragunath K, Wang K, et al. Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: A multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system. Gut. 2008;57(2):167–72.

117. Curvers WL, Herrero LA, Wallace MB, Wong Kee Song L, Ragunath K, Wolfsen HC, et al. Endoscopic Tri-Modal Imaging Is More Effective Than Standard Endoscopy in Identifying Early-Stage Neoplasia in Barrett's Esophagus. Gastroenterology. 2010;139(4):1106-1114.e1.

118. Curvers WL, van Vilsteren FG, Baak LC, Böhmer C, Mallant-Hent RC, Naber AH, et al. Endoscopic trimodal imaging versus standard video endoscopy for detection of early Barrett's neoplasia: a multicenter, randomized, crossover study in general practice. Gastrointestinal Endoscopy. 2011;73(2):195–203.

119. di Pietro M, Boerwinkel DF, Shariff MK, Liu X, Telakis E, Lao-Sirieix P, et al. The combination of autofluorescence endoscopy and molecular biomarkers is a novel diagnostic tool for dysplasia in Barrett's oesophagus. Gut. 2014/04/10. 2015 Jan;64(1):49–56.

120. Boerwinkel DF, Di Pietro M, Liu X, Shariff MK, Lao-Sirieix P, Walker CE, et al. Endoscopic TriModal imaging and biomarkers for neoplasia conjoined: a feasibility study in Barrett's esophagus. Diseases of the Esophagus. 2014 Jul 1;27(5):435–43.

121. Gupta A, Attar BM, Koduru P, Murali AR, Go BT, Agarwal R. Utility of confocal laser endomicroscopy in identifying high-grade dysplasia and adenocarcinoma in Barrett's

esophagus: a systematic review and meta-analysis. European Journal of Gastroenterology & Hepatology. 2014;26(4). 369-77

122. Sharma P, Meining AR, Coron E, Lightdale CJ, Wolfsen HC, Bansal A, et al. Real-time increased detection of neoplastic tissue in Barrett's esophagus with probe-based confocal laser endomicroscopy: final results of an international multicenter, prospective, randomized, controlled trial. Gastrointestinal endoscopy. 2011/07/13. 2011 Sep;74(3):465–72.

123. Canto MI, Anandasabapathy S, Brugge W, Falk GW, Dunbar KB, Zhang Z, et al. In vivo endomicroscopy improves detection of Barrett's esophagus-related neoplasia: a multicenter international randomized controlled trial (with video). Gastrointestinal endoscopy. 2013/11/09. 2014 Feb;79(2):211–21.

124. Bouma BE, Tearney GJ, Compton CC, Nishioka NS. High-resolution imaging of the human esophagus and stomach in vivo using optical coherence tomography. Gastrointestinal Endoscopy. 2000;51(4, Part 1):467–74.

125. Evans JA, Poneros JM, Bouma BE, Bressner J, Halpern EF, Shishkov M, et al. Optical coherence tomography to identify intramucosal carcinoma and high-grade dysplasia in Barrett's esophagus. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2006 Jan;4(1):38–43.

126. Wani S, Qumseya B, Sultan S, Agrawal D, Chandrasekhara V, Harnke B, et al. Endoscopic eradication therapy for patients with Barrett's esophagus–associated dysplasia and intramucosal cancer. Gastrointestinal Endoscopy. 2018;87(4):907-931.e9.

127. Peters FP, Brakenhoff KPM, Curvers WL, Rosmolen WD, Fockens P, ten Kate FJW, et

al. Histologic evaluation of resection specimens obtained at 293 endoscopic resections in Barrett's esophagus. Gastrointestinal Endoscopy. 2008;67(4):604–9.

128. Inoue H, Takeshita K, Hori H, Muraoka Y, Yoneshima H, Endo M. Endoscopic mucosal resection with a cap-fitted panendoscope for esophagus, stomach, and colon mucosal lesions. Gastrointestinal Endoscopy. 1993;39:58–62.

129. Pouw RE, Van Vilsteren FGI, Peters FP, Herrero LA, Ten Kate FJW, Visser M, et al. Randomized trial on endoscopic resection-cap versus multiband mucosectomy for piecemeal endoscopic resection of early Barrett's neoplasia. Gastrointestinal Endoscopy. 2011;74:35–43.

130. Eluri S, Shaheen NJ. Barrett's Esophagus: Diagnosis and Management. Gastrointestinal Endoscopy. 2017;85:889–903.

131. Cook Medical. Duette® Multi-Band Mucosectomy [Internet]. 2018 [cited 2018 Mar 29]. Available from: https://www.cookmedical.com/products/esc_duette_webds/18/08/2019

132. Alvarez Herrero L, Pouw RE, Van Vilsteren FGI, Ten Kate FJW, Visser M, Seldenrijk CA, et al. Safety and efficacy of multiband mucosectomy in 1060 resections in Barrett's esophagus. Endoscopy. 2011;43:177–83.

133. K. Belghazi, M. Everson, R. Haidry, P. Kandel, L.K. Mejia, M.J. Bourke, et al. Safety of the six-shooter multiband mucosectomy device for endoscopic resection in Barrett's esophagus in 4327 resections: a retrospective international multicenter study. United European Gastroenterology Week Conference, Barcelona; 2017.

134. Desai M, Saligram S, Gupta N, Vennalaganti P, Bansal A, Choudhary A, et al. Efficacy and safety outcomes of multimodal endoscopic eradication therapy in Barrett's esophagus-related neoplasia: a systematic review and pooled analysis.

Gastrointestinal Endoscopy. 2017;85:482–95.

135. Tomizawa Y, Konda VJA, Coronel E, Chapman CG, Siddiqui UD. Efficacy, Durability, and Safety of Complete Endoscopic Mucosal Resection of Barrett Esophagus: A Systematic Review and Meta-Analysis. Journal of Clinical Gastroenterology. 2017;(00):1–7.

136. Pech O, May A, Manner H, Behrens A, Pohl J, Weferling M, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology. 2014;146:652-660.e1.

137. Wani, S., Mathur, S.C., Curvers, W.L., Singh, V., Herrero, L.A., Hall, S.B., Ulusarac, O., Cherian, R., McGregor, D.H., Bansal, A., Rastogi, A., Ahmed, B., Singh, M., Gaddam, S., Ten Kate, F.J., Bergman, J., Sharma P. Greater interobserver agreement by endoscopic mucosal resection than biopsy samples in barrett's dysplasia. Clinical Gastroenterology and Hepatology. 2010;8(9):783–8.

138. Mino-Kenudson M, Hull MJ, Brown I, Muzikansky A, Srivastava A, Glickman J, et al. EMR for Barrett's esophagus-related superficial neoplasms offers better diagnostic reproducibility than mucosal biopsy{A figure is presented}. Gastrointestinal Endoscopy. 2007;66(4):660–6.

139. Barret M, Cao DT, Beuvon F, Leblanc S, Terris B, Camus M, et al. Endoscopic submucosal dissection for early Barrett's neoplasia. United European Gastroenterology Journal. 2016;4(2):207–15.

140. Park CH, Kim EH, Kim HY, Roh YH, Lee YC. Clinical outcomes of endoscopic submucosal dissection for early stage esophagogastric junction cancer: A systematic review and meta-analysis. Digestive and Liver Disease. 2015;47(1):37–44.

141. Yang D, Zou F, Xiong S, Forde JJ, Wang Y, Draganov P V. Endoscopic submucosal dissection for early Barrett's neoplasia: a meta-analysis. Gastrointestinal Endoscopy.

2018;87(6):1383–93.

142. Terheggen G, Horn EM, Vieth M, Gabbert H, Enderle M, Neugebauer A, et al. A randomised trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett's neoplasia. Gut. 2016;66(5):783–93.

143. Subramaniam S, Chedgy F, Longcroft-Wheaton G, Kandiah K, Maselli R, Seewald S, et al. Complex early Barrett's neoplasia at 3 Western centers: European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST). Gastrointestinal Endoscopy. 2017;86(4):608–18.

144. Pedro Pimentel-Nunes, Mário Dinis-Ribeiro, Thierry Ponchon, Alessandro Repici, Michael Vieth, Antonella De Ceglie, Arnaldo Amato, Frieder Berr, Pradeep Bhandari, Andrzej Bialek, Massimo Conio, Jelle Haringsma, Cord Langner, Søren Meisner, Helmut Messmann, PHD. Endoscopic submucosal dissection : European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2015;47:829–54.

