Evaluating new technologies in the assessment and endoscopic management of Barrett’s Oesophagus

by

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A thesis submitted in total fulfillment of the requirements for the degree of Doctor of Medicine

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February 2012
Abstract

The assessment and treatment of dysplastic Barrett’s oesophagus (BO) has evolved dramatically over the last decade. Recently, advances in endoscopic imaging techniques have enabled more accurate identification of subtle mucosal abnormalities and provide improved capacity to identify early cancers. This combined with advances in endoscopic resection and ablation techniques have resulted in excellent outcomes for individuals with high grade dysplasia (HGD) and intramucosal cancer (IMC) treated with endoscopic means alone.

The aim of this work was to assess to efficacy and safety of these new technologies in the assessment and management of dysplastic BO.

The first study assessed the accuracy of predicting HGD and IMC in mucosa predicted as being non dysplastic vs. dysplastic by high definition white light (HD WLE), Narrow band imaging (NBI) and confocal endomicroscopy (CEM). A prospective cohort study of 50 consecutive patients was performed. A prediction of likely histology was made for each biopsy point (4 quadrant every 1cm and any visible mucosal abnormality) firstly with HD WLE, then with NBI and finally CEM. 1190 individual biopsy points have been assessed (39 HGD and 52 IMC). For the detection of HGD/IMC the sensitivity, specificity and accuracy for HD WLE were 79.1%, 83.1% and 82.8%, for NBI were 89.0%, 80.1% and 81.4% and for CEM were 75.7%, 80.0% and 79.9% respectively. All mucosal points with IMC and all patients with HGD were detected by targeted biopsies guided by HD WLE and NBI without the need for random Seattle protocol biopsies.

We then assessed the impact that endoscopic mucosal resection (EMR) had on the optimal staging and treatment of dysplastic BO. 71 consecutive patients referred for endoscopic management of dysplastic BO were included in the study. 48 patients had an EMR performed on a visible mucosal abnormality, resulting in upstaging in 20 patients (P= 0.0498). 33/48 patients had a lesion missed by their referring doctor, including 9 cancers. In 24/48 (50%) patients EMR was considered necessary for optimal treatment (12 patients with sub-mucosal invasion, were unsuitable for endoscopic therapy, 12 patients with IMC into the muscularis mucosa or lamina propria may not have been adequately treated by HALO radiofrequency ablation alone.) These results demonstrate
the importance of EMR and secondly that a large proportion lesions are not identified by endoscopists in community practice.

We finally assessed the rate of complete remission of intestinal metaplasia (CR-IM) at 12 months post commencement of HALO radiofrequency ablation (RFA) and secondly looked at factors that may predict resistance to HALO RFA. 92 patients at the time of analysis had been referred for endoscopic treatment of dysplastic BO of which 31 patients had reached the 12 month assessment. CR-IM was achieved in 25/31 patients (80%) within 12 months of the first HALO RFA treatment. A median of 3 therapeutic procedures (1 EMR and 2 HALO ablations sessions) were required to achieve CR-IM. Longer BO segments, median 9cm (range 5-14) predict failure to achieve CR-IM at 12 months (p = 0.04). Our study confirmed good success rates of combination endoscopic therapy comparable with other published studies.
Declaration

This is to certify that

1. The thesis comprises only my original work towards the Doctor of Medicine except where indicated in the Preface
2. Due acknowledgement has been made in the text to all other material used,
3. The thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

.............................

Chatura S Jayasekera
Preface

I have had the leading role in collaboration with my supervisors in conception, design and coordination of all the work presented, as well as analysing the data and writing up the results. The study of endoscopic assessment of Barrett’s oesophagus and the study assessing treatment outcomes required the expertise of other endoscopists. Dr Andrew Taylor and I shared many of the assessment and therapeutic endoscopic procedures performed throughout the study. Prof. Finlay Macrae and I shared many of the confocal endomicroscopy procedures. Dr Alex Thompson assisted in the statistical analysis of the data presented.

Publications arising from this work are:


There are two further papers that have been submitted to international gastroenterological journals that are currently in the process of review at the time of this thesis submission.

This thesis contains no material which has been accepted for any other degree in any university. To the best of my knowledge and belief, this thesis contains no material previously written or published by any other person, except where due reference is given in the text. This thesis is not greater than 100,000 words in length.

Chatura S Jayasekera

February 2012
Acknowledgements

I feel fortunate to have been given the opportunity to undertake this Doctor of Medicine at St Vincent’s Hospital, where I had already spent many years during my pre clinical and basic physician training.

There are many people who have helped me throughout the last two years. To my supervisor, Paul Desmond, who having done this so many times before was able to chart a clear timetable during our regular meetings and always provide insightful feedback whenever a new draft was put on his desk for review. I also enjoyed and gained very much from our Tuesday morning ERCP list.

To Andrew Taylor my co-supervisor. Thank you for a great two years. From our first meetings at your home formulating the study to our last endoscopy list we have worked seamlessly as a team. I will always be grateful for the skills both endoscopic and clinical that I have gained during the project, which now have enabled me to continue working in this field. I hope very much that our friendship and collaboration will continue in the future.

To Alex Thompson thank you for your help with the statistical analysis over a busy Christmas period. Thank you to Richard Williams for his expert pathological opinion and enthusiasm. Thank you to Georgina Cameron for her help with data collection and continuing to drive the work. Thank you to Finlay Macrae for his involvement with the confocal procedures and for involving me at Royal Melbourne. A big thank you to the endoscopy staff, in particular Sally, Fumi and David for their patience with our Monday morning mapping sessions.

Finally to my wonderful wife Lelani and children, Indiana and Luca for their support, patience and necessary distraction needed to enjoy the journey.
# Table of contents

## Chapter 1 .......................................................................................................................... 12

### Literature review: Barrett’s oesophagus ................................................................. 12

1.1 Definition ......................................................................................................................... 12
1.2 Historical evolution .......................................................................................................... 12
1.3 Epidemiology of Barrett’s oesophagus .......................................................................... 13
1.4 Histopathology of Barrett’s oesophagus ..................................................................... 14
   1.4.1 Columnar epithelium ................................................................................................. 14
   1.4.2 Gastric cardia ............................................................................................................ 14
   1.4.3 Intestinal metaplasia ................................................................................................. 15
   4.4 Indefinite for dysplasia ............................................................................................... 18
   1.4.5 Low grade dysplasia ............................................................................................... 18
   1.4.6 High grade dysplasia .............................................................................................. 19
   1.4.7 Intramucosal cancer ................................................................................................. 20
1.5 Aetiology of Barrett’s oesophagus ............................................................................... 20
   1.5.1 Gastro oesophageal reflux disease ...................................................................... 20
1.6 Pathogenesis of Barrett’s Oesophagus ....................................................................... 21
   1.6.1 Molecular pathogenesis ......................................................................................... 21
   1.6.2 The development of metaplasia .............................................................................. 22
   1.6.3 Evidence for acid and bile as pathogenic factors ..................................................... 22
   1.6.4 Molecular changes in metaplasia ........................................................................... 23
1.7 Neoplastic progression of Barrett’s oesophagus ......................................................... 25
   1.7.1 Genetic alterations .................................................................................................. 25
   1.7.2 Inactivation of tumour suppressor genes ................................................................. 25
   1.7.3 Oncogene overactivity ............................................................................................ 27
   1.7.4 Avoidance of Apoptosis ......................................................................................... 28
   1.7.5 Chromosomal abnormalities ............................................................................... 28
   1.7.6 Biomarker panels .................................................................................................. 29
1.8 Risk factors for development of oesophageal adenocarcinoma ................................ 31
   1.8.1 Degree of dysplasia ............................................................................................... 32
   1.8.2 Length of the Barrett’s segment ............................................................................. 34
Chapter 2 – Sequential High Definition White Light and Narrow Band Imaging Enable a Targeted Biopsy Protocol in Dysplastic Barrett’s Oesophagus

2.1 Introduction ................................................................................................................. 87
2.2 My role in the study ...................................................................................................... 88
2.3 Aims .............................................................................................................................. 88
2.4 Materials and Methods ............................................................................................ 89
   2.4.1 Patient Selection .................................................................................................. 89
   2.4.2 Referral forms ...................................................................................................... 89
   2.4.3 Details of endoscopic evaluation ......................................................................... 90
   2.4.4 Equipment ............................................................................................................ 90
   2.4.5 Mapping protocol .............................................................................................. 90
   2.4.7 Data storage and statistical analysis .................................................................... 93
   2.4.8 Economic analysis ............................................................................................. 94
   2.4.9 Ethics committee approval .................................................................................. 94
2.5 Results ......................................................................................................................... 94
   2.5.1 Patient characteristics ....................................................................................... 94
   2.5.2 The accuracy of the three modalities in predicting histology within the Barrett’s segment .................................................................................................................. 96
   2.5.3 Accuracy in diagnosing high grade dysplasia / intramucosal cancer ................. 96
   2.5.4 Are they complementary modalities ..................................................................... 99
   2.5.5 Efficacy and cost effectiveness of targeted biopsy protocol .............................. 100
   2.5.6 The cost of confocal ........................................................................................... 101
2.6 Discussion .................................................................................................................. 102
   2.6.1 Are advanced imaging modalities effective in predicting underlying histology ..... 103
   2.6.2 Targeted biopsy protocol ................................................................................... 104
   2.6.3 Role of confocal endomicroscopy ........................................................................ 106
   2.6.4 What is the optimal protocol considering time and cost ..................................... 107
   2.6.5 Limitations ........................................................................................................... 107
   2.6.6 Future of Barrett’s assessment ............................................................................ 108

Chapter 3 - Visible Mucosal Abnormalities Harbouring Cancer On EMR Are Commonly Identified In Individuals Referred To A
Specialist Centre For Treatment Of Dysplastic Barrett’s Oesophagus, But Frequently Missed By Referring Endoscopists

3.1 Introduction ................................................................................................................. 110
3.2 Aims ............................................................................................................................. 111
3.3 Materials and Methods ............................................................................................... 112
  3.3.1 Patient Selection .................................................................................................... 112
  3.3.2 Details of endoscopic therapy ................................................................................. 112
  3.3.3 Medication .............................................................................................................. 115
  3.3.4 Histological assessment ......................................................................................... 115
  3.3.5 Database ................................................................................................................ 115
  3.3.6 Ethics committee approval ..................................................................................... 115
  3.3.7 Statistical analysis ................................................................................................ 115
3.4 Results .......................................................................................................................... 116
  3.4.1 Patient characteristics ............................................................................................ 116
  3.4.2 Procedural details at referral ............................................................................... 116
  3.4.3 Lesion characteristics ............................................................................................ 117
  3.4.4 Examples of Visible Mucosal Abnormalities according to Paris classification: ...... 119
  3.4.5 EMR characteristics ............................................................................................ 122
  3.4.6 Role of EMR in staging .......................................................................................... 123
  3.4.7 Role of EMR in optimal treatment ........................................................................ 124
  3.4.8 Assessment of safety following EMR .................................................................... 125
3.5 Discussion ..................................................................................................................... 126
  3.5.1 Importance of EMR for accurate staging ............................................................... 126
  3.5.2 Importance of EMR in addition to HALO RFA, for optimal treatment of intramucosal cancer .................................................................................................................... 128
  3.5.3 Safety of EMR ....................................................................................................... 128
3.6 Conclusions .................................................................................................................. 129

Chapter 4: Combination Endoscopic Therapy For Dysplastic Barrett’s Oesophagus - Overall Results

4.1 Introduction .................................................................................................................. 131
4.2 Aims ............................................................................................................................. 132
4.3 Materials and Methods .............................................................................................. 132
  4.3.1 Patient Selection .................................................................................................... 132
4.3.2 Referral forms ........................................................................................................... 133
4.3.3 Details of endoscopic evaluation ............................................................................ 133
4.3.4 Details of endoscopic therapy .................................................................................. 135
4.3.5 Medication .................................................................................................................. 136
4.3.6 Database .................................................................................................................... 137
4.3.7 Ethics committee approval ........................................................................................ 137
4.3.8 Histological assessment ........................................................................................... 137
4.3.9 Statistical analysis ..................................................................................................... 137
4.4 Results ........................................................................................................................... 138
4.4.1 Recruitment ............................................................................................................... 138
4.4.2 Patient characteristics ............................................................................................... 139
4.4.3 Completed treatment at 12 months ......................................................................... 141
4.4.4 Incomplete treatment at 12 months ....................................................................... 142
4.4.5 Yet to reach 12 months of treatment ..................................................................... 143
4.4.6 Staging investigations ............................................................................................... 143
4.4.7 Surface area treated with each ablation session ...................................................... 143
4.5 Assessment of safety following HALO radiofrequency ablation ................................. 145
4.5.1 Methods ................................................................................................................. 145
4.5.2 Results ..................................................................................................................... 146
4.6 Discussion ..................................................................................................................... 148
4.6.1 Interpretation of results ............................................................................................ 149
4.6.2 Patients still within treatment protocol .................................................................. 149
4.6.3 Staging investigations in patients with IMC ............................................................ 150
4.6.4 Side effects profile of HALO RFA ........................................................................ 150
4.7 Conclusion - The future of endoscopic therapy for dysplastic Barrett’s oesophagus .... 151

Bibliography ........................................................................................................................ 155

Appendices ............................................................................................................................. 181

Appendix 1 - Forms used to refer patients into Barrett’s program .................................. 181
Appendix 2 – Equations and Excel tables used in Chapter 2 .............................................. 184
Appendix 3 – Forms used in Chapter 4 .............................................................................. 191
Appendix 4 - Published papers ............................................................................................ 193
Chapter 1

Literature review: Barrett’s oesophagus

The aim of this chapter is to provide a comprehensive background to the central topic of my thesis - Barrett’s oesophagus.

1.1 Definition

Barrett’s oesophagus (BO) is defined as displacement of the squamocolumnar junction proximal to the gastrooesophageal junction correlating with the histological finding of intestinal metaplasia (Wang and Sampliner 2008; Sharma 2009). Despite broad agreement of the endoscopic parameters that define BO, the histological definition does not have the same consensus. The U.S. definition and that held by many centres worldwide requires the histological presence of intestinal metaplasia, which is columnar epithelium containing goblet cells (Spechler 2002). This is in contrast to the British Society of Gastroenterology who published their most recent guidelines in 2006 stating, the presence of columnar mucosa is adequate for the diagnosis of BO without the need of goblet cells (Playford 2006).

1.2 Historical evolution

Barrett’s oesophagus is named after Norman Rupert Barrett, an Australian born thoracic surgeon who worked at St. Thomas’ Hospital in London. Norman Barrett was an influential surgeon who was the editor of the journal Thorax for a number of years. Despite being credited for the discovery of this new pathological disease, he was neither the first to describe the columnar lined oesophagus, nor was he correct in describing the pathogenesis of this disease. A pathologist Wilder Tileston in 1906 was the first to describe the columnar-lined oesophagus in 3 patients which he attributed to gastro-oesophageal reflux (Spechler, Fitzgerald et al. 2010). In Norman Barrett’s publication, he thought the columnar-lined viscous was a tubular segment of stomach that had been tethered within the chest by a congenitally short oesophagus (Barrett 1950). In 1951,
Bosher and Taylor were the first to describe intestinal metaplasia (goblet cells) within the columnar lined oesophagus (Bosher and Taylor 1951). The differentiation of various types of columnar mucosa became apparent in 1976 when Paull et al reported 3 types of columnar epithelia lining the distal oesophagus: (1) a junctional (cardia-type) epithelium, (2) a gastric fundic-type epithelium, and (3) intestinal-type metaplasia, which the authors called specialized columnar epithelium, with prominent goblet cells (Paull, Trier et al. 1976).

### 1.3 Epidemiology of Barrett’s oesophagus

The prevalence of BO in the adult population is 0.4% to 1.6%. These estimates are derived from two of the largest studies, the first was a large Swedish study where a random sample of 1000 patients underwent gastroscopy to determine the prevalence of BO, they found a prevalence of 1.6% (Ronkainen, Aro et al. 2005). The second study by Cameron et al. included both clinical and autopsy diagnoses from the Olmstead County and found a prevalence of 0.4% for the diagnosis of BO (Cameron, Zinsmeister et al. 1990).

However other publications have found a considerably higher prevalence of BO, up to 25% (Gerson, Shetler et al. 2002). This range likely relates to the population tested and their underlying risk factor profile. A study by Rex et al. in which a gastroscopy was performed to assess the prevalence of BO in asymptomatic patients undergoing screening colonoscopy for polyp detection. This study detected BO in 6.8% of the 961 patients undergoing colonoscopy. This cohort of patients were predominantly older, white males which constitute the highest risk group for the development of BO (Rex, Cummings et al. 2003). In patients with chronic gastro-oesophageal reflux disease, the prevalence of BO increases to between 5-15% (Winters, Spurling et al. 1987; Corder, Jones et al. 1996).

Not only is there a significant burden of BO within the general population, the incidence of BO is rising. An Australian retrospective prevalence study conducted in Brisbane showed that the endoscopic frequency of BO increased from 2.9 to 18.9 per 1,000 endoscopies (p<0.001) comparing years 1990 to 2002 (Kendall and Whiteman 2006). The increased incidence of BO was independent of the increased number of
gastroscopies performed. A prospective cohort study showed an increased rate of BO detection from 19.8/1000 endoscopies to 40.5/1000 endoscopies over a 5 year period (van Soest, Dieleman et al. 2005). These studies may reflect a true rise in incidence within the populations studied or instead be in part attributed to the increased awareness of BO by endoscopists.

1.4 Histopathology of Barrett’s oesophagus

Intestinal metaplasia of the normal squamous mucosa is the first step in the evolution to adenocarcinoma. A large multicentre cohort study found 0.5%/year rate of progression from non dysplastic BO to adenocarcinoma (Sharma, Falk et al. 2006) and in many studies oesophagectomy specimens containing adenocarcinoma have adjacent areas with varying degrees of dysplasia and intestinal metaplasia. Hence the concept that adenocarcinoma arises out of intestinal metaplasia (Haggitt, Tryzelaar et al. 1978; Skinner, Walther et al. 1983; Smith, Hamilton et al. 1984; Rosenberg, Budev et al. 1985; Paraf, Flejou et al. 1995).

A study looking at the thickness of BO vs. normal squamous mucosa in 200 patients found Barrett’s columnar epithelium is minimally thicker (mean 0.50mm; range 0.39 to 0.59 mm) than normal squamous epithelium (0.49mm; range 0.42 to 0.58 mm). (Ackroyd, Brown et al. 1999) However this difference is not clinically relevant as it does not influence choice nor efficacy of treatment.

1.4.1 Columnar epithelium

In 1976 Paull et al. showed that the distal oesophagus can harbour 3 types of columnar epithelium – cardia type, fundic type and intestinal metaplasia (Paull, Trier et al. 1976).

1.4.2 Gastric cardia

The gastric cardia is the small area of the stomach that lies below the oesophagus at the gastro-oesophageal junction. The precise location of the cardia is variable depending on the modality used to define the gastro-oesophageal junction. A study comparing the manometric and endoscopic location of the gastro-oesophageal junction in 192 patients with repeat endoscopies 6 weeks apart found a 10% difference in the location at the
second endoscopy by both modalities (Kim, Waring et al. 1994). These differences are likely related to change in position with respiration and peristalsis.

The gastric cardia consists of loosely packed mucous glands with scant functional gastric cells. This is in contrast to the fundic type gastric epithelium which has tightly packed glands with many functional gastric cells (e.g. Parietal cells) (Marsman, Tytgat et al. 2005). Therefore it is important to correlate the location of the biopsy with endoscopic assessment of the gastro-oesophageal junction as all these cell types can be present in the oesophagus.

The size of cardiac mucosa tends to increase with age, and displays marked individual variability influenced by such factors as acid exposure (Chandrasoma, Der et al. 2000; Chandrasoma, Lokuhetty et al. 2000). Intestinal metaplasia of the cardia compared to Barrett’s intestinal metaplasia of the distal oesophagus has a different pathogenesis and natural history, with differing risks of dysplasia and cancer progression. Intestinal metaplasia of the gastric cardia occurs as a result of H. pylori infection and represents a columnar to columnar metaplastic reaction. This is in contrast to Barrett’s intestinal metaplasia of the distal oesophagus which occurs as a result of acid exposure and represents a squamous to columnar cell transition (Odze 2005). A prospective study by Sharma in 2000, found the time to dysplasia progression was significantly longer for intestinal metaplasia of the cardia vs. intestinal metaplasia within BO (Sharma, Weston et al. 2000). Therefore it is not currently recommended that patients with intestinal metaplasia of the cardia undergo endoscopic surveillance.

1.4.3 Intestinal metaplasia

Intestinal metaplasia refers to the presence of goblet cells within columnar epithelium (Yerian 2009). Goblet cells are epithelial cells that have a goblet shaped appearance and are distended with acid mucin filled cytoplasm (Goldblum 2003).
Intestinal metaplasia

The goblet cells can be readily detected on standard haematoxylin-eosin stains, however specialised histochemical stains better identify true goblet cells, which are based on mucin content. Alcian blue at pH 2.5 stain the sialomucins and sulphated mucins within goblet cells (Haggitt, Reid et al. 1988).

Picture of Ab+ve Goblet Cell

The goblet cells are intensely Alcian blue positive. The periodic acid-Schiff portion of the stain outlines a primitive luminal brush border.

The neutral mucins of the columnar cells do not stain with alcian blue, instead they stain strongly positive with the periodic-acid Schiff stain (PAS) (Yerian 2009). Therefore, the
presence of both cell types can be seen within a Barrett’s segment, described as incomplete intestinal metaplasia.

**PAS and AB +ve columnar cell**

![Image of Alcian blue and periodic acid-Schiff stain](image)

Alcian blue and periodic acid-Schiff stain of a segment of Barrett's oesophagus. The goblet cells are intensely Alcian blue positive because of the presence of acid mucin. The cells between the goblet cells are periodic acid-Schiff positive because of the presence of neutral mucin.

The gastric foveolar cells can sometimes be confused with goblet cells as they all contain some acid mucins therefore they will stain weakly with alcian blue. These cells are referred to as “pseudogoblet cells” (Yerian 2009)

It is therefore critical to correctly identify those patients who truly have intestinal metaplasia related to BO – due to the implications for surveillance and cancer risk vs. those with columnar mucosa. This fact was highlighted in a study looking at a community based pathology diagnosis of BO. Gastric metaplasia without intestinal metaplasia was misdiagnosed as Barrett’s in 38% of patients. The misdiagnosis was mainly due to the incorrect characterisation of the pseudogoblet cells (Alikhan, Rex et al. 1999). Despite these findings the American Gastroenterological Association concluded that special histochemical stains are not routinely required to diagnose intestinal metaplasia however may be used when goblet cells are scant or there are many pseudogoblet cells to increase diagnostic certainty (Sharma, McQuaid et al. 2004).
To add to the diagnostic confusion the finding of intestinal metaplasia at the gastro-oesophageal junction is seen in 9% to 36% of patients without endoscopic evidence of BO (Johnston, Hammond et al. 1996; Nandurkar, Talley et al. 1997; Trudgill, Suvarna et al. 1997). It is important that these histological changes are correlated with endoscopic evidence to be called BO (Wang and Sampliner 2008).

4.4 Indefinite for dysplasia

The presence of inflammation and ulceration of the distal oesophageal mucosa secondary to gastro-oesophageal reflux disease can often accompany the finding of BO. These processes result in regenerative changes that can mimic the findings of dysplasia. Therefore caution should be exercised when making the diagnosis of dysplasia in the presence of inflammation and instead indefinite for dysplasia is a more appropriate label (Goldblum 2003). These patients should have six weeks of acid suppression prior to re-biopsy.

The other situation where indefinite for dysplasia is an appropriate diagnosis occurs when glands at the base of BO show atypia – (nuclear enlargement, slight hyperchromasia and stratification, and increased mitotic activity) as these features are not diagnostic for dysplasia without surface involvement (Goldblum 2003; Yerian 2009).

1.4.5 Low grade dysplasia

The histological features of low grade dysplasia (LGD) include generally preserved crypt architecture. The nuclei tend to show variable hyperchromasia, crowding and irregular contours with the atypical nuclei limited to the basal half of the crypts. Dystrophic goblet cells may be seen, although typically goblet cell density is reduced in dysplastic foci (Goldblum 2003).
Low grade dysplasia

1.4.6 High grade dysplasia

In high grade dysplasia (HGD) the degree of cytologic atypia and architectural complexity is more pronounced than in LGD (Yerian 2009). The differentiation of these two grades of dysplasia can be challenging. The crypt architecture is more complex than with LGD with varying crypt patterns including villiform and branched. The nuclear changes are more extreme with more pleomorphism and hyperchromatism than is seen in LGD, and there often is nuclear stratification to the crypt luminal surface (Goldblum 2003).

High grade dysplasia
In HGD the neoplastic glands are irregularly shaped and are more crowded, separated only by thin strands of fibrovascular tissue

1.4.7 Intramucosal cancer

Intramucosal cancer refers to the presence of neoplastic cells that have penetrated through the basement membrane and infiltrate into the lamina propria, typically as single cells or in small clusters (Goldblum 2003). These neoplastic cells may be found within the muscularis mucosae but do not penetrate into the submucosa.

Intramucosal cancer

1.5 Aetiology of Barrett’s oesophagus

Gastro-oesophageal reflux is the only proposed risk factor that exists for the development of BO.

1.5.1 Gastro oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) may be defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the
oesophagus (DeVault and Castell 1999). It is difficult to accurately estimate prevalence of GORD. 10-20% of people describe symptoms weekly (Locke, Talley et al. 1997). Patients with chronic GORD are at increased risk for the development of BO. Studies have found 5-15% of patients with chronic GORD harbour BO (Winters, Spurling et al. 1987; Corder, Jones et al. 1996). Another study found that 12% of patients with erosive oesophagitis had BO at repeat endoscopy after acid suppression at a median of 11 weeks follow up (Hanna, Rastogi et al. 2006).

1.6 Pathogenesis of Barrett's Oesophagus

1.6.1 Molecular pathogenesis

The progression from normal oesophageal squamous mucosa to the intestinal metaplasia of BO is still not completely characterised. Furthermore, the neoplastic progression from non dysplastic BO through to adenocarcinoma is also poorly understood. Unlike the well understood adenoma carcinoma sequence in the development of colorectal cancer, considerable genetic heterogeneity exists in the development and progression of BO with the function of many genetic and epigenetic factors still ambiguous in relation to disease pathogenesis (Spechler, Fitzgerald et al. 2010).

For many years much research has been invested in the search for molecular markers critical in the pathogenesis of BO. It is hoped that these markers would better risk stratify which patients would progress to adenocarcinoma vs. those whose disease would remain quiescent. Furthermore, these markers could be used to assess the mucosa post endoscopic treatment of BO in order to stratify which patients may be at risk of recurrence and hence guide surveillance frequency. Many markers have been identified, however the promise of molecular markers has yet to be realised in clinical practice (Spechler, Fitzgerald et al. 2010).

Clonal evolution in BO is a concept that assumes that it is the accumulation of genetic mutations that drives the neoplastic progression. However an alternate concept is the presence of a cancer stem cell, which sustains tumour growth whereas most cells in the tumour have no capacity for renewal (Hormi-Carver and Souza 2009).
1.6.2 The development of metaplasia

Metaplasia is defined as the replacement of one adult cell type with another and is the first step in the progression to dysplasia and ultimately cancer (Spechler 2004). The resultant metaplastic tissue is more resistant to damage than the squamous epithelium that it has replaced. However, the precursor cell from which intestinal metaplasia in BO develops has yet to be identified.

The currently accepted hypothesis is that abnormal cellular differentiation occurs due to gastric acid and bile reflux that gain exposure to the multipotential stem cells in the basal layers or the ducts of submucosal glands via damage to the tight junctions between epithelial cells (Jankowski, Wright et al. 1999; Glickman, Chen et al. 2001; Pera 2002; Seery 2002). An alternate hypothesis derived from a rat model, found that circulating bone marrow stem cells have been identified as possible progenitor cell for BO (Sarosi, Brown et al. 2008).

P63, a protein that regulates differentiation in epithelial tissue to squamous epithelium, may also be implicated in the pathogenesis of metaplasia within the distal oesophagus. Two studies have supported this hypothesis. Firstly, an ex vivo study of oesophageal cell culture showed that on exposure to acid and bile salts, P63 was down regulated (Roman, Petre et al. 2007). Secondly, a mouse model with p63 (-/-) mice resulted in the development of a columnar oesophagus (Daniely, Liao et al. 2004).

1.6.3 Evidence for acid and bile as pathogenic factors

Acid and bile induced injury drive the development of metaplasia in BO. A study looking at the frequency and severity of acid and bile reflux showed that both acid and bile reflux show a graded increase in severity across the GORD spectrum (Vaezi and Richter 1996). However acid suppression has not definitely been shown to decrease cancer progression (Barbera and Fitzgerald 2009).
There is evidence from both animal and human models that duodenal contents (bile) play an important role in the development of BO. In a rat model where the oesophagus was joined to the duodenum found that columnar epithelium developed in the lower oesophagus exposed to duodenal contents without acid exposure (Seto and Kobori 1993). Furthermore, an ex-vivo study showed that bile acids in the presence of low pH <4 can induce oxidative DNA stress which may be a co-factor in the development of BO (Dvorak, Payne et al. 2007). Finally in animal and ex-vivo human studies, the in the presence of duodenal contents has been shown to up regulate the expression of CDX2 a key factor in the development of BO (Eda, Osawa et al. 2003; Hu, Williams et al. 2007; Pera, de Bolos et al. 2007).

1.6.4 Molecular changes in metaplasia

Homeotic genes are responsible for developmental patterns and sequences in embryological development. The CDX genes which form a part of the homeotic genes are responsible for determining the gastrointestinal cell type from the endoderm (Quinlan, Colleypriest et al. 2007). In adults with BO, it is thought that metaplasia results from differential expression of homeotic genes CDX1 and CDX2 as a result of GORD (acid and bile).

Many animal and human ex-vivo studies have shown increased expression of CDX1 and CDX2 in subjects with Barrett’s metaplasia compared with normal oesophageal cell lines (Eda, Osawa et al. 2003; Phillips, Frierson et al. 2003; Groisman, Amar et al. 2004; Wong, Wilding et al. 2005; Hu, Williams et al. 2007; Kazumori, Ishihara et al. 2009). CDX2 is known to be responsible for the transcription of several intestinal specific genes, including Mucin 2 and Villin which are expressed at increased levels within BO. This process is thought to mediate the development of intestinal metaplasia. However a number of mouse models have demonstrated that increased expression of CDX2 alone cannot itself induce the intestinal phenotype.

The main regulator of CDX1 and CDX2 expression is thought to be via morphogenetic factors (e.g. Bone morphogenetic protein –4 (BMP-4)) (Pillemer, Yelin et al. 1998; Que, Choi et al. 2006). BMP4 belongs to the transforming growth factor – beta (TGF-beta) family – implicated in the regulation of cellular differentiation, migration and proliferation (Milano, van Baal et al. 2007). In a rat model the reflux exposed animals
had increased expression of BMP-4 compared with the normal oesophageal squamous epithelium. (Milano, van Baal et al. 2007) In human ex-vivo squamous tissue cultures when exposed to BMP-4, their gene pattern changes to resemble that seen in BO (Milano, van Baal et al. 2007).

It is thought that BMP4 is derived from tissue fibroblasts under the stimulation of Sonic Hedgehog which is a morphogenic protein critical for normal development and induced by injury and inflammation caused by acid and bile. BMP4 can then stimulate transcriptional factors, such as SOX 9 and increase the production of CDX2 and through co-stimulation induce an intestinal phenotype.

Another proposed factor is the demethylation of the CDX1 gene promoter. In an ex-vivo study, tissue which expressed high levels of CDX1 mRNA under the influence of acid, bile and other pro-inflammatory cytokines were only seen where demethylation of the promoter had occurred. However the initial trigger for CDX1 gene promoter demethylation is unknown (Wong, Wilding et al. 2005).

Therefore our current understanding of the multistep process involved in the pathogenesis of intestinal metaplasia is that GORD induces the production of Sonic Hedgehog which drives fibroblasts to up regulate the production of BMP4 which is likely an early event in the transformation of squamous to columnar mucosa of the distal oesophagus. BMP4 then stimulates the production of transcriptional factors e.g. SOX 9 and in conjunction with the CDX genes, in particular CDX2, up regulate the production of intestinal specific genes, including Mucin 2 and Villin. These all act together with other co-factors such as a chronic inflammatory response leading to the production of oxygen free radicals and oxidative stress and with immune factors, are thought to play an important role in the pathogenesis of intestinal metaplasia and progression to dysplasia (Souza, Krishnan et al. 2008; Barbera and Fitzgerald 2009). However the interrelations of the many cofactors are yet to be determined in this proposed pathway.
1.7 Neoplastic progression of Barrett’s oesophagus

1.7.1 Genetic alterations

BO does not appear to have a clear hereditary basis as no single causative gene has been identified (Badreddine and Wang 2010). Some studies suggest that BO is more prevalent in first degree relatives vs. controls (Chak, Lee et al. 2002; Gerson, Shetler et al. 2002). Environmental factors may be a contributor to the above observation.

