MD (Res)

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Establishing an Evidence Based Technique for Mucosal Landmarks' measurement,

Ethnic Disparity in Segment Length

and

Biopsy Technique

In

Barrett's Oesophagus and Gastrointestinal Endoscopy

by

Dr Humayun Muhammad

A thesis submitted in fulfilment for the requirement for the degree of

Doctor of Medicine (MD)

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BARDOLPH 'Sblood, I would my face were in your belly!

FALSTAFF God-a-mercy! so should I be sure to be heart-burned'.

(Henry IV, Part 1: Act 3 Scene 3)

Sir John Falstaff

Student ID: 20728642

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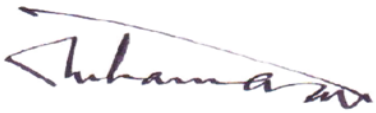

Dr Humayun Muhammad
8th March 2024.

Abstract

Establishing an evidence based technique for mucosal landmarks measurement, ethnic disparity in segment length and endoscopic biopsy technique in Barrett's Oesophagus

Introduction

Barrett's Oesophagus (BO) is a metaplastic condition affecting 1-2% of the UK population with propensity to evolve into dysplasia and Adenocarcinoma of Oesophagus (ACO). Early detection of dysplasia by tissue biopsies is dependent on regular surveillance which is reliant on measuring the correct length of BO and microscopic examination of biopsy specimens. The length of BO is dependent on the position of gastroesophageal junction (GOJ) from incisors, which could be measured in both intubation and extubation of endoscope. However, it is not clear if there is any difference in the position when measured during both phases. Furthermore, it is not clear if taking biopsies in a certain way i.e., single (SBB), or double bite (DBB) affects the histological quality of specimens. Moreover, BO is a global disease and in racial terms there are clinical, demographic, and prognostic differences between White British (WBP) and South Asian populations (SAP). One such specific difference is the progression of BO to ACO. It is noteworthy that segment length strongly correlates with ACO progression, yet literature lacks clarity on segment length differences between the populations.

MD Aim

To assess the quality of histological specimens collected through SBB and DBB, comparing size, orientation, crush artefacts and overall effect on histological diagnosis. It is also aimed to identify oesophageal landmarks in relation to BO in both phases of endoscopy as well as to chart and compare the length of BO segment SAP and WBP using statistical approaches. To achieve these aims, the MD was divided into three studies.

Methods

In study I Patients (>18 years) were assigned randomly to SBB or DBB groups and biopsies were collected prospectively. In addition, patients were also prospectively included for the assessment of oesophageal landmarks (Study II) and finally, segments length of the BO was analysed based on ethnicity, and difference was compared statistically (Study III).

Results:

Study I (n=135, 54% males), aged ranged from 20 to 91 (M 54± 15.8) and 144 procedures were performed. The time taken to collect sets of SBB (n=72) was 74 to 286 seconds (M = 180, SD±55.9) and DBB (n=72) ranged from 39 to 149 seconds (M = 88.5, SD±28.5, IQR = 71-111) with significant difference, suggesting SB takes longer time (P<0.001, r = -.009.). No significant difference was seen when analysed as per size, orientation, crush artefacts, tissue loss and overall effect on diagnosis (p>0.05).

Study II I (n=259, 46.7% males) age for the population ranged from 18 to 95 years (M = 58.9, SD±17.2). GOJ on insertion was located distal in comparison to Intubation (M =40 ±2.8, n =259, IQR=38-42) and extubation (Mdn = 40, M =40 ±2.9, n =258, IQR=38-42), z = -3.9, p<.01). The length of HH was compared Intubation (Mdn = 1, M =1.44 ±.92, n =137, IQR=1-2) and extubation (Mdn = 1, M =1.48 ±.87, n =175, IQR=1-2), z = -2.0 p=.03) and found shorter in intubation.

Study III: 249 cases of BO were identified in both sets of data. Landmarks and biopsy data and age ranged from 18 to 95 years (M = 58.2, SD±17.3, IQR = 25-75). SAP has short MBO as compared to WBP, and this was true for SAP males on subgroup analysis. To assess for significance, both segments were compared and significant difference was observed in both MBO (WBP (Median = 2, n = 221, IQR=2-3) and SAP (Median = 2, n = 28, IQR=1-2), U = 2247, z = -2.4, p =0.01)) and CBO (WBP (Median = 1, n = 219, IQR=1-2) and SAP (Median = 1, n = 28, IQR=1-1), U = 2407, z = -2.0, p <0.01))

Discussion and conclusion:

We show here that there is no significant difference between SBB and DBB biopsies in terms of histological quality however when considering time, SB takes significantly longer to complete number of biopsies per cycle. Therefore, we suggest that when taking large number of biopsies DBB technique should be used. In relation to landmarks, there is proximal displacement of GOJ during the extubation and this changes the number of diagnosed HH, hence it is suggested that for the purpose of standardisation all measurements should be taken in the extubation. This research further suggests that there is a significant difference between WBP and SAP in relation to BO segment length nevertheless comprehensive research to assess BO in different ethnicities in holistic fashion is needed. Such a project may form basis for new guidelines where ethnicity may also be a relevant factor in surveillance of BO.