145. Markar SR, Mackenzie H, Ni M, Huddy JR, Askari A, Faiz O, et al. The influence of procedural volume and proficiency gain on mortality from upper GI endoscopic mucosal resection. Gut. 2016/10/18. 2018 Jan;67(1):79–85.

146. Phoa KN, Pouw RE, Bisschops R, Pech O, Ragunath K, Weusten BLAM, et al. Multimodality endoscopic eradication for neoplastic Barrett oesophagus: Results of an European multicentre study (EURO-II). Gut. 2016;65:555–62.

147. Hamade N, Sharma P. Ablation Therapy for Barrett's Esophagus: New Rules for Changing Times. Current Gastroenterology Reports. 2017;19(12).64

148. Gage AA, Baust J. Mechanisms of Tissue Injury in Cryosurgery. Cryobiology. 1998;37(3):171–86.

149. Baust JG, Gage AA, Klossner D, Clarke D, Miller R, Cohen J, et al. Issues critical to the

successful application of cryosurgical ablation of the prostate. Technology in Cancer Research and Treatment. 2007;6(2):97–109.

150. Evonich RF, Nori DM, Haines DE. A randomized trial comparing effects of radiofrequency and cryoablation on the structural integrity of esophageal tissue. Journal of Interventional Cardiac Electrophysiology. 2007;19(2):77–83.

151. Canto MI, Shaheen NJ, Almario JA, Voltaggio L, Montgomery E, Lightdale CJ. Multifocal nitrous oxide cryoballoon ablation with or without EMR for treatment of neoplastic Barrett's esophagus. Gastrointestinal Endoscopy. 2018;88:438–46.

152. Künzli H, Schölvinck D, Meijer S, Seldenrijk K, Bergman J, Weusten B. Efficacy of the CryoBalloon Focal Ablation System for the eradication of dysplastic Barrett's esophagus islands. Endoscopy. 2016;49:169–75.

153. Schölvinck DW, Künzli HT, Kestens C, Siersema PD, Vleggaar FP, Demeester SR, et al. Treatment of Barrett ' s esophagus with a novel focal cryoablation device : a safety and feasibility study. Endoscopy. 2015;1106–12.

154. van Munster SN, Overwater A, Haidry R, Bisschops R, Bergman JJGHM, Weusten BLAM. Focal cryoballoon versus radiofrequency ablation of dysplastic Barrett's esophagus: impact on treatment response and postprocedural pain. Gastrointestinal Endoscopy. 2018;88:1–9.

155. Sengupta N, Ketwaroo GA, Bak DM, Kedar V. Salvage cryotherapy after failed radiofrequency ablation for Barrett ' s esophagus – related dysplasia is safe and effective. Gastrointestinal Endoscopy. 2015;82(3):443–8.

156. Dumot JA, Vargo JJ, Falk GW, Frey L, Lopez R, Rice TW. An open-label, prospective trial of cryospray ablation for Barrett's esophagus high-grade dysplasia and early esophageal cancer in high-risk patients. Gastrointestinal Endoscopy. 2009;70(4):635–

44.

157. Visrodia K, Zakko L, Ms SS, Leggett CL, Ms PGI, Wang KK. Cryotherapy for persistent Barrett's esophagus after radiofrequency ablation : a systematic review and meta-analysis. Gastrointestinal Endoscopy. 2018;87:1396–404.

158. Manner H, Rabenstein T, Pech O, Braun K, May A, Pohl J, et al. Ablation of residual Barrett ' s epithelium after endoscopic resection : a randomized long-term follow- up study of argon plasma coagulation vs . surveillance (APE study). Endoscopy. 2014;6–12.

159. McPherson SJ, Sinclair MT, Smith NCE, Kelly K, Ellis D, Mason M. Gastrointestinal Haemorrhage: Time to Get Control ? NCEPOD. 2015. https://www.ncepod.org.uk/2015report1/downloads/TimeToGetControlFullReport.pdf. Accessed 12/06/2019

160. Hwang JH, Fisher DA, Ben-Menachem T, Chandrasekhara V, Chathadi K, Decker GA, et al. The role of endoscopy in the management of acute non-variceal upper GI bleeding. Gastrointestinal Endoscopy. 2012;75(6):1132–8.

161. Khamaysi I, Lecturer S, Gralnek IM, Medicine A. Best Practice & Research Clinical Gastroenterology Acute upper gastrointestinal bleeding (UGIB) – Initial evaluation and management. Best Practice & Research Clinical Gastroenterology. 2013;27(5):633–8.

162. Marmo R, Koch M, Cipolletta L, Capurso L, Pera A, Bianco MA, et al. Predictive factors of mortality from nonvariceal upper gastrointestinal hemorrhage: A multicenter study. American Journal of Gastroenterology. 2008;103(7):1639–47.

163. Sugawa C, Benishek D, Walt AJ. Mallory-Weiss syndrome. A study of 224 patients. The American Journal of Surgery. 1983;145(1):30–3.

164. Feinman M, Haut ER. Upper Gastrointestinal Bleeding. Surgical Clinics of North America. 2014;94(1):43–53.

165. Szura M, Pasternak A. Upper gastrointestinal bleeding - state of the art. Folia Med Cracov. 2014;54(4):59–78.

166. van Leerdam ME. Epidemiology of acute upper gastrointestinal bleeding. Best Practice & Research Clinical Gastroenterology. 2008;22(2):209–24.

167. Ion D, Mavrodin CI, Serban MB, Marinescu T, Pãduraru DN. Haemobilia - A Rare Cause of Upper Gastro-Intestinal Bleeding. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques. 2011;21(5):e286–7.

168. Campbell HE, Stokes EA, Bargo D, Logan RF, Mora A, Hodge R, et al. Costs and quality of life associated with acute upper gastrointestinal bleeding in the UK: cohort analysis of patients in a cluster randomised trial. BMJ open. 2015;5(4):e007230.

169. Hearnshaw S, Murphy M, Travis S, Dalton D, Lowe D, Grant-Casey J, et al. Uk Comparative Audit of Upper Gastrointestinal Bleeding and the use of Blood. British society of Gastroenterolgy. 2007;7(4)1–88.

170. Lin H, Wang K, Perng C, Chua R, Lee F, Lee C, et al. Early or delayed endoscopy for patients with peptic ulcer bleeding. A prospective randomized study. Journal of Clinical Gastroenterology. 1996;22(4):267–71.

171. Sung J, Tsoi K, Ma T, Yung M-Y, Lau J, Chiu P. Causes of mortality in patients with peptic ulcer bleeding: a prospective cohort study of 10,428 cases. The American journal of gastroenterology. 2010;105(1):84–9.

172. Hearnshaw S a, Logan RF a, Lowe D, Travis SPL, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. Gut. 2011;60:1327–35.

173. Wallis JP, Wells AW, Chapman CE. Changing indications for red cell transfusion from 2000 to 2004 in the North of England. Transfusion Medicine. 2006;16(6):411–7.

174. Villanueva C, Colomo A, Bosch A, Concepcion M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11–21.

175. Gralnek I, Dumonceau J-M, Kuipers E, Lanas A, Sanders D, Kurien M, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2015;47(10):1–46.

176. Lee JM, Kim ES, Chun HJ, Hwang Y-J, Lee JH, Kang SH, et al. Discharge hemoglobin and outcome in patients with acute nonvariceal upper gastrointestinal bleeding. 2016;4(8):865–9.

177. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ETTL. New oral anticoagulants increase risk for gastrointestinal bleeding: A systematic review and meta-analysis. Gastroenterology. 2013;145(1):105-112

178. Abraham N, Horsley-Silva J. Gastrointestinal bleeding secondary to the new anticoagulants. Current Opinion in Gastroenterology. 2016;32(6):1-6

179. Cuker A. Laboratory measurement of the non-vitamin K antagonist oral anticoagulants: selecting the optimal assay based on drug, assay availability, and clinical indication. Journal of Thrombosis and Thrombolysis. 2016;41(2):241–7.

180. Stanley AJ, Ashley D, Dalton HR, Mowat C, Gaya DR, Thompson E, et al. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. The Lancet. 2009;373(9657):42–7.