Many genetic alterations have been identified as factors in the neoplastic progression of non dysplastic BO through to oesophageal adenocarcinoma, however none have been identified as critical (Barbera and Fitzgerald 2009). This fact, has to date limited the role of molecular markers in crossing over from the domain of research into clinical practice.

1.7.2 Inactivation of tumour suppressor genes

The inactivation of tumour suppressor genes, which is a universal phenomenon seen in all cancers, is a critical step for the development of uncontrolled cell proliferation as they block cell cycle progression from G1 to S phase. Inactivation occurs via three mechanisms. Firstly, mutation which causes a nucleotide base excision or deletion that results in DNA nucleotide sequence change. Secondly, the deletion of a chromosomal region containing the gene ie. Loss of heterozygosity (LOH). Finally promoter hypermethylation, which refers to the attachment of a methyl group to DNA cytosine residues of the promoter region of genes (Hormi-Carver and Souza 2009).

1.7.2.1 The role of P53

P53 is a central regulator of the cell cycle and many other factors mediate its expression and therefore function (Barbera and Fitzgerald 2009). P53 is located on the small arm of chromosome 17. Abnormalities of p53 are generally associated with neoplastic progression of BO but are also seen in non dysplastic BO at high frequency, between
50% to 90% in one study (Tannapfel 2004). Ex-vivo studies have shown that majority of P53 abnormalities occur due to mutation or loss of heterozygosity, however the latter appears to be a better predictor of neoplastic progression (Hormi-Carver and Souza 2009). Cells that lose P53 expression often display aneuploidy or tetraploidy (Spechler, Fitzgerald et al. 2010).

In a large prospective study of 325 patients with BO, the prevalence of P53 LOH detected by flow cytometry at baseline, increased from 6% in non dysplastic BO to 57% in high-grade dysplasia (p < 0.001). Patients with P53 LOH had increased rates of progression to cancer (relative risk = 16, p < 0.001) (Reid, Prevo et al. 2001). A recent study compared the intensity and distribution of staining of the non functional P53 protein that accumulates in the cell nucleus associated with an abnormally functioning gene, in 35 patients with adenocarcinoma / high grade dysplasia, compared to controls. The staining intensity of the abnormally functional P53 protein was substantially elevated in biopsies from patients who developed oesophageal adenocarcinoma compared with controls (odds ratio 11.7 (95% confidence interval 1.93 - 71.4)). However P53 staining has a low sensitivity where only 32.4% of cases had an intense / diffuse staining pattern on the initial biopsy, potentially limiting its possible use as a biomarker (Murray, Sedo et al. 2006).

The best method for assessing P53 abnormalities is by flow cytometry. A study looking at P53 abnormalities in oesophagectomy samples found flow cytometry had a higher sensitivity compared to fluorescence in situ hybridization (Wongsurawat, Finley et al. 2006).

### 1.7.2.2 The role of P16

P16 is a regulator of P53 with inactivation occurring most commonly through hypermethylation of its promoter, which is an epigenetic event (Barbera and Fitzgerald 2009). However P16 inactivation also commonly occurs due to loss of heterozygosity (Wong, Barrett et al. 1997). A study of oesophagectomy specimens harbouring adenocarcinoma found hypermethylation of the P16 promoter in 43% (9/21) of normal tissue, in 77% (14/18) of associated BO, and in 85% (18/21) of oesophageal adenocarcinomas (Hardie, Darnton et al. 2005).
Abnormalities of P16 appear to be one of the first steps in the neoplastic progression of BO. A study assessing DNA sequencing found that P16 mutations have the ability to undergo clonal expansion, creating a field in which other abnormalities can arise that may lead to oesophageal adenocarcinoma. The prevalence of established biomarkers increased from 0% to 20% to 44% in patients whose biopsies were p16+/+, p16+-, and p16-/-, respectively (P < 0.001) (Wong, Paulson et al. 2001). Therefore P16 abnormalities are unlikely to serve as a good biomarker as alteration in P16 occurs very commonly.

1.7.2.3 The role of P27

The cyclin-dependent kinase inhibitor P27 is a negative regulator of the cell division cycle (Hormi-Carver and Souza 2009). Less data exists on abnormalities of these genes. A study showed 45 (83%) of 54 invasive carcinomas had low P27 protein levels which correlated with poor tumour characteristics and patient outcomes (Singh, Lipman et al. 1998).

1.7.3 Oncogene overactivity

1.7.3.1 Cyclin D1, A, E

The cyclin family of oncogenes are an important regulator of cell cycle progression from G1 to S phase. Many studies have demonstrated increased expression of Cyclin D1, A and E in both metaplastic and dysplastic BO compared with normal squamous epithelium (Arber, Lightdale et al. 1996; Lao-Sirieix, Brais et al. 2004; Lao-Sirieix, Lovat et al. 2007). Cyclin A appears to be the most important oncogene in dysplastic progression of BO. A study showed that presence of cyclin A in non dysplastic BO had a 7.6 fold increased risk of progression to high grade dysplasia or cancer vs. biopsies with absent cyclin A expression (Lao-Sirieix, Lovat et al. 2007). A larger case control study of patients with high grade dysplasia / adenocarcinoma found no significant difference in the level of cyclin D1 compared with matched controls (Murray, Sedo et al. 2006).
1.7.4 Avoidance of Apoptosis

Avoidance of apoptosis is another step in neoplastic progression to cancer. COX-2 appears to be a possible mechanism for avoidance of apoptosis via its prostaglandin products. A study of BO biopsies showed that COX-2 protein expression was significantly higher in patients with Barrett's metaplasia, dysplasia, and adenocarcinoma compared with normal squamous oesophageal mucosa. Furthermore, higher levels were inducible by exposure to acid and bile (Shirvani, Ouatu-Lascar et al. 2000). These findings have provided the rationale for using COX-2 inhibitors as a chemoprevention strategy.

1.7.5 Chromosomal abnormalities

Aneuploidy refers to a cell whose chromosomal content is abnormal. Polyploidy refers to increased number of whole set of chromosomes. Aneuploidy and polyploidy (tetraploidy – 92 chromosomes) has been shown in BO to be a factor in both the development of metaplasia and the progression to cancer (Reid, Haggitt et al. 1987; Fennerty, Sampliner et al. 1989). The method of detecting chromosomal abnormalities is best done on fresh tissue with flow cytometry rather than by fluorescence in situ hybridization on paraffin set tissues.

A study which looked at the 5 year risk of cancer progression found that the presence of aneuploidy / tetraploidy had most impact in patients who had low grade, indefinite for dysplasia or no dysplasia. In patients with these levels of dysplasia and normal chromosomes had 0%, 5 year cancer incidence vs. the same histopathological findings and aneuploidy / tetraploidy where the risk of cancer progression was 28%. In contrast chromosomal instability had little to add in patients with high grade dysplasia as their risk of progression was far higher (Reid, Levine et al. 2000).

The presence of chromosomal abnormalities increases the risk of oesophageal cancer among patients with BO. A relative risk of 4.4 for tetraploidy, 11 for aneuploidy and 20 was found when both chromosomal abnormalities were present (Spechler, Fitzgerald et al. 2010).
Therefore these markers may have a role in further stratifying low risk patients into those who may progress earlier to cancer. This may then impact surveillance intervals and timing of treatment.

Generalised DNA damage is also commonly seen in BO. In a controlled study, DNA damage was higher in Barrett's mucosa compared with normal oesophageal and gastric mucosa ($P < 0.001$). In addition higher levels of DNA damage had an odds ratio of 9.4 ($1.1$-83.4; $p = 0.044$) for progression to high grade dysplasia or adenocarcinoma vs. lower levels (Olliver, Hardie et al. 2003; Olliver, Hardie et al. 2005).

Microsatellite instability a form of genetic instability which is most notably implicated in the development of colorectal cancer has also been shown to be present in patients with dysplastic BO. In a cohort of patients with oesophageal adenocarcinoma within BO, only low levels of microsatellite instability were detected limiting its use as a biomarker (Gleeson, Sloan et al. 1996).

1.7.6 Biomarker panels

One of the main reasons that the development of biomarkers has not progressed further into phase 4 studies is the fact that individual research centres are performing different tests often using local assays with results that have been unable to be reproduced by other centres (Souza 2010).

All of the above markers are inadequate to use as lone biomarker. Therefore studies have assessed panels of biomarkers developed with the aim of risk stratifying patients in the following settings. Firstly to assess which patients are likely to undergo neoplastic progression to cancer. Secondly to assess which patients are likely to respond to ablative therapies and which patients are at risk of recurrence after eradication, due to persistence of molecular abnormalities in the neosquamous mucosa.

In a study of 243 patients with BO, 3 biomarkers from oesophageal biopsies at baseline for P53 LOH, P16 LOH and aneuploidy were assessed. A combination of all 3 abnormalities had a cancer incidence of 80% at 6 years cf. cancer risk of 20% for 1 and 36% for 2 abnormalities at 10 years (Galipeau, Li et al. 2007).
Another study assessing a gene promoter hypermethylation on a biomarker panel of six genes (APC, TIMP3, CRBP1, p16, RUNX3, and HPP1) in a retrospective longitudinal study of 99 BO and nine low grade dysplasia specimens obtained from 53 BO patients undergoing surveillance endoscopy. Only high-grade dysplasia or adenocarcinoma was defined as progression end points. Multivariate analyses revealed hypermethylation of p16, RUNX3, and HPP1 in BO or low grade dysplasia may represent independent risk factors for the progression of BO to high grade dysplasia or adenocarcinoma (Schulmann, Sterian et al. 2005).

In regards to predicting which patients will respond favourably to endoscopic therapy. A study by Prasad of patients undergoing Photodynamic therapy (PDT) of dysplastic BO found on a multivariate analysis that P16 allelic loss detected by fluorescence in situ hybridization (odds ratio [OR], 0.32; 95% confidence interval [CI], 0.10-0.96) predicted decreased response to PDT (Prasad, Wang et al. 2008).

There have been a number of studies assessing the molecular profile of the neosquamous mucosa after endoscopic ablative therapies. In patients whom APC was used as the ablative modality, studies have found P53 expression and P16 deletion persisted in the neosquamous mucosa (Lopes, Pereira-Lima et al. 2005; Paulson, Xu et al. 2006). In a study by Pouw, 22 patients post RFA ablation were assessed 2 months post complete eradication of BO. The baseline BO and post-RFA neosquamous mucosa were evaluated for immunohistochemical expression of Ki-67 and P53, and genetic abnormalities (DNA-fluorescent in situ hybridization: chromosome 1 and 9, P16 and P53). All pre-treatment specimens from all 22 patients showed abnormalities on immunohistochemical staining and fluorescent in situ hybridization, whereas all post-RFA neosquamous mucosa specimens were normal. The finding of a normal molecular profile is reassuring in those labelled as having complete eradication of BO. Further prospective studies are needed so that we can document the natural history in particular time to recurrence of BO of those whose molecular profile returns to normal vs. those whose abnormalities persist. This would then provide further information to risk stratify these patients for ongoing surveillance protocols.

A genome wide approach is being adopted by a number of studies to identify new biomarkers which feature dominantly in patients with Barrett’s compared to healthy
controls. Studies have looked into single nucleotide polymorphisms (SNPs) and methylation profiling.

miRNAs- are small naturally occurring RNAs that can stop multiple target genes by destabilising that target genes mRNA or preventing translation into a protein. Changes to the miRNA levels have observed in different tissue types and have been associated with dysplasia and in cancer (Feber, Xi et al. 2008). miRNAs have been identified that are found in higher levels in tumour tissue vs. controls – i.e. Oncogenic miRNAs and those expressed in lower levels – ie. Tumour suppressor miRNA (Kan and Meltzer 2009).

In a study of colorectal cancer miRNA sequences, miR-143 and miR-145, consistently display reduced steady-state levels of the mature miRNA at the adenomatous and cancer stages of colorectal neoplasia compared to control tissue (Michael, SM et al. 2003).

A study looking at a genome wide approach of miRNA expression in normal squamous, gastric mucosa, non dysplastic BO and oesophageal adenocarcinoma. From 377 miRNAs, 44 miRNAs were thought likely to have altered expression between various mucosal samples. Expression of miR-143, miR-145 and miR-215 was lower in oesophageal adenocarcinoma than in BO. Levels of miR-203 and miR-205 were high in normal squamous epithelium and low in columnar epithelia (Wijnhoven, Hussey et al. 2010). Another study by this group looking at the expression of miR-143 post APC ablation found that the proximal squamous mucosa and neosquamous mucosa of post ablation patients had higher miR-143 levels compared to squamous mucosa from controls without Barrett’s – suggesting a field change.

1.8 Risk factors for development of oesophageal adenocarcinoma

BO is the precursor lesion that progress to oesophageal adenocarcinoma (Shaheen and Ransohoff 2002). Patients with BO have a high relative risk 30 -40x of progressing to adenocarcinoma (Reid 1991). However it is important to note that the absolute risk is low in most studies between 0% to 3%. The incidence of adenocarcinoma is increasing rapidly with poor 5 year survival rates in the order of 14.9% (American Cancer Society. American Cancer Society;2005). There have been no studies to suggest any geographic
variation in cancer progression (Thomas, Abrams et al. 2007). Much research has focused on risk factors for progression to adenocarcinoma in patients with BO.

1.8.1 Degree of dysplasia

1.8.1.1 Intestinal metaplasia

A meta-analysis found a significant publication bias in the data with smaller studies quoting higher risks of progression to adenocarcinoma in the setting of non dysplastic BO. Their conclusion was 0.5%/year risk in non dysplastic BO (Shaheen, Crosby et al. 2000). This rate of progression was echoed in a large multicentre cohort study that also found a 0.5%/year rate of progression of non dysplastic BO to adenocarcinoma (Sharma, Falk et al. 2006). A recent population based cohort study from Denmark published in the New England Journal of Medicine in 2011, demonstrated an even lower annual risk of progression to oesophageal adenocarcinoma of 0.12% (95% CI, 0.09 to 0.15) (Hvid-Jensen, Pedersen et al. 2011). Therefore the risk of progression may be lower than first thought which may have future implications on screening intervals.

It is currently widely accepted that the presence of intestinal metaplasia is required for neoplastic progression, hence the inclusion of this histological finding in the definition. However, a large Norwegian study of 712 patients compared patients with intestinal metaplasia vs. glandular (columnar) mucosa in lower oesophageal biopsies. No difference was found in the development of adenocarcinoma between the two groups at a median of 12 years of follow up. The oesophageal malignancy rate was 0.34% per year (specialised intestinal metaplasia 0.37%, gastric metaplasia 0.30%; p =NS). The major limitation of the study was its retrospective design and the limited number of biopsies taken which may have under diagnosed intestinal metaplasia in the group with columnar epithelium (Kelty, Gough et al. 2007). This finding supports the position of the British Society of Gastroenterology who do not require intestinal metaplasia to diagnose BO. A prospective study will be needed to definitively answer this question.

The biggest risk factor for malignant progression of BO to adenocarcinoma is the degree of dysplasia (Reid, Levine et al. 2000). This is currently the only useful
parameter for identifying patients at increased risk of adenocarcinoma in clinical practice and affects the surveillance protocol recommended (Falk 2009). In resection based studies up to 50% of patients with adenocarcinoma had varying degrees of dysplasia in the surrounding mucosa (Miros, Kerlin et al. 1991; Cameron, Lomboy et al. 1995; Lagergren, Bergstrom et al. 1999).

1.8.1.2 Low grade dysplasia

The presence of low grade dysplasia increases the risk of neoplastic progression over time. However the magnitude of this risk has been inconsistently reported in the literature from different cohort studies (Falk 2009). Some studies have demonstrated as high as 66-75% of patients have regression of previously diagnosed low grade dysplasia back to intestinal metaplasia at a subsequent endoscopy (Schnell, Sontag et al. 2001; Conio, Blanchi et al. 2003; Sharma, Falk et al. 2006). However a recently published study highlighted the inaccuracy of community based pathologists where after expert review of biopsies assessed as low grade dysplasia, 75% were down staged to intestinal metaplasia, these patients had risk of progression to high grade dysplasia or cancer of 0.49% / year compared to those confirmed to have true low grade dysplasia, where the risk of progression was far greater at 13.4%/year (Curvers, Ten Kate et al. 2010). Other cohort studies have also echoed the finding that the rate of progression is higher when low grade dysplasia is confirmed by expert and multiple pathologists (Skacel, Petras et al. 2000; Montgomery, Goldblum et al. 2001). In a systemic review of the literature the authors found 0.6%-1.6%/year rate of progression of low grade dysplasia to cancer (Wani, Mathur et al. 2009).

1.8.1.3 High grade dysplasia

The finding of high grade dysplasia, is well established as a risk factor for progression to cancer and therefore serves as a trigger for definitive therapy of the BO segment. A variety of rates of progression are quoted in the literature, reflecting different study designs and sample sizes. A number of resection based studies have shown that the presence of unsuspected cancer in patients with high grade dysplasia approximates 40%,
up to 73% in some studies. A recent meta-analysis of the data found a 6.6%/year rate of progression from high grade dysplasia to adenocarcinoma (Rastogi, Puli et al. 2008).

The finding of high grade dysplasia can be further stratified according to the extent of high grade dysplasia within the Barrett’s segment. A study of 67 patients examined this question. The extent of high grade dysplasia was defined as focal if cytologic and/or architectural changes of high grade dysplasia were limited to a single focus of 5 or fewer crypts and diffuse if more than 5 crypts were involved in a single biopsy specimen or if high grade dysplasia was considered multifocal (involving more than one biopsy fragment). Cancer-free survival rates at 1 and 3 years were 93% and 86% for focal high grade dysplasia compared with 62% and 44% for diffuse high grade dysplasia (P < 0.001) Diffuse high grade dysplasia had a 3.7-fold increase in the risk of oesophageal cancer compared with focal high grade dysplasia (P = 0.02) on multivariate analysis. Multifocal high grade dysplasia had increased risk of progression to cancer at 12 months vs. focal high grade dysplasia (Buttar, Wang et al. 2001).

1.8.2 Length of the Barrett’s segment

The previous classification of segment length into short segment <3cm vs. long segment >3cm bares no clinically utility. As neoplastic progression and progression to cancer can be seen in all lengths of BO, a recent AGA expert panel recommended that these terms no longer be used (Cameron, Lomboy et al. 1995; Sharma, McQuaid et al. 2004).

However, studies have conflicting results regarding importance of length of BO on risk of adenocarcinoma. A study by Weston showed that the prevalence of dysplasia was higher for long segment BO at index endoscopy (P < 0.007) and on subsequent surveillance the development of high grade dysplasia / cancer occurred only in those with long segment BO (P<0.05). However the two groups were not well matched for race, with the short segment BO group having a significantly higher proportion of African Americans (Weston, Krmpotich et al. 1997) Another observational study found that the length of segment was an independent predictor of progression p=0.012 (Weston, Sharma et al. 2004). Another study by Rudolph showed a small increased risk with >5cm of BO (Rudolph, Vaughan et al. 2000).
In contrast, a large prospective cohort study of 309 patients showed no significant difference in progression to adenocarcinoma based on length after adjusting for histological diagnosis at entry (Rudolph, Vaughan et al. 2000). A recent meta-analysis concluded no significant association between cancer risk and length of segment (Thomas, Abrams et al. 2007). Therefore it appears that length of segment is not a risk factor for neoplastic progression of BO.

### 1.8.3 Biomarkers

Biomarkers have the potential to predict risk of progression to adenocarcinoma however none have been validated in large clinical studies (Falk 2009). Refer to previous discussion in the literature review.

### 1.8.4 Gastro oesophageal reflux disease

GORD may be defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the oesophagus (DeVault and Castell 1999). The true prevalence of GORD is difficult to accurately estimate. In population studies up to 10-20% of people describe symptoms weekly (Locke, Talley et al. 1997). GORD results in a spectrum of oesophageal disorders ranging from reflux oesophagitis, stricture formation and the development BO with the potential to develop adenocarcinoma of the oesophagus.

A number of case control studies have looked at GORD as a risk factor for adenocarcinoma. Patients with recurrent severe reflux had odds ratio of 7.7 for the development of adenocarcinoma of the oesophagus vs. matched controls (Lagergren, Bergstrom et al. 1999). Another study found the adjusted Odds ratio of patients with oesophageal adenocarcinoma having daily reflux was 5.5 (Farrow, Vaughan et al. 2000).
The development of intestinal metaplasia appears to improve the severity of symptoms experienced by patients with GORD (Shaheen and Palmer 2009). In a study of patients with GORD with and without BO, the patients without BO were more symptomatic of GORD despite having better DeMeester scores compared to patients with BO (Brandt, Darling et al. 2004). These findings have been echoed in other studies (Johnson, Winters et al. 1987; Eloubeidi and Provenzale 2000). Therefore the patients experiencing severe GORD are less likely to have developed intestinal metaplasia. This finding may also explain the observation that around half the cancers develop in patients without significant GORD symptoms (Lagregren, Bergstrom et al. 1999).

Other factors that confound using GORD as a risk factor for progression is that the absolute risk for those with GORD developing adenocarcinoma is low due to low overall incidence of cancer vs. the high prevalence of patients with symptoms of GORD (Shaheen and Ransohoff 2002). Furthermore, studies have failed to show a reduction in deaths from oesophageal cancer as a result of screening (Lagregren, Bergstrom et al. 1999). Therefore screening patients for BO with GORD is controversial and not cost effective (Sharma 2009).

1.8.5 Demographic considerations

1.8.5.1 The age of the patient

A review of two large databases provides the best data on the effect of age on risk of developing adenocarcinoma of the oesophagus. The Danish Cancer Registry and The Surveillance, Epidemiology and End Results (SEER) program show risk of adenocarcinoma increases with age and peaks at 75-79 years (El-Serag, Mason et al. 2002; van Blankenstein, Looman et al. 2005). They also found that the incidence of cancer among younger patients aged between 45-65 years, was higher than historical levels (El-Serag, Mason et al. 2002).

1.8.5.2 The gender of the patient
Oesophageal adenocarcinoma has a strong male predominance. Large population studies have found that the male gender has 6-8 fold risk of oesophageal adenocarcinoma vs. the female gender (El-Serag, Mason et al. 2002; van Blankenstein, Looman et al. 2005). Despite this large overall difference in risk, the SEER database showed that in both genders of white race, the rate of increase / year of oesophageal adenocarcinoma were of similar magnitude. In white males an increase of 7.8%/year, P < 0.0001; and in white females an increase of 6.48%/year; P < 0.0001 was found (Younes, Henson et al. 2002).

1.8.5.3 The ethnic background of the patient

The white race has far greater risk of adenocarcinoma compared with other racial groups. A study of the SEER database between 1992 to 1998 compared the incidence of oesophageal adenocarcinoma among five ethnic groups. In Caucasian males the oesophageal adenocarcinoma rate was 4.2 per 100,000 population/yr which was double that of Hispanics and four-fold higher than those of black racial origin, Asians, and Native Americans (p < 0.01) (Kubo and Corley 2004). In regards to the rate of increase of adenocarcinoma amongst the different racial groups further data from the SEER database between 1973-1998 showed increase rate in whites and Hispanics but not in blacks (Younes, Henson et al. 2002).

Previously squamous cell carcinoma was the predominant cause of oesophageal cancer in all ethnic groups. However, adenocarcinoma is now the predominant cause of oesophageal cancer in whites whereas the black race continues to be more susceptible to squamous cell carcinoma than adenocarcinoma. A small retrospective study looking at demographics of patients with oesophageal cancer over a 5 year period – 12/13 patients with histological proven adenocarcinoma were white, cf. 1/5 of the patients with squamous cell cancer being of white racial origin (Rogers, Goldkind et al. 1986). A larger retrospective study of patients with oesophageal cancer showed that in whites, 66% of patients had adenocarcinoma vs. 32% of patients who had squamous cell cancer. This was in contrast to black patients in whom 92% had squamous cell cancer (Chalasani, Wo et al. 1998).
1.8.5.4 The Family history

The effect that family history has in the development of oesophageal adenocarcinoma is conflicting in the literature. 2 large case control studies found no increased risk if a family member is affected with oesophageal adenocarcinoma. The first was a US study of 293 patients (Dhillon, Farrow et al. 2001). The second was a Swedish study of 189 patients (Lagergren, Ye et al. 2000).

In contrast a smaller case control study of 58 patients which regarded a positive finding as the presence of any one of BO, oesophageal adenocarcinoma, or cardia adenocarcinoma, found a significantly higher rate among case subjects compared with controls (24% v 5%; p<0.005) (Chak, Lee et al. 2002). There are also multiple case reports in the literature from individual families clusters showing high rate of GORD / BO / adenocarcinoma in successive generations (Crabb, Berk et al. 1985; Fahmy and King 1993). One such family cluster had 6 members affected with BO of which 3 developed cancer, suggestive of autosomal dominant inheritance (Jochem, Fuerst et al. 1992).

However there is no current evidence to suggest that family members should be screened for BO or oesophageal adenocarcinoma.

1.8.6 Modifiable Factors in cancer development

1.8.6.1 Obesity

Obesity is emerging as a pathogenic factor in many disease states in particular in the development of a variety of cancer subtypes. It is thought that the increased risk is in part related to the dysregulation of hormonal factors and pro-inflammatory cytokines which are seen in higher levels in obese patients – e.g. role of leptin, IGF-1 (Frystyk, Skjaerbaek et al. 1999; Kendall, Macdonald et al. 2008).
In oesophageal adenocarcinoma the mechanism of increased cancer risk is likely multifactorial. Two main factors are increased GORD related to increased intra-abdominal pressure coupled with the molecular effects of adiposity relating to inflammation and oxidate stress (Falk 2009). A systematic review and meta-analysis of the literature of obesity and adenocarcinoma compared to GORD controls proposed that main increase risk related to GORD rather than obesity itself (Moayyedi 2008).

Another meta-analysis showed that a high body mass index (BMI) >25 was associated with an increased risk of oesophageal adenocarcinoma (males, OR, 2.2; 95% CI, 1.7-2.7; females, OR, 2.0; 95% CI, 1.4-2.9). With higher levels of BMI associated with increased risk (Kubo and Corley 2006). This relationship between level of BMI and oesophageal cancer risk was also found in an Australian case control study, where the oesophageal adenocarcinoma risk increased in a linear fashion with increased BMI. The highest risks were seen for BMI >or=40 kg/m2 (odds ratio (OR) = 6.1, 95% CI 2.7 to 13.6) compared with "healthy" BMI (18.5-24.9 kg/m2). The increased risk was independent of GORD, however the presence of high BMI in the presence of GORD had a synergist effect on cancer risk (Whiteman, Sadeghi et al. 2008).

Obesity as measured by waist circumference has also been shown to increase the risk of oesophageal cancer independent of BMI (Falk 2009).

**1.8.6.2 Helicobacter Pylori**

Helicobacter pylori mediates a number of gastrointestinal diseases. It is classified as a carcinogen, critical in the development of gastric cancer and MALToma and is a major cause of peptic ulcer disease. However helicobacter pylori appears to be protective against oesophageal adenocarcinoma. It is thought to mediate this protective effect via gastric atrophy therefore decreasing gastric acid production and hence less acidic refluxate. However the protective effects of helicobacter pylori were also seen in gastric atrophy negative subjects – suggesting another mechanism (McColl, Watabe et al. 2008).

In a study looking at this relationship, patients with adenocarcinoma had inverse significant relationships with both the helicobacter pylori prevalence (pooled odds ratio
[OR], 0.52; 95% CI 0.37-0.73; P < .001) and the prevalence of the virulent cagA-positive strain of helicobacter pylori (pooled OR, 0.51; 95% CI, 0.31-0.82; P = .006). These inverse relationships were also found in patients with BO (Rokkas, Pistiolas et al. 2007).

Therefore the data may suggest that in patients with BO who are found to have helicobacter pylori, not eradicating the bacteria may decrease the risk of neoplastic progression. However the magnitude of the benefit is unclear and needs to be balanced with the negative effects of helicobacter pylori. The Maastricht 3 consensus report on helicobacter pylori infection concluded that helicobacter pylori eradication does not cause nor worsen GORD symptoms – therefore eradication should not increase risk of BO (Malfertheiner, Megraud et al. 2007).

1.8.6.3 Smoking

A multicentre population based case control study found a positive association between cigarette smoking and the risk of oesophageal and gastric cardia adenocarcinoma combined (OR = 2.4; 95% = 1.7-3.4). The risk appeared to correlate with increasing intensity and duration of smoking (Gammon, Schoenberg et al. 1997). However another Swedish population based case controlled study found no clear association between tobacco smoking and the development of oesophageal adenocarcinoma (Lagergren, Bergstrom et al. 2000).

1.8.6.4 Alcohol consumption

The duration and amount of alcohol consumption does not appear to be a factor in the development of oesophageal adenocarcinoma in a number of case controlled studies (Gammon, Schoenberg et al. 1997; Lagergren, Bergstrom et al. 2000).

1.8.6.5 Diet

A population based case control study from Nebraska suggested that greater intake of dietary fibre, certain carotenoids, and vitamins may decrease the risk of oesophageal adenocarcinoma, whereas greater intake of saturated fat may increase the risk of

40
oesophageal adenocarcinoma (Chen, Tucker et al. 2002). Another population based case control study found an increased risk of oesophageal adenocarcinoma for diet low in fruit and vegetables (Engel, Chow et al. 2003).

1.8.6.6 Medications

A number of different medications and multivitamins have been shown to mediate the risk of oesophageal adenocarcinoma. A systemic review and meta-analysis of observational studies support a protective association between aspirin and NSAIDs with a 33% reduction in the Odds ratio for developing oesophageal adenocarcinoma and provide evidence for a dose effect (Corley, Kerlikowske et al. 2003; Sadeghi, Bain et al. 2008). However a prospective, nested case-control study did not show any benefit of NSAIDs in risk reduction of adenocarcinoma (Lindblad, Lagergren et al. 2005).

The cyclo-oxygenase pathways have been implicated in the pathogenesis of BO via their effects on apoptosis of cells. COX-2 appears to be a possible mechanism for avoidance of apoptosis via its prostaglandin products (Shirvani, Ouatu-Lascar et al. 2000). These findings have provided the rationale for using COX-2 inhibitors as a chemoprevention strategy. This was concept was tested in a multicentre, randomised control trial of celecoxib 200mg bd vs. placebo for 48 weeks in patients with BO. Their results failed to show a protective effect of celecoxib in preventing progression of Barrett's dysplasia to cancer. No increased cardiovascular complications were seen in the celecoxib group (Heath, Canto et al. 2007).

A large prospective cohort study of 339 patients evaluated the association between supplemental vitamins and minerals on neoplastic progression of BO. Patients were followed for a mean of 5 years in which 37 cases of oesophageal adenocarcinoma were diagnosed. Patients who took 1 or more multivitamin pills/day had a significantly decreased risk oesophageal adenocarcinoma (HR = 0.38; 95% CI = 0.15-0.99] compared to those not taking multivitamins. Significant inverse associations were also observed with supplemental vitamin C and vitamin E (Dong, Kristal et al. 2008).
1.9 Screening at risk populations for the development of Barrett’s oesophagus

The principles of an effective screening program require the following four components. 1. An identifiable at risk population 2. A screening tool that is reliable, acceptable to the patient and cost effective. 3. An effective treatment exists for early stage disease. 4. There is evidence of improved outcomes with intervention that outweighs harm of the process (Wilson and Jungner 1968).

1.9.1 Identifiable at risk population

Targeting the at risk population is difficult, due to a number of factors that impair screening. Gastro-oesophageal reflux disease is the most significant risk factor for the development of BO. Therefore it would be expected that this group would be at the greatest risk of neoplastic progression. However around half the cancers develop in patients without significant GORD (Lagergren, Bergstrom et al. 1999). Therefore screening patients only with chronic GORD will miss a large group of at risk patients (Shaheen and Palmer 2009).

1.9.2 Screening tool that is reliable, acceptable to the patient and cost effective

The endoscopic features of BO can be subtle and easily overlooked. In a study of white patients with dyspepsia, white light endoscopy with standard definition scopes has a sensitivity of 82% and a positive predictive value of 32% for detecting BO (Eloubeidi and Provenzale 1999). It would be expected that these percentages would improve with the advent of high definition endoscopes and advanced imaging techniques. Among patients with long segments of oesophageal columnar metaplasia, over 20% may not have intestinal metaplasia detected on a single set of endoscopic biopsies (Kim, Waring et al. 1994; Chandrasoma, Der et al. 2001; Jones, Sharma et al. 2002) due to sampling error or interim development of intestinal metaplasia after the first examination. Biopsy protocols have been developed to optimise detection rates in particular of dysplasia,
however only 27% of practising gastroenterologists in a U.S. survey adhere to these biopsy guidelines (Cruz-Correa, Gross et al. 2001).