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Acronyms:

ACO	Adeno carcinoma Oophagous	IBD	Inflammatory Bowel Disease
ACG	American College of Gastroenterology	IM	Intestinal Metaplasia
ASG	Australian Society of Gastroenterology	LGD	Low Grade Dysplasia
BO	Barrett's esophagus	LSBO	Long Segment Barrett's Oesophagus
BSG	British Society of Gastroenterology	LOS	Lower Oesophageal Sphincter
BMI	Body Mass Index	MBO	Maximum Barrett's Oesophagus
CBO	Circumferential Barrett's Oesophagus	NERD	Non erosive Reflux Disease
CD	Coeliac Disease	NHS	National Health Service
CI	Confidence Interval	OGD	Oesophago-gastro-duodenoscopy
CT	Computed Tomography	OR	Odds ratio
DBB	Double Bite Biopsy	PPI	Proton Pump Inhibitor
DI	Diaphragmatic Indentation	PV	Palisade vessels
ES	Epithelial Stripping	REC	Research and Ethics Committee
EMR	Endo Mucosal Resection	SAP	South Asian Population
GI	Gastrointestinal	SBB	Single Bite Biopsy
GLF	Gastric Longitudinal Folds	SCJ	Squamo Columnar Junction
GOJ	Gastro Oesophageal Junction	SSBO	Short Segment Barrett's Oesophagus
GORD	Gastro Oesophageal Reflux Disease	UHL	University Hospitals of Leicester
HGD	High Grade Dysplasia	UK	United Kingdom
HH	Hiatus Hernia	USA	United States of America
HP	Helicobacter pylori	WBP	White British population
HRQoL	Health Related Quality of Life	WHO	World Health Organization

Publications and presentations associated with the MD.

Articles

H Muhammad, N Burch, V Gordon, S Umar, J Jankowski "One bite or two? A comparison of single bite and double bite biopsy techniques in gastrointestinal endoscopy (BITES)." Scandinavian Journal of Gastroenterology (2022): 1-4.

H Muhammad, S Umar, S Ahmad, J Mayberry. A Comparison of Single Bite and Double Bite Biopsy Techniques in Gastrointestinal Endoscopy: A Scoping Review. Journal of Gastroenterology Research 6 (1), (2022) 229-233

Ghaus, S., Neumann, H., Muhammad, H., Tontini, G. E., & Ishaq, S. (2016). Diagnosis and surveillance of Barrett's esophagus: addressing the transatlantic divide. Digestive diseases and sciences, 61(8), 2185-2193.

Abstract/ Poster Publications/ Presentations

Humayun Muhammad, S Umar, Adele Costabile, Yvonne Jeanes. Histological quality of single- and double-bit duodenal biopsies. ICDS 2022 Sorrento Abstract book, 2022.

Burch, N. E., et al. "Salahadeen (Study Assessing Landmark Height Alteration During Endoscopic Evaluation)." Gut 60.Suppl 1 (2016): A126-A126.

Humayun Muhammad, Asma Asghar, Priyanka Prakash and Janusz Jankowski. Comparison of segment Length in Columnar lined oesophagus between South Asian and White populations using Prague's criteria (LUMBAEE) Gut 72 (Suppl 2), A174-A175.

Humayun Muhammad. Barrett's Oesophagus. Presentation to Barrett's Oesophagus Wessex at Southampton General Hospital on 19th June 2018.