181. NICE. Acute upper gastrointestinal bleeding in over 16s : management. 2012.

https://www.nice.org.uk/guidance/cg141/resources/acute-upper-gastrointestinal-bleeding-in-over-16s-management-pdf-35109565796293. Accessed 04/05/2019

182. Mokhtare M, Bozorgi V, Agah S, Nikkhah M, Faghihi A, Boghratian A, Shalbaf N, Khanlari A SH. Comparison of Glasgow-Blatchford score and full Rockall score systems to predict clinical outcomes in patients with upper gastrointestinal bleeding. Clinical and Experimental Gastroenterology. 2016;9:337–43.

183. Martinez-Cara JG, Jimenez-Rosales R, Ubeda-Munoz M, de Hierro ML, de Teresa J, Redondo-Cerezo E. Comparison of AIMS65, Glasgow-Blatchford score, and Rockall score in a European series of patients with upper gastrointestinal bleeding: performance when predicting in-hospital and delayed mortality. United European Gastroenterology Journal. 2015; 4(5):1-8

184. Robertson M, Majumdar A, Boyapati R, Chung W, Worland T, Terbah R, et al. Risk stratification in acute upper GI bleeding: Comparison of the AIMS65 score with the Glasgow-Blatchford and Rockall scoring systems. Gastrointestinal Endoscopy. 2016;83(6):1151–60.

185. Stanley AJ, Laine L, Dalton HR, Ngu JH, Schultz M, Abazi R, et al. Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study. Bmj. 2017;3(6):45-53

186. Tai CM, Huang SP, Wang HP, Lee TC, Chang CY, Tu CH, et al. High-risk ED patients with nonvariceal upper gastrointestinal hemorrhage undergoing emergency or urgent endoscopy: a retrospective analysis. American Journal of Emergency Medicine. 2007;25(3):273–8.

187. Schacher GM, Ortner MA, Wasserfallen JB, Blum AL, Dorta G. Is Early Endoscopy in the Emergency Room Beneficial in Patients with Bleeding Peptic Ulcer ? A “

Fortuitously Controlled ” Study. Endoscopy. 2005; 3(2):145-53

188. Jairath V, Kahan B, Logan R, Hearnshaw S, Doré C, Travis S, et al. Outcomes following acute nonvariceal upper gastrointestinal bleeding in relation to time to endoscopy: results from a nationwide study. Endoscopy. 2012;44(8):723–30.

189. Bjorkman DJ, Zaman A, Fennerty MB, Lieberman D, DiSario JA, Guest-Warnick G. Urgent vs. elective endoscopy for acute non-variceal upper-GI bleeding: An effectiveness study. Gastrointestinal Endoscopy. 2004;60(1):1–8.

190. Laursen SB, Leontiadis GI, Stanley AJ, Møller MH, Hansen JM, Schaffalitzky de Muckadell OB. Relationship between timing of endoscopy and mortality in patients with peptic ulcer bleeding: a nationwide cohort study. Gastrointestinal Endoscopy. 2016; 4(2):246-52

191. Cooper GS, Chak A, Way LE, Hammar PJ, Harper DL RG. Early endoscopy in upper gastrointestinal hemorrhage: associations with recurrent bleeding, surgery, and length of hospital stay. Gastrointest Endosc. 1999;49(2):145–52.

192. Lim LG, Ho KY, Chan YH, Teoh PL, Khor CJL, Lim LL, et al. Urgent endoscopy is associated with lower mortality in high-risk but not low-risk nonvariceal upper gastrointestinal bleeding. Endoscopy. 2011;43(4):300–6.

193. Sonnenberg A. Timing of endoscopy in gastrointestinal bleeding. United European gastroenterology journal. 2014;2(1):5–9.

194. Wong SH, Sung JJY. Management of GI emergencies: Peptic ulcer acute bleeding. Best Practice and Research: Clinical Gastroenterology. 2013;27(5):639–47.

195. Campbell IW, Nairn M. Scottish Intercollegiate Guidelines network: management of diabetes (SIGN 55). The British Journal of Diabetes & Vascular Disease. 2002;2(1):50-6

196. Laine L, Jensen DM. Management of patients with ulcer bleeding. The American

Journal of Gastroenterology. 2012;107(3):345–60; quiz 361.

197. Hu D. Emergency medicine questions: Can tranexamic acid be used to treat upper gastrointestinal bleeds? American Journal of Emergency Medicine. 2016;34(9):1892–3.

198. Bennett C, Klingenberg LS, Langholz E, Gluud LL. Tranexamic acid for upper gastrointestinal bleeding. Cochrane Database of Systematic Reviews. 2014;21(11):CD006640.

199. Gluud LL, Klingenberg SL, Langholz E. Tranexamic acid for upper gastrointestinal bleeding. Cochrane database of systematic reviews Online. 2012;1(1):CD006640.

200. Forrest J, Finlayson N, Shearman D. ENDOSCOPY IN GASTROINTESTINAL BLEEDING. The Lancet. 1974;4(3)394–7.

201. Nayor J, Saltzman JR. Determining the endpoint of endoscopic therapy for upper GI bleeding: Are our eyes as good as our ears? Gastrointestinal Endoscopy. 2016;83(1):137–9.

202. Jensen DM, Stuart R, Ahlbom H, Eklund S. Inter-Observer Agreement On Assessment of Photo Documentation in Bleeding Peptic Ulcer. Gastrointestinal Endoscopy. 2009;69(5):1-8

203. Lin HJ, Hsieh YH, Tseng GY, Perng CL, Chang FY, Lee SD. A prospective, randomized trial of large-versus small-volume endoscopic injection of epinephrine for peptic ulcer bleeding. Gastrointestinal Endoscopy. 2002;55(6):615–9.

204. Liou TC, Lin SC, Wang HY, Chang WH. Optimal injection volume of epinephrine for endoscopic treatment of peptic ulcer bleeding. World Journal of Gastroenterology. 2006;12(18):3108–13.

205. Park JM, Huo SM, Lee HH, Lee B-I, Song HJ, Choi M-G. Longer Observation Time

Increases Proportion of Neoplasms Detected by Esophagogastroduodenoscopy. Gastroenterology. 2017;153(2):460-469.

206. http://www.gastrotraining.com/category/gastro-duodenal/upper-gi-bleed-endoscopy/gold-probe-upper-gi-bleed-endoscopy-gastro-duodenal. Accessed 12/03/2019

207. Ginsberg G, Alan Barkun, Bosco J, Burdick S, Isenberg G, Nakao N, et al. The argon plasma coagulator. Gastrointestinal Endoscopy. 2002;55(February):807–10.

208. Marmo R, Rotondano G, Piscopo R, Bianco MA, Angella RD, Cipolletta L. Dual Therapy Versus Monotherapy in the Endoscopic Treatment of High-Risk Bleeding Ulcers : A Meta-Analysis of Controlled Trials. American Journal of Gastroenterology. 2007;(9):279–89.

209. Sung J, Tsoi K, Lai L, Wu J, Lau J. Endoscopic clipping versus injection and thermo-coagulation in the treatment of non-variceal upper gastrointestinal bleeding: a meta-analysis. Gut. 2007;(January):4(3):1364–72.

210. Wedi E, Fischer A, Hochberger J, Jung C, Orkut S, Richter-Schrag HJ. Multicenter evaluation of first-line endoscopic treatment with the OTSC in acute non-variceal upper gastrointestinal bleeding and comparison with the Rockall cohort : the FLETRock study. Surgical Endoscopy. 2017; 5(4):34-41

211. Calvet X, Vergara M, Brullet E, Gisbert JP, Campo R. Addition of a Second Endoscopic Treatment Following Epinephrine Injection Improves Outcome in High-Risk Bleeding Ulcers. Gastroenterology. 2004;126(2):441–50.

212. Vergara M, Bennett C, Calvet X, Gisbert JP. Epinephrine injection versus epinephrine injection and a second endoscopic method in high-risk bleeding ulcers. The Cochrane database of systematic reviews. 2014;10(10):57-71

213. Kohler B, Maier M, Benz C. Acute Ulcer Bleeding A Prospective Randomized Trial to Compare Doppler and Forrest Classifications in Endoscopic Diagnosis and Therapy. Digestive Diseases. 1997;42(7):1370–4.

214. Wong R, Chak A, Kobayashi K, Isenberg G, Cooper G, Carr-Locke D, et al. Role of Doppler US in acute peptic ulcer hemorrhage: can it predict failure of endoscopic therapy? Gastrointest Endosc. 2000;52(3):315–21.