Furthermore endoscopic localization of the gastrooesophageal junction and measurement of z-line displacement is moderately reproducible, with mild to substantial variation in measured segment lengths between examinations (Kim, Waring et al. 1994). The Prague classification was developed to overcome this variability. It involves a circumferential length measurement – C and a maximal length measurement – M. The Prague classification has a high reliability co-efficient between observers (around 0.95) especially with BO segments >2cm (Sharma, Dent et al. 2006).

In addition to endoscopic variability, pathologist variability further limits population screening. Inter-observer variability exists when assessing BO – between expert and non expert pathologists (Reid, Haggitt et al. 1988). The variability is most notable when diagnosing non dysplastic, indefinite and low grade dysplasia (Kerkhof, van Dekken et al. 2007). In a study comparing interobserver agreement between patients with high grade dysplasia vs. borderline for dysplasia (indefinite) found a kappa score of 0.65 for high grade dysplasia vs. 0.32 for borderline for dysplasia between pathologists (Montgomery, Bronner et al. 2001). Therefore in difficult cases, a second opinion should be sought from an expert pathologist experienced in BO (Yerian 2009).

Studies have looked at cost effectiveness models, generally targeted at patients >50 years with GORD symptoms. One study looking at screening this high risk group with subsequent surveillance limited to patients with BO with dysplasia required $10 440 per quality-adjusted life-year (QALY) saved compared to no screening or surveillance. The cost of surveillance after initial screening in patients found to have non dysplastic BO at a 5 yearly interval was $596 000 per QALY saved compared to no surveillance (Inadomi, Sampliner et al. 2003; Inadomi, Somsouk et al. 2009).

At this stage the weight of evidence appears to be against endoscopic screening for BO at both the population level and also in presumed high risk groups. This is mainly due to the potential morbidity associated with an invasive screening test such as an endoscopy and secondly due to the considerable cost to the community. Less expense and invasive techniques are currently being assessed and developed.
One such method is the cytosponge test which has been developed with collaboration between Australian and U.K. centres. This technique involves ingestion of a pill connected to a string. The pill is coated with gelatine which is broken by acid in the stomach. This releases the cytosponge which is then pulled back out of the mouth and during its passage through the oesophagus samples cells that can be assessed for the presence of a protein that is expressed in non dysplastic BO (TFF3). In a feasibility study in the UK. 3% of patients with history of GORD had BO. The sensitivity and specificity of the cytosponge test was 90.0% (55.5% to 99.7%) and 93.5% (90.9% to 95.5%) respectively for clinically relevant segments of 2 cm or more. Patients reported minimal psychological distress throughout the study (Kadri, Lao-Sirieix et al. 2010).

With the validation of these techniques in larger randomised studies – population screening may become safe and cost effective.

1.9.3 Treatment is effective in early stage disease

Early stage treatment of dysplastic BO relies on endoscopic therapy. Ablation therapies rely on the fact that squamous mucosa will replace the ablated BO in a non-acid environment. Older endoscopic therapies include argon plasma coagulation, photodynamic therapy and multipolar electrocoagulation. These techniques all have significant drawbacks including variable mucosal ablation and “buried Barrett’s” under squamous mucosa. More recently HALO radiofrequency ablation of BO appears to have emerged as the treatment of choice. Energy delivery is automated, which leads to a more predictable and uniform ablation, enhancing safety (stricture rate 6%) and efficacy compared to other ablative therapies. A randomized controlled trial of HALO RFA compared to a sham procedure has shown much higher rates of complete remission after 12 months in individuals with high grade dysplasia (81%) and low grade dysplasia (91%) compared to the control groups (Shaheen, Sharma et al. 2009). However, issues surrounding, durability of remission, rate of relapse and progression to cancer, the need for ongoing endoscopic surveillance and finally the cost effectiveness are still yet to be fully determined pending more longitudinal data.
1.9.4 Evidence of improved outcomes

The risk of progression to cancer in patients with non dysplastic BO is low with the absolute risk in most studies between 0-3%. A large multicentre cohort study found a rate of 0.5%/year progression of non dysplastic BO to adenocarcinoma (Sharma, Falk et al. 2006). Therefore many patients with BO die from other causes than adenocarcinoma of the oesophagus. Patients with BO have a hazard ratio for death 1.37 (CI 1.12-1.66) compared with general population, with <45% of this slightly increased of risk of death due to adenocarcinoma (Solaymani-Dodaran, Logan et al. 2004).

No randomised controlled trials that shows screening for BO has improved mortality from adenocarcinoma (Lagergren, Bergstrom et al. 1999; Sharma, McQuaid et al. 2004; Shaheen and Palmer 2009). A study showing that a prior gastroscopy was associated with an improved stage at the diagnosis of adenocarcinoma but did not alter long-term survival. This study suggests the effect of lead time bias. In the absence of prospective randomized controlled trials, the benefit of screening to decrease mortality from adenocarcinoma cannot be confirmed (Rubenstein, Sonnenberg et al. 2008).

1.10 Diagnosis of Barrett’s Oesophagus

1.10.1 Clinical features

Patients with BO are generally asymptomatic, however a proportion of patient’s may describe symptoms of GORD as this is the most well described risk factor for the development of BO (Winters, Spurling et al. 1987; Corder, Jones et al. 1996).

The presence of oesophageal symptoms such as dysphagia and odynophagia likely represents the progression to cancer.

As with symptoms there are no physical signs to detect the presence of BO. Again patients with advanced adenocarcinoma may have signs of loco-regional spread such as lymphadenopathy.
1.10.2 Endoscopic diagnosis

The endoscopic features of BO can be subtle and easily overlooked. In a study of white patients with dyspepsia, white light endoscopy with standard definition scopes has a sensitivity of 82% and a positive predictive value of 32% for detecting BO (Eloubeidi and Provenzale 1999). It would be expected that these percentages would improve with the advent of high definition endoscopes and advanced imaging techniques.

Within a columnar lined segment of oesophagus intestinal metaplasia is not uniformly distributed (Chandrasoma, Der et al. 2001). Among patients with long segments of oesophageal columnar metaplasia, over 20% may not have intestinal metaplasia detected on a single set of endoscopic biopsies (Kim, Waring et al. 1994; Chandrasoma, Der et al. 2001; Jones, Sharma et al. 2002) due to sampling error or interim development of intestinal metaplasia after the first examination. Therefore it is recommended repeat endoscopy with systemic biopsies in patients with columnar lining in the distal oesophagus without confirmed intestinal metaplasia on the initial biopsies should be done (Sharma, McQuaid et al. 2004).

1.10.3 Biopsy protocols

Biopsy protocols have been developed to optimise detection rates of BO in particular of dysplasia. Random biopsy protocol’s have been adopted due to the concern that the subtle mucosal changes associated with dysplasia are undetectable endoscopically and therefore would be missed be a targeted biopsy protocol. With the advent of high definition endoscopes and advanced imaging techniques such as narrow band imaging, new categories of mucosal and vascular patterns that correlate with histology have been developed (Sharma, Bansal et al. 2006). These new techniques may enable a targeted biopsy protocol to be adopted in the near future.

There are many limitations of a random biopsy protocol such as the endoscopist spending more time biopsying the mucosa rather than carefully assessing it for visible mucosal abnormalities, as well as the extra time taken to biopsy and the cost and time associated with pathological interpretation. The extra time taken to biopsy would likely
explain the fact that only 27% of practising gastroenterologists in a U.S. survey adhere to biopsy guidelines (Cruz-Correa, Gross et al. 2001).

1.10.3.1 Seattle Protocol

The Seattle protocol consists of 4 quadrant biopsies every 1-2cm of BO and targeted biopsies of any visible mucosal abnormality. A resection based study of patients with high grade dysplasia who proceeded to surgery found no significant difference in the undetected cancer rate of patients who had Seattle protocol biopsies prior to surgery vs. a non protocol, less intensive biopsy program (Kariv, Plessec et al. 2009). However other studies have shown that the greater the number of biopsies taken the increased chance of detecting dysplasia or early cancer (Levine, Haggitt et al. 1993; Sharma, McQuaid et al. 2004). An observational study aiming to assess optimum number of biopsies to diagnose intestinal metaplasia in BO with a mean length of 4cm found 8 random biopsies per endoscopy, resulted in a mean of 67.9% endoscopies having intestinal metaplasia. In contrast, if only four were taken the yield of intestinal metaplasia was 34.7% (Harrison, Perry et al. 2007).

1.10.4 Prague classification

Furthermore endoscopic localization of the gastrooesophageal junction and measurement of z-line displacement is moderately reproducible, with mild to substantial variation in measured segment lengths between examinations (Kim, Waring et al. 1994). The Prague classification was developed to overcome this variability. It involves a circumferential length measurement – C and a maximal length measurement – M. The Prague classification has a high reliability co-efficient between observers ( around 0.95) especially with BE segments >2cm (Sharma, Dent et al. 2006).

1.10.5 Pathologist variability

Many studies have shown inter-observer variability and well as intra-observer variability exists when assessing Barrett’s oesophagus. These differences are most
notable between expert and non expert pathologists (Reid, Haggitt et al. 1988). Furthermore the degree of dysplasia impacts in the diagnostic certainty and accuracy between pathologists. The variability is most notable when diagnosing non dysplastic, indefinite and low grade dysplasia (Kerkhof, van Dekken et al. 2007). A recently published study highlighted the inaccuracy of community based pathologists where after expert review of biopsies assessed as low grade dysplasia, 75% were down staged to intestinal metaplasia – these patients had risk of progression to high grade dysplasia or cancer of 0.49% / year compared to those confirmed to have true low grade dysplasia, where the risk of progression was far greater at 13.4%/year (Curvers, Ten Kate et al. 2010). In contrast interobserver agreement is better with high grade dysplasia (kappa score 0.65) than with indefinite for dysplasia (kappa 0.32) between pathologists (Montgomery, Bronner et al. 2001). Therefore in difficult cases, a second opinion should be sought from an expert pathologist experienced in BO (Yerian 2009).

1.11 Advanced imaging techniques in the assessment of Barrett’s oesophagus

Aim of endoscopic surveillance is to detect dysplastic BO, in particular to identify high grade dysplasia or intramucosal cancer which can then be treated before progression to invasive cancer. These pre cancerous lesions are often subtle and difficult to detect with standard white light endoscopy therefore a random biopsy protocol has been adopted as standard of care despite its flaws. Advanced imaging techniques enhance visualisation of mucosal and vascular patterns, improving detection of dysplastic BO and precancerous lesions.

1.11.1 White Light endoscopy

A video endoscope uses a charge coupled device surface that is comprised of pixels that generate an electrical charge in proportion to light exposure (Wolfsen 2009). Standard video endoscope consist of 100,000 to 300,000 pixels compared to high density / definition endoscopes which have 600,000 to 1,000,000 pixels thereby enhancing image quality and resolution. In a study of white patients with dyspepsia, white light
endoscopy with standard definition scopes has a sensitivity of 82% and a positive predictive value of 32% for detecting BO (Eloubeidi and Provenzale 1999).

1.11.2 Narrow Band Imaging

Narrow band imaging (NBI) has been the most widely studied advanced imaging technique. The penetration depth of light is dependent on its wavelength. The use of blue light in conjunction with a special narrow-band filter which only passes (blue (440-460 nm), green (540-560 nm), and red (610-630 nm) wavelengths, enables imaging of the superficial tissue structures – mucosal, glandular and vascular patterns. The absorption spectrum of haemoglobin is also included, which adds to the vascular details (Gono, Obi et al. 2004).

NBI has been shown to be superior to white light endoscopy for the detection of dysplasia within a Barrett’s segment. In a prospective, blinded tandem endoscopy study of 65 patients, targeted biopsies with NBI compared to standard resolution white light endoscopy with random biopsies detected more dysplasia, 57% vs. 43%, detected higher grades of dysplasia, 18% vs. 0% and took less biopsies, mean 8.5 versus 4.7 (P < .001) (Wolfsen, Crook et al. 2008).

There have been a number of studies which have used different mucosal and vascular pattern characteristics to determine the presence of dysplasia within a Barrett’s segment. Intestinal metaplasia without high grade dysplasia has a regular vascular pattern, with a ridge villous mucosal pattern. Whereas high grade dysplasia has an irregular / distorted mucosal and vascular pattern. The circular mucosal pattern represents cardia mucosa (Sharma, Dent et al. 2006).
Regular Vascular Pattern

Irregular Vascular Pattern
Ridge / Villous Mucosal Pattern

Circular Pit Pattern
Irregular / Distorted Mucosal Pattern

Based on the above characterisations most of the studies have been able to differentiate non dysplastic BO vs. high grade dysplasia. Studies have found for the diagnosis of non dysplastic BO without high grade dysplasia sensitivity between 93.5% - 100%, specificity between 78.8% - 86.7% and positive predictive valve between 93.5 - 94.7%. For the diagnosis of high grade dysplasia a sensitivity between 90% - 100%, specificity 76% - 100% and positive predictive valve 64% - 99.2% (Kara, Ennahachi et al. 2006; Sharma, Bansal et al. 2006; Anagnostopoulos, Yao et al. 2007). In Sharma’s study if biopsies were limited to areas with irregular/distorted pattern, no patient with high grade dysplasia would have been missed (Sharma, Bansal et al. 2006).

1.11.3 Chromoendoscopy

The technique of chromoendoscopy involves staining the oesophageal surface to provide fine detail of the mucosal surface and therefore enhance detection of subtle mucosal abnormalities that may harbour early neoplastic changes. Methylene blue is the most studied of the different mucosal stains. As yet, there is no uniformity in the method, concentration of the stain, and classification of staining patterns by
chromoendoscopy, making it difficult to compare various studies (Sharma and Bansal 2006).

1.11.3.1 Methylene blue

0.1%-1.0% methylene blue solution selectively stains specialised columnar epithelium but has variable / heterogeneous uptake in dysplastic tissue. Studies have shown conflicting results comparing methylene blue targeted biopsies vs. random biopsy protocols for both the detection of intestinal metaplasia and dysplasia. One of the main reasons for the inconsistent results is that interpretation of methylene blue staining is operator dependant, like many of the advanced imaging techniques (Canto and Kalloo 2006).

Positive results for the detection of intestinal metaplasia have been shown in a number of studies with high sensitivity (91%-98%) and variable specificity (43%-97%) (Canto, Setrakian et al. 2000; Canto, Setrakian et al. 2001; Kiesslich, Hahn et al. 2001; Kouklakis, Kountouras et al. 2003; Ragunath, Krasner et al. 2003). A randomised controlled trial comparing methylene blue targeted biopsies vs. random biopsies found methylene blue detected more intestinal metaplasia 75 % compared to random biopsies 68 % (P = 0.032). However, no significant differences were found for the diagnosis of dysplasia and carcinoma (Ragunath, Krasner et al. 2003).

Poorer results for the detection of intestinal metaplasia are seen in some smaller studies (sensitivity, 53%-72%; specificity, 32%-51%) (Gangarosa, Halter et al. 2000; Dave, Shousha et al. 2001; Wo, Ray et al. 2001). In a study assessing the yield of dysplasia in 30 patients, a random biopsy protocol found dysplasia in 17 patients, whereas methylene blue targeted biopsies of unstained areas found dysplasia in only 9, regardless of what technique was used first (Lim, Rotimi et al. 2006).

Safety issues have been raised with the use of methylene blue which causes the mucosa to be photosensitised by white light resulting in oxidative damage of DNA within BO mucosa (Olliver, Wild et al. 2003). However, Olliver’s study did not demonstrate that the DNA changes persist and result in an elevated cancer risk. Furthermore there has not been any reported increased incidence of malignancy in patients undergoing
surveillance with methylene blue chromoendoscopy for BO or chronic ulcerative colitis (Canto and Kalloo 2006).

Overall it appears the methylene blue targeted biopsies are superior to random biopsies for the detection of intestinal metaplasia however are of no benefit in the diagnosis of dysplasia or early cancer.

1.11.3.2 Indigo carmine

There is little data in the literature on this technique. A study by Sharma with magnification endoscopy with indigo carmine showed that high grade dysplasia was able to be differentiated from non dysplastic BO in six patients with an irregular/distorted pattern. However 18 patients with low grade dysplasia had ridged villous pattern which was incorrectly characterised as intestinal metaplasia (Sharma, Weston et al. 2003).

1.11.3.3 Acetic acid

Combination of acetic acid and magnification endoscopy characterised 4 pit patterns in BO. The detection of intestinal metaplasia with this combination technique had a sensitivity of 87% and was significantly superior to standard white light endoscopy however failed to differentiate the higher neoplastic grades of dysplasia (Guelrud, Herrera et al. 2001).

1.11.4 Autofluorescence endoscopy

Autofluorescence endoscopy (AFI) differentiates tissue types based on their differences in fluorescence emission (Wolfsen 2009). AFI involves stimulation of certain molecules (fluorophores) by short wavelength light (ultraviolet or blue light). On excitation, these fluorophores emit fluorescent light spread over a range of longer wavelengths from the green to the red spectrum. This is called autofluorescence, and responsible endogenous
fluorophores include collagen, reduced nicotinamide adenine dinucleotide, elastin, flavin, aromatic amino acids, and porphyrins (Sharma and Bansal 2006). The endoscopy processor incorporates the charge coupled device signal into a real time pseudocolour image – normal mucosa = green, dysplasia/neoplasia = red/purple tones.

A study of 35 consecutive patients with BO showed no benefit of AFI over white light and random biopsies for the detection of dysplasia (Egger, Werner et al. 2003). Another study by Kara of 22 patients with high grade dysplasia / intramucosal cancer found AFI increased the detection rate of high grade dysplasia / intramucosal cancer from 63% to 91% over random biopsies, however this increased sensitivity was associated with a high false positive rate of 51% (Kara, Peters et al. 2005).

1.11.5 Multimodality endoscopic assessment

Advanced imaging techniques when used in combination for the detection of dysplasia, may provide complementary information. This may improve accuracy enough to support a targeted biopsy protocol rather than the currently accepted random Seattle protocol. In a single centre, cross sectional study of 20 patients with BO, AFI was used to red flag lesions and then NBI used to further characterise lesions. This dual technique led to a reduction in the false positive rate from 40% to 10%. All of the 14 patients with high grade dysplasia were detected by a combination of AFI and NBI (Kara, Peters et al. 2006).

A multicentre study feasibility study of a trimodal imaging approach in 84 patients with BO showed AFI identified 27/30 patients with high grade dysplasia / intramucosal cancer compared with high definition white light endoscopy which identified only 16 patients. The three patients with high grade dysplasia which were missed by AFI were detected by random biopsies. The increase in lesion detection by AFI is associated with a low positive predictive value, however this can be improved with NBI (Curvers, Singh et al. 2008).
1.11.6 Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) is a new endoscopic technique that provides cross sectional mucosal images at a microscopic level, at and below the surface epithelium to a depth of 250μm. The images obtained are up to 1250 fold magnification, well beyond that of a conventional endoscope (Kiesslich, Goetz et al. 2005). The mucosal images are obtained in a cross sectional manner in contrast to standard histopathologic sections, where sections are perpendicular to the mucosal surface.

1.11.6.1 Technical principles

Confocal endomicroscopy utilises a low power blue laser (488 nm) that focuses one single point onto the tissue to be assessed. The laser beam is reflected back to a pinhole which is at the identical focal length to the laser which is then transmitted to a detector. The surrounding white light is not at the same focal length to that of the pinhole and is therefore excluded from the confocal image. In order to create a digital cross-sectional image within the tissue layers the beam path maps out a microscopic square by scanning from left to right and then top to bottom,(typically, 50 μm-1.0 mm across) (Polglase, McLaren et al. 2005).

1.11.6.2 Confocal laser endomicroscopy systems

Two confocal endomicroscopy systems have been developed, the confocal endoscope (eCLE), the EC3870CILK (Pentax, Tokyo, Japan) and the probe-based confocal endomicroscopy (pCLE), the Cellvizio system (Mauna Kea Technologies, Paris, France). Both systems have their own strengths and weaknesses.

The Pentax endomicroscope has the confocal lens incorporated within the framework of the endoscope. The confocal lens protrudes slightly from the end of the endoscope, developed by Optiscan (Australia). With this system, images can be collected from the mucosal surface to a depth of 250 μm, moving in depth by 7-μm increments. Alternatively, the probe based confocal endomicroscopes are passed down the biopsy
channel of a standard endoscope. The different probes have varying depth of image capture which ranges from 55 to 65 μm from the surface for the Gastroflex/Coloflex UHD probe to 70-130 μm for the Gastroflex/Coloflex probe. The image resolution is higher with the Pentax endomicroscope than the probe based system, with a lateral resolution of 0.7 μm compared with 1-3.5 μm. The main advantage of the probe based system is the rapid acquisition of images with a video frame rate of 12 images per second compared with the Pentax endomicroscope which has an imaging rate of 0.8–1.6 images per second. The other advantage of a probe based confocal endomicroscope is that a new endoscope doesn’t need to be purchased as it can be passed down the biopsy channel of a standard endoscope.

1.11.6.3 Contrast agents

In order to obtain images at depths below the surface an exogenous fluorescent contrast agent is required which is excited by the laser light. Intravenous fluorescein, used for many years in ophthalmology to better visualise retinal vasculature, is the most commonly used agent which correlates with the blue region of the light spectrum. The recommended dose is 5ml of 10% fluorescein sodium which is injected intravenously immediately pre procedure which usually lasts around 30min. The intravenous fluorescein binds avidly to serum albumin within the circulation. A small proportion is free and traverses capillaries to enter tissue. Within the tissue the fluorescein localizes within the extracellular matrix of the surface epithelium and the lamina propria. Intravenous fluorescein highlights blood vessels, intracellular spaces, and lamina propria but does not stain nuclei, however mucin appears dark, therefore goblet cells of BO are dark. Other less commonly used agents are acriflavine, which is a topical antiseptic agent and cresyl violet.

1.11.6.4 Confocal classification systems

Prior to its use in the assessment of patients with BO, confocal endomicroscopy was first used to assess colonic polyps. In an initial study of 27 patients assessing colonic pathology, all 390 areas assessed with confocal endomicroscopy were biopsied for histopathological correlation. This study found that confocal endomicroscopy had a
high accuracy (sensitivity, 97.4%; specificity, 99.4%; accuracy, 99.2%) for prediction of neoplastic changes when compared to histopathology used as the gold standard (Kiesslich, Burg et al. 2004).

The first study of patients with BO was performed by Kiesslich in 2006 on 63 patients, using fluorescein based contrast agent. For the detection of non dysplastic Barrett’s oesophagus they found a sensitivity of 98.1%, specificity of 94.1% and an accuracy 96.8%. For the detection of neoplasia, they found sensitivity 92.9%, a specificity of 98.4% and an accuracy of 97.4%. They also demonstrated a very good interobserver agreement for the prediction of the histopathological diagnosis with a kappa score of 0.843. The captured confocal images were not assessed in real time but instead selected high-quality confocal images were chosen after the procedure to be assessed (Kiesslich, Gossner et al. 2006).

Based on this initial study Kiesslich developed the Confocal Barrett’s Classification. Findings suggestive of the presence of high grade dysplasia or cancer include the presence of irregular, black cells with a loss of the normal cellular pattern and distorted subepithelial capillaries with leakage of fluorescein (Kiesslich, Gossner et al. 2006).
Confocal classification system (Kiesslich, Gossner et al. 2006)

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<tr>
<th>Confocal diagnosis</th>
<th>Vessel architecture</th>
<th>Image Examples</th>
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<tbody>
<tr>
<td><strong>Gastric type epithelium</strong></td>
<td>Capillaries of regular shape only visible in deeper parts of the mucosal layer.</td>
<td><img src="image1.png" alt="Image examples" /> <img src="image2.png" alt="Image examples" /></td>
</tr>
<tr>
<td><strong>Barrett’s epithelium</strong></td>
<td>Subepithelial capillaries of regular shape beneath columnar lined epithelium visible in upper and deeper parts of the mucosal layer</td>
<td><img src="image3.png" alt="Image examples" /> <img src="image4.png" alt="Image examples" /></td>
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<tr>
<td><strong>Neoplasia</strong></td>
<td>Irregular capillaries visible in upper and deeper parts of the mucosal layer. Leakage of vessels leads to a heterogeneous and brighter signal intensity within the lamina propria.</td>
<td><img src="image5.png" alt="Image examples" /> <img src="image6.png" alt="Image examples" /></td>
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<tr>
<th>Cell architecture</th>
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<tr>
<td><strong>Gastric type epithelium</strong></td>
<td>Regular columnar lined epithelium with round glandular openings and typical cobble stone appearance</td>
</tr>
<tr>
<td><strong>Barrett’s epithelium</strong></td>
<td>Columnar lined epithelium with in between dark mucin in goblet cells in upper parts of the mucosal layer. In deeper parts, villous like, dark shaped regular cylindrical Barrett’s epithelial cells are present.</td>
</tr>
<tr>
<td><strong>Neoplasia</strong></td>
<td>Black cells with irregular apical and distal borders and shapes with high dark contrast to surrounded tissue</td>
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A probe based study looking at the diagnosis of high grade dysplasia / cancer on images obtained were read by two independent observers and then correlated with histology. In a per-biopsy analysis, the sensitivity and specificity for the two independent investigators were 75.0% and 88.8%, and 75.0% and 91.0%, respectively, translating at best into a positive predictive value of 44.4% and a negative predictive value of 98.8%. Therefore a low sensitivity but high negative predictive valve. The inter-observer agreement was considered good with a kappa score of 0.6 (Pohl, Rosch et al. 2008).

1.11.6.5 Real time studies of Confocal assessment

The Confocal Barrett’s Classification was first validated by an Italian group that presented their results in abstract form at DDW in 2008. This study included 39 patients and found BO and associated neoplasia could be predicted with a sensitivity of 96.4%. The agreement between endomicroscopic and histological results was substantial with a kappa score of 0.74. A prospective, randomized controlled, crossover study comparing targeted biopsies with CLE vs. a random 4 quadrant biopsy protocol. CLE with targeted mucosal biopsies increased the yield of neoplasia from 17% to 34% and required 59% fewer biopsies to achieve a diagnosis. Two thirds of patients in the surveillance group did not need any mucosal biopsies at all as assessed by CLE (Dunbar, Okolo et al. 2009).

1.11.6.6 Limitations of Confocal laser endomicroscopy

These real time studies are single centre studies performed by expert endoscopists in the practice of CLE. Performing CLE in real time requires a clear understanding of the Confocal Barrett’s Classification system and the ability to acquire and assess the images rapidly in vivo, which has anecdotally a long learning curve. Other limitations include the reduced image quality with either endomicroscopy system due to movement artefact. Furthermore the difficulty in distinguishing low grade dysplasia from non dysplastic BO is challenging with the lack of nuclear staining with fluorescein. The difficulty in assessing lower grades of dysplasia is also seen with histopathological interpretation of biopsies, with poor inter-observer agreement.
1.11.7 Endocytoscopy

Involves highly magnified probes up to x1125 to evaluate cellular and nuclear characteristics. The main limitation of this technique is difficulty obtaining good quality images. Not many studies exist in BO. In a study of 16 patients, 166 biopsy sites were assessed. At most, 23% of images with lower magnification were interpretable to identify characteristics of neoplasia, and 41% with higher magnification. Interobserver agreement was fair at best (kappa from < 0 to 0.45). Limited by poor image quality affecting between 22%-49% of images captured (Pohl, Koch et al. 2007).

1.12 Staging of Barrett’s oesophagus

Accurate neoplastic staging in the current era is the cornerstone for the successful endoscopic management of patients with dysplastic BO. This ensures that those in whom endoscopic therapy is undertaken are treated with the appropriate modality depending on the depth of invasion and that patients with invasion into the sub mucosa are referred for curative surgical oesophagectomy.

1.12.1 The importance of accurate T-staging

The oesophagus unlike other parts of the gastrointestinal tract has lymphatic vessels within the lamina propria as well as larger channels within the submucosa and muscularis propria. Therefore intramucosal carcinoma has the potential to metastasize (Spechler and Davila 2009). In a large retrospective German study of 290 patients with early oesophageal cancer, of the 157 patients with adenocarcinoma, 70 patients had intramucosal cancer and none had lymph node spread. In patients with submucosal invasion 21% had lymph node spread. The remaining patients had squamous cell carcinoma, where the rate of lymph node metastases was higher for both intramucosal cancer (7.7%) and for those with submucosal invasion (36.4%) (Stein, Feith et al. 2005). In the literature the rates quoted of lymph node metastases in patients with
intramucosal adenocarcinoma range from 0% to 7% - with the approximately 2% being the median percentage. Once the submucosa is breached the rate of lymph node metastases increases to >20% (Rice, Zuccaro et al. 1998; Feith, Stein et al. 2003; Stein, Feith et al. 2005; Oh, Hagen et al. 2006; Peyre, DeMeester et al. 2007). This highlights the importance of accurate T-staging in choosing the correct treatment modality.

Further research has aimed to expand the indications of endoscopic therapy by analysing whether invasion into the superficial layers of the submucosa carries the same risk of nodal metastases as it does for deeper submucosal invasion. A number of studies have separated the levels of the submucosa into upper third (SM1), middle third (SM2) and lower third (SM3) hoping to demonstrate that the risk of nodal disease may be less in SM1 cancers and therefore amenable to endoscopic therapy.

A recent retrospective study from the Rochester group of 51 patients with T1 adenocarcinoma assessing nodal metastases found that nodal metastases were present in 0% (0 of 25) of intramucosal cancers , 21% (3 of 14) of SM1, 36% (4 of 11) of SM2, and 50% (2 of 4) of SM3 tumours. The differences were significant between intramucosal and submucosal tumours (p < 0.0001), however not between the 3 depths of submucosal invasion (p = 0.503).(Sepesi, Watson et al. 2010). Another study retrospective study of oesophagectomy specimens of 80 patients with T1 disease found 12.9% LN metastases in SM1 disease and 20.4% LN metastases in SM3 disease (Badreddine, Prasad et al. 2010).

1.12.1.1 The utility of endoscopic ultrasound

Endoscopic ultrasound (EUS) incorporates an ultrasound probe into the tip of an endoscope. Because of the proximity of the EUS transducer to the organ(s) of interest, the images obtained are frequently more accurate and more detailed than the ones obtained by traditional ultrasound. The EUS also can obtain information about the layers of the intestinal wall as well as adjacent areas such as lymph nodes and the blood vessels. Other uses of EUS include studying the flow of blood inside blood vessels using Doppler ultrasound and to obtain tissue samples by passing a needle (fine needle aspiration), under ultrasound guidance, into enlarged lymph nodes or suspicious tumours.
EUS is an important tool for accurate staging of patients with invasive BO. The largest study in the literature was from the Wiesbaden group who conducted a retrospective review of 179 patients who had EUS prior to oesophagectomy for staging of oesophageal cancer (Barrett’s adenocarcinoma (n = 134) and squamous cell cancer (n = 45)). The overall accuracy for EUS in identifying the correct T stage was 74% (95%CI 66-80%). T2 cancers in particular are frequently over staged, which would impact significantly on the subsequent treatment strategy (Pech, Gunter et al. 2010). Another large resection based study of 100 patients found similar results with an accuracy 79.6% for EUS staging and low sensitivity of 48% for patients with sub mucosal tumours (n=25) (May, Gunter et al. 2004).

Smaller studies also have demonstrated this modest accuracy when compared with pathologic specimens both from oesophagectomy specimens and endoscopic mucosal resection specimens (Larghi, Lightdale et al. 2005; Waxman, Raju et al. 2006).

Therefore these studies have shown that EUS is inadequate in determining accurately the T-stage of invasive BO however it is the best modality for the assessment of local and regional lymph node metastases, with the ability to provide a fine needle aspirate to determine tumour involvement of the lymph node (Spechler and Davila 2009).

1.12.1.2 The utility of Endoscopic Mucosal Resection

Endoscopic mucosal resection has been shown to be the best technique for accurate T-staging of invasive neoplastic BO. Two techniques exist. The cap and suck technique which involves a submucosal injection of saline to lift the mucosa, the mucosa is then sucked into an endoscopic mucosal resection cap mounted on the end of the endoscope. A snare is deployed through the biopsy channel and over the sucked up mucosa and the mucosa is then resected. The Duette system (band ligation) is similar to variceal band ligation. The mucosa is sucked into the cap and a band is deployed. The mucosa is then snared either over or under the applied band and then resected. This system allows multiple resections within a single intubation.
Compared to standard biopsy endoscopic mucosal resection provides a large mucosal specimen which usually involves the submucosal layer, to be assessed by the pathologist, which has been shown to improve diagnostic accuracy and result in lower interobserver variability. A study comparing 251 endoscopic mucosal resection specimens vs. 269 biopsy samples showed that submucosa was present in the majority of endoscopic mucosal resections, compared with biopsy specimens (88% vs. 1%, P < .0001). Almost all biopsy specimens (99%) included lamina propria. However, the muscularis mucosa was observed in only 58% of biopsy specimens. Interobserver agreement on the diagnosis of dysplasia was significantly greater for endoscopic mucosal resection specimens than biopsy specimens (low-grade dysplasia, 0.33 vs. 0.22, P < .001; high-grade dysplasia, 0.43 vs. 0.35, P = .018) (Wani, Mathur et al. 2010). Due to the larger pathological specimen, endoscopic mucosal resection results in upstaging of the depth of invasion compared to biopsy alone. A study of 40 patients undergoing endoscopic mucosal resection – 6/25 (24%) with high grade dysplasia were upstaged to intramucosal carcinoma and 6/15 (40%) with intramucosal carcinoma were upstaged to submucosal cancer (Larghi, Lightdale et al. 2005).