CHAPTER I

1.1 SECTION 1

Introduction

Barrett's oesophagus (BO) is a metaplastic condition where normal stratified squamous epithelium of the distal oesophagus is replaced by an intestinal-type epithelium with or without goblet cells (Eluri and Shaheen, 2017; Shaheen *et al.*, 2016). It usually develops as a complication of chronic gastroesophageal reflux disease (GORD) (Kadri *et al.*, 2010; Jankowski *et al.*, 2010) and affects 1-2% of the general population (Ronkainen *et al.*, 2011; Jankowski *et al.*, 2010). Although, it is frequently found in White males (Coleman *et al.*, 2011; Corley *et al.*, 2009), it has also been reported in other ethnicities (Rajendra, 2011). Clinically, BO may present with symptoms of GORD (Connor *et al.*, 2004) but this is not always the case (Zagari *et al.*, 2008); in asymptomatic cases the diagnosis may be delayed (Dulai *et al.*, 2002; Jankowski *et al.*, 2000) or it may even remain undiagnosed (Shaheen, 2002). Consequently, endoscopic, and supportive histological examinations remain the only reliable ways to diagnose BO (Lee *et al.*, 2010).

Endoscopy, in addition to its use in the diagnostic workup, is also essential in the surveillance of BO (El-Serag *et al.*, 2016) as, being a metaplastic process, it may evolve into dysplasia (Odze, 2006), which may then progress to Adenocarcinoma of the Oesophagus (ACO) (Reid *et al.*, 2010). Progression to ACO is a multifactorial process associated with genetic (Ek *et al.*, 2013) and demographic factors (Krishnamoorthi *et al.*, 2016). Among other associations, the length of the BO segment and presence of dysplasia in BO are two objective variables which are strongly associated with this transformation (Theron *et al.*, 2016; Anaparthy *et al.*, 2013). Naturally, longer segment BO will need closer surveillance to detect dysplasia (Fitzgerald *et al.*,

2014; Sharma *et al.*, 2004) for which effective endoscopic treatments are available (Peters *et al.*, 2005; Ell *et al.*, 2000; Conio *et al.*, 2005). ACO, once it develops, is a lethal condition with 15 to 25% mortality at five years (Pennathur *et al.*, 2013).

For this reason, it is important to accurately measure and document the length of BO segment for risk stratification by using the Prague system (Sharma *et al.*, 2006) which objectively measures BO segment relative to the distal-most oesophageal landmark: the Gastro Oesophageal Junction (GOJ). It is noteworthy that the GOJ is not a fixed landmark, and it is possible that it may alter its position during different phases of endoscopy, i.e., during intubation (insertion) or extubation (withdrawal). Since this area lacks standardisation, it may affect BO length and, as a result, surveillance intervals.

Surveillance intervals, depending multiple factors, may range between six months and five years (Fitzgerald et al., 2014) and not only involve gross endoscopic inspection, but also taking biopsies to monitor possible progression to dysplasia or ACO (Roumans *et al.*, 2019; Jankowski *et al.*, 2010). For this purpose, following the Seattle protocol (Levine *et al.*, 2000), biopsies may be taken in a single (SBB) or double bite (DBB). As expected, the latter technique may collect more biopsies per unit time, and hence may reduce endoscopy intubation time. However, DBB may affect the histological quality of the collected specimens (Latorre et al., 2015) which may then affect dysplasia detection (Hookey *et al.*, 2007). That said, the former technique may prolong the intubation time (Pappas *et al.*, 2021) and may expose patients to possible endoscopic complications (Eisen *et al.*, 2002).

BO is a global disease and several differences have been observed in diagnosis and surveillance of BO in clinical practice worldwide (Voutilainen, 2010). On a histological level, there is clear disagreement in statements from the United Kingdom (UK) and the United States of America (USA) on the inclusion of intestinal metaplasia (IM) in the definition of BO (Ghaus *et al.*,

2016). Secondly, most of the research on BO to date has not clearly mentioned the way in which the biopsies were taken (i.e., SBB or DBB) to diagnose BO; the use of DBB may have affected diagnostic accuracy and the presence of dysplasia in tissue samples.

In endoscopic terms, there exists a controversy between studies regarding the true identification of the GOJ (Amano et al., 2006; Kusano *et al.*, 2009). The differences could be due to different ethnicities of the study populations and hence the ethnic contributions towards the better identification of GOJ needs to be considered. Similarly, possible displacement of the GOJ during phases of endoscopy may well affect the length of BO segment. Since these variables have also not been considered in the reported literature, there is a possibility that the length of BO might not have been charted correctly. It is noteworthy that the length of BO is also important from the point of view of other ethnicities such as South Asians, as (if different) it may partly explain the difference in progression to ACO in comparison to Whites (Hongo, Nagasaki & Shoji, 2009).

To explore some of these aspects of BO, this thesis aims to give an overview of BO in the context of its malignant potential. We, furthermore, conducted a literature search to explore the evidence behind controversies: such as why GOJ is measured differently and the effect of SBB and DBB tissue collection on the histological quality of specimens. Informed by this, the BO was evaluated with special reference to the length relation to two different ethnicities, the South Asian Population (SAP) and White British Population (WBP) and three studies were undertaken to address formulated research questions.