215. van Leerdam ME, Rauws EAJ, Geraedts AAM, Tijssen JGP, Tytgat GNJ. The role of endoscopic Doppler US in patients with peptic ulcer bleeding. Gastrointestinal endoscopy. 2003;58(5):677–84.

216. Ramaswamy RS, Choi HW, Mouser HC, Narsinh KH, McCammack KC, Treesit T, et al. Role of interventional radiology in the emergent management of acute upper gastrointestinal bleeding. Seminars in Interventional Radiology. 2012;29(3):169–77.

217. Krämer SC, Görich J, Rilinger N, Siech M, Aschoff AJ, Vogel J, et al. Embolization for gastrointestinal hemorrhages. European Radiology. 2000;10(5):802–5.

218. Bezerra KB, Júnior EAB, Pereira NC de S, Costa FA da. Gastric arteriovenous malformation: treatment by embolization. Radiologia Brasileira. 2012;45(Figure 2):126–8.

219. Lau J, Sung J, Lee K, Yung M-Y, Wong S, Wu J, et al. Effect of Intravenous Omeprazole on Recurrent Bleeding After Endoscopic Treatment of Bleeding Peptic Ulcers. The New England Journal of Medicine. 2000;343:310–6.

220. Rubin M, Hussain SA, Shalomov A, Cortes RA, Smith MS, Kim SH. Live view video capsule endoscopy enables risk stratification of patients with acute upper GI bleeding in the emergency room: A pilot study. Digestive Diseases and Sciences. 2011;56(3):786–91.

221. Gralnek I, Ching J, Maza I, Wu J, Rainer T, Israelit S, et al. Capsule endoscopy in acute upper gastrointestinal hemorrhage: a prospective cohort study. Endoscopy. 2013;45:12–9.

222. Meltzer A, Ali A, Kresiberg R, Patel G, Smith J. Video Capsule Endoscopy in the Emergency Department : A Prospective Study of Acute Upper Gastrointestinal Hemorrhage. YMEM. 2013;61(4):438-443.e1.

223. Sung JJ, Tang RS, Ching JY, Rainer T, Lau JY. The use of capsule endoscopy in the emergency department as a triage of patients with GI bleeding. Gastrointestinal Endoscopy. 2016;84(6):907–13.

224. Beg S, Al-bakir I, Bhuva M, Patel J, Fullard M, Leahy A, et al. Early clinical experience of the safety and efficacy of EndoClot in the management of non-variceal upper gastrointestinal bleeding. Endoscopy International Open. 2015;3:605–9.

225. Garber A, Jang S. Novel Therapeutic Strategies in the Management of Non-Variceal Upper Gastrointestinal Bleeding. Clin Endosc. 2016;49:421–4.

226. Prei JC, Barmeyer C, Bürgel N, Daum S, Epple HJ, Günther U, et al. EndoClot polysaccharide hemostatic system in nonvariceal gastrointestinal bleeding. Journal of Clinical Gastroenterology. 2016;50(10):e95–100.

227. Kim YJ, Park JC, Kim EH, Shin SK, Lee SK, Lee YC. Hemostatic powder application for control of acute upper gastrointestinal bleeding in patients with gastric malignancy. Endoscopy international open. 2018/05/25. 2018 Jun;6(6):E700–5.

228. S Giday , Y Kim, D Krishnamurty, R Ducharme, D Liang, E Shin, et al. A long-term randomized controlled trial of a novel nanopowder hemostatic agent for control of severe upper gastrointestinal bleeding in a porcine model. Gastrointestinal Endoscopy. 2009;69(5):296–9.

229. Smith LA, Stanley AJ, Bergman JJ, Kiesslich R, Hoffman A, Tjwa ET, et al. Hemospray application in nonvariceal upper gastrointestinal bleeding: results of the Survey to Evaluate the Application of Hemospray in the Luminal Tract. Journal of clinical gastroenterology. 2014;48(10):e89-92.

230. Haddara S, Jacques J, Lecleire S, Branche J, Leblanc S, Le Baleur Y, et al. A novel hemostatic powder for upper gastrointestinal bleeding: a multicenter study (the GRAPHE registry). Endoscopy. 2016;48(12):1084–95.

231. Barkun AN, Moosavi S, Martel M. Topical hemostatic agents: A systematic review with particular emphasis on endoscopic application in GI bleeding. Gastrointestinal Endoscopy. 2013;77(5):692–700.

232. Sung JJY, Luo D, Wu JCY, Ching JYL, Chan FKL, Lau JYW, et al. Early clinical experience of the safety and effectiveness of Hemospray in achieving hemostasis in patients with acute peptic ulcer bleeding. Endoscopy. 2011;43(4):291–5.

233. Chen YI, Barkun A, Nolan S. Hemostatic powder TC-325 in the management of upper and lower gastrointestinal bleeding: A two-year experience at a single institution. Endoscopy. 2015;47(2):167–71.

234. Arena M, Masci E, Eusebi LH, Iabichino G, Mangiavillano B, Viaggi P, et al. Hemospray for treatment of acute bleeding due to upper gastrointestinal tumours. Digestive and Liver Disease. 2017;49(5):514–7.

235. Holster IL, Kuipers EJ, Tjwa ETTL. Hemospray in the treatment of upper gastrointestinal hemorrhage in patients on antithrombotic therapy. Endoscopy. 2013;45:63–6.

236. Ibrahim M, El-mikkawy A, Hamid MA, Abdalla H, Lemmers A, Mostafa I, et al. Early application of haemostatic powder added to standard management for

oesophagogastric variceal bleeding: a randomised trial. Gut. 2018;1–10.

237. Facciorusso A, Straus Takahashi M, Eyileten Postula C, Buccino VR, Muscatiello N. Efficacy of hemostatic powders in upper gastrointestinal bleeding: A systematic review and meta-analysis. Digestive and Liver Disease. 2019 Dec 1;51(12):1633–40.

238. Alzoubaidi D, Magee C, Gulati S, Haji A, Morris J, Lovat L, et al. Outcomes from an international multicentre registry with gastrointestinal bleeding undergoing endoscopic treatment with Hemospray. Gut. 2017;66(Suppl 2):30–1.

239. Spechler SJ. Barrett 's Esophagus and Esophageal Adenocarcinoma: pathogenesis, diagnosis, and therapy. The medical clinics of north America. 2002;86:1423–45.

240. Fernando HC, Murthy SC, Hofstetter W, Shrager JB, Bridges C, Mitchell JD, et al. The Society of Thoracic Surgeons Practice Guideline Series: Guidelines for the Management of Barrett's Esophagus With High-Grade Dysplasia. Annals of Thoracic Surgery. 2009;87:1993–2002.

241. G. Prasad, K. Wang, N. Buttar, L. Wongkeesong, K. Krishnadath, F. Nichols, L. Lutzke LB. Long-Term Survival Following Endoscopic and Surgical Treatment of High-Grade Dysplasia in Barrett's Esophagus. Gastroenterology. 2007;132:1226–33.

242. Stein HJ, Hutter J, Feith M, von Rahden BHA. Limited Surgical Resection and Jejunal Interposition for Early Adenocarcinoma of the Distal Esophagus. Seminars in Thoracic and Cardiovascular Surgery. 2007;19:72–8.

243. Shimada H, Nabeya Y, Matsubara H, Okazumi SI, Shiratori T, Shimizu T, et al. Prediction of lymph node status in patients with superficial esophageal carcinoma: Analysis of 160 surgically resected cancers. American Journal of Surgery. 2006;191:250–4.

244. Peters FP, Kara MA, Rosmolen WD, Aalders MCG, Ten Kate FJW, Bultje BC, et al.

Endoscopic treatment of high-grade dysplasia and early stage cancer in Barrett's esophagus. Gastrointestinal Endoscopy. 2005;61:506–14.

245. Rice T, Falk G, Achkar E PR. Surgical management of high-grade dysplasia in Barrett's esophagus. American Journal of Gastroenterology. 1993;88:1832–6.

246. Schölvinck DW, Belghazi K, Pouw RE, Curvers WL, Weusten BL a. M, Bergman JJGHM. In vitro assessment of the performance of a new multiband mucosectomy device for endoscopic resection of early upper gastrointestinal neoplasia. Surgical Endoscopy. 2016;30(2):471–9.