Therefore endoscopic mucosal resection is superior to EUS in T-staging due to improved accuracy in the assessment of submucosal invasion, a critical determinant excluding patients from definitive endoscopic therapy (Spechler and Davila 2009).

1.12.2 Other staging investigations

The other investigations commonly used for loco regional staging are computed tomography (CT) and positron emission tomography (PET). These modalities have not been specifically studied in a Barrett’s population however are regarded as standard of care in cancer management in excluding distant disease and loco regional lymph nodes which would preclude curative endoscopic therapy.
1.13 Treatment of Barrett’s oesophagus

The decision to treat BO and by what method is based on a number of factors. At present there is a clear consensus that patients with high grade dysplasia need definitive treatment due to the risk of progression to cancer. With the advent of safer more efficacious endoscopic therapies treating patients with low grade dysplasia is currently being debated. Treatment needs to be individualised depending on the following considerations (Wang and Sampliner 2008).

Patient factors, including age, co morbidities and preference for particular treatment. For example a patient who is not considered a surgical candidate due to co-morbidities may undergo endoscopic therapy even in the presence of submucosal disease. Oesophageal factors, including length of BO, presence of visible mucosal abnormalities that require endoscopic mucosal resection, presence of anatomical considerations such as strictures. Finally institutional factors / local expertise as surgical oesophagectomy is best performed in a high volume centre.

The key determining factor of choice of treatment is the T-stage of the dysplastic Barrett’s oesophagus. A recent systematic review performed by Dunbar has further re-enforced the position of the safety of endoscopic therapy even in patients with intramucosal cancer. They found that in the 524 patients who had an oesophagectomy for HGD none had lymph node metastases identified and in the 1350 patients in who an oesophagectomy performed for intramucosal cancer, lymph node metastases were found in 26 (1.93 %, 95 % CI 1.19 - 2.66 %). The authors rightly concluded that as the mortality of oesophagectomy often exceeds 2%, the concern of undiagnosed lymph node metastases in these two groups is no longer a justification for surgical therapy over an endoscopic approach (Dunbar and Spechler 2012). This data also highlights that endoscopic ultrasound may not be necessary if an EMR only shows HGD or intramucosal cancer.

Patients with submucosal cancer, especially with high risk features such as lympho-vascular invasion and poor tumour differentiation are beyond the scope of endoscopic therapy and should be referred for surgery after extensive staging with endoscopic ultrasound, CT and PET scanning.
he management options available include endoscopic surveillance, pharmacological therapy, endoscopic therapy and surgical therapy.

1.13.1 Surveillance endoscopy

Endoscopic surveillance is designed to detect cancer at earlier stage in patients with BO (Sharma 2009). This involves careful inspection of the Barrett’s segment with targeted biopsies of any area with a visible mucosal abnormality and random biopsies of the remaining mucosa adhering to the Seattle protocol.

ACG guidelines published in 2008 suggested that if two endoscopies 12 months apart demonstrated non dysplastic BO then surveillance can be at a frequency of 3 yearly (Wang and Sampliner 2008). If low grade dysplasia is detected, then an endoscopy should be repeated in 6 months. If low grade dysplasia is confirmed at the repeat endoscopy then yearly surveillance is recommended (Wang and Sampliner 2008). The presence of high grade dysplasia is an indication for definitive management and should not be monitored due to high risk of progression to cancer.

1.13.1.1 Utility of surveillance endoscopy

There are no randomised controlled trials that evaluate the efficacy of surveillance. A number of studies have shown that cancers detected during surveillance had better survival compared to cancers that presented with symptoms (Peters, Clark et al. 1994; van Sandick, van Lanschot et al. 1998; Ferguson and Durkin 2002). A non randomised retrospective analysis found 5 year survival up to 80% in surveillance diagnosed cancers (Streitz, Andrews et al. 1993; Fountoulakis, Zafirellis et al. 2004). There is however the potential for lead time and length time bias in these studies as they are retrospective and non randomised (Sampliner 2009). Other studies have shown that patients with BO have similar survival and no decrease in disease related mortality in those undergoing surveillance compared with those without surveillance (Cameron, Ott et al. 1985; Van der Veen, Dees et al. 1989; Eckardt, Kanzler et al. 2001).
1.13.1.2 Cost of surveillance endoscopy

Due to the lack of prospective randomised trials a number of studies have used modelling estimates to determine the cost effectiveness of surveillance. These studies have found that surveillance strategies in BO are cost effective when compared to other surveillance programs for cancer detection.

A Markov model was formulated for a hypothetical 50 year old man with chronic GORD. They found that screening and surveillance of patients with both dysplastic and nondysplastic BO followed by oesophagectomy for surgical candidates with high-grade dysplasia or oesophageal cancer and endoscopic therapy for cancer patients who were not operative candidates cost $12,140 per life-year gained compared to no screening (Gerson, Groeneveld et al. 2004). Another Markov model found the incremental cost-effectiveness of bi-annual endoscopy is $16,695/ life-year saved from oesophageal cancer compared to no surveillance (Sonnenberg, Soni et al. 2002).

1.13.2 Acid suppression

GORD is a well described risk factor for BO and disease progression as discussed in earlier chapters. Acid suppression has been shown in both molecular and clinical studies to have beneficial effects on BO.

In cell line models acid suppression has been shown to increase cell differentiation, decrease COX-2 expression and proliferation in non dysplastic BO tissue (Ouatu-Lascar, Fitzgerald et al. 1999; Shirvani, Ouatu-Lascar et al. 2000; Lao-Sirieix, Lovat et al. 2007).

A number of cohort studies have shown acid suppression tends to reduce the risk of progression to dysplasia and may decrease the area of BO affected (Peters, Ganesh et al. 1999; El-Serag, Aguirre et al. 2004; Hillman, Chiragakis et al. 2004; Hillman, Chiragakis et al. 2008). One of the larger cohort studies was an Australian study of 350
patients, with a median follow-up of 4.7 years. Patients who delayed using a proton pump inhibitor (PPI) for 2 years or more after diagnosis with BO had 5.6 times (95% CI, 2.0-15.7) the risk of developing low-grade dysplasia at any given time as those who used a PPI in the first year. Similar results were found for the risk of developing high-grade dysplasia or adenocarcinoma (Hillman, Chiragakis et al. 2004). There is currently a large multicentre, randomised controlled trial underway in its 5th year - The AspECT trial, looking at the long-term chemoprevention effect of esomeprazole with or without aspirin.

1.13.2.1 Degree of acid suppression

Acid suppression with PPI has been shown to be superior to H2 receptor antagonists. A double blinded randomised study comparing high dose PPI (40mg bd omeprazole vs. 150mg bd ranitidine) with 2 year follow up – 53/61 patients completed study. Small regression of BO was seen in the PPI group vs. no change in ranitidine group (Peters, Ganesh et al. 1999). A longitudinal study over a 6 year period found that omeprazole 20mg daily resulted in no change in the area of BO vs. baseline findings, however the study did not look at progression of dysplasia (Cooper, Neumann et al. 1998). Therefore until the results of the AspECT trial become available the optimal dose is still unclear.

1.13.3 Chemoprevention

A number of different medications and multivitamins have been shown to mediate the risk of oesophageal adenocarcinoma. A systemic review and meta-analysis of observational studies support a protective association between aspirin and NSAIDs with a 33% reduction in the Odds ratio for developing oesophageal adenocarcinoma and provide evidence for a dose effect (Corley, Kerlikowske et al. 2003; Sadeghi, Bain et al. 2008). However a prospective, nested case-control study did not show any benefit of NSAIDs in risk reduction of adenocarcinoma (Lindblad, Lagergren et al. 2005). A recent study by Rothwell showed that aspirin reduced the overall risk of fatal
adenocarcinoma in the trial populations (HR 0.65, 95% CI 0.53-0.82, \( p=0.0002 \)).(Rothwell, Wilson et al. 2012)

The cyclo-oxygenase pathways have been implicated in the pathogenesis of BO via their effects on apoptosis of cells. COX-2 appears to be a possible mechanism for avoidance of apoptosis via its prostaglandin products (Shirvani, Ouatu-Lascar et al. 2000). These findings have provided the rationale for using COX-2 inhibitors as a chemoprevention strategy. This was concept was tested in a multicentre, randomised control trial of celecoxib 200mg bd vs. placebo for 48 weeks in patients with BO. Their results failed to show a protective effect of celecoxib in preventing progression of Barrett's dysplasia to cancer. No increased cardiovascular complications were seen in the celecoxib group (Heath, Canto et al. 2007).

A large prospective cohort study of 339 patients evaluated the association between supplemental vitamins and minerals on neoplastic progression of BO. Patients were followed for a mean of 5 years in which 37 cases of oesophageal adenocarcinoma were diagnosed. Patients who took 1 or more multivitamin pills/day had a significantly decreased risk oesophageal adenocarcinoma (HR = 0.38; 95% CI = 0.15-0.99) compared to those not taking multivitamins. Significant inverse associations were also observed with supplemental vitamin C and vitamin E (Dong, Kristal et al. 2008).

1.13.4 Endoscopic therapy

A study looking at the thickness of BO in 200 patients found Barrett columnar epithelium is 0.50mm; range 0.39 to 0.59 mm. (Ackroyd, Brown et al. 1999). Therefore endoscopic therapies need to adequately ablate to a minimum of this depth for epithelial disease and below this for invasive disease that may extend to the muscularis mucosa which has an estimated depth of 1.0mm.

Despite the recent interest in a number of endoscopic therapies, no study has demonstrated a decreased risk of cancer progression for patients with dysplastic BO treated with endoscopic therapy. This is predominantly due to the design of the studies,
their limited follow up periods and relatively small numbers treated (Spechler and Davila 2009).

Many factors influence the success of endoscopic therapy. Endoscopic treatment of BO should be performed in tertiary referral centres that have the required expertise and resources. Furthermore these centre have access to expert surgical staff, multidisciplinary meetings and expert gastrointestinal pathologists which all play a significant role in management (Pouw, Seewald et al. 2010).

1.13.4.1 Thermal based therapy

1.13.4.1.1 Argon Plasma Coagulation

Argon plasma coagulation (APC) is delivered to the mucosa via a probe that is passed down the working channel of a standard endoscope. The probe applies a high frequency, monopolar current of ionized argon gas that coagulates the mucosa to a depth between 1 to 3mm. The main determinants of the depth of coagulation are the argon gas flow rate, generator setting, distance to the mucosa and duration of application. Most studies in the literature use energy settings from 40W to 90W.

Non dysplastic Barrett’s oesophagus

Most of the literature for treatment of BO with APC is in non dysplastic BO, however most of these studies are case series with a few randomised controlled trials. Most of the case series differ in their methodology and follow up. Complete eradication rates within the randomised controlled trials ranges from 36% to 97% in non dysplastic BO (Ackroyd, Tam et al. 2004; Hage, Siersema et al. 2004; Dulai, Jensen et al. 2005; Sharma, Wani et al. 2006; Bright, Watson et al. 2007; Bright, Watson et al. 2008). In a randomised study comparing APC to a control group treated with PPI found at 12 months, 14 of 23 APC patients had at least 95% regression, and nine of 23 had complete regression of BO. No surveillance patient had more than 95% regression (Bright,
Another study comparing APC and multipolar electro coagulation found that in 24 months follow up both had similar outcomes regarding eradication rates (63% vs. 75%), number of sessions and adverse events (Sharma, Wani et al. 2006).

The study with the longest follow up period of 68 months, compared APC to endoscopic surveillance after anti-reflux surgery. This study found 40% complete remission of intestinal metaplasia (CR-IM) vs. 20% in the surgical group. 2 patients in the surgical group progressed to high grade dysplasia vs. 1 patient in the APC group who progressed to low grade dysplasia. 2 patients in the APC group developed an oesophageal stricture requiring dilatation (Bright, Watson et al. 2007).

**Low grade dysplasia**

In patients with low grade dysplasia the largest case series was of 32 patients with 24 months of follow up who received APC at 3 weekly intervals until complete eradication was achieved. The ablation of BO was achieved with a median of 2.0 APC sessions, without side-effects, however recurrence of BO was detected in 3 patients (Familiari, Scaffidi et al. 2003). In a randomised control trial of 26 patients comparing APC to photo dynamic therapy (PDT). At 12 months there was no statistical difference in eradication rates of BO: APC 56%, PDT 60% or dysplasia APC 67%, PDT 77%. Side effects were more commonly seen in the PDT group. Importantly buried Barrett’s was seen in both groups, with one patient in the PDT arm developing adenocarcinoma under the neo-squamous epithelium (Ragunath, Krasner et al. 2005).

**High grade dysplasia**

No randomised controlled trials have been performed in patients with high grade dysplasia treated with APC. The largest case series of 29 patients with longest follow up of median 37 months treated with a median of 2 sessions. They achieved 86% complete remission of high grade dysplasia and 76% CR-IM. However 4 patients progressed to adenocarcinoma and one patient had an oesophageal perforation (Attwood, Lewis et al. 2003).
1.13.4.1.2 Multipolar electrocoagulation

The mechanism of multipolar electrocoagulation is thermal contact with a probe that transmits electrical energy directly to the tissue surface resulting in increased temperature and destruction of the tissue. As with APC, the depth of burn is dependent on contact duration, pressure of the probe and generator settings (Dumot and Greenwald 2008).

The only studies of this modality have been in non-dysplastic BO. There are 2 small case studies with median follow up of under 2 years which demonstrate a complete remission rate of 100% (11/11 and 14/14). In one study 3 patients developed “buried BO” containing intestinal metaplasia (Montes, Brandalise et al. 1999; Sharma, Bhattacharyya et al. 1999). The largest case series is a multicentre study of 58 patients with intestinal metaplasia and short follow up of 6 months of which 78% achieved CR-IM, however no longer term results are available (Sampliner, Faigel et al. 2001). The main limitation of the technique is that it is time consuming, therefore not practical to treat long segments of BO.

1.13.4.1.3 Lasers (Nd:YAG, KTP:YAG)

The two most commonly used lasers are the Neodymium: yttrium aluminium garnet laser which results in depth of injury up to 4-6mm and the Potassium titanyl phosphate laser which causes a more superficial injury. The data involving laser therapy is confined to small case series. The largest series was of 31 patients where BO was eradicated in 21 patients after 6.5 +/- 1.2 laser sessions. Complications included one perforation, one upper gastrointestinal bleed and one stricture. Of eight post-laser recurrences, seven were successfully re-ablated; however one developed adenocarcinoma requiring oesophageal resection (Fisher, Bromer et al. 2003).
1.13.4.1.4 RADIOFREQUENCY ABLATION (RFA)

Technical aspects

The Barrx Halo system consists of 2 ablation systems. The HALO 360 consists of a 4cm balloon which has a 3cm RFA segment which consists of 60 independent electrodes that are tightly spaced with alternating polarity. 5 different balloon diameters can be chosen after the patient’s oesophagus is firstly assessed with an automated sizing balloon. Once inflated the balloon flattens the oesophageal mucosa. The energy delivered is controlled by the RF generator at 12J/cm² and is delivered in less than 1sec. After the first ablation the balloon is removed and cleaned and the oesophagus is cleared with a cap mounted onto the endoscope to provide a clean surface to deliver the second ablation. The automation of this system leads to enhanced safety and efficacy compared to other ablative therapies.

The HALO 90 has an endoscope mounted electrode (20mm x 13mm) which allows focal delivery of RFA for small areas of BO. The same energy and automation are used as for the HALO 360.

Dosimetry studies

Prior to the first human studies of HALO RFA, porcine models were initially used to assess optimal radiofrequency ablation dose. Ganz performed a multiphase study assessing optimal dose of RFA. Phases 1-3 in porcine model and phase 4 human study. The human study assessed completeness of ablation and ablation depth in patients 48 hours prior to oesophagectomy for cancer. 3 patients showed complete ablation of epithelium with 12 J/cm² with one ablation with variable depth into the lamina propria and not beyond the muscularis mucosae (Ganz, Utley et al. 2004). A study by Dunkin in patient’s pre-oesophagectomy for cancer assessed 3 energy densities of 8, 10 or 12 J/cm² and also compared 1 vs. 2 ablations. They also found that ablation depth was related to energy delivered. With 10J/cm² x2 and 12J/cm² with both 1 or 2 ablations resulting in complete epithelial ablation (Dunkin, Martinez et al. 2006). A final
dosimetry study by Smith showed that complete removal or ablation of all intestinal metaplasia and high grade dysplasia was achieved in 9 of 10 ablation zones with the minimum delivered energy of 10J/cm² x 2 ablations and maximum of 14J/cm² x 4 ablations. There was a graded increase in depth of ablation with higher energy and multiple applications. The 10J/cm² x 2 ablations resulted in complete ablation of epithelium and minimally into the lamina propria whereas the maximal ablation of 14J/cm² x 4, ablated into the muscularis mucosa with associated oedema in the superficial submucosa, but no submucosal ablation. In one patient a single focus of HGD within the lamina propria was detected at the ablation margin (Smith, Bejarano et al. 2007).

Clinical/Efficacy studies

Non dysplastic

AIM trial (Ablation of intestinal metaplasia trial) had an initial dosimetry arm which assessed 32 patients then a second effectiveness phase (AIM-2) after selecting 10J/cm² x 2 ablations. This energy dose was derived from their results and the previous dosimetry studies. Results at 12 months (mean 1.5 ablations) 48/69 (70%) had complete eradication of intestinal metaplasia after treatment with the HALO 360 device (Sharma, Wang et al. 2007). After 12 months, focal ablation with the HALO 90 device was performed for remaining areas of intestinal metaplasia. Results at 30 months after further focal ablation therapy (mean number of 1.9 ablations) 60/61 (98%) of remaining patients had CR-IM. (Fleischer, Overholt et al. 2008). The 5 year results were presented at DDW 2010 – 50/60 patients agreed to enter this phase. 46/50 (92%) had CR-IM, 4/50 (8%) had intestinal metaplasia detected. The 4 patients with recurrent intestinal metaplasia underwent further focal RFA with CR-IM achieved at next biopsy session. This study has provided the best longitudinal data of the efficacy of HALO RFA ablation. These results suggest that the technique has good durability of response once CR-IM is achieved. However a small group of patients developed recurrent intestinal metaplasia therefore highlighting the need for ongoing surveillance and retreatment as required.
Low grade dysplasia

A small single centre study of 10 patients with confirmed low grade dysplasia (median BO segment 4.4 cm) underwent circumferential ablation with the HALO 360 device at baseline and then at 4 months as required. 9/10 required focal ablation with the HALO 90 device after 1 year due to persistent BO. Repeat endoscopy with Seattle protocol biopsies were undertaken throughout the treatment period to assess for residual disease. At 2 years, CR-dysplasia was 100 % and CR-IM was 90 %. There were no strictures or buried intestinal metaplasia at follow-up (Sharma, Kim et al. 2008).

High grade dysplasia

A multicenter study of HALO RFA in 142 patients with high grade dysplasia with a median Barrett’s segment length of 6 cm, underwent circumferential ablation at 3 monthly intervals if persistent Barrett’s was detected at each endoscopy (median 1 session, IQR 1-2). No serious adverse events were reported. At a median follow-up 12 months complete remission of high grade dysplasia was achieved in 90.2% of patients, complete remission of dysplasia in 80.4%, and CR-IM in 54.3%. For this study the HALO 90 device was not available which may have increased the rates of CR-IM and CR-dysplasia if the study continued beyond 12 months as did the study by Sharma in patients with low grade dysplasia (Ganz, Overholt et al. 2008).

Randomized control trials

The AIM – dysplasia trial was the first double blinded randomized study of RFA in BO. The study had a multicentre design with a sham-control arm. 127 patients were selected for the study, 64 with LGD (mean length of Barrett’s 4.6cm) and 63 with HGD (mean length of Barrett’s 5.3cm). Patients were then randomised in a 2:1 ratio to receive either radiofrequency ablation (ablation group) or a sham procedure (control group). Patients were able to receive up to four ablations with either the HALO 360 device or the HALO 90 device depending on the characteristics of the remaining BO. Outcomes were
assessed at 12 months after re biopsy of the treated area. In patients with high grade dysplasia, complete eradication occurred in 81.0% of those in the ablation group, as compared with 19.0% of those in the control group (P<0.001). In patients with low-grade dysplasia, complete eradication of dysplasia occurred in 90.5% of those in the ablation group, as compared with 22.7% of those in the control group (P<0.001). Overall, 77.4% of patients in the ablation group had complete eradication of intestinal metaplasia, as compared with 2.3% of those in the control group (P<0.001). Patients in the ablation group had less disease progression (3.6% vs. 16.3%, P = 0.03) and fewer cancers (1.2% vs. 9.3%, P = 0.045). Side effects were generally minor the more serious side effects included one patient with an upper gastrointestinal haemorrhage, and five patients (6.0%) had an oesophageal stricture (Shaheen, Sharma et al. 2009).

The follow up results of the AIM-dysplasia study were presented at DDW 2010 with 2 - 3 years follow up of patients who remained in the study. 65 patients achieved CR-IM at 12 months. 62/65 patients with CR-IM were assessed 59/62 (95.2%) remained CR-IM at 2 years. The 3/62 who relapsed (2x low grade dysplasia, 1x intestinal metaplasia) all had multifocal high grade dysplasia with BO segments 5-6 cm at baseline. 13/13 patients with follow up to 3 years all had a persistent CR-IM. 13 patients failed to achieve CR-IM at 1 year. 11/13 achieved CR-IM at 2 years with a mean of 1.2 further focal ablation sessions.

Cost effectiveness of HALO RFA

A cost utility analysis using a decision analysis model found that endoscopic ablation for patients with high grade dysplasia could increase life expectancy by 3 quality-adjusted years at an incremental cost of <$6,000 compared with no intervention. For low grade dysplasia the incremental cost effectiveness ratio for RFA was $2677 / quality adjusted life years gained vs. $8193 for surveillance (Inadomi, Somsouk et al. 2009). Using a Markov model, ablation for nondysplastic BO is more cost-effective than endoscopic surveillance, however many assumptions have been made in particular no data exists on the degree of cancer risk reduction secondary to ablative therapy (Das, Wells et al. 2009).
1.13.4.1.6 Combination endoscopic therapy

The principle of combination therapy is to remove any visible mucosal abnormalities with endoscopic mucosal resection that harbour’s dysplastic BO as these lesions may invade beyond the epithelium, thereby limiting the efficacy of ablative therapies. Once the visible abnormalities are removed the remaining BO is treated with ablation.

The reason for total Barrett’s ablation after focal EMR is to reduce the risk of recurrent disease. Rates of recurrence vary between studies but are accepted to occur from 11% to 30% at a mean follow up of 3 years (May, Gossner et al. 2002; Peters, Kara et al. 2005). Studies have shown that total ablation reduces the risk of recurrence (Pech, Behrens et al. 2008; Shaheen, Sharma et al. 2009; Pouw, Wirths et al. 2010).

The benefit of the combination approach over pure endoscopic mucosal resection of the entire Barrett’s segment is to limit the complications of endoscopic mucosal resection in particular its high stricture rate. HALO RFA should be delayed 2 months after initial endoscopic mucosal resection to allow the mucosal wound to heal, thereby reducing the risk of oesophageal perforation secondary to balloon insufflations (Spechler and Davila 2009). Many of the combination studies are from European groups.

In a single centre study, 6/11 patients underwent endoscopic mucosal resection for visible mucosal abnormalities leaving the worst pathological grade of residual BO prior to ablation of low grade dysplasia (n = 2) and high grade dysplasia (n = 9). Patients underwent a median of two circumferential and two focal ablation sessions. CR-IM was achieved in all patients which persisted for median follow-up period of 14 months after the last treatment session. No adverse events or strictures, and in none of the 473 biopsies of neo-squamous mucosa demonstrated subsquamous BO (Gondrie, Pouw et al. 2008).

In a European multicenter study of 23 patients who underwent pre-RFA endoscopic mucosal resection of visible lesions; 16 patients had early cancer and 7 patients had HGD. Serial RFA resulted in complete remission of dysplasia in 95% and CR-IM in 88% of patients. In 2 patients small Barrett’s islands persisted despite repeated RFA therefore an escape endoscopic mucosal resection was performed which improved
outcomes with complete remission of dysplasia of 100% and CR-IM of 96%. Complications after RFA included upper gastrointestinal bleeding (n = 1) and dysphagia (n = 1). After additional follow-up (median, 22 months; there was no recurrence of neoplasia (Pouw, Wirths et al. 2010).

This study by Pouw reinforces the efficacy of endoscopic therapy in patients with advanced BO with disease confined to the muscularis mucosa. In the past these patients would be treated with an oesophagectomy. Long term follow up of these patients is required to assess durability of remission rates and need for further treatment.

A recently published, multicenter randomised study of patients with short segments of Barrett’s containing high grade dysplasia / intramucosal cancer, compared combination therapy to stepwise radical endoscopic resection of the entire Barrett’s segment. They found at 12 months, CR-neoplasia was achieved in 25/25 (100%) and CR-IM was achieved in 23/25 (92%) of patients treated with stepwise radical endoscopic resection. CR-neoplasia and CR-IM was achieved in 21/22 (96%) of patients who received combination treatment. In patients who underwent stepwise radical endoscopic resection the stenosis rate was significantly higher (88%) versus (14%) in patients treated with combination therapy,(p<0.001).These results demonstrate the efficacy and non-inferiority of combination therapy to radical stepwise endoscopic mucosal resection (van Vilsteren, Pouw et al. 2011).

1.13.4.2 Photochemical based therapies

1.13.4.2.1 Photo Dynamic therapy

Photodynamic therapy (PDT) involves the destruction of the oesophageal epithelium by photochemical energy. This energy is generated by 2 elements. A photosensitiser is used (either IV porfimer sodium or oral 5-aminolevulinic acid (5-ALA ) which is taken up by the tissues. Then exposure and endoscopy to light results in local generation of toxic, singlet oxygen molecules that lead to tissue destruction. The main limitation of this technique is photosensitivity. Therefore patients need to remain out of sunlight after the procedure to avoid skin and other mucosal sensitivity. Other adverse events include
stricture formation and buried glands. Most studies in PDT are limited to small case series and the photosensitiser, IV porfirmer sodium.

Non dysplastic Barrett's Oesophagus

In a head to head study of 68 patients with 5-ALA comparing PDT vs. APC. 17/33 of patients achieved CR-IM at median 12 months follow up after a median of 2 sessions with PDT vs. 33/34 of patients who achieved CR-IM with a median 3 sessions with APC. This difference had a P<0.0001. Both groups had buried BO between 21-24% of patients (Kelty, Ackroyd et al. 2004).

Low grade dysplasia

A randomised controlled trial of 26 patients comparing APC to PDT. At 12 months eradication of BO was achieved in 56% of patients treated with APC vs. 60% of patients treated with PDT. The difference in eradication rates of dysplasia at 12 months was not statistically significant. Side effects occurred in both groups, severe adverse events included for APC, 2/13 (15%) stricture, 1/13 (8%) odynophagia, chest pain and fever; for PDT 2/13 (15%) photosensitivity, 2/13 (15%) stricture. Buried columnar glands with intestinal metaplasia were seen in both groups, with one patient in the PDT arm developing adenocarcinoma under the neo-squamous epithelium (Ragunath, Krasner et al. 2005).

High grade dysplasia

The largest randomised controlled trial was a multicenter study involving 30 sites, of 208 patients with high grade dysplasia comparing PDT (IV porfimer sodium) plus omeprazole with omeprazole alone. The main outcome measured was complete remission of high grade dysplasia. There was a significant difference (p < 0.0001) in favour of PDT (106/138 [77%]) compared with omeprazole alone (27/70 [39%]) in achieving complete remission of high grade dysplasia. There was still a significant rate of progression in the PDT arm in order of 13% (n=18) and a high rate of documented adverse events with 94% of patients in PDT arm vs. 13% in PPI group (Overholt, Lightdale et al. 2005). 5 year follow up results showed sustainable eradication rates with PDT (77% [106/138] vs. PPI (omep) 39% [27/70], P<.0001). 3 more patients in the
PDT arm progressed to adenocarcinoma (21/138 [15%]) compared with no further patients on omeprazole (20/70 [29%]) (Overholt, Wang et al. 2007). This study highlights the limitations of PDT with high adverse effects, incomplete eradication of Barrett’s leading to buried glands and significant rates of neoplastic progression.

1.13.4.3 Mechanical based therapies

1.13.4.3.1 Endoscopic mucosal resection

The technique of endoscopic mucosal resection and its utility in T-staging has been previously discussed. Endoscopic mucosal resection has a number of advantages over ablative therapies for treatment of invasive BO. The ablative therapies, especially HALO RFA ablate consistently to a depth of 500um which correlates with the epithelium, however variable ablation depths have been noted within the lamina propria which lies between 500um to 1000um – the level of the muscularis mucosa. Therefore if invasion extends in to the lamina propria or to the muscularis mucosa HALO RFA cannot reliably ablate to this depth. This results in the potential to leave buried glands and incompletely eradicate the disease. As described earlier the depth of endoscopic mucosal resection includes the submucosa in up to 88% of specimens therefore invasive Barrett’s oesophagus confined to the muscularis mucosa (intramucosal cancer) will be completely removed by endoscopic mucosal resection (Wani, Mathur et al. 2010). In a study looking at resection margins, negative margins on endoscopic mucosal resection pathology correlate with absence of residual disease at the endoscopic mucosal resection site at oesophagectomy – therefore a cure has been achieved. Submucosal carcinoma on endoscopic mucosal resection specimens was associated with a high prevalence of residual disease at surgery (50%) and metastatic lymphadenopathy (31%) (Prasad, Buttar et al. 2007).

The use of endoscopic mucosal resection in invasive dysplastic BO can be separated into two types of procedures. The first is local resection a visible mucosal abnormality which harbours dysplastic / invasive BO with variable treatment of the remaining Barrett’s segment. The second strategy is stepwise radical complete endoscopic mucosal resection of the entire Barrett’s segment usually confined to shorter segments. The data for endoscopic mucosal resection is limited to a few large European centers.
A non blinded, non randomized study from the Weisbaden group of 100 consecutive patients with low-risk adenocarcinoma of the oesophagus arising in Barrett's metaplasia, were treated with endoscopic mucosal resection for local resection with the suck-and-cut technique. A total of 144 resections (1.47 per patient) were performed without technical problems. No major complications and only 11 minor ones (bleedings without decrease of Hb >2 g/dL; treated with injection therapy) occurred. The decision to treat the remaining non neoplastic BO was individualised with 49/100 patients receiving either APC or PDT. Complete local remission was achieved in 99 of the 100 patients after 1.9 months (range, 1-18 months) and a maximum of 3 resections. During a mean follow-up period of 36.7 months, recurrent or metachronous carcinomas were found in 11% of the patients, but successful repeat treatment with endoscopic resection was possible in all of these cases. The calculated 5-year survival rate was 98% (Ell, May et al. 2007).

In another publication by the Wiesbaden group from 2008 evaluating curative endoscopic therapy in Barrett’s oesophagus with high grade dysplasia / intramucosal cancer. Endoscopic mucosal resection alone was performed in 231 patients (mean age 64.1 years) with intramucosal Barrett’s neoplasia. Complete response could be achieved in 225 patients (97.4%) after a median of 3 months. After a median follow-up of 61 months, 201 patients (87%) are still alive and 30 (13%) died from other causes. Metachronous neoplasia was found in 49 patients (21.2%) but after endoscopic retreatment, 221 patients (95.7%) achieved long-term complete response. The risk factors most frequently associated with recurrence were piecemeal resection (RR 2.4), long-segment Barrett's oesophagus (RR 1.9), no ablative therapy of Barrett's oesophagus after complete remission (RR 2.5), time until complete remission achieved >10 months (RR 0.3) and multifocal neoplasia (RR 2.1) (Pech, Behrens et al. 2008).