Study one: the quality of histological specimens collected through SBB and DBB were compared in terms of size, orientation, crush artefacts and overall effect on diagnosis (if any). In study two, identification of landmarks in relation to BO were explored in a prospective manner, in both phases of endoscopy. In study three, the length of BO segment was compared

between South Asian (SAP) and White British populations (WBP) and differences analysed for significance.

1.2 An overview of clinical aspects of BO and its progression to ACO.

BO is named after Norman Rupert Barrett (1903 –1979), a London based Australian surgeon (Lord, 1999) who reported a columnar lined distal ulcerated viscus in a group of patients almost 75 years ago (Barrett, 1950). Nevertheless, he might not be the first researcher who referred to this condition (Schmidt, 1805). In pathological terms, BO results from metaplastic transformation of the normal stratified squamous epithelium of the distal oesophagus, which may or may not have goblet cells (Eluri and Shaheen, 2017; Shaheen *et al.*, 2016). Although clinically, when symptomatic, BO is associated with heartburn, dyspepsia, water brash and regurgitation, the metaplastic mucosa *per se* does not cause any symptoms (Toruner *et al.*, 2004; Irvanloo *et al.*, 2011).

From an objective viewpoint, nonetheless, mucosal visualisation with an endoscope remains the most reliable method by which to diagnose BO (Lee *et al.*, 2010) and mandatory to confirm the diagnosis of BO, and this is endorsed by US, Australian and British gastrointestinal bodies (Fitzgerald *et al.*, 2014; Shaheen *et al.*, 2016; Whiteman *et al.*, 2015). Endoscopically speaking, BO, if present, is reddish in colour (so called salmon pink), has a velvet-like texture, and is easily identifiable with some experience (Halum *et al.*, 2006). Additionally, it is a valid method of diagnosis with good interobserver agreement (Vahabzade et al., 2012). **Figure 1** below shows the endoscopic appearance of BO compared with normal oesophagus.

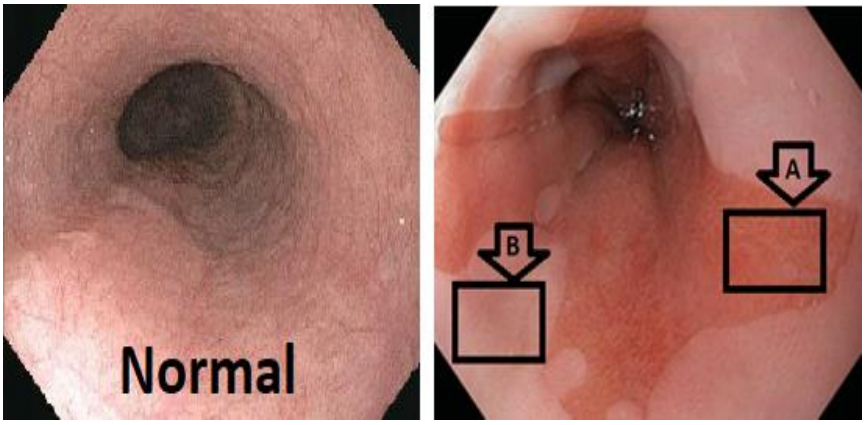

Figure 1: Normal oesophagus and Barrett's Oesophagus as seen endoscopically. Arrow A shows the salmon-pink mucosa of BO, whereas arrow B shows normal oesophageal mucosa. (Courtesy www.gastrolab.net).

1.2.1 Risk factors associated with BO.

Several risk factors are associated with BO and among them GORD has the strongest association (Jankowski *et al.*, 2010). This is based on several population-based studies (Lieberman and Sampliner, 2001; Cossentino and Wong, 2003; Crabb *et al.*, 1985; Anderson *et al.*, 2007; Zagari *et al.*, 2008). Whether acid reflux influences the metaplastic evolution of Barrett's epithelium is uncertain; nevertheless, effective acid suppression with a proton pump inhibitor (PPI) has been associated with increased normal epithelial cell differentiation and decreased abnormal proliferation, suggesting that low pH may have a favourable effect on dysplasia regression (Ouatu–Lascar, Fitzgerald & Triadafilopoulos, 1999; Menges, Müller & Zeitz, 2001).