247. HRA. HRA Decision Tools [Internet]. Available from: http://www.hra-decisiontools.org.uk/research/docs/DefiningResearchTable_Oct2017-1.pdf. Accessed 21/05/2019

248. Participants in the paris work shop. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon. Gastrointestinal Endoscopy. 2003;58:3–43.

249. Vahabzadeh B, Seetharam AB, Cook MB, Wani S, Rastogi A, Bansal A, et al. Validation of the Prague C&M Criteria for the endoscopic grading of Barrett's esophagus among gastroenterology trainees: A multicenter study. Gastrointestinal Endoscopy. 2015;75(2):236–41.

250. Stanley R Hamilton; Lauri A Aaltonen. WHO classification of Tumours, Pathology and Genetics of Tumours of the Digestive System. IARC Press. 2000.

251. Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, et al. Risk of malignant progression in Barrett's Esophagus patients: Results from a large population-based study. Journal of the National Cancer Institute. 2011;103:1049–57.

252. Femke P. Peters; Mohammed A. Kara; Wouter L. Curvers; Wilda D. Rosmolen; Paul

Fockens; Kausilia K. Krishnadath; Fiebo J.W. ten Kate; Jacques J.G.H.M. Bergman. Multiband mucosectomy for endoscopic resection of Barrett's esophagus: feasibility study with matched historical controls. European Journal of Gastroenterology & Hepatology. 2007;19:311–5.

253. Haidry RJ, Butt MA, Dunn JM, Gupta A, Lipman G, Smart HL, et al. Improvement over time in outcomes for patients undergoing endoscopic therapy for Barrett's oesophagus-related neoplasia: 6-year experience from the first 500 patients treated in the UK patient registry. Gut. 2015;64:1192–9.

254. Matsuzaki K, Nagao S, Kawaguchi A, Miyazaki J, Yoshida Y, Kitagawa Y, et al. Newly designed soft prelooped cap for endoscopic mucosal resection of gastric lesions. Gastrointest Endosc. 2003;57:242–6.

255. Manner H, Pech O, Heldmann Y, May A, Pohl J, Behrens A, et al. Efficacy, safety, and long-term results of endoscopic treatment for early stage adenocarcinoma of the esophagus with low-risk sm1 invasion. Clinical Gastroenterology and Hepatology. 2013;11:630–5.

256. Crane SJ, Locke GR, Harmsen WS, Zinsmeister AR, Romero Y, Talley NJ. Survival trends in patients with gastric and esophageal adenocarcinomas: A population-based study. Mayo Clinic Proceedings. 2008;83:1087–94.

257. Pouw RE, Wirths K, Eisendrath P, Sondermeijer CM, Ten Kate FJ, Fockens P, et al. Efficacy of Radiofrequency Ablation Combined With Endoscopic Resection for Barrett's Esophagus With Early Neoplasia. Clinical Gastroenterology and Hepatology. 2010;8:23–9.

258. Poehlmann A, Kuester D, Malfertheiner P, Guenther T, Roessner A. Inflammation and Barrett's carcinogenesis. Pathology Research and Practice. 2012;208(5):269–80.

259. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. Journal of the National Cancer Institute. 2005;97(2):142–6.

260. Hur C, Miller M, Kong CY, Dowling EC, Nattinger KJ, Dunn M, et al. Trends in esophageal adenocarcinoma incidence and mortality. Cancer. 2013;119(6):1149–58.

261. Lipman G, Haidry R. Endoscopic management of Barrett's and early oesophageal neoplasia. Frontline Gastroenterology. 2017;8(2):138–42.

262. Ganz RA, Utley DS, Stern RA, Jackson J, Batts KP, Termin P. Complete ablation of esophageal epithelium with a balloon-based bipolar electrode: A phased evaluation in the porcine and in the human esophagus. Gastrointestinal Endoscopy. 2004;60(6):1002–10.

263. Haidry RJ, Lipman G, Banks MR, Butt MA, Sehgal V, Graham D, et al. Comparing outcome of radiofrequency ablation in Barrett's with high grade dysplasia and intramucosal carcinoma: A prospective multicenter UK registry. Endoscopy. 2015;47(11):980–7.

264. Sarina Pasricha, William J. Bulsiewicz, Kelly E. Hathorn, Srinadh Komanduri, V. Raman Muthusamy, Richard I. Rothstein, Herbert C. Wolfsen, Charles J. Lightdale, Bergein F. Overholt, Daniel S. Camara, Evan S. Dellon, William D. Lyday, Atilla Ertan, Gary W. NJS. Durability and Predictors of Successful Radiofrequency Ablation for Barrett's Esophagus. Clinical Gastroenterology and Hepatology. 2014;12:1840–7.

265. Krishnamoorthi R, Singh S, Ragunathan K, David A, Wang KK, Iyer PG, et al. Risk of recurrence of Barrett's esophagus after successful endoscopic therapy. Gastrointestinal Endoscopy. 2016;83:1090–106.

266. Friedland S, Triadafilopoulos G. A novel device for ablation of abnormal esophageal

mucosa (with video). Gastrointestinal Endoscopy. 2011;74(1):182–8.

267. Cormac Magee, Charles Gordon, Jason Dunn, Sebastian Zeki, Ian Penman, Robert Willert, Howard Smart, Jacobo Fernandez-Sorto, Krish Ragunath, Mirela Pana, Massimiliano Di Pietro, Narayanasamy Ravi, Allan Morris, Sharmila Subramanian, Pradeep Bhandari, David RH. OUTCOMES OF 360 HALO EXPRESS RADIO-FREQUENCY ABLATION FOR BARRETT'S OESOPHAGUS RELATED NEOPLASIA. Gut. 2018;67-69

268. Inadomi, J.M, Somsouk, M, Madanick, R.D, Thomas, J.P, Shaheen N. A Cost-Utility Analysis of Ablative Therapy for Barrett's Esophagus. Gastroenterology. 2009;136(7):2101–14.

269. Rehan Haidry LL. Long-term durability of radiofrequency ablation for Barrett's-related neoplasia. Current Opinion in Gastroenterology. 2015;31:316–320.

270. C Magee, C Gordon, J Dunn, I Penman, R Willert, H Smart, J Fernandez-Sorto, MDI Pietro, A Moriis, P Dunne, S Subramaniam, K Kandiah, P Bhandari, L Lovat RH. HALO 360 EXPRESS RADIO-FREQUENCY ABLATION IN THE TREATMENT OF BARRETT'S OESOPHAGUS – THE FIRST 100 CASES TREATED IN THE UNITED KINGDOM. BSG Annual Meeting June 2017; 66: 1-288

271. Orman, Eric; Li, Nan; Shaheen N. Efficacy and Durability of Radiofrequency Ablation for Barrett's Esophagus: Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology. 2013;11:1–20.

272. Milli Gupta, Prasad G. Iyer, Lori Lutzke, Emmanuel C. Gorospe, Julian A. Abrams, Gary W. Falk, Gregory G. Ginsberg, Anil K. Rustgi, Charles J. Lightdale TC, Wang, David I. Fudman, John M. Poneros KKW. Recurrence of Esophageal Intestinal Metaplasia After Endoscopic Mucosal Resection and Radiofrequency Ablation of Barrett's Esophagus: Results From a US Multicenter Consortium Recurrence of Barrett's Esophagus after

EMR and RFA. Gastroenterology. 2013;145:79–86.

273. Pech O, Behrens A, May A, Nachbar L, Gossner L, Rabenstein T, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut. 2008;57:1200–6.

274. Cotton CC, Wolf WA, Pasricha S, Li N, Madanick RD, Spacek MB, et al. Recurrent intestinal metaplasia after radiofrequency ablation for Barrett's esophagus: endoscopic findings and anatomic location. Gastrointestinal Endoscopy. 2015;81:1362–9.

275. K Fasanella, K McGrath. The Ice Age reborn? Gastrointestinal Endoscopy. 2019;90:213–4.

276. Kerry B. Dunbar SJS. The Risk of Lymph Node Metastases in Patients with High Grade Dysplasia or Intramucosal Carcinoma in Barrett's Esophagus: A Systematic Review. American Journal of Gastroenterology. 2012; 9(2):87-91

277. Yong ELC, Han XP, Watson DI, Devitt PG, Jamieson GG, Thompson SK. Outcome following surgery for squamous cell carcinoma of the oesophagus. ANZ Journal of Surgery. 2009;79(10):724–8.