Number of case series suggest that endoscopic mucosal resection is able to achieve CR-IM between 76%-100% and complete remission of high grade dysplasia / intramucosal carcinoma in 86%-100% (Seewald, Akaraviputh et al. 2003; Giovannini, Bories et al. 2004; Conio, Repici et al. 2005; Peters, Kara et al. 2006; Lopes, Hela et al. 2007).
A large multicentre study from Amsterdam with 169 patients from four tertiary referral centres performed stepwise radical circumferential endoscopic mucosal resection. Median BE length 3 cm (IQR 2-5), with high grade dysplasia / intramucosal carcinoma, without deep submucosal infiltration or lymph node metastases. Endoscopic mucosal resection was performed every 4-8 weeks, until complete endoscopic and histological eradication of BO and neoplasia. Complete eradication of all neoplasia achieved in 97.6% (165/169) and all CR-IM in 85.2% (144/169) of patients after median follow-up of 32 months complete eradication of neoplasia was sustained in (161/169) 95.3% and CR-IM was sustained in 80.5% (136/169) of patients. Acute, severe complications occurred in 1.2% of patients (bleeding, perforation), and 49.7% of patients developed symptomatic stenosis, requiring dilatation. 1 patient (0.6%) had progression of neoplasia during treatment and died of metastasised adenocarcinoma (Pouw, Seewald et al. 2010).

The endoscopic mucosal resection procedure is technically demanding and should be performed in highly specialized centers. The proceduralist needs to have the skills to recognize and manage complications such as bleeding, perforation and stricture dilatation. The impressive results seen in these studies are offset by oesophageal stenosis which is seen up to half of the patients and recurrent disease. The risk of stricture is related to the extent of resection with some centers advocating endoscopic mucosal resection if the segment length is <5cm (Peters, Kara et al. 2006). A number of factors influence recurrent disease, but this highlights the advantage of combination therapy to eradicate the remaining Barrett’s epithelium.

1.13.4.3.2 Endoscopic submucosal dissection

This technique was pioneered in Japan initially for the en bloc resection of gastric neoplasm’s. It is technically challenging, with long procedural times. Endoscopic submucosal dissection (ESD) in the oesophagus provides further challenges to that encountered in gastric ESD, due mainly to the narrow oesophageal lumen. It provides the opportunity to remove large lesions en bloc allowing for accurate histological assessment of both depth and lateral margin clearance.
In a prospective cohort of 24 patients with adenocarcinoma located at the gastro-oesophageal junction treated with ESD, the en bloc resection rate was 100%. 17 patients were free of disease at 30.1 months follow up. No complications except stenosis occurred (Yoshinaga, Gotoda et al. 2008).

1.13.4.4 Other endoscopic techniques

1.13.4.4.1 Cryoablation

This technique involves the application of liquid nitrogen or carbon dioxide to the oesophageal mucosal surface which is delivered endoscopically via spraying catheters passed through the working channel. The aim of this treatment is to destroy the Barrett’s mucosa by initial freezing and then apoptosis.

The largest study was a multicentre retrospective cohort study involving ninety-eight patients with high grade dysplasia within their Barrett’s segment. Each patient underwent a mean of 3.4 treatments. Sixty patients were included in the efficacy analysis of which 97% had achieved complete remission of high grade dysplasia, 87% had achieved complete remission of dysplasia and 57% had CR-IM. There were few minor complications which occurred at a low frequency (Shaheen, Greenwald et al. 2010).

In another multicentre study of liquid nitrogen spray which assessed the safety, tolerability and efficacy of the procedure, found similar efficacy data to the Shaheen study. The main adverse events include 1x perforation, 3 strictures and transient dysphagia and chest pain in around 15% of subjects (Greenwald, Dumot et al. 2010).

The safety profile of cryoablation appears to compare favourably to such techniques as PDT and APC. However the procedure is technically challenging with uncertainty around the optimal dose to deliver. At this stage the efficacy data appears to be inferior to HALO RFA therefore further studies are required showing improved outcomes before this technique can be considered a reliable therapy.

1.13.5 Complications of endoscopic therapy
Overall the endoscopic therapies are comparatively well tolerated with superior morbidity and mortality rates to that seen with surgical oesophagectomy. The main adverse events encountered range from minor pain and discomfort post procedure to bleeding, perforation and stricture formation. The complication type and rates have been addressed within the discussion of each endoscopic modality.

1.13.6 Buried Barrett’s

Buried Barrett’s is defined as “specialized columnar epithelium covered by a layer of squamous epithelium with no communication with the surface” (Sharma, Wang et al. 2007). In addition to buried metaplastic BO there have been case reports of buried dysplasia and neoplasia (Van Laethem, Peny et al. 2000).

Rates of buried Barrett’s have been identified at baseline in many of the studies of endoscopic therapy. In Shaheen’s randomised study of HALO RFA, found buried glands at study entry in 25% of patients which decreased with RFA to 5% but increased in the control group treated with PPI to 40% (Shaheen, Sharma et al. 2009). From this data it would appear the endoscopic therapy decreases the risk of buried Barrett’s, however in a study of 52 patients treated with PDT, pre treatment buried glands were noted in 1 patient and post ablation 13 patients had buried glands (Mino-Kenudson, Ban et al. 2007).

It is important to recognise that the true incidence of buried glands after any endoscopic therapy is difficult to quantify due to variations in sampling technique, pathological interpretation and confusion regarding definition (Wani, Sayana et al. 2010).

1.13.6 Surgical management of Barrett’s oesophagus and cancer

1.13.6.1 Definitive treatment of dysplasia / early cancer

The basis for oesophagectomy being the standard of care for patients with high grade dysplasia is high rate of occult cancer both intramucosal and submucosal in resection specimens. A meta analysis of resection based studies found 23 articles, among the 441 that reported rates of invasive cancer (sub mucosal invasion) with a pooled average of
39.9%. Reported rates varied from 0% to 73%. Fourteen studies provided differentiation between intramucosal and submucosal invasion. Among 213 patients in these studies only 12.7% had invasion into the submucosa whereas 87.3% were found to harbour high grade dysplasia or intramucosal cancer which may have been successfully treated with endoscopic techniques. Patients with a visible lesion were more likely to have submucosal invasion with rates of 11% vs. 3% in patients with no lesion identified (Konda, Ross et al. 2008).

However most of these studies were prior to the advent of high definition endoscopes and advanced imaging techniques, such as narrow band imaging and confocal endomicroscopy. These techniques are better able to identify visible mucosal abnormalities which can often harbour intramucosal or submucosal cancer.

1.13.6.2 Commonly performed surgical operations

Two types of operation are frequently performed depending on institutional preference. The transthoracic approach allows the creation of an anastomosis between stomach and oesophagus either in the left or right pleural space whereas the transhiatal approach only allows an anastomosis between stomach and oesophagus at the level of the neck (Gilbert and Jobe 2009). Much of the morbidity and mortality is due to anastomotic failure / leak. A metaanalysis of 7500 oesophagectomy patients found that transthoracic oesophagectomy had 50% relative risk reduction in leak rates compared with the transhiatal approach. This technique however was associated with higher early pulmonary morbidity and mortality rates. Overall 5 year survival was found to be similar between techniques (Hulscher, Tijssen et al. 2001). Whereas a large prospective randomised study of 83 patients found no difference in leak rates and survival between the two surgical approaches (Walther, Johansson et al. 2003).

A number of centres have published their outcomes following oesophagectomy for Barrett’s with high grade dysplasia. The overall cancer free survival was determined by the presence of occult cancer within the resected specimen. In patients with high grade dysplasia alone the 5 year survival rate was >95%, however this dropped to around 64% when an occult cancer was detected. The limiting factor of oesophageal surgery
compared to endoscopy therapy is the morbidity and mortality rates encountered. These rates have been closely linked to volume of procedures done / year by both the institution and more importantly the surgeon (Swisher, Deford et al. 2000; Birkmeyer, Stukel et al. 2003). The weighted average across the studies for morbidity was 33% and mortality was 1.4% at a median follow up between 12 to 59 months (Thomson and Cade 2003; Tseng, Wu et al. 2003; Sujendran, Sica et al. 2005; Westerterp, Koppert et al. 2005; Chang, Oelschlager et al. 2006; Moraca and Low 2006; Peyre, DeMeester et al. 2007; Williams, Watson et al. 2007).

It is important to note that an oesophagectomy does not result in a lifetime cure. A number of follow up studies post oesophagectomy have found both recurrence of BO in the order of 18% to 50% as well as recurrence of cancer. This likely relates to the re-exposure of the oesophageal mucosa to acid and bile reflux (O'Riordan, Tucker et al. 2004; Wolfsen, Hemminger et al. 2004; Westerterp, Koppert et al. 2005). Therefore follow up endoscopic assessment with biopsy is required in patients who have undergone an oesophagectomy in a similar manner to those who have undergone endoscopic ablative therapies (Gilbert and Jobe 2009).

1.13.6.3 Control of gastro oesophageal reflux disease

The Nissen fundoplication is the most commonly performed anti-reflux surgery and it is performed laparoscopically in the majority of cases. Longitudinal studies have shown both dysplastic progression and progression to cancer in patients treated with a fundoplication for GORD symptoms (Spechler, Lee et al. 2001; Ye, Chow et al. 2001; Lord 2003).
Chapter 2 – Sequential High Definition White Light and Narrow Band Imaging Enable a Targeted Biopsy Protocol in Dysplastic Barrett’s Oesophagus.

2.1 Introduction

The aim of endoscopic surveillance in BO is to detect dysplasia, in particular to identify high grade dysplasia (HGD) and intramucosal cancer (IMC) which can then be treated before progression to invasive cancer (Buttar, Wang et al. 2001; Rastogi, Puli et al. 2008). These high risk lesions are often subtle and difficult to detect with standard white light endoscopy as reflected in a recent meta-analysis of resection based studies, that found occult cancer in an average of 39.9% of patients in whom oesophagectomy was performed for BO that harboured HGD (Konda, Ross et al. 2008). Therefore based on this principle, a random biopsy protocol (the Seattle protocol) has been adopted as standard of care despite many limitations, which include extra time and cost to acquire and interpret the many biopsies and consequently, poor adherence (Cruz-Correa, Gross et al. 2001; Spechler, Sharma et al. 2011).

The Seattle protocol consists of 4 quadrant biopsies every 1 or 2cm of BO and targeted biopsies of any visible mucosal abnormality (VMA). A resection based study of patients with HGD who proceeded to surgery found no significant difference in the undetected cancer rate of patients who had Seattle protocol biopsies prior to surgery vs. a non protocol, less intensive biopsy program (Kariv, Plesec et al. 2009). However other studies have shown that the greater the number of biopsies taken the increased chance of detecting dysplasia or early cancer (Levine, Haggitt et al. 1993; Sharma, McQuaid et al. 2004).

With the advent of high definition endoscopes and advanced imaging techniques such as narrow band imaging (NBI) and confocal endomicroscopy (CLE), new categories of mucosal and vascular patterns that correlate closely with histology have been developed (Kiesslich, Burg et al. 2004; Kara, Ennahachi et al. 2006; Kiesslich, Gossner et al. 2006; Sharma and Bansal 2006; Anagnostopoulos, Yao et al. 2007). This ability to detect
more subtle visible mucosal abnormalities that harbour HGD/IMC may enable endoscopists, skilled in BO assessment to perform targeted biopsies alone.

A prospective assessment of the accuracy of 3 imaging techniques in the evaluation of Barrett’s oesophagus is presented. The decision was made during the formulation of the study design not to blind each endoscopist to the others findings. This protocol was chosen so as to best emulate real life practice in which the three imaging modalities would be used in a sequential manner rather than in isolation, with the aim of increasing diagnostic certainty after each assessment. The implications of these results are then discussed.

2.2 My role in the study

My role in the study began with the formulation of a study design in collaboration with Dr Andrew Taylor. Once finalised the next step was preparation of the study design and supporting documents for ethics submission. Ethics approval was granted prior to the commencement of the study.

Throughout the duration of the study I was responsible for the co-ordination and implementation of the study including; patient bookings, data collection which occurred during endoscopy lists, performance of procedures, multidisciplinary meetings and the maintenance of the database. Database maintenance involved basic data entry, production of quarterly quality assurance reports, and finally data analysis.

2.3 Aims

The aims of this study were to assess:

1. The accuracy of the high definition white light, narrow band imaging and confocal endomicroscopy in predicting histology within the Barrett’s segment.

2. The yield of high grade dysplasia (HGD) / intramucosal cancer (IMC) in mucosa assessed as non dysplastic vs. dysplastic by each modality.
3. The efficacy and cost benefit of a targeted biopsy protocol using advanced imaging techniques over standard Seattle protocol (random) biopsies.

4. To assess whether confocal endomicroscopy adds additional accuracy above HD white light and NBI in the assessment of dysplastic Barrett’s oesophagus.

2.4 Materials and Methods

2.4.1 Patient Selection

Patients included in this prospective cohort study were those referred to St Vincent’s Hospital Melbourne for endoscopic evaluation and treatment of dysplastic BO previously diagnosed by their referring physician. All patients were over the age of 18 years. The study was approved by the St Vincent’s Human Research Ethics Committee.

The decision was made during the formulation of the study design to perform the endoscopic assessments sequentially in an unblinded manner. This protocol was chosen so as to best emulate real life practice in which the three imaging modalities would be used in a sequential manner rather than in isolation, with the aim of increasing diagnostic certainty after each assessment.

2.4.2 Referral forms

A majority of patients included in the study were referred to the principle investigator (A.T.) using a form previously devised as part of the successful grant obtained through the Victorian Government which has funded the HALO procedures for 100 patients, since the program’s inception (Appendix 1). On this form, the referring doctor was asked to indicate past history, previous endoscopic procedures and most recent histology. For the remaining patients, details of previous endoscopies and biopsy results were forwarded to the principle investigator directly by the referring doctor. All patients were then assessed by the principle investigator prior to entry into the study.
2.4.3 Details of endoscopic evaluation

Initial mapping procedures were performed by two expert endoscopists. All patients had signed informed consent for both the initial procedure and also to be included within the overall study framework. A dedicated anaesthetist was used in all cases with the majority of patients undergoing general anaesthesia, due mainly to the duration of the mapping protocol.

2.4.4 Equipment

The initial white light and narrow band imaging components of the mapping protocol were performed using an Olympus H180 (PCF-Q180AL/I) endoscope which had the NBI feature incorporated into the endoscope and was able to be activated by a touch of a button mounted on the controls of the endoscope.

Confocal endomicroscopy was performed using the Pentax confocal endomicroscope (EC3870k system; Pentax, Toyko, Japan with the ISC-1000 confocal endomicroscopy processor), developed by Optiscan (Australia), which has the confocal lens incorporated within the framework of the endoscope. In order to obtain images at depths below the surface an exogenous fluorescent contrast agent was required. 10% Fluorescein sodium was used at a dose of 5ml injected intravenously prior to commencement of CLE. The contrast agent usually lasted 30min.

2.4.5 Mapping protocol

In order to accurately compare a targeted biopsy protocol to the Seattle protocol we systematically mapped the distribution of the BO by dividing the oesophagus into a grid which was based on two methods. Firstly diathermy (argon plasma coagulation or the tip of a snare) was used to mark the oesophageal mucosa along the length of the BO in 1-2cm levels (picture 1) which correlated with the centimetre measurements along endoscope. Secondly the endoscope was maintained in a neutral position from which the 12 o’clock position was determined to be at the superior aspect of the oesophagus, analogous to a clock face (picture 2)
A data collection grid was created which matched with the oesophageal grid (figure 2.1). The y-axis denoted the depth in centimetres of the BO and the x-axis denoted the o’clock positions. Due to the convention of the Seattle protocol to biopsy in four quadrants, the 3,6,9 and 12 o’clock were the positions evaluated at each centimetre of BO in addition to those found to be visibly abnormal. The data collection grid was identical to the one stored in the database which allowed comparison of the predictions of each modality to the underlying histology. The data collection grid is shown below.

The top of the gastric folds was used as the landmark denoting the gastro-oesophageal junction, finally Prague classification for each patient was determined.

Therefore the entry endoscopic assessment (mapping protocol) involved a detailed reassessment of the oesophagus utilising the three imaging modalities in a sequential manner (high definition white light followed by NBI and finally CLE).

The white light and NBI assessment were performed according to the Sharma Classification outlined in the literature review (Sharma, Bansal et al. 2006). The CLE examination was performed according to the Confocal Classification system also detailed in the literature review (Kiesslich, Gossner et al. 2006).

As the primary aim of the study was to identify areas of HGD/IMC, areas with low grade dysplasia were considered together with non dysplastic BO. However it must be noted that the finding of LGD is important and has significant clinical implications.
Initial assessment was performed with high definition white light endoscopy by the first endoscopist (A.T.). A prediction of likely histology was made for each mucosal point according to the Seattle protocol (4 quadrant every 1cm and any visible mucosal abnormality). These findings were documented by a scribe on the data collection grid. The second assessment was then conducted with NBI by the same endoscopist (A.T.). Again a prediction of likely histology was made for each mucosal point according to the Seattle protocol. As the first endoscopist performed both the white light and NBI
assessments, any abnormal areas identified by white light were able to be evaluated in more detail with NBI.

The third assessment was with CLE in which the real time prediction of histology of the same mucosal points made by the second endoscopist (F.M.) The second endoscopist was aware of the location of any abnormal mucosal areas which had been identified by either HD WLE or NBI prior to the assessment with CLE, to allow reassessment of those same areas. Again a prediction of likely histology was made for each mucosal point according to the Seattle protocol in addition to the abnormal mucosal areas identified. There was no post procedure review of images as the aim was to assess real time interpretation.

The final step in the mapping protocol was to biopsy all the mucosal points assessed by each modality according to the Seattle protocol. This was performed with the Olympus endoscope. Each biopsy was placed in a separate specimen pot, labelled with the location according to depth in centimetres and o’clock position with the endoscope in a neutral position. The histological assessment, by an expert GI pathologist (R.W.), was used as the gold standard to determine the accuracy of the other imaging modalities. The histological assessment was also stored in the same grid pattern in the database, in order to make comparisons to the predictions by each modality.

2.4.6 Data storage and statistical analysis

A computerised database was designed by an external I.T. consultant based on Microsoft Access 2007. The database was password protected and all data was entered, stored and analysed using this programme.

Categorical variables were compared using the Chi square / Fisher's exact test. Continuous variables were compared using the Kruskal Wallis test. All statistical testing was 2 sided at a significance level of 5% using SAS statistical software, v9.2 (SAS, Cary, NC, USA)
2.4.7 Economic analysis

The costing system used to derive the economic data was “Power Performance Management”, a product from Power Health Solutions which has been licensed to St Vincent’s Hospital Melbourne. This software was able to provide a cost per minute calculation for endoscopic utilisation. The gastroenterology medical costs are derived from the Human Resources department’s sessional rates for gastroenterologists. Day Procedures costing, including nursing costs, are derived from the money received by the Day Procedures Cost Centre based on each patient episode relative to the length of stay. Anaesthetic costs are costed using the times entered onto the centralised system which calculates anaesthetic start time and finish time per case. Overheads in the system like Finance and Payroll are also considered by the software programme. The cost of biopsy specimen processing and histological interpretation was obtained for the Department of Pathology. The costs are presented in Australian dollars, the current U.S. exchange rate at the time of article submission was 1 U.S. dollar = 1.002 Australian dollars.

2.4.8 Ethics committee approval

The study was approved by the St Vincent’s Human Research Ethics Committee (HREC-D) – Protocol Number 161/09.

2.5 Results

2.5.1 Patient characteristics

Between February 2010 and September 2011, a total of 50 consecutive patients were prospectively enrolled in the study, of which 50 patients had HD WLE and NBI assessment and 46 patients had CLE (in 1 patient CLE not performed due to anaesthetic issues, 3 patients time restraints).
As outlined in table 2.1 the majority of patients were middle aged males which is consistent with those at highest risk for the development of Barrett’s oesophagus in the literature. The mean age of the patients was 66 years (range 41 to 86 years), and 84.4% were male. The median length of BO was 7cm (range 1 to 16cm) All patients were referred with dysplastic BO for consideration of combination endoscopic therapy.

A total of 1190 individual biopsy points have been assessed from the 50 patients, with a median of 25 biopsy points per patient, of which 39 biopsy points were found to harbour HGD and 52 biopsy points were found to harbour IMC after histological assessment. As CLE was only performed in 46/50 patients, fewer biopsy points (1117) were assessed.

### Table 2.1 - Details of demographic and worst pathology at the time of referral according to referring clinician

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Number (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>50</td>
</tr>
<tr>
<td>Male</td>
<td>42 (84 %)</td>
</tr>
<tr>
<td>Age</td>
<td>Median 66 years (range 41 - 86)</td>
</tr>
<tr>
<td>Length of Barrett’s</td>
<td>Median 7 cm (range 1 - 16)</td>
</tr>
<tr>
<td>Referral pathology</td>
<td></td>
</tr>
<tr>
<td>Intramucosal cancer</td>
<td>8</td>
</tr>
<tr>
<td>High grade dysplasia</td>
<td>18</td>
</tr>
<tr>
<td>Low grade dysplasia</td>
<td>23</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>1</td>
</tr>
<tr>
<td>Percentage of visible lesions identified by referring doctors</td>
<td></td>
</tr>
<tr>
<td>Intramucosal cancer</td>
<td>8 (62.5%)</td>
</tr>
<tr>
<td>High grade dysplasia</td>
<td>18 (22.2%)</td>
</tr>
<tr>
<td>Low grade dysplasia</td>
<td>23 (0%)</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>1 (0%)</td>
</tr>
</tbody>
</table>
2.5.2 The accuracy of the three modalities in predicting histology within the Barrett’s segment

The results of overall accuracy of each modality in predicting underlying histology are outlined in table 2.2

<table>
<thead>
<tr>
<th>Modality</th>
<th>Correct</th>
<th>Incorrect</th>
<th>Total biopsies</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>WLE</td>
<td>395</td>
<td>795</td>
<td>1190</td>
<td>33.2%</td>
</tr>
<tr>
<td>NBI</td>
<td>523</td>
<td>637</td>
<td>1190</td>
<td>44.0%</td>
</tr>
<tr>
<td>CLE</td>
<td>546</td>
<td>571</td>
<td>1117</td>
<td>48.9%</td>
</tr>
</tbody>
</table>

These results show that all modalities performed poorly in predicting the underlying histology at each mucosal point assessed. CLE appeared to perform the best of the three modalities with an overall accuracy of 48.9% with WLE performing the with the least accuracy.

2.5.3 Accuracy in diagnosing high grade dysplasia / intramucosal cancer

The accuracy of each modality in the assessment of HGD/ IMC is outlined in table 2.3.

The most important results outlined in table 2.3 were that no cancers were missed. All modalities detected the mucosal points that harboured IMC. WLE had already made the initial correct prediction with the other modalities agreeing this initial finding as the assessments were performed sequentially without blinding.

The three modalities performed with less consistency in the detection of HGD. Seven patients had 16 points of HGD missed by HD WLE assessment. Two of the seven patients had HGD missed on a per case basis by white light alone, however points of HGD were detected by NBI and CLE in these two patients. One patient with 6 points of HGD did not have confocal performed. CLE missed 16 points of HGD in seven patients. Four of the six patients had HGD missed on a per case basis by CLE alone. However it is important to note that the confocal examination occurred after sequential WLE and NBI assessment. Therefore any areas of concern (nodules /VMAs ) had been already mapped and the location disclosed to the second endoscopist.
Table 2.3 - Details of accuracy of each modality’s sequential assessment in identifying HGD/IMC

<table>
<thead>
<tr>
<th>Modality</th>
<th>White light assessment</th>
<th>Narrow Band Imaging</th>
<th>Confocal Endomicroscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total biopsy points assessed</td>
<td>1190</td>
<td>1190</td>
<td>1117</td>
</tr>
<tr>
<td>• Predicted as non dysplastic</td>
<td>931</td>
<td>901</td>
<td>859</td>
</tr>
<tr>
<td>• Predicted as HGD/IMC</td>
<td>259</td>
<td>289</td>
<td>258</td>
</tr>
<tr>
<td>Total biopsy points with HGD /IMC at histology</td>
<td>91</td>
<td>91</td>
<td>66</td>
</tr>
<tr>
<td>• Predicted as non dysplastic</td>
<td>16</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>o HGD</td>
<td>16</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>o IMC</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>• Predicted as HGD/IMC</td>
<td>75</td>
<td>81</td>
<td>50</td>
</tr>
<tr>
<td>o HGD</td>
<td>23</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>o IMC</td>
<td>52</td>
<td>52</td>
<td>30</td>
</tr>
<tr>
<td>Diagnostic yield = Number of biopsies to detect one point of HGD/IMC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random</td>
<td>13.1</td>
<td>13.1</td>
<td>16.9</td>
</tr>
<tr>
<td></td>
<td>(1190/91)</td>
<td>(1190/91)</td>
<td>(1117/66)</td>
</tr>
<tr>
<td>Targeted</td>
<td>3.5</td>
<td>3.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Number of extra biopsies to detect one point of HGD in mucosa assessed as flat</td>
<td>58.2</td>
<td>90.1</td>
<td>53.7</td>
</tr>
</tbody>
</table>

The NBI assessment was most accurate, missing the least biopsy points (10 biopsy points) that harboured HGD in the least number of patients (4 patients). Importantly
with NBI, every patient had HGD detected at another biopsy point in all of the 4 patients with missed HGD, therefore all patients would have undergone definitive combination endoscopic therapy. See figure 2.2.

Figure 2.2 Per patient negative predictive value for High grade dysplasia / intramucosal cancer

Narrow Band Imaging

| Table of NBI by Histology |  
|----------------------------|---|---|---|
| **NBI(NBI)** | **Histology** | **Total** |  |
|  | 1 | 0 |  |
| **1** | 23 | 25 | 48 |
|  | 46 | 50 | 96 |
|  | 47.92 | 52.08 | 100 |
|  | 100 | 92.59 |  |
| **0** | 0 | 2 | 2 |
|  | 0 | 4 | 4 |
|  | 0 | 100 |  |
|  | 0 | 7.41 |  |
| **Total** | 23 | 27 | 50 |
|  | 46 | 54 | 100 |

<table>
<thead>
<tr>
<th><strong>Sensitivity</strong></th>
<th><strong>Specificity</strong></th>
<th><strong>Accuracy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.074074</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The accuracy of the predictions made with the three modalities was further reflected by the high negative predictive values and high diagnostic yield of HGD/IMC obtained, as outlined in table 2.4.
Table 2.4. Per location analysis of sensitivity and specificity for the detection of HGD/IMC by each modality.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>NPV (95%CI)</th>
<th>PPV (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Definition White Light</td>
<td>79.1% (72.7% – 89.3%)</td>
<td>83.1% (80.9% – 85.4%)</td>
<td>98.3% (97.2% – 99.0%)</td>
<td>28.1% (23.6% – 35.0%)</td>
</tr>
<tr>
<td>Narrow Band Imaging</td>
<td>89.0% (80.3% - 94.3%)</td>
<td>81.0% (78.6% – 83.3%)</td>
<td>98.9% (97.9% - 99.4%)</td>
<td>27.9% (23.0% - 33.6%)</td>
</tr>
<tr>
<td>Confocal Endomicroscopy</td>
<td>75.7% (63.4% - 85.1%)</td>
<td>80.0% (77.6% - 82.6%)</td>
<td>98.1% (96.9% - 98.9%)</td>
<td>19.4% (14.8% - 24.8%)</td>
</tr>
</tbody>
</table>

The negative predictive value of HD WLE was 98.3% (97.2% –99.0%), NBI was 98.9% (97.9% - 99.4%) and CLE was 98.1% (96.9% - 98.9%). The diagnostic yield, (i.e. number of biopsies required to detect one point of HGD/IMC) was superior with a targeted biopsy protocol to the Seattle protocol across all modalities, as outlined in table 3. NBI again performed the best of the three modalities with 90.1 further random biopsies required to diagnose one point of HGD, not detected by NBI assessment.

2.5.4 Are they complementary modalities

In order to evaluate the most efficacious targeted biopsy protocol we assessed the incremental diagnostic yield of each modality as they were used in a sequential protocol. The maximal number of mucosal points that harboured HGD/IMC was detected by using a combination of all three modalities. However the benefit of CLE above NBI was minimal. CLE resulted in finding one further point of HGD in a patient in whom HGD had already been detected by NBI. This findings had no impact on patient outcomes and occurred at considerable time and cost. Therefore it was concluded that targeted biopsy protocol guided by HD WLE and NBI was the most efficacious.
2.5.5 Efficacy and cost effectiveness of targeted biopsy protocol

An assessment of cost benefit was then made between a targeted biopsy protocol guided by HD WLE and NBI versus the Seattle protocol. (Table 2.5)

### Table 2.5: Mean cost per patient

<table>
<thead>
<tr>
<th></th>
<th>Seattle protocol</th>
<th>Targeted Biopsy protocol</th>
<th>Mean cost saving per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cost of biopsies per patient</td>
<td>$1030.50</td>
<td>$250.20</td>
<td>$780.30</td>
</tr>
<tr>
<td>Mean cost of time taken to biopsy per patient</td>
<td>$239.00</td>
<td>$57.60</td>
<td>$181.40</td>
</tr>
<tr>
<td>Overall mean cost per patient</td>
<td>$1269.50</td>
<td>$307.80</td>
<td><strong>$961.70</strong></td>
</tr>
</tbody>
</table>

Cost per minute required for endoscopy utilisation = $13.39/min
Cost of processing and histological interpretation of each biopsy = $43.30.

The cost of processing and histological interpretation of each biopsy was $43.30. Therefore the total cost of all the biopsies taken in our group of 50 patients, according to the Seattle protocol was $51,527.00. The total cost of a targeted biopsy protocol as guided by HD WLE and NBI was $12,513.70. The average cost saving per patient achieved by using a targeted biopsy protocol compared to Seattle protocol biopsies, was $780.30.

In addition to the cost of processing and histological interpretation of biopsies, another factor in favour of a targeted biopsy protocol was the extra time taken to biopsy the entire Barrett’s segment according to the Seattle protocol. A biopsy rate was determined by calculating the average time taken to biopsy a segment of Barrett’s across the group of patients. For the mapping protocol two endoscopy nursing staff were available, one
guiding the forceps and the second labelling and closing the specimen pots. Therefore the biopsy rate calculated was 45 seconds per biopsy. Therefore a targeted biopsy protocol would have taken a mean of 4.3 minutes per patient to acquire the targeted biopsies versus 17.8 minutes with the Seattle protocol. The cost per minute required for endoscopy utilisation which includes, gastroenterology medical costs, day procedure costs (including nursing, administration and consumables) and anaesthetic costs (including medical, nursing, pharmacy and consumable costs) was $13.39 per minute. Therefore a targeted biopsy protocol resulted in a mean cost saving of $961.70 per patient over the Seattle protocol.

2.5.6 The cost of confocal

The cost of confocal endomicroscopy had already been evaluated by Prof Finlay Macrae in his “proposal for statewide introduction of a new health technology” which was submitted to the Department of Health for the financial year of 2010-2011. The cost of confocal endomicroscopy incorporates a number of factors as outlined in table 2.6.

Therefore assuming 80 cases / year for 5 years the total cost per patient of each procedure based on the results from table 10 is $559.53 + $714.63 = Total - $1274.16 / case
2.6 Discussion

The main aim of this work has been to assess whether the new advanced imaging technologies provide us with the ability to accurately perform targeted biopsies alone in Barrett’s assessment, thereby dispensing with the more expensive and time consuming Seattle biopsy protocol. This methodology provides an accurate representation of the real life decision making in Barrett’s assessment due to two key factors. Firstly the study protocol adopted an unblinded, sequential, multimodality endoscopic protocol. The aim of this protocol was to assess whether each endoscopic modality provided an incremental diagnostic yield, thereby increasing the diagnostic certainty of the histological prediction made for each mucosal point assessed, in order to determine which mucosal areas needed to be biopsied. The second factor was that the predictions of histology were made in real time by each endoscopist, rather than assessment of carefully chosen pictures after the procedure.

All mucosal points with IMC and all patients with HGD were detected by targeted biopsies without the need for random Seattle protocol biopsies, demonstrating that a targeted biopsy protocol can be performed accurately and efficaciously dispensing with

<table>
<thead>
<tr>
<th><strong>Table 2.6: Cost of Confocal Endomicroscopy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confocal equipment</strong></td>
</tr>
<tr>
<td>Purchasing cost</td>
</tr>
<tr>
<td>A cost per case based on 400 cases over 5 years</td>
</tr>
<tr>
<td>CLE cleaner</td>
</tr>
<tr>
<td><strong>Procedural costs / case</strong></td>
</tr>
<tr>
<td>Outpatient costs - Avg per case (40min)</td>
</tr>
<tr>
<td>Episode costs - Avg DRG cost per case</td>
</tr>
<tr>
<td>Total Procedural Costs for Confocal Endomicroscopy/case</td>
</tr>
</tbody>
</table>
the need to perform random Seattle protocol biopsies during the routine surveillance of BO. In addition to its efficacy, a targeted biopsy protocol would have resulted in a mean cost saving of $961.70/patient over the Seattle protocol.