278. Kumar Krishnan, John E. Pandolfino, Peter J. Kahrilas, Laurie Keefer, Lubomyr Boris and SK. Increased Risk for Persistent Intestinal Metaplasia in Patients with Barrett's Esophagus and Uncontrolled Reflux Exposure before Radiofrequency Ablation. Gastroenterology. 2012;143:576–81.

279. Komanduri S, Kahrilas PJ, Krishnan K, Mcgorisk T, Bidari K. Recurrence of Barrett ' s Esophagus is Rare Following Endoscopic Eradication Therapy Coupled With Effective Reflux Control. The American journal of gastroenterology. 2017;112:556–66.

280. Gosain S, Mercer K, Twaddell WS, Uradomo L, Greenwald BD. Liquid nitrogen spray cryotherapy in Barrett's esophagus with high-grade dysplasia: Long-term results. Gastrointestinal Endoscopy. 2013;78(2):260–5.

281. Greenwald BD, Dumot JA, Abrams JA, Lightdale CJ, David DS, Nishioka NS, et al. Endoscopic spray cryotherapy for esophageal cancer: safety and efficacy. Gastrointestinal Endoscopy. 2010;71(686–693).

282. van Munster SN, Overwater A, Raicu MGM, Seldenrijk KCA, Nagengast WB, Schoon EJ, et al. A novel cryoballoon ablation system for eradication of dysplastic Barrett's esophagus: a first-in-human feasibility study. Endoscopy. 2020;52(3):193-201

283. Canto M. Cryotherapy for Barrett's Esophagus. Gastrointestinal Endoscopy Clinics of North America. 2017;27:503–13.

284. Truesdale CM, Soulen MC, Clark TWI, Mondschein JI, Wehrenberg-Klee E, Bruce Malkowicz S, et al. Percutaneous computed tomography-guided renal mass radiofrequency ablation versus cryoablation: Doses of sedation medication used. Journal of Vascular and Interventional Radiology. 2013;24(3):347–50.

285. Bastani H, Drca N, Insulander P, Schwieler J, Braunschweig F, Kennebäck G, et al. Cryothermal vs. radiofrequency ablation as atrial flutter therapy: A randomized comparison. Europace. 2013;15(3):420–8.

286. Erinjeri JP, Clark TWI. Cryoablation: Mechanism of action and devices. Journal of Vascular and Interventional Radiology. 2010;21(SUPPL. 8):S187–91.

287. Allaf ME, Varkarakis IM, Bhayani SB, Inagaki T, Kavoussi LR, Solomon SB. Pain control requirements for percutaneous ablation of renal tumors: cryoablation versus radiofrequency ablation--initial observations. Radiology. 2005;237(1):366–70.

288. Wani S, Drahos J, Cook MB, Rastogi A, Bansal A, Yen R, et al. Comparison of

endoscopic therapies and surgical resection in patients with early esophageal cancer: A population-based study. Gastrointestinal Endoscopy. 2014;79(2):224-232.e1.

289. Wolf WA, Pasricha S, Cotton C, Li N, Triadafilopoulos G, Muthusamy VR, et al. Incidence of Esophageal Adenocarcinoma and Causes of Mortality after Radiofrequency Ablation of Barrett's Esophagus. Gastroenterology. 2015;149(7):1752-1761e1.

290. Antony A, Pohanka C, Keogh S, Klein R, Alshelleh M, Lee C, et al. Adherence to quality indicators in endoscopic surveillance of Barrett's esophagus and correlation to dysplasia detection rates. Clinics and Research in Hepatology and Gastroenterology. 2018;1–6.

291. Bennett C, Vakil N, Bergman J, Harrison R, Odze R, Vieth M, et al. Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a delphi process. Gastroenterology. 2012;143(2):336–46.

292. Wani S, Muthusamy VR, Shaheen N, Yadlapati R, Wilson RH, Abrams JA, et al. Development of Quality Indicators for Endoscopic Eradication Therapies (EET) in Barrett's Esophagus: The TREAT-BE (Treatment with Resection and Endoscopic Ablation Techniques for Barrett's Esophagus) Consortium. Gastrointestinal Endoscopy. 2016;83(5):AB129–30.

293. Fitch K, Bernstein SJJ, Aguilar MDD, Burnand B, LaCalle JRR, Lazaro P, et al. The RAND / UCLA Appropriateness Method User's Manual. 2001. 109 p. Published by RAND.

294. Harris PA, Ph D, Taylor R, Thielke R, Ph D, Payne J, et al. Research Electronic Data Capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support Paul. Journal of biomedical Information. 2010;42(2):377–81.

295. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J DSRedcC. The REDCap Consortium: Building an International Community of Software Platform Partners. Journal of biomedical Information. 2019; 12(4):65-79

296. Pasricha S, Cotton C, Hathorn KE, Li N, Bulsiewicz WJ, Wolf A, et al. Effects of Learning Curve on Efficacy of Radiofrequency Ablation for Barrett's Esophagus. Gastroenterology. 2016;149(4):890–6.

297. Abrams J, Kapel R, Lindberg G, Saboorian M, Genta R, Neugut A, et al. Adherence to Biopsy Guidelines for Barrett's Esophagus Surveillance in the Community Setting in the United States. Clinical Gastroenterology and Hepatology. 2011;7(7):736–710.

298. Pohl H, Aschenbeck J, Drossel R, Schröder A, Mayr M, Koch M, et al. Endoscopy in Barrett's oesophagus: Adherence to standards and neoplasia detection in the community practice versus hospital setting. Journal of Internal Medicine. 2008;264(4):370–8.

299. Singh M, Gupta N, Gaddam S, Balasubramanian G, Wani S, Sinh P, et al. Practice patterns among U.S. gastroenterologists regarding endoscopic management of Barrett's esophagus. Gastrointestinal Endoscopy. 2013;78(5):689–95.

300. G. Lipman, A. Gupta, M. Banks, R. Sweis, J. M. Dunn, D. Morris, H. Smart, P. Bhandari, R. P. Willert, G. Fullarton, A. J. Morris, M. Di Pietro, P. Mundre, C. Gordon, I. Penman, H. Barr, P. Patel, P. Boger, N. Kapoor, B. S. Mahon, J. Hoare, R. Narayanasamy LL. Specialist centre patient volume does not impact on endoscopic outcomes for treatment of barrett's dysplasia. Results from the UK RFA registry. In: BSG annual conference. 2016.

301. NICE guideline. Barrett's Oesophagus: Ablative Therapy for the treatment of Barrett's

Oesophagus. National Insititue for Health and Clinical excellence. 2010. https://www.nice.org.uk/guidance/cg106/resources/barretts-oesophagus-ablative-therapy-pdf-35109332329669. Accessed 03/05/2018

302. Sharma P, Dent J, Armstrong D, Bergman JJGHM, Gossner L, Hoshihara Y, et al. The Development and Validation of an Endoscopic Grading System for Barrett's Esophagus: The Prague C & M Criteria. Gastroenterology. 2006;131(5):1392–9.

303. Herrero LA, Curvers WL, Frederike G. I. van Vilsteren, Wolfsen H, Ragunath K, Song5 L-MK, et al. Validation of the Prague C & M classification of Barrett ' s esophagus in clinical practice. Endoscopy. 2013;50:876–82.

304. Ooi J, Wilson P, Walker G, Blaker P, Demartino S, O'Donohue J, et al. Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate. Endoscopy. 2017;49(6):524–8.

305. R. Lambert. Update on the Paris Classification of Superficial Neoplastic Lesions in the Digestive Tract. Endoscopy. 2005;37(6):570–8.

306. Pech O, Gossner L, Manner H, May A, Rabenstein T, Behrens A, et al. Prospective evaluation of the macroscopic types and location of early Barrett ' s neoplasia in 380 lesions. Endoscopy. 2007;51:588–93.

307. Sami SS, Subramanian V, Butt WM, Bejkar G, Coleman J, Mannath J, et al. High definition versus standard definition white light endoscopy for detecting dysplasia in patients with Barrett's esophagus. Diseases of the Esophagus. 2015;28(8):742–9.

308. Qumseya BJ, Wang H, Badie N, Uzomba RN, Parasa S, White DL, et al. Dysplasia and Neoplasia in Patients with Barrett's Esophagus: Meta-Analysis and Systematic Review. Clinical Gastroenterology and Hepatology. 2013;6(244):1–16.