2.6.1 Are advanced imaging modalities effective in predicting underlying histology

To date predicting histology at each biopsy point with the currently available advanced imaging techniques is challenging. Throughout the histological spectrum from non dysplastic BO through to intramucosal cancer, overlap exists between the corresponding mucosal and vascular features seen at endoscopy. This overlap makes it difficult to differentiate with certainty the various grades of dysplasia. These difficulties are also encountered by pathologists where high rates of inter-observer variability have been demonstrated especially when assessing non dysplastic BO and low grade dysplasia (Kerkhof, van Dekken et al. 2007) (Montgomery, Bronner et al. 2001). Therefore the first aim of the study was to assess whether each modality was able to predict with accuracy the histology of the underlying mucosa. Our results confirmed this difficulty with an accuracy of less than 50% for all modalities when predicting the exact histology for each mucosal point assessed. Given these findings we focused on the accuracy of detecting high grade dysplasia / intramucosal cancer with the three advanced imaging techniques. The finding of high grade dysplasia within a segment of Barrett’s is the most potent risk factor for the progression to cancer (Rastogi, Puli et al. 2008; Wang and Sampliner 2008). Therefore routine surveillance endoscopy of BO should be performed with the intent to find HGD or early cancers and if found acts as a trigger for definitive therapy.

The results of our study confirm that of previous studies that careful assessment of the mucosal pattern and vascular pattern with advanced imaging techniques has the ability to predict HGD / IMC (Kara, Ennahachi et al. 2006; Sharma, Falk et al. 2006; Anagnostopoulos, Yao et al. 2007). All modalities detected the mucosal points that harboured IMC. As the mapping protocol involved sequential examination with the three modalities, HD WLE had already made the initial correct prediction with the other modalities confirming this finding. The three modalities performed with less consistency in the detection of HGD. Compared to cancers, which occurred in areas
with discrete mucosal abnormalities, HGD was often detected in mucosal areas with more subtle mucosal and vascular abnormalities. NBI performed the best of the three modalities missing the least biopsy points that harboured HGD in the least number of patients. Importantly with NBI, on a per patient basis, HGD was detected in all patients using an NBI-based targeted biopsy approach, therefore all patients would have undergone definitive combination endoscopic therapy. On a per patient basis, HGD was missed in 2 patients using WLE alone and in 4 patient if targeted biopsies were taken based on CLE findings

2.6.2 Targeted biopsy protocol

In order for a targeted biopsy protocol to be considered a viable alternative to random biopsies, it must not miss any cancers, as these lesions require an EMR to ensure clearance of the focal lesion prior to ablation and for staging purposes, to determine suitability for ongoing endoscopic therapy in cases of mucosal cancer or surgical resection where submucosal invasion is present. A targeted protocol must also detect the presence of HGD, as this is the critical finding that escalates the management strategy from intensified endoscopic surveillance for low grade dysplasia (LGD) to definitive treatment.

The results of our study echo the findings of previous studies which show that careful assessment of the mucosal pattern and vascular pattern with advanced imaging techniques has the ability to predict HGD and IMC. Targeted biopsies increased the diagnostic yield of HGD/IMC per biopsy taken. A targeted protocol guided by WLE required 3.5 targeted biopsies to detect 1 point of HGD vs. 13.1 random biopsies to detect 1 point of HGD. NBI required 3.6 targeted biopsies to detect 1 point of HGD. CLE required 5.2 targeted biopsies to detect 1 point of HGD vs. 16.9 random biopsies to detect 1 point of HGD.

However, endoscopic identification of LGD, especially when differentiating LGD from non dysplastic BO, has proven to be difficult.[5, 8, 9] It must be noted that our study did not set out to evaluate the accuracy of detecting LGD. Therefore, one potential limiting factor of only performing targeted biopsies would be missing LGD which has increasingly been shown to have important management implications. These problems
differentiating LGD from non dysplastic BO are also encountered by pathologists (Kerkhof, van Dekken et al. 2007). A recently published study highlighted the inaccuracy of community based pathologists where after expert review of biopsies previously assessed as LGD, 75% were down staged to non dysplastic BO (Curvers, Ten Kate et al. 2010). In contrast interobserver agreement is better with HGD (kappa score 0.65) than with indefinite for dysplasia (kappa 0.32) between pathologists (Montgomery, Bronner et al. 2001).

The traditional approach for LGD has been intensified endoscopic surveillance due to the commonly held belief that progression to HGD and cancer was low (Wang and Sampliner 2008; Sharma 2009). However a recently published study by Curvers et al. has shown that the rate of progression of LGD may be higher than previously thought, with those confirmed to have true LGD by two expert GI pathologists, having a 13.4%/year risk of progression (Curvers, Ten Kate et al. 2010). The study by Curvers et al., in the context of promising short to medium term results with HALO RFA, strengthens the argument for radiofrequency ablation therapy for LGD. A recent American Gastroenterological Association (AGA) medical position statement has recommended that HALO RFA should be considered a valid therapeutic option in BO with LGD (Spechler, Sharma et al. 2011). A large UK based multicenter randomised controlled trial co-ordinated by Bergman is currently underway, comparing HALO RFA to surveillance in LGD. This study will likely define our approach to LGD in near future.

The maximal number of mucosal points that harboured HGD/IMC was detected by using a combination of all three modalities. However the benefit of CLE above NBI was minimal. CLE resulted in finding one further point of HGD in a patient in whom HGD had already been detected by NBI, therefore this finding had no impact on patient outcomes and came at considerable time and cost.

Therefore consideration needs to be given to the most efficacious protocol which takes into account cost associated with the CLE technology, cost of random biopsies and which modalities provide the ability to perform a targeted biopsy protocol with an acceptable diagnostic yield. In order to further evaluate the most efficacious protocol we looked at the role of CLE in our analysis.
2.6.3 Role of confocal endomicroscopy

Confocal endomicroscopy was performed by an expert endoscopist (F.M.) who has been involved with the development of the technology, including a number of publications. CLE was performed in real time which differs from many other studies of CLE in which confocal images are read after the procedure with the best images selected. The challenges of performing real time CLE include speed of interpretation, poor image acquisition and difficulty in the interpretation of an inflamed segment of BO. Despite many years of use of CLE the endoscopist anecdotally noticed an improvement in interpreting images in real time as the study progressed suggesting a long learning curve of this new technique.

CLE failed to perform better than NBI in the assessment of HGD/IMC by a number of measures, including accuracy, time taken and cost. From our results CLE cost an extra $1274.16 / case. Therefore for the entire study the extra cost of CLE was $58611.36 for the 46 patients. CLE only found one biopsy point not detected by NBI without any impact on patient outcome. Therefore it is a large cost to justify the tiny incremental diagnostic benefit. Above the extra cost, the CLE procedure is time consuming, on average adding 30min to the procedural time.

CLE is a new technology that is still yet to establish its role in the assessment of BO and is currently only being studied in few highly specialised international centres by endoscopists skilled and trained in the technique, predominantly in the US and Europe. The probe based CLE system may have merit in that it can be passed down the biopsy channel to perform localised assessment. A recent study by Sharma et al. demonstrated increased diagnostic yield of HGD/IMC with this method over HD WLE alone (Sharma, Meining et al. 2011). However further study is required, ideally in the form of randomised controlled trials, to determine the role of CLE in the assessment and management of BO. In addition, specialised training programs will need to be developed to ensure competency with this technique.
2.6.4 What is the optimal protocol considering time and cost

A targeted biopsy protocol with NBI alone carries high diagnostic accuracy with least expense. Our assessment with NBI was mainly focused on the interpretation of the mucosal pattern according to Sharma’s classification. NBI is easy to perform and activated by the touch of a button on the controls of the endoscope.

Targeted biopsies guided by NBI would have had a mean cost saving of $961.70 per patient, with all patients with HGD diagnosed on a per patient basis. The most biopsies taken on an individual patient was 58 biopsies, this patient had 6 biopsy points that NBI thought were abnormal and 2 points of HGD were detected within these 6 points and none in the remaining biopsies. Therefore this highlights the time and cost savings in a patient with a long segment of BE. This patient’s biopsies cost $2,511.40 to process and interpret as well as an extra 43 minutes to acquire and label the biopsies. Whereas a targeted protocol guided by NBI alone would have required 4.5min to take the 6 biopsies and cost $259.80 to process and interpret. This equates to a significant cost and time saving for both the endoscopy and pathology staff.

2.6.5 Limitations

There were some limitations of our study. Our study group was an enriched cohort, primarily consisting of patients with known dysplastic BO with a high proportion harbouring HGD/IMC. Secondly, the sequential unblinded endoscopic design of the study, whilst reflecting real life application of these technologies, restricted a true head to head comparison of the three modalities which would be possible if each assessment was blinded. Furthermore, we did not have the availability of the magnifying NBI scopes which allows stable magnification of the image 100 to 150x. This advanced imaging technique that aids in pit pattern characterisation, may have further improved the diagnostic yield of the NBI assessment.

Despite our best attempts to ensure that the same mucosal points were assessed by each modality, some degree of variability was likely to have occurred. In a similar way, the location of the biopsy may differ from the mucosal point that was visually assessed due to surface blood which can obscure the measuring landmarks. These factors may have
introduced error into the analysis however these barriers are difficult to overcome. Another potential limiting factor was the lack of a true gold standard. One method to reduce error would be to perform circumferential endoscopic mucosal resection of the entire BO or perform the assessment in patients prior to oesophagectomy.

A further limitation regarding the economic analysis, was that the cost of histology may have been over estimated as frequently endoscopists would put 4 biopsies per level in a single pot than all in separate pots.

2.6.6 Future of Barrett’s assessment

Despite the possibility of a targeted biopsy protocol raised by the promising results of our study, it is still premature to advocate a targeted biopsy protocol beyond expert tertiary centres to community gastroenterologists. Our study was performed by skilled endoscopists with expertise in the endoscopic assessment of BO aided by advanced imaging techniques in an enriched population. In addition the significance of LGD is yet to be answered. If the currently underway randomised study shows no long term benefit of HALO RFA in reducing cancer progression versus a sham treatment then a targeted biopsy protocol may be applied looking for HGD and IMC, however if there is a considerable benefit of HALO RFA in the management of LGD then random biopsies (perhaps 1 biopsy every cm) will still need to be performed in order to detect LGD in addition to meticulous inspection looking for any subtle mucosal or vascular abnormalities.

I would make the following recommendations based on our study and the current barriers that exist to performing optimal assessment BO by community gastroenterologists. In order for a targeted protocol to be more widely applicable, a training program would be required to teach gastroenterologists how to assess the mucosal and vascular pattern with high definition white light and narrow band imaging. This would increase the diagnostic yield of dysplasia in the biopsies taken as already the adherence rate to the Seattle protocol is very low. Currently confocal endomicroscopy should remain a research tool and be limited to use in specialised centres, due mainly to
the long learning curve required to assess the images in real time and the additional time and cost required to use the equipment.

There is currently much interest in developing non-invasive methods of population screening for Barrett’s which will in turn increase the demand on endoscopic procedures. One such method is the cytosponge test which has been developed with collaboration between Australian and U.K. centres. This technique involves ingestion of a pill connected to a string. The pill is coated with gelatine which is broken by acid in the stomach. This releases the cytosponge which is then pulled back out of the mouth and during its passage through the oesophagus samples cells that can be assessed for the presence of a protein that is expressed in non-dysplastic BO (TFF3). (Kadri, Lao-Sirieix et al. 2010)

The evaluation of BO is likely to change dramatically during the next decade, as CLE is refined and other advanced imaging techniques such as autofluorescence are further studied. Already there are studies demonstrating the benefit of autofluorescence as a red flag technique to detect areas of dysplasia then using NBI or CLE to improve the specificity of these findings (Kara, Peters et al. 2006; Curvers, Singh et al. 2008). Evaluation will likely incorporate multiple modalities including endoscopic and biomarker assessment. Each of the emerging modality’s place in the diagnostic algorithm of BO assessment will not only depend on its efficacy but also factors such as cost, safety and practicalities of its implementation.
3.1 Introduction

Endoscopic therapy for BO harbouring high grade dysplasia (HGD) and intramucosal cancer (IMC) has emerged as a credible alternative to surgery in recent years. These include the new ablative techniques such as radiofrequency ablation and cryotherapy (Ganz, Overholt et al. 2008; Shaheen, Sharma et al. 2009; Greenwald, Dumot et al. 2010; Shaheen, Greenwald et al. 2010). Despite the promise of these new techniques, endoscopic mucosal resection (EMR) remains an essential component of the optimal endoscopic management of dysplastic BO, either as a single therapy with stepwise radical endoscopic resection or focal EMR in combination with ablation techniques (Ell, May et al. 2007; Pech, Behrens et al. 2008; Pouw, Seewald et al. 2010; Pouw, Wirths et al. 2010; van Vilsteren, Pouw et al. 2011). EMR is a technically demanding procedure requiring skills to recognize and manage complications such as bleeding, perforation and stricture formation.

EMR plays two critical roles in the management of patients with dysplastic BO. Firstly, EMR has been shown to be the best diagnostic modality to assess the depth of invasion within the mucosal and submucosal layers (Spechler and Davila 2009; Wani, Mathur et al. 2010). Non endoscopic treatment with either surgery or definitive chemoradiotherapy is required if invasion into the submucosa is detected, as the rate of lymph node metastases is >20%, whereas endoscopic treatment alone is likely to be curative, if disease is confined to the muscularis mucosae, as the rate of lymph node metastases is only approximately 2% (Rice, Zuccaro et al. 1998; Feith, Stein et al. 2003; Stein, Feith et al. 2005; Oh, Hagen et al. 2006; Peyre, DeMeester et al. 2007).

The second important role of EMR is in the treatment of Barrett’s neoplasia that invades beyond the epithelium. HALO RFA has been shown in dosimetry studies to ablate
consistently to a depth of 500µm, which correlates with the epithelium. However, deeper to the epithelium, there is variable ablation depth to between 500µm and 1000µm, corresponding to the lamina propria and muscularis mucosa (Ganz, Utley et al. 2004; Dunkin, Martinez et al. 2006; Smith, Bejarano et al. 2007). Therefore, if Barrett’s neoplasia invades into the lamina propria or to the muscularis mucosa, treatment with HALO RFA alone may result in inadequately treated invasive cancer. This hypothesis underpins the importance of combination endoscopic therapy that requires EMR to completely excise these focal invasive areas prior to ablation of the remaining epithelial BO.

A prospective assessment of the diagnostic and therapeutic impact of EMR in patients with dysplastic BO is presented. This is followed by data on the safety and side effect profile of the procedure. Finally the implications of these findings are discussed.

### 3.2 Aims

The aims of this study were to assess

1. the importance of endoscopic mucosal resection in accurate assessment of dysplastic Barrett’s oesophagus
2. the importance of endoscopic mucosal resection in the treatment of dysplastic Barrett’s oesophagus.
3. the safety of endoscopic mucosal resection.
3.3 Materials and Methods

3.3.1 Patient Selection

Patients included in this study were those referred to St Vincent’s Hospital for endoscopic evaluation and treatment of dysplastic BO previously diagnosed by their referring physician. Patients were over the age of 18 years. Prior to entry into the study, patients underwent a detailed endoscopic assessment at St Vincent’s Hospital as detailed in chapter 2. The patients in this study consisted of the 50 patients assessed in Chapter 2 as well as a further 21 patients. The decision to perform EMR was based on the finding of a visible mucosal abnormality (VMA) that harboured dysplastic BO at histological assessment. EMR was generally performed at a second endoscopy, however later in the series, this was performed at the initial mapping procedure if there was a clear lesion to resect. External pathology was generally reviewed by our expert G.I pathologist (R.W.)

3.3.2 Details of endoscopic therapy

The EMR procedures were performed by one of two endoscopists (A.T. and C.J.) The procedures were performed on an outpatient basis with a dedicated anaesthetist used in all cases. The mode of sedation was left at the discretion of the attending consultant anaesthetist. The majority of patients underwent propofol based sedation with a few patients requiring general anaesthesia.

EMR was performed using an Olympus H180 (PCF-Q180AL/I) endoscope with resections performed using the multi-band mucosectomy technique (figure 3.1) (Duette Multiband Mucosectomy kit; Cook Endoscopy) or the cap and snare technique (figure 3.2) (oblique cap diameter 12.8/14.8/18mm, MAJ-296/297; Olympus).

The BO segment was reassessed with a high definition endoscope to identify the mucosal area of concern (image 1). The margins of larger lesions were then marked by diathermy (image 2), with the tip of a snare, if the lesion required greater than one EMR. The gastroscope was then removed and the Duette EMR kit was loaded onto the
endoscope. The Duette cap consists of 6 bands allowing 6 resections to be performed in one session if required. The mucosal area of concern was then sucked into the cap and a rubber band deployed around the base of the mucosa creating a pseudo polyp (image 3). The braided snare was then passed through the biopsy channel and the pseudopolyp snared either above or below the rubber band at the discretion of the endoscopist. The lesion was resected (image 4) with ERBE settings at Endocut effect 3 (blended current). The mucosa resected was then retrieved by suction into the cap and removal of the endoscope. This procedure was repeated for larger areas requiring contiguous resection.

Figure 3.1 EMR performed with the Duette device:
The procedures performed earlier in the study were predominantly performed using the Olympus cap and snare technique. In this procedure a clear cap was placed over the mucosal area to be resected (image A). A submucosal injection of saline was then performed to lift the mucosa off the underlying muscle layers (image B). The mucosa was then suctioned into the cap and a snare deployed over the suctioned mucosa (image C) and then the mucosa was resected (image D).

**Figure 3.2 – EMR performed with the cap and snare technique (Waxman and Konda 2009)**

In one patient with a latex allergy the “Speed Band Super View Super 7 Multiple Band Ligator” from Boston Scientific was used in conjunction with the snare from the Duette system, as the Boston bands were latex free.

Patients were interviewed 2 hours post procedure to ensure safety for discharge. Patients were given instructions on diet, medications and the clinical signs of bleeding or perforation.
3.3.3 Medication

All patients within the treatment protocol were placed on twice daily proton pump inhibitors in order to promote optimal healing of the oesophagus with neosquamous mucosa in a non acid environment. Antiplatelet agents, both aspirin and clopidogrel were withheld 7 days prior to EMR procedures. In patients where the clinical need to restart antiplatelet agents was thought the outweigh the risk of delayed oesophageal bleeding, aspirin was commenced the day after the procedure. If the patient was previously on clopidrogrel, aspirin was used as an alternate agent in the first 7 days.

3.3.4 Histological assessment

The EMR specimens were fixed in formalin for routine histological evaluation by an expert GI pathologist (R.W.). Careful pathological assessment was made documenting the depth of invasion, clearance of resection margins both lateral and deep and lymphovascular invasion.

3.3.5 Database

A computerised database was designed by an external I.T. consultant based on Microsoft Access 2007. The database was password protected and all data was entered, stored and analysed using this programme.

3.3.6 Ethics committee approval

The study was approved by the St Vincent’s Human Research Ethics Committee (HREC-D) – Protocol Number 161/09.

3.3.7 Statistical analysis
Categorical variables were compared using the Chi square / Fisher's exact test. Continuous variables were compared using the Kruskal Wallis test. All statistical testing was 2 sided at a significance level of 5% using SAS statistical software, v9.2 (SAS, Cary, NC, USA)

3.4 Results

3.4.1 Patient characteristics

Between November 2008 and September 2011, a total 71 patients have been referred with dysplastic BO for consideration of combination endoscopic therapy St Vincent's hospital. The mean age of the patients was 70 years (range 41 to 86 years), and 88.7% were male. The median length of BO was 7cm (range 1 to 16cm) (Table 3.1).

Table 3.1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Number (percentage)</th>
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<tbody>
<tr>
<td>Male</td>
<td>63 (88.7%)</td>
</tr>
<tr>
<td>Age</td>
<td>Median 70 years (range 41 - 86)</td>
</tr>
<tr>
<td>Length of Barrett’s</td>
<td>Median 7 cm (range 1 - 16)</td>
</tr>
</tbody>
</table>

This data confirms that males are the highest risk group for the development of BO.

3.4.2 Procedural details at referral

The characteristics of the referral endoscopy are presented in table 3.2.
Table 3.2: Characteristics of endoscopy findings by referring physicians

<table>
<thead>
<tr>
<th>Referral endoscopy</th>
<th>Number (71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral pathology</td>
<td></td>
</tr>
<tr>
<td>Sub mucosal cancer</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Intra mucosal cancer</td>
<td>16 (22.5%)</td>
</tr>
<tr>
<td>High grade dysplasia</td>
<td>28 (39.4%)</td>
</tr>
<tr>
<td>Low grade dysplasia</td>
<td>20 (28.7%)</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>6 (8.5%)</td>
</tr>
<tr>
<td>Seattle protocol followed</td>
<td>0</td>
</tr>
<tr>
<td>Number of biopsies</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>6</td>
</tr>
<tr>
<td>Range</td>
<td>2 – 10</td>
</tr>
<tr>
<td>Discrete lesions identified at referral</td>
<td>13 (18.3%)</td>
</tr>
</tbody>
</table>

These findings highlight the fact that the Seattle protocol was never followed by the community based gastroenterologists who referred the patients for treatment. Given a median of 7cm of Barrett’s, 28 biopsies would be expected if the Seattle protocol was followed. The majority of patients were referred with high grade dysplasia or intramucosal cancer.

3.4.3 Lesion characteristics

Of the 71 patients referred for assessment and management of dysplastic BO, 48 patients underwent an EMR for resection of 48 visible mucosal abnormalities that harboured dysplastic BO. The endoscopic characteristics of the lesions identified which
were resected by EMR and the subsequent proportion in which invasive cancer was detected are outlined in table 3.3. Furthermore the characteristics and pathology of the lesions identified and lesions missed by the referring doctors are also presented in table 3.3

Table 3.3: Characteristics of visible mucosal abnormalities removed by EMR

<table>
<thead>
<tr>
<th>Characteristics of lesions resected with EMR</th>
<th>Number</th>
<th>Number identified by referring doctors</th>
<th>Number with invasive cancer IMC / SMC</th>
<th>Number of missed cancers by referring doctors IMC / SMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat / subtle lesions – Paris 0-2B</td>
<td>17</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Raised lesions</td>
<td>31</td>
<td>15</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Paris 1s</td>
<td>12</td>
<td>10</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Paris 0-2A</td>
<td>14</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Paris 0-2A+C</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>15</td>
<td>24</td>
<td>9</td>
</tr>
</tbody>
</table>

These results highlight a number of important findings. Firstly of the 48 lesions identified after careful endoscopic assessment with sequential high definition white light, narrow band imaging and confocal endomicroscopy, only 15 lesions were
identified by the referring doctors. Of the 33 lesions missed by the referring doctors, 16 were regarded as raised lesions whereas 17 were flat/subtle lesions. Secondly, 24 of the 48 lesions identified were found to harbour invasive cancer (12 IMC and 12 SMC). The referring doctors identified 15 raised lesions that harboured invasive cancer and missed 9 cancers which consisted of 4 flat/subtle lesions and 5 raised lesions. Importantly 4 patients with SMC were not identified by the referring doctors. Finally, the presence of a nodule (Paris 1s) as well as the presence of a nodular area with a depressed component (Paris 0-2A+C) correlated strongly with the finding of invasive cancer.

3.4.4 Examples of Visible Mucosal Abnormalities according to Paris classification:

3.4.4.1 Subtle lesions (Paris 0-2B) that harboured invasive cancer beyond the epithelium

Intramucosal cancer into the muscularis mucosae
Intramucosal cancer into the muscularis mucosae

3.4.4.2 Discrete lesions (Paris 1s) that harboured invasive cancer beyond the epithelium

Submucosal cancer
Submucosal cancer

Intramucosal cancer
3.4.4.3 Discrete lesions (Paris 0-2A+C) that harboured invasive cancer beyond the epithelium

Submucosal cancer

3.4.5 EMR characteristics

The characteristics of the EMR procedure are shown in table 3.4.

Early in the study protocol the procedure was performed with the cap and snare technique which was then replaced by the multiband mucosectomy technique with the “Duette” system. There were a median number of 3 contiguous resections to ensure adequate clearance of the peripheral margins of the mucosal lesion identified on a per lesion basis.
Table 3.4: Characteristics of EMR procedures

<table>
<thead>
<tr>
<th>Number of EMR sessions performed</th>
<th>61</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMR Technique</strong></td>
<td></td>
</tr>
<tr>
<td>Duette system</td>
<td>53</td>
</tr>
<tr>
<td>Cap and snare</td>
<td>8</td>
</tr>
<tr>
<td><strong>Size of lesion for resection</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>20mm</td>
</tr>
<tr>
<td>Range</td>
<td>5 – 40mm</td>
</tr>
<tr>
<td><strong>Number of pieces resected</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
</tr>
<tr>
<td>Range</td>
<td>1-6</td>
</tr>
<tr>
<td><strong>Number of EMR specimens containing submucosal tissue</strong></td>
<td>158/192 (82.3%)</td>
</tr>
</tbody>
</table>

3.4.6 Role of EMR in staging

After careful endoscopic assessment in combination with EMR 25/71 (35.2%) patients referred had upstaging of their neoplastic grade of dysplasia compared with the referral pathology. 8/71 patients had downstaging of their neoplastic grade of dysplasia. In 38/71 patients there was concordance between the most advanced pathology at assessment and the referral pathology. Figure 3.3 outlines the changes in neoplastic stage of dysplasia that occurred due to an EMR procedure being performed on a mucosal area that harboured a visible mucosal abnormality.
This data highlights the diagnostic impact of EMR in the assessment of dysplastic BO. 20 of the 25 patients that were upstaged after assessment occurred as a result of the EMR procedure ($P=0.0498$). 4 of the 8 patients down staged occurred as a result of the EMR procedure. In 24 patients EMR had no diagnostic impact.

3.4.7 Role of EMR in optimal treatment

The role of EMR in optimal treatment of dysplastic BO has been well established. The ability to resect into the submucosa and clear superficially invasive cancers that remain confined to the muscularis mucosae is the clear advantage that EMR holds over the other ablative techniques.

In 24/48 (50%) EMR was considered necessary for optimal treatment. 12 patients found to have sub-mucosal invasion, were unsuitable for endoscopic therapy and therefore referred for either surgery or definitive chemo radiotherapy depending on fitness for
surgery. 11 patients with intra-mucosal cancer and invasion to muscularis mucosa (M3) and 1 patient with invasion into lamina propria (M2) may not have been adequately treated by HALO ablation alone. 24/48 patients in whom dysplasia was confined to epithelium (M1), EMR would not have changed outcome as HALO RFA would probably have adequately treated epithelial dysplasia, if all the lesions were flat. However EMR is still important in M1 lesions which are raised.

3.4.8 Assessment of safety following EMR

48 patients in whom an EMR was performed were included in the analysis. The adverse events were separated into intraprocedural events, early (<24hours) and late (>24hours).

8 patients had intraprocedural events that required endoscopic therapy, these included 5 patients with minor bleeding controlled with the coagulation grasper, 2 patients with suspected perforation based on the appearance of a deeper submucosal defect post EMR. Endoclips were applied to these areas and both patients had normal gastrograffin studies performed post procedure and were discharged the next day without complication.

There was 1 serious complication of an oesophageal perforation that was suspected during the procedure. The patient was referred with a subtle mucosal abnormality that was found to harbour HGD. The area that was resected in this patient was located at the gastrooesophageal junction. Three contiguous resections were performed without complication however the fourth resection resulted in a focal mucosal defect which was thought to represent a perforation. Endoscopic closure was attempted with the use of endoclips however gastrograffin swallow performed immediately post procedure revealed extravasation of contrast into the mediastinum. Antibiotics were immediately given and patient taken to theatre for primary repair including a fundoplication wrap. The histology from the EMR specimens only demonstrated LGD. The patient required a total of 6 days in hospital and he had a successful recovery. Follow up endoscopies have been performed with CR-IM achieved after x2 HALO 90 treatments.

There were no early post-procedural complications with one late complication identified. This patient had an episode of melaena 10 days post EMR, repeat
gastroscopy was performed however no endoscopic therapy was necessary and the patient recovered without need for a blood transfusion. No patient developed symptomatic dysphagia post EMR that required dilatation. At repeat gastroscopy, few patients had minor scarring noted after EMR, but no significant strictures were identified.

3.5 Discussion

The main aim of this work has been to evaluate the importance of EMR in the assessment and treatment of dysplastic BO. This methodology provides an accurate representation of the real life application of EMR both as a diagnostic and therapeutic tool.

The two principle findings of this study are that experienced endoscopists using high definition endoscopes find more lesions than community based gastroenterologists and secondly, EMR is needed to adequately stage lesions prior to choosing optimal therapy.

3.5.1 Importance of EMR for accurate staging

EMR has been shown to be the best modality for determining both the grade of dysplasia and the depth of neoplastic invasion within the mucosal and submucosal layers as EMR provides a large specimen for pathological interpretation. EMR specimens have been shown to increase the accuracy and inter observer agreement between the interpreting pathologists as the majority of EMR specimens (88%) contain submucosa compared to a standard biopsy <1% (Pech 2010).

The majority of patients in our study cohort were referred with HGD/IMC for consideration of definitive endoscopic therapy. Meticulous endoscopic reassessment was performed in order to best select which patients were suitable for endoscopic therapy, as the presence of adenocarcinoma with submucosal invasion is associated with up to a 20 to 30% risk of lymph node metastases, and should therefore be considered an indication for surgical resection in fit patients (Rice, Zuccaro et al. 1998; Stein, Feith et
al. 2000; Stein, Feith et al. 2005). Twelve patients who had an EMR performed were found to harbour adenocarcinoma that had invaded into the submucosal layer, precluding endoscopic therapy and were therefore referred for either surgery or chemoradiotherapy.

The identification of both flat (often subtle) and raised lesions after careful assessment endoscopy in combination with EMR of these lesions, led to upstaging in 25/71 patients (35.2%), of whom 20/25 were upstaged directly as a result of EMR. 33/48 of these lesions were not identified on previous endoscopy by the referring doctors, resulting in 9/24 cancers being missed. Due to the larger pathological specimen, endoscopic mucosal resection results in upstaging of the depth of invasion compared to biopsy alone (Nijhawan and Wang 2000). A study of 40 patients undergoing endoscopic mucosal resection – 6/25 (24%) with high grade dysplasia were upstaged to intramucosal carcinoma and 6/15 (40%) with intramucosal carcinoma were upstaged to submucosal cancer (Larghi, Lightdale et al. 2005).

There are many possible factors contributing to these findings. The referring physicians were not likely to have performed their assessment gastroscopy as a dedicated procedure but instead would have formed part of a busy general list, without the availability of advanced imaging techniques and knowledge of the diagnosis. In addition many of the physicians may have not been familiar with the mucosal assessment of BO, in particular the mucosal patterns that correlate with HGD or IMC. Our assessment was aided by two key factors. Firstly, knowledge of the referral pathology and longer assessments in fully sedated patients may have lead to a better yield of detecting subtle mucosal abnormalities. Despite these possible biases our findings highlight the importance of quality upper endoscopy which is even more important when performing surveillance of BO. Increasing awareness amongst community gastroenterologists through ongoing education of the mucosal features that correlate with HGD / IMC and reinforcing the need to allocate adequate time to perform surveillance endoscopy will likely improve diagnostic yield.
The rates of upstaging in our study are consistent with those reported in resection based studies where up to 30-40% of patients with HGD who underwent an oesophagectomy were found to harbour invasive cancer (Konda, Ross et al. 2008). The similarity of the surgical resection figures to the rates of IMC and SMC diagnosed by endoscopic mapping and EMR, suggests that cancers which in the past were not detected prior to surgical resection, are now being diagnosed with high definition endoscopy aided by advanced imaging techniques and EMR. The results of our study support the principle of performing an EMR in a region with a visible mucosal abnormality that harbours dysplasia in order to exclude occult cancers that would most likely be inadequately treated by a superficial ablative therapy such as HALO RFA.

3.5.2 Importance of EMR in addition to HALO RFA, for optimal treatment of intramucosal cancer.

Dosimetry studies assessing the depth of radiofrequency ablation with the HALO 360 device have shown that 12J x 2 ablations is the optimal dose delivered at each session (Ganz, Utley et al. 2004; Dunkin, Martinez et al. 2006; Smith, Bejarano et al. 2007). At this dose the HALO device ablates reliably the epithelium of the Barrett’s mucosa, ablates variably within the lamina propria and muscularis mucosa and does not ablate into the submucosal layer, as it is at this depth that the rate of stricture formation increases. Our study identified 11 patient with dysplastic BO that invaded into the muscularis mucosae and 1 patient with invasion into the lamina propria. These patients may not have been adequately treated by HALO RFA alone, with its variable depth of ablation beyond the epithelium, which raises concerns about the application of HALO RFA without meticulous endoscopic assessment and EMR of even subtle visible mucosal lesions. Rates of cancer recurrence, especially early cancer recurrence may in part be due to untreated invasive BO. There is currently little data in the literature that addresses this issue.