309. Coletta M, Sami SS, Nachiappan A, Fraquelli M, Casazza G, Ragunath K. Acetic acid

chromoendoscopy for the diagnosis of early neoplasia and specialized intestinal metaplasia in Barrett's esophagus: A meta-analysis. Gastrointestinal Endoscopy. 2016;83(1):57–67.

310. Kandiah K, Chedgy FJQ, Subramaniam S, Longcroft-Wheaton G, Bassett P, Repici A, et al. International development and validation of a classification system for the identification of Barrett's neoplasia using acetic acid chromoendoscopy: the Portsmouth acetic acid classification (PREDICT). Gut. 2017 Sep;

311. Sharma P, Bergman JJGHM, Goda K, Kato M, Messmann H, Alsop BR, et al. Development and Validation of a Classification System to Identify High-Grade Dysplasia and Esophageal Adenocarcinoma in Barrett's Esophagus Using Narrow-Band Imaging. Gastroenterology. 2016;150(3):591–8.

312. Lipman G, Bisschops R, Sehgal V, Ortiz-Fernández-Sordo J, Sweis R, Esteban JM, et al. Systematic assessment with I-SCAN magnification endoscopy and acetic acid improves dysplasia detection in patients with Barrett's esophagus. Endoscopy. 2017;49(12):1219–28.

313. Subramaniam S, Kandiah K, Chedgy F, Bhattacharyya R, Basford P, Longcroft-Wheaton G BP. BLUE LIGHT IMAGING FOR BARRETT'S NEOPLASIA CLASSIFICATION (BLINC): THE DEVELOPMENT AND VALIDATION OF A NEW ENDOSCOPIC CLASSIFICATION SYSTEM TO IDENTIFY BARRETT'S NEOPLASIA. 2020;91(2):310-320

314. Qumseya BJ, Brown J, Abraham M, White D, Wolfsen H, Gupta N, et al. Diagnostic performance of EUS in predicting advanced cancer among patients with Barrett's esophagus and high-grade dysplasia/early adenocarcinoma: Systematic review and meta-analysis. Gastrointestinal Endoscopy. 2015;81(4):865–74.

315. May A, Günter E, Roth F, Gossner L, Stolte M, Vieth M, et al. Accuracy of staging in

early oesophageal cancer using high resolution endoscopy and high resolution endosonography: A comparative, prospective, and blinded trial. Gut. 2004;53(5):634–40.

316. Larghi A, Lightdale CJ, Memeo L, Bhagat G, Okpara N, Rotterdam H. EUS followed by EMR for staging of high-grade dysplasia and early cancer in Barrett's esophagus. Gastrointestinal Endoscopy. 2005;62(1):16–23.

317. Thosani N, Singh H, Kapadia A, Ochi N, Lee JH, Ajani J, et al. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: A systematic review and meta-analysis. Gastrointestinal Endoscopy. 2012;75(2):242–53.

318. Liu L, Hofstetter WL, Rashid A, Swisher SG, Correa AM, Ajani J a, et al. Significance of the depth of tumor invasion and lymph node metastasis in superficially invasive (T1) esophageal adenocarcinoma. The American journal of surgical pathology. 2005;29(8):1079–85.

319. Westerterp M, Koppert LB, Buskens CJ, Tilanus HW, Ten Kate FJW, Bergman JJHGM, et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Archiv. 2005;446(5):497–504.

320. Manner H, Pech O, Heldmann Y, May A, Pauthner M, Lorenz D, et al. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submucosal invasion (pT1b sm1) depending on histological risk patterns. Surgical Endoscopy. 2014; 29:1888-96

321. Manner H, Wetzka J, May A, Pauthner M, Pech O, Fisseler-Eckhoff A, Stolte M, Vieth M, Lorenz D EC. Early-stage adenocarcinoma of the esophagus with mid to deep submucosal invasion (pT1b sm2-3): the frequency of lymph-node metastasis depends

on macroscopic and histological risk patterns. Diseases of the Esophagus. 2016;21:1–11.

322. Schölvinck D, Künzli H, Meijer S, Seldenrijk K, van Berge Henegouwen M, Bergman J, et al. Management of patients with T1b esophageal adenocarcinoma: a retrospective cohort study on patient management and risk of metastatic disease. Surgical Endoscopy. 2016;30(9):4102–13.

323. Nicholas J. Shaheen, M.P.H., Prateek Sharma, Bergein F. Overholt, Herbert C. Wolfsen, Richard E. Sampliner, Kenneth K. Wang, Joseph A. Galanko, Mary P. Bronner, John R. Goldblum, Ana E. Bennett, Blair A. Jobe, Glenn M. Eisen, M. Brian Fennerty, John G. Hu VRM, Steven A. Edmundowicz, Stuart J. Spechler, Ali A. Siddiqui, Rhonda F. Souza, Anthony Infantolino, Gary W. Falk, Michael B. Kimmey, Ryan D. Madanick, Amitabh Chak and CJL. Radiofrequency Ablation in Barrett's Esophagus with Dysplasia. The New England Journal of Medicine. 2009;30:2277–88.

324. Haidry RJ, Dunn JM, Butt MA, Burnell MG, Gupta A, Green S, et al. Radiofrequency ablation and endoscopic mucosal resection for dysplastic Barrett's esophagus and early esophageal adenocarcinoma: Outcomes of the UK national halo RFA registry. Gastroenterology. 2013;145(1):87–95.

325. Nicholas J. Shaheen, MD, MPH, Bergein F. Overholt, MD, Richard E. Sampliner, MD, Herbert C. Wolfsen, MD, Kenneth K. Wang, MD, David E. Fleischer, MD, Virender K. Sharma, MD, Glenn M. Eisen, MD, MPH, M. Brian Fennerty, MD, John G. Hunter, MD, Mary P. Bronn M. Durability of Radiofrequency Ablation in Barrett's Esophagus with Dysplasia. Gastroenterology. 2011;141(2):460–8.

326. Van Vilsteren FGI, Phoa KN, Alvarez Herrero L, Pouw RE, Sondermeijer CMT, Visser M, et al. A simplified regimen for focal radiofrequency ablation of Barrett's mucosa: A

randomized multicenter trial comparing two ablation regimens. Gastrointestinal Endoscopy. 2013;78(1):30–8.

327. van Vilsteren FG, Phoa KN, Alvarez Herrero L, Pouw RE, Sondermeijer CM, van Lijnschoten I, Seldenrijk KA, Visser M, Meijer SL, van Berge Henegouwen MI, Weusten BL, Schoon EJ BJ. Circumferential balloon-based radiofrequency ablation of Barrett's esophagus with dysplasia can be simplified, yet efficacy maintained, by omitting the cleaning phase. Clinical Gastroenterology and Hepatology. 2013; 11(5):491-98

328. Pouw RE, Künzli HT, Bisschops R, Sondermeijer CM, Koch AD, Didden P, et al. Simplified versus standard regimen for focal radiofrequency ablation of dysplastic Barrett's oesophagus: a multicentre randomised controlled trial. The Lancet Gastroenterology and Hepatology. 2018;3(8):566–74.

329. Belghazi K, Pouw RE, Koch AD, Weusten BL, Schoon EJ, Curvers W, et al. SELF-SIZING RADIOFREQUENCY ABLATION BALLOON FOR ERADICATION OF BARRETT'S ESOPHAGUS: RESULTS OF AN INTERNATIONAL MULTICENTER RANDOMIZED TRIAL COMPARING THREE DIFFERENT TREATMENT REGIMENS. Gastrointestinal Endoscopy. 2019;90(3):415-423

330. Cotton CC, Wolf WA, Overholt BF, Li N, Lightdale CJ, Wolfsen HC, et al. Late Recurrence of Barrett's Esophagus After Complete Eradication of Intestinal Metaplasia is Rare: Final Report From Ablation in Intestinal Metaplasia Containing Dysplasia Trial. Gastroenterology. 2017;153(3):681-688.e2.

331. Lyday WD, Corbett FS, Kuperman DA, Kalvaria I, Mavrelis PG, Shughoury AB, et al. Radiofrequency ablation of Barrett ' s esophagus : out- comes of 429 patients from a multicenter community practice registry. 2009;32:272–8.

332. Qumseya BJ, Panossian AM, Rizk C, Cangemi DJ, Wolfsen C, Raimondo M, et al.

Survival in esophageal high-grade dysplasia/adenocarcinoma post endoscopic resection. Digestive and Liver Disease. 2013;45(12):1028–33.

333. Qumseya BJ, Wani S, Desai M, Qumseya A, Bain P, Sharma P, et al. Adverse Events After Radiofrequency Ablation in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology. 2016;14(8):1086-1095.e6.

334. Komatsu Y, Landreneau R, Jobe BA. Buried Barrett Metaplasia After Endoluminal Ablation: a Ticking Time Bomb or Much Ado About Nothing? Journal of Gastrointestinal Surgery. 2016; 21:78-90

335. Gray NA, Odze RD, Spechler SJ. Buried metaplasia after endoscopic ablation of barrett's esophagus: A systematic review. American Journal of Gastroenterology. 2011;106:1899–908.

336. Kohoutova D, Haidry R, Banks M, Bown S, Sehgal V, Butt MA, et al. Esophageal neoplasia arising from subsquamous buried glands after an apparently successful photodynamic therapy or radiofrequency ablation for Barrett's associated neoplasia. Scandinavian Journal of Gastroenterology. 2015;50(11):1315–21.

337. Titi M, Overhiser A, Ulusarac O, Falk GW, Chak A, Wang K, et al. Development of subsquamous high-grade dysplasia and adenocarcinoma after successful radiofrequency ablation of Barrett's esophagus. Gastroenterology. 2012;143(3):564-566.e1.

338. Cotton CC, Haidry R, Eluri S, Dellon E, Lovat L, Shaheen N. Evidence-based surveillance intervals following radiofrequency ablation (RFA) of Barrett's esophagus (BE): An analysis of recurrence in the us RFA registry with validation in the UK national halo registry. Gastrointestinal Endoscopy. 2016;83(5):1-8

339. Phoa KN, Pouw RE, Van Vilsteren FGI, Sondermeijer CMT, Ten Kate FJW, Visser M, et al. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: A Netherlands cohort study. Gastroenterology. 2013;145(1):96–104.

340. Cotton CC, Haidry R, Thrift AP, Lovat L, Shaheen NJ. Development of Evidence-Based Surveillance Intervals After Radiofrequency Ablation of Barrett's Esophagus. Gastroenterology. 2018;155(2):316-326.e6.

341. Belghazi K, van Vilsteren FGI, Weusten BLAM, Meijer SL, Bergman JJGHM, Pouw RE. Long-term follow-up results of stepwise radical endoscopic resection for Barrett's esophagus with early neoplasia. Gastrointestinal Endoscopy. 2018;87(1):77–84.

342. Fleischer D, Overholt B, Sharma V, Reymunde A, Kimmey M, Chuttani R, Chang K, Muthasamy R, Lightdale C, Santiago N, Pleskow D, Dean P WK. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. Endoscopy. 2010;42:781-88

343. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ (Clinical research ed). 1995;311(7001):376–80.

344. Everson MA, Ragunath K, Bhandari P, Lovat L, Haidry R. How to Perform a High-Quality Examination in Patients With Barrett's Esophagus. Gastroenterology. 2018;154(5):1222–6.

345. NICE. Epithelial radiofrequency ablation for Barrett 's oesophagus. 2010. https://www.nice.org.uk/guidance/IPG344. Accessed 13/05/2018

346. Cahyadi O, Bauder M, Meier B, Caca K, Schmidt A. Effectiveness of TC-325 (Hemospray) for treatment of diffuse or refractory upper gastrointestinal bleeding – a single center experience. Endoscopy International Open. 2017;05(11):E1159–64.

347. Shi K, Shen Z, Zhu G, Meng F, Gu M, Ji F. Systematic review with network meta-analysis: Dual therapy for high-risk bleeding peptic ulcers. BMC Gastroenterology. 2017;17(1):1–8.

348. Lau JYW, Barkun A, Fan DM, Kuipers EJ, Yang YS, Chan FKL. Challenges in the management of acute peptic ulcer bleeding. The Lancet. 2013;381(9882):2033–43.

349. Hemospray® Endoscopic Hemostat [Internet]. Cook Medical. [cited 2018 Jun 12]. Available from: https://www.cookmedical.com/products/35a4a7f2-867b-4c81-a983-44ea06277852/

350. Laine L, Spiegel B, Rostom A, Moayyedi P, Kuipers EJ, Bardou M, et al. Methodology for randomized trials of patients with nonvariceal upper gastrointestinal bleeding: Recommendations from an international consensus conference. American Journal of Gastroenterology. 2010;105(3):540–50.

351. Pittayanon R, Rerknimitr R, Barkun A. Prognostic factors affecting outcomes in patients with malignant GI bleeding treated with a novel endoscopically delivered hemostatic powder. Gastrointestinal Endoscopy. 2017;20:1–9.

352. Hagel AF, Albrecht H, Nagel A, Vitali F, Vetter M, Dauth C, et al. The Application of Hemospray in Gastrointestinal Bleeding during Emergency Endoscopy. Gastroenterology Research and Practice. 2017; 18:34-39

353. Barkun AN, Adam V, Lu Y, Chen YI, Martel M. Using Hemospray Improves the Cost-effectiveness Ratio in the Management of Upper Gastrointestinal Nonvariceal Bleeding. Journal of Clinical Gastroenterology. 2018;52(1):36–44.

354. Hearnshaw SA, Logan RFA, Lowe D, Travis SPL, Murphy MF, Palmer KR. Use of endoscopy for management of acute upper gastrointestinal bleeding in the UK: Results of a nationwide audit. Gut. 2010;59(8):1022–9.

355. Laine L, Jensen DM. Management of patients with ulcer bleeding. American Journal of Gastroenterology. 2012;107(3):345–60.

356. Meng ZW, Marr KJ, Mohamed R, James PD. Long-Term Effectiveness, Safety and Mortality Associated with the Use of TC-325 for Malignancy-Related Upper Gastrointestinal Bleeds: A Multicentre Retrospective Study. Journal of the Canadian Association of Gastroenterology. 2018;(July):12:1–7.

357. Alzoubaidi D, Lovat LB, Haidry R. Management of non-variceal upper gastrointestinal bleeding : where are we in 2018 ? Frontline Gastroenterology. 2018;0:1–8.

358. Shaheen NJ, Falk GW, Iyer PG GL. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. American Journal of Gastroenterology. 2016;111(7):98-106

359. Belghazi K, Schölvinck DW, van Berge Henegouwen MI, Gisbertz SS, Weusten BL, Meijer SL, et al. Results of a two-phased clinical study evaluating a new multiband mucosectomy device for early Barrett's neoplasia: a randomized pre-esophagectomy trial and a pilot therapeutic pilot study. Surgical endoscopy. 2018/11/19. 2019 Sep;33(9):2864–72.

360. Westerveld DR, Nguyen K, Banerjee D, Jacobs C, Kadle N, Draganov P V, et al. Safety and effectiveness of balloon cryoablation for treatment of Barrett's associated neoplasia: systematic review and meta-analysis. Endoscopy international open. 2020/01/22. 2020 Feb;8(2):E172–8.

361. Alzoubaidi D, Hussein M, Rusu R, Napier D, Dixon S, Rey JW, et al. Outcomes from an international multicenter registry of patients with acute gastrointestinal bleeding undergoing endoscopic treatment with Hemospray. Digestive Endoscopy. 2020;32(1):96–105.

362. Wani S, Muthusamy VR, Shaheen NJ, Yadlapati R. Development of quality indicators

for endoscopic eradication therapies in Barrett ' s esophagus : the TREAT-BE (Treatment with Resection and Endoscopic Ablation Techniques for Barrett ' s Esophagus) Consortium. Am J Gasterol. 2017:112(7):1032-1048

363. Pasricha S, Cotton C, Hathorn KE, Li N, Bulsiewicz WJ, Wolf WA, et al. Effects of the Learning Curve on Efficacy of Radiofrequency Ablation for Barrett's Esophagus. Gastroenterology. 2015/06/25. 2015 Oct;149(4):890-6.e2.

364. Van Vilsteren FGI, Pouw RE, Herrero LA, Peters FP, Bisschops R, Houben M, et al. Learning to perform endoscopic resection of esophageal neoplasia is associated with significant complications even within a structured training program. Endoscopy. 2012;44(1):4–14.