3.5.3 Safety of EMR

The safety profile of oesophageal EMR has been well documented in the literature with the procedure performed on large numbers of patients in multicenter studies. The
currently accepted rates of serious complications of bleeding and perforation are in the order of 1%. In studies where complete stepwise circumferential EMR of the entire Barrett’s segment is performed without ablation therapies, a stricture rate of 50% has been reported (Pouw, Seewald et al. 2010). The results of our study again demonstrate that EMR can be performed safely in expert hands. The 2 suspected perforations and the 1 definite perforation all occurred at the gastro-oesophageal junction. The gastro-oesophageal junction has an inner muscle layer that is less supported than in the more proximal oesophagus. Therefore there is a relative anatomical weakness which makes performing EMR at this location, theoretically a higher risk. However there is no published data in the literature that supports higher rates of perforation at the gastro-oesophageal junction. The episode of perforation resulted in a change of practice where we now will lift the submucosa with a saline cushion prior to EMR resection, in order to minimise this risk in resections performed near the gastro-oesophageal junction.

No patient in our study cohort has developed symptomatic dysphagia which likely reflects the use of focal EMR rather than circumferential EMR. This approach relies of the endoscopist’s ability to identify areas that harbour intramucosal cancer and utilises the best aspects of each modality and minimises the limitations and possible adverse events associated with both EMR and HALO RFA. A recent randomised multicenter study compared stepwise complete EMR to combination therapy and found similar therapeutic outcomes with a much lower rate of stricture formation with focal EMR followed by Halo RFA (14%) compared to total circumferential EMR (88%) (van Vilsteren, Pouw et al. 2011).

3.6 Conclusions

This data demonstrates the importance of EMR in the adequate staging of dysplastic BO and in optimal treatment even of intramucosal cancer prior to mucosal ablation therapy such as HALO RFA. Our data show clearly that a large proportion of visible mucosal abnormalities harbouring cancer are not identified by endoscopists in community practice. This raises serious concern about the widespread use of endoscopic ablation therapy for BO in the community gastroenterology and surgical setting. Poor long term results can be anticipated following HALO RFA performed outside specialist centres,
though this needs to be confirmed by long-term follow-up studies specifically addressing this question. Our data indicates that individuals with dysplastic BO should be referred to centres specialising in and highly skilled in identification of mucosal detail in BO and in endoscopic mucosal resection techniques.
Chapter 4: Combination Endoscopic Therapy For Dysplastic Barrett’s Oesophagus - Overall Results

4.1 Introduction

The previous management of dysplastic BO harbouring high grade dysplasia (HGD) and intramucosal cancer (IMC) was surgical oesophagectomy, however in recent years this treatment paradigm has shifted since the development of effective endoscopic therapies such as HALO radiofrequency ablation (RFA) and cryotherapy (Ganz, Overholt et al. 2008; Shaheen, Sharma et al. 2009; Greenwald, Dumot et al. 2010; Shaheen, Greenwald et al. 2010). Despite the promise of these new techniques, endoscopic mucosal resection (EMR) remains an essential component of the optimal endoscopic management of dysplastic BO, both for staging and therapeutic purposes (Ell, May et al. 2007; Pech, Behrens et al. 2008; Pouw, Seewald et al. 2010; Pouw, Wirths et al. 2010; van Vilsteren, Pouw et al. 2011).

The initial phase of development of HALO RFA involved a series of dosimetry studies which focused on optimising depth of ablation and the development of an ablation protocol (Ganz, Utley et al. 2004; Dunkin, Martinez et al. 2006; Smith, Bejarano et al. 2007). Subsequent clinical trials, from which most of the safety and efficacy data is derived, have been large multicenter studies based in US and European centres, all of which have produced extremely encouraging short term results, with success rates greater than 90% (Sharma, Wang et al. 2007; Fleischer, Overholt et al. 2008; Ganz, Overholt et al. 2008; Shaheen, Sharma et al. 2009).

In patients with dysplastic BO, the principle of combination therapy is to remove visible mucosal abnormalities that may harbor invasive cancer with EMR and then ablate the remaining BO with HALO RFA, to reduce the risk of metachronous neoplasia. A recent randomised study of patients with short segment BO containing HGD/IMC, compared combination therapy to stepwise radical EMR of the entire Barrett’s segment. This study found similar efficacy between the two techniques with complete eradication of BO of 92% with EMR alone and 96% with combination therapy. However the stricture
rate was 88% in the EMR group compared with 14% in patients treated with the combination approach (van Vilsteren, Pouw et al. 2011).

Our study is the first Australian based study prospectively assessing the efficacy and safety of combination therapy with EMR and HALO RFA, in the treatment of dysplastic BO. The outcomes of this cohort are presented in the following chapter, looking in particular at efficacy and safety of this approach.

4.2 Aims

The aims of this study were to assess:

1. the rate of complete remission of intestinal metaplasia (CR-IM) at 12 months post commencement of HALO RFA.
2. factors that may predict resistance to HALO RFA.
3. the safety and tolerability of HALO radiofrequency ablation

4.3 Materials and Methods

4.3.1 Patient Selection

Patients included in this study were those referred to St Vincent’s Hospital for endoscopic evaluation and treatment of dysplastic Barrett’s oesophagus previously diagnosed by their referring physician. Patients were over the age of 18 years. Prior to entry into the study, patients underwent a detailed endoscopic assessment at St Vincent’s Hospital as detailed in chapter 2. The decision to perform endoscopic mucosal resection was based on the finding of a visible mucosal abnormality (VMA) that harboured dysplastic Barrett’s oesophagus at histological assessment as outlined in chapter 3. Patients then entered the HALO ablation program once it was thought that all invasive dysplastic Barrett’s oesophagus had been adequately resected by endoscopic mucosal resection.
4.3.2 Referral forms

A majority of patients included in the study were referred to the principle investigator using a form previously devised from the Victorian Government’s New Technologies Grant which has funded the HALO procedures for 100 patients, since the program’s inception (Appendix 1). On this form, the referring doctor was asked to indicate past history, previous endoscopic procedures and most recent histology. For the remaining patients, details of previous endoscopies and biopsy results were forwarded to the principle investigator directly by the referring doctor. All patients were then assessed by the principle investigator prior to entry into the study.

4.3.3 Details of endoscopic evaluation

The initial endoscopic assessment (mapping protocol) and endoscopic mucosal resection has been described in detail in chapters 2 and 3 respectively.

Prior to commencement of endoscopic therapy the mapping assessment biopsies and previous pathology were assessed in a multidisciplinary meeting involving an expert GI pathologist (R.W.), upper GI surgeons and gastroenterologists. A management strategy was then formulated for each patient based on the management algorithm outlined below and any future concerns reviewed in the same meeting process.

Staging investigations were also performed based on the neoplastic grade of dysplasia. In general staging investigations beyond an EMR were performed only in patients with the finding of intramucosal cancer. In these patients loco-regional staging were performed, including endoscopic ultrasound and imaging studies (PET and CT). If these tests detected evidence of submucosal invasion or of loco-regional disease, then referral for consideration of surgery and /or chemoradiotherapy was made.

The management algorithm formulated at the inception of the study is outlined in figure 4.1.
Figure 4.1: Management algorithm

POST HALO ALGORITHM

- Repeat endoscopy every 2-3 months

- No residual BO
  - Seattle protocol biopsies of neosquamous mucosa

- Residual dysplastic BO
  - No visible mucosal abnormality (Flat Mucosa)
  - HALO Focal 90 or 360 if extensive BE

- Residual dysplastic BO + Visible endoscopic abnormality

- No BO
  - Repeat process in 6 months

- No BO again repeat process in 12 months
  - If HGD initially continue annual endoscopy

- EMR
4.3.4 Details of endoscopic therapy

4.3.4.1 Equipment

4.3.4.1.1 HALO radiofrequency ablation:

The HALO RFA procedures were performed with the The Barrx Halo system, which consists of 2 ablation devices. The HALO 360 consists of a 4cm balloon which has a 3cm RFA segment which contains 60 independent electrodes that are tightly spaced with alternating polarity. 5 different balloon diameters can be chosen after the patients oesophagus is firstly assessed with an automated sizing balloon. Once inflated the balloon flattens the oesophageal mucosa. The energy delivered is controlled by the radiofrequency generator at 12J/cm², which is delivered in less than 1sec. After the first ablation the balloon is removed and cleaned and the burnt oesophageal mucosa is cleared with a cap mounted onto the endoscope to provide a clean surface to deliver the second ablation. The HALO 90 system consists of an endoscope mounted electrode (20mm x 13mm) which allows focal delivery of radio frequency energy to small areas of BO. The same energy and automation are used as for the HALO 360.

HALO 360
4.3.4.1.2 Endoscopic mucosal resection

Endoscopic mucosal resection was predominantly performed with an Olympus “Duette” EMR kit as outlined in Chapter 3.

4.3.4.1.3 Argon plasma coagulation

Argon plasma coagulation (APC) is another ablative therapy that has proven efficacy in Barrett’s oesophagus. In some patients with few tiny islands of Barrett’s remaining after successful HALO RFA, APC was used from the ERBE system at 30W as a cost saving measure.

4.3.5 Medication

All patients within the treatment protocol were placed on twice daily proton pump inhibitors in order to promote optimal healing of the neosquamous mucosa in a non acid environment.

Antiplatelet agents were withheld 7 days prior to HALO RFA and EMR procedures.
4.3.6 Database

A computerised database was designed by an external I.T. consultant based on Microsoft Access 2007. The database was password protected and all data was entered, stored and analysed using this programme.

4.3.7 Ethics committee approval

The study was approved by the St Vincent’s Human Research Ethics Committee (HREC-D) – Protocol Number 161/09.

4.3.8 Histological assessment

The EMR and biopsy specimens were fixed in formalin for routine histological evaluation by an expert GI pathologist (R.W.). Careful pathological assessment was made in particular for EMR specimens, documenting the depth of invasion, clearance of resection margins both lateral and deep and lymphovascular invasion.

4.3.9 Statistical analysis

Categorical variables were compared using the Chi square / Fisher's exact test. Continuous variables were compared using the Kruskal Wallis test. All statistical testing was 2 sided at a significance level of 5% using SAS statistical software, v9.2 (SAS, Cary, NC, USA)
4.4 Results

4.4.1 Recruitment

Between November 2008 and February 2012, a total 92 patients have been referred with dysplastic BO for consideration of combination endoscopic therapy to St Vincent’s hospital, Melbourne.

A flow diagram demonstrating recruitment is presented in figure 4.2. Of the 92 patients referred for assessment and management of dysplastic BO, 26 were deemed unsuitable for endoscopic therapy. 19 patients were found to have invasive cancer that precluded curative endoscopic therapy, these patients were referred for surgery or chemoradiotherapy depending on their fitness for surgery. 4 patients were found to harbour non dysplastic BO and were sent back to the referring doctor for ongoing surveillance endoscopy. The final 3 patients were found to be medically unfit for ongoing endoscopic procedures and were excluded on this basis after discussion with both patient and referring doctor.
**Figure 4.2 – Recruitment of patients**

**4.4.2 Patient characteristics**

An assessment at 12 months post commencement of HALO RFA, looking at the single outcome of complete eradication of intestinal metaplasia (CR-IM) is outlined in table 4.3. The baseline characteristics of those who achieved CR-IM at 12 months were compared to those with resistant BO at 12 months looking for factors that may contribute to resistance to HALO RFA.
### Table 4.3 – Comparison of baseline factors of patients with CR-IM at 12 months vs. persistent Barrett’s Oesophagus

<table>
<thead>
<tr>
<th></th>
<th>Achieved CR-IM</th>
<th>Nil CR-IM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>23</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>67 (41 - 86)</td>
<td>66 (64 - 80)</td>
<td>0.5685</td>
</tr>
<tr>
<td>Male Gender (n,%)</td>
<td>20 (87%)</td>
<td>4 (66%)</td>
<td>0.1156</td>
</tr>
<tr>
<td>Length-C</td>
<td>2 (0-7)</td>
<td>7 (3-14)</td>
<td>0.0071</td>
</tr>
<tr>
<td>Length-M</td>
<td>3 (1-10)</td>
<td>9 (5-14)</td>
<td>0.0413</td>
</tr>
<tr>
<td>Hernia</td>
<td>19 (82%)</td>
<td>6 (100%)</td>
<td>0.4486</td>
</tr>
<tr>
<td>Referral pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IM</td>
<td>2 (9%)</td>
<td>0</td>
<td>0.7181</td>
</tr>
<tr>
<td>LGD</td>
<td>5 (21%)</td>
<td>2 (33%)</td>
<td></td>
</tr>
<tr>
<td>HGD</td>
<td>14 (61%)</td>
<td>4 (66%)</td>
<td></td>
</tr>
<tr>
<td>IMC</td>
<td>2 (9%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>N(HALO) treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (13%)</td>
<td>0</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>14 (61%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (26%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>2 (33%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>3 (50%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>1 (17%)</td>
<td></td>
</tr>
</tbody>
</table>
4.4.3 Completed treatment at 12 months

At the time of writing there were 23 patients who had successfully completed eradication of dysplastic BO at or prior to 12 months since first therapeutic intervention with HALO RFA. 2 patients with short tongues of BO were treated with EMR alone. The majority of patients were middle aged males with a hiatus hernia. The median length of BO was 3cm with a wide range of 1 to 10cm. Table 4.4 outlines the treatment required to achieve complete remission at 12 months.

**Table 4.4: Treatment required to achieve CR-IM at 12 months.**

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic mucosal resection alone</td>
<td>2 patients</td>
</tr>
<tr>
<td>Number of EMR sessions</td>
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In 16/25 patients an EMR was performed prior to HALO RFA to resect an area with a visible mucosal abnormality. In 2 of these patients with short tongues of BO less than 3cm, no further HALO was required as the EMR had completely resected the entire BO segment. As a result of previous EMR, 4 patients who proceeded to HALO 360 had appropriate downsizing of the 360 ablation balloon as per manufacturer’s instructions to reduce the risk of perforation, with the median size of ablation balloon of 28mm, range 25 to 31mm.

Patients who achieved CR-IM with either EMR alone or HALO RFA alone required a median of 2 procedures, range 1-3 procedures. Patients treated with combination of EMR and HALO RFA required a median of 1 EMR and 2 HALO RFA procedures to achieve CR-IM by 12 months.

4.4.4 Incomplete treatment at 12 months

At the time of writing there were 6 patients who had not achieved CR-IM at 12 months since first therapeutic intervention with HALO RFA. The most notable difference between the baseline characteristics of this cohort and those who achieved CR-IM at 12months, is the longer median length of Barrett’s at 9cm. All patients had a hiatus hernia with a median size of 5cm (range 3cm to 7cm).

An EMR was required in 3 of the 6 patients to remove a visible mucosal abnormality prior to commencement of HALO RFA. One patient required four EMR sessions to ensure clearance of the lesion, the other 2 patients required a single EMR session. As a result of previous EMR, the 3 patients who proceeded to HALO 360 required downsizing of the HALO 360 ablation balloon with a median size of 28mm range 25 to 31mm. All 6 patients have undergone a combination of HALO 360 and HALO 90 with a median of 4 sessions at the 12 month assessment point. As patients were not routinely biopsied until endoscopic eradication of the BO segment, it is uncertain the rates of complete remission of dysplasia in this small group at the 12 month mark. One patient subsequently achieved CR-IM at 18 months after a total of 6 HALO RFA sessions.

The residual BO in those patients who did not achieve CR-IM at 12 months, 1 patient had residual dysplasia the remaining patients had residual IM. The residual BO was
located at the gastrooesophageal junction in 2 patients, tubular oesophagus in 3 patients and combination of both locations in 1 patient.

APC was used in 2 patients with a few tiny islands of Barrett’s both within the tubular oesophagus and at the gastro oesophageal junction.

4.4.5 Yet to reach 12 months of treatment

There are currently 35 patients who are still within the treatment protocol who are yet to reach 12 months since first therapeutic intervention with HALO RFA.

4.4.6 Staging investigations

Staging investigations were performed in the 6 patients who were found to harbour intramucosal cancer after detailed assessment including EMR. These tests were performed in order to exclude the presence of metastatic or locoregional disease which would preclude endoscopic therapy. Endoscopic ultrasound performed in these patients did not reveal any pathological lymph nodes and staging with PET and CT found no evidence of metastatic spread.

4.4.7 Surface area treated with each ablation session

An estimation of the surface area (cm2) treated with each HALO RFA ablation was made comparing those who achieved complete eradication at 12 months to those who needed further treatment. The surface area treated was used as a surrogate measure to estimate the surface area of Barrett’s.

The surface area calculations were made in the following way.

1. The HALO 90 ablation device is 20mm x 13mm = surface area 4.6cm2

HALO 90 surface area calculation = 4.6cm2 x number of locations treated
2. The HALO 360 is a circumferential balloon which when inflated estimates the diameter of the oesophagus. For example the 28mm balloon refers to a diameter of 28mm.

Radius = Diameter / 2

\[ \text{Surface area treated with HALO 360} = 2\pi r \left( \frac{\text{diameter of balloon}}{2} \right) \times \text{length of Barrett’s segment} \]

Figure 4.5 below compares reduction of surface area with each ablation between the 2 groups after commencement of HALO ablation. This estimation does not account for previous number or extent of EMR prior to commencement of HALO ablation. The number at the top of each column within the graph refers to the number of patients treated with each HALO ablation, The x-axis refers to the HALO number i.e. first, second and third HALO and the y-axis refers to the surface area of Barrett’s ablated. All 6 patients who did not achieve complete eradication required HALO, whereas 23/25
that completed treatment required HALO RFA as 2 patients achieved complete eradication with EMR alone.

**Figure 4.5 Surface area treated at each HALO session**

The figure above demonstrates the stepwise reduction in surface area of Barrett’s treated with each HALO RFA ablation session. As expected the group who have completed eradication at 12 months had a more rapid response to each ablation session.

### 4.5 Assessment of safety following HALO radiofrequency ablation

#### 4.5.1 Methods

**4.5.1.1 Patient selection**

All patients who had undergone an HALO RFA ablation session were asked to be included in the assessment.

**4.5.1.2 Follow up forms**
Patients undergoing HALO RFA were interviewed 2 hours post procedure with an exit survey rating symptoms on a visual analogue scale from 0-10 (Appendix 3). On discharge patients were given a 14 day symptom diary using the same visual analogue scale (Appendix 3). The symptom diaries were then returned in the mail following completion.

4.5.2 Results

4.5.2.1 Patient characteristics

There were 26 patients who had a total of 63 ablation sessions included in the analysis in figure 4.6.

Figure 4.6: Visual analogue scale depicting symptoms and severity post HALO RFA

The visual analogue severity scale from 0 to 10 is represented along the y-axis. The days of the weeks are represented along the x-axis. Patients generally experienced mild symptoms post ablation, with chest and throat pain the most commonly experienced side effects at both the exit survey and in the first few days post ablation. These symptoms were generally short lived with all symptoms resolving by day 5. On a per ablation assessment, out of 63 ablations, 46 caused some chest or throat pain whereas 17 patients were completely asymptomatic.
There were 2 patients who had superficial mucosal tears as a consequence of the HALO 360 sizing balloon, recognised before the HALO RFA balloon was used. Neither of these patients had previous EMR. At follow up endoscopy, both of these patients had healing of the previous mucosal tear and were able to proceed to receive HALO ablation without complication.

**Patient 1**

![Image of Patient 1](image1)

**Patient 2**

![Image of Patient 2](image2)
4.6 Discussion

The main aim of this work has been to evaluate the efficacy and safety of combination endoscopic therapy in the management of dysplastic Barrett’s oesophagus.

In patients with HGD /IMC, oesophagectomy had previously been regarded as standard treatment because of studies showing that cancer is discovered in approximately 30-40% of oesophagectomy specimens after a pre-operative diagnosis of HGD (Konda, Ross et al. 2008). Oesophagectomy in high volume centres now carries a low mortality rate of around 1%, however morbidity rates still remain around 30% (Thomson and Cade 2003). Recently, improved capacity to identify early cancers with modern endoscopes, combined with advances in endoscopic resection and ablation techniques have resulted in excellent outcomes for individuals with HGD / IMC treated with endoscopic therapies alone, providing a credible alternative to surgical oesophagectomy (Sharma, Wang et al. 2007; Fleischer, Overholt et al. 2008; Ganz, Overholt et al. 2008; Gondrie, Pouw et al. 2008; Shaheen, Sharma et al. 2009; Pouw, Wirths et al. 2010; van Vilsteren, Pouw et al. 2011).

The principle of combination therapy is to remove visible mucosal abnormalities that may harbor invasive cancer with EMR and then ablate the remaining BO with HALO RFA, to reduce the risk of metachronous neoplasia. EMR plays two critical roles in the management of patients with dysplastic BO. Firstly, EMR has been shown to be the best diagnostic modality to assess the T stage of invasive dysplastic BO (Spechler and Davila 2009; Wani, Mathur et al. 2010). The second important role of EMR is in the treatment of invasive BO that invades into the lamina propria or to the muscularis mucosa as we believe that HALO RFA cannot reliably ablate to this depth, which may result in untreated and buried dysplastic BO with the potential to progress to invasive cancer. This combination technique optimizes the beneficial aspects of HALO RFA and EMR whilst reducing the complications associated with each, in particular stricture rates with EMR (van Vilsteren, Pouw et al. 2011).
4.6.1 Interpretation of results

The two principle findings of this study were that combination endoscopic therapy was able to achieve CR-IM in 80% of patients at 12 months with a median of 1 EMR and 2 HALO RFA procedures and secondly, longer BO segments predict failure to achieve CR-IM at 12 months (p = 0.04).

In our study CR-IM was achieved in 25/31 patients (80%) within 12 months of the first HALO RFA treatment. A median of 3 therapeutic procedures (1 EMR and 2 HALO ablations sessions) was required to achieve CR-IM. The 6 patients who failed to achieve CR-IM at 12 months had similar baseline characteristics to the group who achieved CR-IM, in regard to the common variables of age, gender, degree of dysplasia, need for EMR, presence of hiatus hernia and median size of hiatus hernia. The clear baseline difference between the groups was the median length of BO which was 9 cm (range 5-14 cm) in the group who failed to achieve CR-IM compared with 3 cm (range 1-10 cm) in the successfully treated group (p = 0.04). Korst et al. recently reported that the length of BO was a factor predicting resistance to ablation or the need for more ablations with HALO RFA. They also found that a large hiatus hernia predicted slow response to HALO RFA (Korst, Santana-Joseph et al. 2011).

Complete eradication in our study not only refers to complete eradication of dysplasia but also complete eradication of intestinal metaplasia. This endpoint was confirmed both at endoscopy with visual re-epithelisation of the oesophagus with neo-squamous mucosa and secondly with re biopsy of the length of the mucosa to allow for histological confirmation. Histological confirmation is critical, as it provides an objective measure of successful treatment and provides an assessment for buried BO.

4.6.2 Patients still within treatment protocol

It is difficult to draw many hard conclusions from this group of patients for the following reasons. Patients still within the treatment protocol represent a heterogeneous group at various stages along their treatment journey. Therefore the characteristics of this group, number of EMR sessions and number of ablations sessions will change depending on the time point at which the data is analysed. Other studies of HALO
ablation performed re-biopsy at pre defined time points, usually at 12 and 24 months in order to determine the rates of complete remission of dysplasia and complete remission of intestinal metaplasia. Our study only performed re-biopsy once all endoscopically visible Barrett’s had been eradicated. It may be that many patients have already achieved complete remission of dysplasia and only have remaining intestinal metaplasia to ablate, which in other studies is an endpoint in itself.

4.6.3 Staging investigations in patients with IMC

The staging investigations performed in patients with IMC after assessment generally had a low yield of detecting loco-regional and distal spread. In all patients disease was confirmed to be confined to the oesophagus, therefore these patients proceeded to endoscopic therapy. The 13 patients in whom sub mucosal cancer was detected, usually after EMR were referred on to the surgeons for ongoing assessment and management.

4.6.4 Side effects profile of HALO RFA

The side effect profile that we encountered was similar in type and magnitude to other studies of HALO RFA (Fleischer, Overholt et al. 2008; Shaheen, Sharma et al. 2009). The most common side effects of chest and throat discomfort post procedure only lasted a few days and were mild enough to be treated with simple analgesia. Oesophageal strictures are another advantage of this combination approach which appears to be an uncommon side effect. Higher stricture rates are commonly seen in circumferential EMR and following photodynamic therapy and argon plasma coagulation (Ragunath, Krasner et al. 2005; Sharma, Wani et al. 2006).

2 patients had superficial oesophageal mucosal tears that occurred after inflation with the automated sizing balloon. These complications resulted in cancellation and delay of the procedure to allow time for the oesophageal mucosa to heal prior to future ablation. The company currently recommend estimations with the sizing balloon be performed every 3cm along the BO segment and downsizing of the ablation catheter if the patient has had previous EMR.
4.7 Conclusion - The future of endoscopic therapy for dysplastic Barrett’s oesophagus

The assessment and treatment of dysplastic Barrett’s oesophagus (BO) has evolved dramatically over the last decade. Recently, advances in endoscopic imaging techniques have enabled more accurate identification of subtle mucosal abnormalities and provide improved capacity to identify early cancers. This combined with advances in endoscopic resection and ablation techniques have resulted in excellent outcomes for individuals with high grade dysplasia (HGD) and intramucosal cancer (IMC) treated with endoscopic means alone.

The aim of this work was to assess to efficacy and safety of these new technologies in the assessment and management of dysplastic BO.

The first study assessed the accuracy of predicting HGD and IMC in mucosa predicted as being non dysplastic vs. dysplastic by high definition white light (HD WLE), Narrow band imaging (NBI) and confocal endomicroscopy (CEM). A prospective cohort study of 50 consecutive patients was performed. A prediction of likely histology was made for each biopsy point (4 quadrant every 1cm and any visible mucosal abnormality) firstly with HD WLE, then with NBI and finally CEM. 1190 individual biopsy points have been assessed (39 HGD and 52 IMC). For the detection of HGD/IMC the sensitivity, specificity and accuracy for HD WLE were 79.1%, 83.1% and 82.8%, for NBI were 89.0%, 80.1% and 81.4% and for CEM were 75.7%, 80.0% and 79.9% respectively.

This study demonstrated that all mucosal points with IMC and all patients with HGD were detected by targeted biopsies guided by HD WLE and NBI without the need for random Seattle protocol biopsies. This study highlights the major improvement in the endoscopic assessment of BO which has mirrored the advances in technology and optical resolution of the endoscopes over the years. The limited additional benefit of CEM over the other imaging techniques in the detection of HGD and IMC draws into question its utility in real life practice outside the academic setting. Furthermore CEM has other limiting factors which include cost of the equipment, additional time to
perform the procedure and expertise required to interpret the images in real time. Further studies are required to fully characterise the role of CEM. A limitation of our study was that the detection of LGD was not a pre-defined endpoint. As this is now a critical finding that may trigger the commencement of endoscopic therapy, the detection of LGD with a targeted protocol needs to be fully studied before advocating the end to random Seattle protocol biopsies.

We then assessed the impact that endoscopic mucosal resection (EMR) had on the optimal staging and treatment of dysplastic BO. 71 consecutive patients referred for endoscopic management of dysplastic BO were included in the study. 48 patients had an EMR performed on a visible mucosal abnormality, resulting in upstaging in 20 patients (P = 0.0498). 33/48 patients had a lesion missed by their referring doctor, including 9 cancers. In 24/48 (50%) patients EMR was considered necessary for optimal treatment (12 patients with sub-mucosal invasion, were unsuitable for endoscopic therapy, 12 patients with IMC into the muscularis mucosa or lamina propria may not have been adequately treated by HALO radiofrequency ablation alone.)

These results highlight the critical role of EMR in the assessment and management of BO which are consistent with the published literature. Furthermore, the important finding that a large proportion lesions were not identified by endoscopists in community practice, reinforces the need to educate and update these practitioners on taking time and looking carefully for visible mucosal abnormalities that may harbour occult cancer.

We finally assessed the rate of complete remission of intestinal metaplasia (CR-IM) at 12 months post commencement of HALO radiofrequency ablation (RFA) and secondly looked at factors that may predict resistance to HALO RFA. 92 patients at the time of analysis had been referred for endoscopic treatment of dysplastic BO of which 31 patients had reached the 12 month assessment. CR-IM was achieved in 25/31 patients (80%) within 12 months of the first HALO RFA treatment. A median of 3 therapeutic procedures (1 EMR and 2 HALO ablations sessions) were required to achieve CR-IM. Longer BO segments, median 9cm (range 5-14) predict failure to achieve CR-IM at 12 months (p = 0.04).

Our study confirmed good success rates of combination endoscopic therapy comparable with other published studies. However further critical studies are required to identify factors that may lead to poor response to endoscopic therapy. These studies will need
not only to assess the mechanical factors of resistance such as a large hiatus hernia but also must focus on the molecular profile of the BO which may ultimately explain resistance to therapy. These studies need to be performed prospectively and compare biomarker profiles or molecular profiles of patients who are responders vs non responders.

At this stage the most widely accepted indication for endoscopic therapy is in patients with HGD or IMC. However there is a strong movement by some international experts to push the boundaries of endoscopic therapy. Treating patients with LGD or non dysplastic Barrett’s will ultimately come down to a cost effectiveness argument, as many of these patients may never progress to HGD or cancer. However a recently published study sought to stratify risk of progression to cancer in those with LGD confirmed by expert GI pathology review. This study found the risk of progression was far greater than previous noted in the literature at 13.4%/year (Curvers, Ten Kate et al. 2010). The development of biomarkers may help stratify those with LGD or non dysplastic Barrett’s that may progress more rapidly to cancer and therefore be suitable for treatment earlier. The other boundary is whether endoscopic therapy can be successfully performed in patient with superficial sub mucosal invasion. Currently invasion into but not beyond the muscularis mucosae is the limit of successful endoscopic therapy as these patients have a low risk of lymph node metastases.

There are however a number of questions that need to be answered in order to consolidate the position of endoscopic therapy. These include what is the durability of response to ablation? Do we need to continue endoscopic surveillance of these patients and at what frequency, to monitor for recurrence? Has the cancer risk been eliminated, if not what is the rate of cancer progression? These questions will only be answered as medium to long term efficacy data emerges from the large international multicenter cohorts.

One of the biggest concerns that I see for the future of endoscopic therapy in BO is, how are we going to ensure the quality and safety of therapy is maintained once HALO RFA derives an MBS item number. This will open the procedure up to individual practitioners who may not have the required training and expertise. For example will they be able to identify reliably subtle visible mucosal abnormalities that harbour IMC and subsequently remove them with EMR. Inability to do so may result in higher rates
of inadequate treatment potentially leading to progressive and incurable disease. Therefore endoscopic treatment of dysplastic Barrett’s oesophagus should be limited to use by expert endoscopists with an interest in Barrett’s oesophagus in tertiary hospitals, with access to multi disciplinary meetings, expert GI pathologists and upper GI surgeons.
Bibliography


Appendices

Appendix 1 - Forms used to refer patients into Barrett’s program

The Royal Melbourne and St Vincent’s Hospitals

Halo Radio Frequency Ablation of Dysplastic Barrett’s Oesophagus

The Royal Melbourne and St Vincent’s Hospitals advise that the Halo 360 radiofrequency ablation system is available for treatment of dysplastic Barrett’s oesophagus.

Referrals for consideration of treatment should be made directly to Professor Finlay Macrae or Dr Andrew Taylor using the attached referral form, or by mail to GE Unit at RMH or St Vincent’s Hospital. Either of us can be contacted on pager 93871000 if you wish to discuss specific patients or the programme in general.
The HALO Ablation System

The HALO radiofrequency ablation system provides uniform and controlled therapy at a consistent depth, which can remove Barrett’s mucosa from the oesophagus and allow the regrowth of normal cells.

The HALO360 Ablation System uses a balloon-based electrode to ablate Barrett’s tissue circumferentially within the oesophagus. This is used as the initial treatment for circumferential Barrett’s mucosa.

The HALO360 Ablation System is an electrode system that is mounted on the end of an endoscope, allowing the physician to treat focal areas of diseased tissue. This is generally used at follow-up endoscopies, for any remaining focal Barrett’s mucosa.

Published results to date

The Halo system has been extensively evaluated in North America and Europe for treatment of dysplastic and non-dysplastic Barrett’s. In summary, the Halo system has the following attributes:

- Stricture formation is rare with incidence of strictures approximately 1/200
- Biured glands appear very uncommon, with only one biopsy among several thousand biopsies in the published results showing intestinal metaplasia under squamous mucosa
- Non-dysplastic Barrett’s – eradication of all intestinal metaplasia at 2.5 years in 60 of 61 patients (Resch et al. Gastrointestinal Endoscopy 2008)
- Barrett’s with low grade dysplasia – eradication of dysplasia in 10/10 patients and eradication of all Barrett’s mucosa in 9/10 patients at 1 year (Sharma et al. Endoscopy 2008)
- Barrett’s with high grade dysplasia
  - Garcia et al. Gastro 2008
    - 142 patients treated at 14 USA institutions and collected in data registry
    - 99 patients with follow-up biopsy data median 12 months
    - Complete loss of HGD 50%
    - 1 cancer diagnosed after 5 months (considered prevalent)
    - Complete loss of any dysplasia 80%
    - Complete loss of intestinal metaplasia 14%

- Note: there was much lower proportion with complete eradication of Barrett’s in this study than in other studies above. Probably due to (i) differences in technique of Halo treatment, (ii) lack of availability of Halo 24 during the study period, (iii) shorter time period for repeated treatments to fully eradicate Barrett’s.

- Combination of endoscopic mucosal resection (EMR) with Halo RFA for high grade dysplasia or early oesophageal adenocarcinoma
  - Gondire, Berjman et al, Endoscopy, 2008
  - Combination of EMR for residual high grade dysplasia or mucosal cancer and halo radiofrequency ablation for remaining Barrett’s mucosa
  - 23 of 23 patients (100%) had complete eradication of dysplasia and Barrett’s mucosa after 14 months follow-up.
- Dysplasia in squamous mucosa – case reports only.

Indications for the Halo procedure

- High grade dysplasia or early stage carcinoma in individuals considered unfit to have oesophagectomy. May be combined with EMR
- High grade dysplasia in patients fit for surgery
  - In carefully selected patients, treatment with Halo radiofrequency ablation may be considered as an alternative to surgery, after careful workup and with full informed consent. For visible focal lesions, EMR is useful to remove the lesion and to obtain detailed histology. The small risk of missed cancer must be weighed against the morbidity and mortality of oesophagectomy.
- Low grade dysplasia in Barrett’s oesophagus
- Non-dysplastic Barrett’s oesophagus is not considered an indication for ablation at this stage
- Dysplastic squamous mucosa

Workup of patients prior to Halo radiofrequency ablation

Careful assessment of patients with dysplastic Barrett’s is essential to ensure that Halo RFA is the appropriate and optimal treatment. Decision making is complex in individuals with high grade dysplasia. Therefore, the usual workup after referral will include:

- Consultation in GE Clinic or private rooms
- Endoscopic assessment including high resolution endoscopy and narrow band imaging and further biopsy mapping
- Endoscopic ultrasound
- CT
- Endoscopic mucosal resection for visible dysplastic lesions
- Detail discussion of potential treatments, sometimes including surgical consultation.

The Halo RFA procedure and follow-up

1. Halo 360 RFA procedure is performed with standard endoscopy under routine sedation as a day procedure. The initial procedure takes approximately 45 minutes. Transient chest discomfort is not uncommon, but serious complications are extremely rare.

2. Follow-up gastroscopy at 2-3 months, with treatment of any residual Barrett’s islands with Halo 90 RFA. Follow-up gastroscopy examinations thereafter 3-6 monthly for 2 years then longer intervals.

Barrett’s column before treatment

Barrett’s eradicated by HALO RFA
The Royal Melbourne and St Vincent's Hospitals Referral Form
For consideration of Halo Radio Frequency Ablation of Dysplastic Barrett's Oesophagus

St V

St Vincent's

Dr Andrew Taylor
Gastroenterology Department
Fax 9899 3999
Pager 9387 1000

The Royal Melbourne Hospital

Professor Finlay Macrae
Gastroenterology Department
Fax 9348 2004
Pager 9387 1000

Patient details

Name ______________________________________ DOB __________
Address __________________________________________
_________________________________________________________________
Phone ________________ Mobile ____________
Medications ____________________________________________
Further information including major medical problems ___________________________________________________________________

Barrett's Details

Last gastroscopy date ____________________________ (Please include reports of recent gastroscopies)
Proximal and distal extent of Barrett's (CM classification optional) __________________________________________
Any nodularity present __________________________________________

Histology

Low grade dysplasia □ Yes □ No
High grade dysplasia □ Yes □ No
Early Cancer □ Yes □ No (Please include all pathology reports)

Referring doctor details

Name __________________________ Telephone __________ Pager __________
Address ____________________________________________
Referral date ________________ Referral to Hospital □ STV □ RMH
Appendix 2 – Equations and Excel tables used in Chapter 2

Per sample assessment – overall accuracy

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Legend

CA – cancer, G- gastric mucosa, IM – intestinal metaplasia, LGD – low grade dysplasia, HGD – high grade dysplasia, SQ – squamous mucosa

WLE – white light endoscopy, NBI – Narrow Band Imaging, CLE – confocal endomicroscopy
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**Legend**

CA – cancer, G- gastric mucosa, IM – intestinal metaplasia, LGD – low grade dysplasia, HGD – high grade dysplasia, SQ – squamous mucosa

WLE – white light endoscopy, NBI – Narrow Band Imaging, CLE – confocal endomicroscopy
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**Legend**

CA – cancer, G - gastric mucosa, IM – intestinal metaplasia, LGD – low grade dysplasia, HGD – high grade dysplasia, SQ – squamous mucosa

WLE – white light endoscopy, NBI – Narrow Band Imaging, CLE – confocal endomicroscopy
Per sample assessment – accuracy of detecting HGD/IMC

High definition White Light

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WLE – white light endoscopy, NBI – Narrow Band Imaging, CLE – confocal endomicroscopy
Narrow Band Imaging

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Legend

WLE – white light endoscopy, NBI – Narrow Band Imaging, CLE – confocal endomicroscopy

Confocal Laser Endomicroscopy

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Legend

WLE – white light endoscopy, NBI – Narrow Band Imaging, CLE – confocal endomicroscopy
Per patient assessment – diagnosis of HGD/IMC

High Definition White Light

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**Accuracy** 0.530612
Appendix 3 – Forms used in Chapter 4

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Scale

Unbearable Distress

No Distress

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14 DAY SYMPTOM DIARY

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Barrett’s oesophagus (BO) is the precursor lesion that can progress to oesophageal adenocarcinoma. BO affects approximately 1% of the population and is believed to be due to chronic gastro-oesophageal reflux disease. (Lagergren, Bergstrom et al. 1999) Patients with BO have a 30 – 40 fold relative risk of developing oesophageal adenocarcinoma which usually occurs via progression through low grade dysplasia (LGD) and then high grade dysplasia (HGD). (Reid, Levine et al. 2000)

The management of non-dysplastic BO comprises surveillance endoscopy and biopsies every 2-3 years along with acid suppression. The traditional approach for LGD has been intensified endoscopic surveillance.

A new trend has evolved in the management of HGD / intra-mucosal cancer. In these patients, oesophagectomy has been standard treatment because of studies showing that cancer is discovered in approximately 40% of oesophagectomy specimens after a pre-operative diagnosis of HGD. (Konda, Ross et al. 2008) Oesophagectomy in high volume centres now carries a low mortality rate of around 1%, however morbidity rates still remain up to 30%. (Thomson and Cade 2003) Recently, improved capacity to identify early cancers with modern endoscopes, combined with advances in endoscopic resection and ablation techniques have resulted in excellent outcomes for individuals with HGD / intra-mucosal cancer treated with endoscopy alone.

The staging of dysplastic BO requires meticulous endoscopic assessment, using the newest generation of high definition endoscopes to identify nodules and subtle mucosal abnormalities which can harbor cancer. Biopsies are taken from visible abnormalities as well as 4 quadrant biopsies from every 1cm of BO. New endoscopic technologies such as narrow band imaging and confocal endomicroscopy appear to aid in identification of dysplastic areas and may reduce the need for random biopsies.
Endoscopic mucosal resection is a technique to remove 10-15mm areas of mucosa, to the depth of the submucosa. Larger areas, or the entire BO up to 3-5cm in length, can be completely removed by this method with several contiguous resections. Endoscopic mucosal resection of focal mucosal abnormalities is essential to identify and remove early cancers and to determine the depth of invasion. If dysplasia or cancer is confined to the mucosal layer, the chance of spread to peri-oesophageal lymph nodes is <5%. On the other hand, if cancer extends into the submucosal layer, the chance of lymph node involvement is approximately 30% and oesophagectomy is therefore indicated. (Feith, Stein et al. 2003; Oh, Hagen et al. 2006)

In expert hands, focal endoscopic mucosal resection achieved complete removal of HGD and intra-mucosal cancer in 96% of 279 patients. However, metachronous lesions occurred in 21%, with incomplete removal of the residual BO the main risk factor at mean follow up of 63 months. This highlights the importance of removal of the entire Barrett’s segment. (Pech, Behrens et al. 2008) To address this issue, a few European centres have advocated stepwise complete resection of short segments of BO. In a recent multicentre study complete eradication of all neoplasia was achieved in 97.6% (165/169) of patients after median follow-up of 32 months. (Pouw, Seewald et al. 2010)

Endoscopic mucosal resection has a 1% risk of serious complications such as major bleeding or perforation. Symptomatic stenosis requiring dilatation develops in up to 50% of patients following stepwise complete resection. (Peters, Kara et al. 2006)

Endoscopic ablation therapies rely on the fact that squamous mucosa will replace the ablated BO in a non-acid environment. Older endoscopic therapies include argon plasma coagulation, photodynamic therapy and multipolar electrocoagulation. These techniques are limited by variable mucosal ablation and “buried Barrett’s” under squamous mucosa.

The HALO radiofrequency ablation system consists of two devices for delivering radiofrequency energy to the BO. The HALO 360 device is a balloon which is inflated in the oesophagus to deliver a 3cm circumferential burn, which can be repeated to treat long segments. The HALO 90 is a flat device attached to the tip of the endoscope to ablate smaller areas of BO. Energy delivery is automated, which leads to a more
predictable and uniform ablation, enhancing safety and efficacy compared to other ablative therapies.

A randomized controlled trial of HALO radiofrequency ablation compared to a sham procedure has shown much higher rates of complete remission after 12 months in individuals with HGD (81%) and LGD (91%) compared to the control groups. The 2-3 year follow up of patients who remained in the study has confirmed durability of response with 95% of patients who achieved complete remission of BO at 12 months remained so at 2 years. Furthermore, 85% of those who failed to eradicate their BO at 12 months achieved complete eradication at 2 years with a mean of 1.2 further focal ablation sessions. Longer term follow up beyond 5 years is required to address maintenance of remission and reduction in cancer progression. (Shaheen, Sharma et al. 2009)

The principle of combination therapy is to remove visible mucosal abnormalities with endoscopic mucosal resection that may harbor invasive cancer, then ablating the remaining BO with HALO radiofrequency ablation. Using this approach, 96% of 23 patients with early cancer of HGD achieved complete remission of BO, with no neoplasia recurrence after 22 months. (Pouw, Wirths et al. 2010)

Endoscopic therapy with HALO radiofrequency ablation and/or endoscopic mucosal resection has now emerged as a credible alternative to surgical oesophagectomy and should be considered as a valid alternative to surgery for patients with HGD / intramucosal cancer. Our institution favours the combination endoscopic approach.

The optimal management of patients with dysplastic Barrett’s requires meticulous assessment and an individualised approach. Patients that undergo endoscopic therapy will need to be informed, motivated and compliant, as careful endoscopic surveillance post eradication is required to ensure that any recurrence is detected and treated early. Therefore endoscopic therapy is best performed at tertiary centres with expertise in this evolving area.
Added value of NBI and confocal laser microscopy in detecting Barrett esophagus neoplasia – in press Endoscopy

Jayasekera CS, Macrae FA, Williams R, Desmond PV, Taylor AC.

INTRODUCTION

Barrett’s oesophagus (BO) is defined as displacement of the squamocolumnar junction proximal to the gastrooesophageal junction correlating with the histological finding of intestinal metaplasia (Wang and Sampliner 2008; Sharma 2009). BO is the precursor lesion that can progress through the development of dysplasia, to oesophageal adenocarcinoma, the incidence of which is increasing rapidly in Western populations (Reid 1991; Shaheen and Ransohoff 2002).

The aim of endoscopic surveillance in BO is to detect dysplasia, in particular to identify high grade dysplasia (HGD) and intramuscosal cancer (IMC) which can then be treated before progression to invasive cancer (Buttar, Wang et al. 2001; Rastogi, Puli et al. 2008). These high risk lesions are often subtle and difficult to detect with standard white light endoscopy as reflected in a recent meta-analysis of resection based studies, that found occult cancer in an average of 39.9% of patients in whom oesophagectomy was performed for BO that harboured HGD (Konda, Ross et al. 2008). Therefore based on this principle, a random biopsy protocol (the Seattle protocol) has been adopted as standard of care despite many limitations, which include extra time and cost to acquire and interpret the many biopsies and consequently, poor adherence (Cruz-Correa, Gross et al. 2001; Spechler, Sharma et al. 2011). The Seattle protocol consists of 4 quadrant
biopsies every 1 or 2cm of BO and targeted biopsies of any visible mucosal abnormality (VMA).

With the advent of high definition endoscopes and advanced imaging techniques such as narrow band imaging (NBI) and confocal endomicroscopy (CEM), new categories of mucosal and vascular patterns that correlate closely with histology have been developed. (Kiesslich, Burg et al. 2004; Kara, Ennahachi et al. 2006; Kiesslich, Gossner et al. 2006; Sharma and Bansal 2006; Anagnostopoulos, Yao et al. 2007) This ability to detect more subtle visible mucosal abnormalities that harbour HGD/IMC may enable endoscopists, skilled in BO assessment to perform targeted biopsies alone.

This prospective cohort study was designed to address whether targeted biopsies alone can be performed in BO assessment. Our objectives were to assess (a) the yield of HGD/IMC in mucosa predicted as being non dysplastic vs. dysplastic by three consecutive endoscopic imaging modalities which included high definition white light (HD WLE), NBI and CEM and (b) the efficacy and cost benefit of a targeted biopsy protocol using advanced imaging techniques over standard Seattle protocol biopsies.

METHODS

Patients included in this cross sectional study were those referred to St Vincent’s Hospital Melbourne for endoscopic evaluation and treatment of dysplastic BO previously diagnosed by their referring physician. All patients were over the age of 18 years. The study was approved by the St Vincent’s Human Research Ethics Committee.

The decision was made during the formulation of the study design to perform the endoscopic assessments sequentially in an unblinded manner. This protocol was chosen
so as to best emulate real life practice in which the three imaging modalities would be used in a sequential manner rather than in isolation, with the aim of increasing diagnostic certainty after each assessment.

**Endoscopic equipment**

The initial white light and narrow band imaging components of the mapping protocol were performed using an Olympus H180 (PCF-Q180AL/I) endoscope which had the NBI feature incorporated into the endoscope and was able to be activated by a touch of a button mounted on the controls of the endoscope.

Confocal endomicroscopy was performed using the Pentax confocal endomicroscope (EC3870k system; Pentax, Toyko, Japan with the ISC-1000 confocal endomicroscopy processor), developed by Optiscan (Australia), which has the confocal lens incorporated within the framework of the endoscope. In order to obtain images at depths below the surface an exogenous fluorescent contrast agent was required. 10% Fluorescein sodium was used at a dose of 5ml injected intravenously prior to commencement of CEM. The contrast agent usually lasted 30min.

**Details of endoscopic assessment**

The mapping procedures were performed by two expert endoscopists (A.T. and F.M.) utilising the three imaging modalities in a sequential manner. All patients had signed informed consent and a dedicated anaesthetist was used in all cases with the majority of patients undergoing general anaesthesia, due mainly to the duration of the mapping protocol.
In order to accurately compare a targeted biopsy protocol to the Seattle protocol we systematically mapped the distribution of the BO by dividing the oesophagus into a grid (figure 1) which was based on two methods. Firstly, diathermy (argon plasma coagulation or the tip of a snare) was used to mark the oesophageal mucosa along the length of the BO in 1-2cm levels which correlated with the centimetre measurements along endoscope. Secondly the endoscope was maintained in a neutral position from which the 12 o’clock position was determined to be at the superior aspect of the oesophagus, analogous to a clock face.

Initial assessment was performed with HD WLE by the first endoscopist (A.T.). A prediction of likely histology was made for each visible mucosal abnormality identified and each mucosal point according to the Seattle protocol. These findings were documented by a scribe on the data collection grid (figure 1). The second assessment was then conducted with NBI by the same endoscopist (A.T.). Again a prediction of likely histology was made for each visible mucosal abnormality identified and then each mucosal point according to the Seattle protocol. As the first endoscopist performed both the white light and NBI assessments, any abnormal areas identified by white light were able to be evaluated in more detail with NBI. We based our interpretation of the mucosal and vascular pattern according to Sharma’s classification where, intestinal metaplasia without high grade dysplasia has a regular vascular pattern, with a ridge villous mucosal pattern. Whereas high grade dysplasia has an irregular / distorted mucosal and vascular pattern, with the circular mucosal pattern representing cardia mucosa. (Sharma, Bansal et al. 2006)

The final assessment was with CEM by the second endoscopist (F.M.), in which the prediction of histology of the same mucosal points were made in real time. The second
endoscopist was aware of the location of any abnormal mucosal areas which had been identified by either HD WLE or NBI prior to the assessment with CEM, to allow reassessment of these same areas. (figure 2)

The final step in the mapping protocol was to biopsy all the mucosal points assessed by each modality according to the Seattle protocol. As every prediction and the evaluation of the incremental yield over the previous technique was made in comparison to the Seattle protocol. This was performed with the Olympus endoscope. Each biopsy was placed in a separate specimen pot, labelled with the location according to depth in centimetres and o’clock position with the endoscope in a neutral position. The histological assessment, by an expert GI pathologist (R.W.), was used as the gold standard to determine the accuracy of endoscopic predictions by each imaging modality.

Statistics

The study was formulated as a hypothesis generating study thereby collecting pilot data. The sample size chosen was determined by practical considerations as the study needed to complete enrolment rather than a power calculation. Accuracy was defined as the correct prediction of histology made by an imaging technique at a mucosal point using histological assessment as the gold standard. Diagnostic yield was defined as the number of biopsies required to detect one point of HGD/IMC. 95% confidence intervals were calculated according to the efficient score method. Categorical variables were compared using the Chi square / Fisher's exact test. Continuous variables were compared using the Kruskal Wallis test. All statistical testing was 2 sided at a significance level of 5% using SAS statistical software, v9.2 (SAS, Cary, NC, USA)
Economic analysis

The costing system used to derive the economic data was “Power Performance Management”, a product from Power Health Solutions which has been licensed to St Vincent’s Hospital Melbourne. This software was able to provide a cost per minute calculation for endoscopic utilisation. The gastroenterology medical costs are derived from the Human Resources department’s sessional rates for gastroenterologists. Day Procedures costing, including nursing costs, are derived from the money received by the Day Procedures Cost Centre based on each patient episode relative to the length of stay. Anaesthetic costs are costed using the times entered onto the centralised system which calculates anaesthetic start time and finish time per case. Overheads in the system like Finance and Payroll are also considered by the software programme. The cost of biopsy specimen processing and histological interpretation was obtained for the Department of Pathology. The costs are presented in Australian dollars, the current U.S. exchange rate at the time of article submission was 1 U.S. dollar = 1.002 Australian dollars.

RESULTS

Between February 2010 and September 2011, a total of 50 consecutive patients were prospectively enrolled in the study, of which 50 patients had HD WLE and NBI
assessment and 46 patients had CEM (in 1 patient CEM not performed due to anaesthetic issues, 3 patients time restraints).

The mean age of the patients was 66 years (range 41 to 86 years), and 84.4% were male. The median length of BO was 7cm (range 1 to 16cm) All patients were referred with dysplastic BO for consideration of combination endoscopic therapy. (Table 1)

**Table 1 - Details of demographic and worst pathology at the time of referral according to referring clinician**

A total of 1190 individual biopsy points have been assessed from the 50 patients, with a median of 25 biopsy points per patient, of which 39 biopsy points were found to harbour HGD and 52 biopsy points were found to harbour IMC after histological assessment. As CEM was only performed in 46/50 patients, fewer biopsy points (1117) were assessed.

**Table 2 - Details of accuracy of each modality’s sequential assessment in identifying HGD/IMC**

**Table 3. Per location analysis of sensitivity and specificity for the detection of HGD/IMC by each modality.**

The most important results outlined in table 2 were that no cancers were missed. All modalities detected the mucosal points that harboured IMC. WLE had already made the initial correct prediction with the other modalities agreeing this initial finding as the assessments were performed sequentially without blinding. The three modalities
performed with less consistency in the detection of HGD. The NBI assessment was most accurate, missing the least biopsy points (10 biopsy points) that harboured HGD in the least number of patients (4 patients). Importantly with NBI, every patient had HGD detected at another biopsy point in all of the 4 patients with missed HGD, therefore all patients would have undergone definitive combination endoscopic therapy. Whereas, HGD was not detected at another biopsy point in 2 patients with HD WLE and 4 patients with CEM.

The accuracy of the predictions made with the three modalities was further reflected by the high negative predictive values and high diagnostic yield of HGD/IMC obtained, as outlined in table 2 and 3. The negative predictive value of HD WLE was 98.3% (97.2% –99.0%), NBI was 98.9% (97.9% - 99.4%) and CEM was 98.1% (96.9% - 98.9%). The diagnostic yield, (ie. number of biopsies required to detect one point of HGD/IMC) was superior with a targeted biopsy protocol to the Seattle protocol across all modalities, as outlined in table 2. NBI again performed the best of the three modalities with 90.1 further random biopsies required to diagnose one point of HGD, not detected by NBI assessment.

In order to evaluate the most efficacious targeted biopsy protocol we assessed the incremental diagnostic yield of each modality as they were used in a sequential protocol. The maximal number of mucosal points that harboured HGD/IMC was detected by using a combination of all three modalities. However the benefit of CEM above NBI was minimal. CEM resulted in finding one further point of HGD in a patient in whom HGD had already been detected by NBI. The accuracy of CEM for the detection of HGD/IMC was 79.9%. This findings had no impact on patient outcomes.
and occurred at considerable time and cost. Therefore it was concluded that targeted biopsy protocol guided by HD WLE and NBI was the most efficacious.

**Cost effectiveness analysis:**

An assessment of cost benefit was then made between a targeted biopsy protocol guided by HD WLE and NBI versus the Seattle protocol. (Table 4)

**Table 4: Mean cost per patient**

The cost of processing and histological interpretation of each biopsy was $43.30. Therefore the total cost of all the biopsies taken in our group of 50 patients, according to the Seattle protocol was $51,527.00. The total cost of a targeted biopsy protocol as guided by HD WLE and NBI was $12,513.70. The average cost saving per patient achieved by using a targeted biopsy protocol compared to Seattle protocol biopsies, was $780.30. In addition to the cost of processing and histological interpretation of biopsies, another factor in favour of a targeted biopsy protocol was the extra time taken to biopsy the entire Barrett’s segment according to the Seattle protocol. A biopsy rate was determined by calculating the average time taken to biopsy a segment of Barrett’s across the group of patients. For the mapping protocol two endoscopy nursing staff were available, one guiding the forceps and the second labelling and closing the specimen pots. Therefore the biopsy rate calculated was 45 seconds per biopsy. Therefore a targeted biopsy protocol would have taken a mean of 4.3 minutes per patient to acquire the targeted biopsies versus 17.8 minutes with the Seattle protocol. The time and cost saving of a targeted biopsy protocol was partially offset by the additional time taken to perform NBI which is not a part of the standard Seattle
protocol. The mean time to perform NBI was 5 minutes per patient. The cost per minute required for endoscopy utilisation which includes, gastroenterology medical costs, day procedure costs (including nursing, administration and consumables) and anaesthetic costs (including medical, nursing, pharmacy and consumable costs) was $13.39 per minute. Therefore a targeted biopsy protocol resulted in a mean cost saving of $894.75 per patient over the Seattle protocol.

**DISCUSSION**

All mucosal points with IMC and all patients with HGD were detected by targeted biopsies without the need for random Seattle protocol biopsies, demonstrating that a targeted biopsy protocol can be performed accurately and efficaciously dispensing with the need to perform random Seattle protocol biopsies during the routine surveillance of BO. In addition to its efficacy, a targeted biopsy protocol would have resulted in a mean cost saving of $961.70/patient over the Seattle protocol. Importantly our study demonstrated that CEM had little impact on the diagnostic yield of IMC and HGD further questioning its clinical utility beyond that of a research tool. The decision to adopt an unblinded, sequential endoscopic protocol with real time predictions was chosen so as to best emulate real life practice thereby evaluating the incremental diagnostic impact of each modality in the detection of HGD/IMC at each mucosal point assessed in comparison to the Seattle protocol.

In order for a targeted biopsy protocol to be considered a viable alternative to random biopsies, it must not miss any cancers, as these lesions require an EMR to ensure clearance of the focal lesion prior to ablation and for staging purposes, to determine suitability for ongoing endoscopic therapy in cases of mucosal cancer or surgical
resection where submucosal invasion is present. A targeted protocol must also detect the presence of HGD, as this is the critical finding that escalates the management strategy from intensified endoscopic surveillance for low grade dysplasia (LGD) to definitive treatment.

The results of our study echo the findings of previous studies which show that careful assessment of the mucosal pattern and vascular pattern with advanced imaging techniques has the ability to predict HGD and IMC. However, endoscopic identification of LGD, especially when differentiating LGD from non dysplastic BO, has proven to be difficult.[5, 8, 9] It must be noted that our study did not set out to evaluate the accuracy of detecting LGD. Therefore, one potential limiting factor of only performing targeted biopsies would be missing LGD which has increasingly been shown to have important management implications. These problems differentiating LGD from non dysplastic BO are also encountered by pathologists(Kerkhof, van Dekken et al. 2007). A recently published study highlighted the inaccuracy of community based pathologists where after expert review of biopsies previously assessed as LGD, 75% were down staged to non dysplastic BO(Curvers, Ten Kate et al. 2010). In contrast interobserver agreement is better with HGD (kappa score 0.65) than with indefinite for dysplasia (kappa 0.32)between pathologists(Montgomery, Bronner et al. 2001).

The traditional approach for LGD has been intensified endoscopic surveillance due to the commonly held belief that progression to HGD and cancer was low (Wang and Sampliner 2008; Sharma 2009). However a recently published study by Curves et al. has shown that the rate of progression of LGD may be higher than previously thought, with those confirmed to have true LGD by two expert GI pathologists, having a 13.4%/year risk of progression.(Curvers, Ten Kate et al. 2010). The study by Curves et
al., in the context of promising short to medium term results with HALO RFA, strengthens the argument for radiofrequency ablation therapy for LGD. A recent American Gastroenterological Association (AGA) medical position statement has recommended that HALO RFA should be considered a valid therapeutic option in BO with LGD. (Spechler, Sharma et al. 2011) A large UK based multicenter randomised controlled trial co-ordinated by Bergman is currently underway, comparing HALO RFA to surveillance in LGD. This study will likely define our approach to LGD in near future.

All modalities detected the mucosal points that harboured IMC. As the mapping protocol involved sequential examination with the three modalities, HD WLE had already made the initial correct prediction with the other modalities confirming this finding. The three modalities performed with less consistency in the detection of HGD. Compared to cancers, which occurred in areas with discrete mucosal abnormalities, HGD was often detected in mucosal areas with more subtle mucosal and vascular abnormalities. In the more prominent lesions in which cancer was detected by HD WLE, it could be thought that the HD WLE influenced the NBI prediction at these points. However NBI detected a further 6 points of HGD/IMC in 30 mucosal points which were predicted to harbour HGD/IMC. Therefore despite the lack of randomization in the order of the endoscopic assessment it is unlikely to conclude that NBI would have missed the cancers if it were performed prior to HD WLE. NBI performed the best of the three modalities missing the least biopsy points that harboured HGD in the least number of patients. Importantly with NBI, on a per patient basis, HGD was detected in all patients using an NBI-based targeted biopsy approach, therefore all patients would have undergone definitive combination endoscopic therapy. On a per
patient basis, HGD was missed in 2 patients using WLE alone and in 4 patient if targeted biopsies were taken based on CEM findings

NBI has been the most widely studied advanced imaging technique in the endoscopic assessment of BO. NBI has been shown to be superior to white light endoscopy for the detection of dysplasia within a Barrett’s segment. (Wolfsen, Crook et al. 2008) Using mucosal and vascular pattern classifications developed with NBI, previous studies have found, a sensitivity between 93.5% - 100%, specificity between 78.8% - 86.7% and positive predictive valve between 93.5 - 94.7% for the diagnosis of non-dysplastic BO. For the diagnosis of HGD a sensitivity between 90% - 100%, specificity 76% - 100% and positive predictive valve 64% - 99.2% has been found. (Kara, Ennahachi et al. 2006; Sharma, Bansal et al. 2006; Anagnostopoulos, Yao et al. 2007) In Sharma’s study if biopsies were limited to areas with irregular/distorted pattern, no patient with HGD would have been missed. (Sharma, Bansal et al. 2006)

In addition to NBI other advanced imaging techniques and modalities such as chromoendoscopy, autofluorescence and CEM have been studied in the assessment of BO. When used in combination advanced imaging techniques have also been shown to provide complementary information improving the diagnostic yield of dysplasia. (Kara, Peters et al. 2006; Curvers, Singh et al. 2008) A recent study by Curvers et al. using trimodal imaging with HD WLE, autofluorescence and NBI demonstrated an increased targeted detection of HGD / cancer over standard definition WLE. However, 17% of lesions harbouring HGD/cancer were misclassified as non suspicious lesions which was a shortcoming that led the authors to conclude that random biopsies remain as standard of care. (Curvers, Herrero et al. 2010) A similar study by the same author performed on
patients with LGD found that the diagnosis of dysplasia was still being made in many patients with random biopsies, in spite of the increased diagnostic yield with trimodal imaging. (Curvers, van Vilsteren et al. 2011) However, despite these promising advances a recent American Gastroenterological Association position statement did not encourage the use of advanced imaging techniques above HD WLE assessment with Seattle protocol biopsies. (Spechler, Sharma et al. 2011)

Our study found minimal additional diagnostic impact of CEM above HD WLE and NBI. CEM resulted in finding one further point of HGD in a patient in whom HGD had already been detected by NBI at another site, therefore this finding had no impact on patient outcomes and came at considerable time and cost. Another major limiting factor of CEM is that significant training and expertise is required to accurately interpret the CEM images, which is only made more challenging when interpreting the images in real time. Therefore it must be concluded that the widespread clinical application of CEM in the assessment of BO appears to be limited; instead it is likely that CEM will remain a research tool applied by few highly specialised BO centres. The probe based CEM system may have merit in that it can be passed down the biopsy channel to perform localised assessment. A recent study by Sharma et al. demonstrated increased diagnostic yield of HGD/IMC with this method over HD WLE alone. (Sharma, Meining et al. 2011)

There were some limitations of our study. Our study group was an enriched cohort, primarily consisting of patients with known dysplastic BO with a high proportion harbouring HGD/IMC. Secondly, the sequential unblinded endoscopic design of the study, whilst reflecting real life application of these technologies, restricted a true head to head comparison of the three modalities which would be possible if each assessment
was blinded. Despite our best attempts to ensure that the same mucosal points were assessed by each modality, some degree of variability was likely to have occurred. In a similar way, the location of the biopsy may differ from the mucosal point that was visually assessed due to surface blood which can obscure the measuring landmarks. These factors may have introduced error into the analysis however these barriers are difficult to overcome. Another potential limiting factor was the lack of a true gold standard. One method to reduce error would be to perform circumferential endoscopic mucosal resection of the entire BO or perform the assessment in patients prior to oesophagectomy.

Despite the possibility of a targeted biopsy protocol raised by the promising results of our study, it is still premature to advocate a targeted biopsy protocol beyond expert tertiary centres to community gastroenterologists. Our study was performed by skilled endoscopists with expertise in the endoscopic assessment of BO aided by advanced imaging techniques in an enriched population. In addition the significance of LGD is yet to be answered. If the currently underway randomised study shows no long term benefit of HALO RFA in reducing cancer progression versus a sham treatment then a targeted biopsy protocol may be applied looking for HGD and IMC, however if there is a considerable benefit of HALO RFA in the management of LGD then random biopsies (perhaps 1 biopsy every cm) will still need to be performed in order to detect LGD in addition to meticulous inspection looking for any subtle mucosal or vascular abnormalities.

Many community endoscopy centres may not have access to the required technology (HD WLE, NBI) to closely evaluate the mucosa and perform targeted biopsies. In order for a targeted biopsy protocol to be more widely applicable, training is required in the recognition of mucosal and vascular patterns that correlate with dysplasia using both
HD WLE and NBI. This form of training would need to be coordinated by local gastroenterological societies, aimed not only at registrars and fellows, but more importantly community based gastroenterologists in clinical practice, currently performing surveillance endoscopy in patients with BO. This will likely improve surveillance endoscopy in BO by increasing the diagnostic yield and in turn improve patient outcomes.
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Title: 
Evaluating new technologies in the assessment and endoscopic management of Barrett’s oesophagus

Date: 
2012

Citation: 
Jayasekera, C. S. (2012). Evaluating new technologies in the assessment and endoscopic management of Barrett’s oesophagus. Doctorate, Medicine, Dentistry & Health Sciences, Departments of Gastroenterology and Medicine (St Vincent's Hospital), The University of Melbourne.

Persistent Link: 
http://hdl.handle.net/11343/37711

File Description: 
Evaluating new technologies in the assessment and endoscopic management of Barrett’s oesophagus

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