Among other factors, obesity, a risk factor for GORD itself (El-Serag, 2008) may also indirectly lead to the development of BO, as shown by a systematic review and meta-analysis (Kamat *et al.*, 2009). In addition, other lifestyle variables such as smoking and alcohol use have also been investigated as causative agents for the development of BO and contrasting results were reported (Gray, Donnelly & Kingsnorth, 1993; Kubo *et al.*, 2009). An important, but relatively less reported - especially in relation to SSBO - is Helicobacter pylori infection (Souza and Spechler, 2005; Usui *et al.*, 2019).

Looking at the studies above, there is evidence to suggest that although GORD is related to the development of BO in both population and experimental studies, the exact mechanism of its development is not clear, and this area needs prospective, high-powered population-based studies with long term endoscopic and histopathologic follow up. Main studies related to risks associated with BO are presented in Table 1 below.

Table 1: Risks factors associated with Barrett's Oesophagus

No	Author, year, Country	number	Description and methods	Associated risk factor and comments
1	Mantynen et al., 2002 Finland	3378	Prospective study. To examine the prevalence of GORD-related findings on endoscopy according to the volume of referrals to upper GI endoscopy.	GORD, Gender: 254 (33.4%) had endoscopy positive (erosive) GORD, 11 (1.4%) BO. Independent risk factors for BO were male sex (OR = 2.6, 95% CI = 1.1-6.1) and GORD symptoms (OR = 2.9, 95% CI = 1.3-6.6).
2	Romero et al., 2002 USA	200	Prospective study. GORD questionnaire in individuals with family history of BO. Control with reflux symptoms but no family history of BO. Equal arm study.	GORD/ Family history: BO (8%) from 53 families and in 5% controls. (adjusted OR = 1.58, 95% CI = 0.46–5.45). No significant increase associated with family history.
3	Rex et al., (2003) USA	961	Prospective study: Prevalence of BO in a volunteer population to examine the relationship of age.	Age, GORD: prevalence of BO was 65 of 961 (6.8%). Among 556 subjects who had never had heartburn. Age >40 a risk factor.
4	Chak et al., 2004 USA	198	Cross sectional: First-degree relatives of BO/ Ca oesophagus who reported no prior upper endoscopy were offered screening.	Family history: BO was identified significantly more often in siblings/offspring of probands, p≤ 0.05.
5	Ronkainen et al., 2005 Sweden	21,610	Retrospective, computerised national population register histological evidence of BO.	GORD. 40% reported reflux symptoms. BE was present in 16 subjects (1.6%; 95% CI, 0.8–2.4)
6	Fouad et al., 2005 Egypt	1000	Prospective: To determine the prevalence and possible risk factors of BO in patients with GORD	GORD: BO was present in 7.3% of patients with chronic GORD symptoms, associated with > age and male.
7	Ang et al., 2005 Singapore	690	Prospective: Clinical spectrum of GORD and compare erosive (ERD) with non-erosive (NERD) in terms of clinical, demographic and BO. Patients on PPI were excluded.	GORD: BO: 1.7%. Compared to patients with non-GORD, patients with GORD were significantly older (45 *vs* 39.4 years), more likely to be male.
8	Anderson et all 2007 Ireland	711	Prospective. To investigate risk factors associated with Barrett's oesophagus and oesophageal adenocarcinoma.	GORD/ Obesity: Gastro-oesophageal reflux was associated with Barrett's [OR 12.0 (95% CI 7.64-18.7)] and oesophageal adenocarcinoma [OR 3.48 (95% CI 2.25-5.41)].
9	Johansson et al., 2007 Sweeden	604	Prospective: To investigate risk factors for incident BO diagnosed in a defined population. Consecutive patients (aged 18–79 years) who were endoscoped with new indications at units exclusively responsible for all gastroscopies in defined catchment area populations were invited	Smoking/ age: reflux symptoms and smoking indicated a 10.7- and 3.3-fold risk, respectively, for BO (95% confidence interval (CI) 3.5–33.4 and 1.1–9.9, respectively). The BO prevalence increased by 5% per year of age (95% CI 1–9%).
10	Zagari, et al., 2008 Italy	1533	Retrospective Endoscopy-based data on gastro-oesophageal reflux disease (GORD) in the general population analysed.	GORD. Prevalence rates or reflux a44% and BO 1.3%. No GORD reported by 46.2% of those with BO. relative risk (RR) 2.6; 95% confidence interval (CI) 1.7 to 3.9.

11	Galmiche et al., 2008 France	89	**Prospective study: To evaluate the diagnostic yield of Capsule endoscopy in patients with chronic reflux symptoms.**	GORD: Oesophagitis in 24 and suspected BO in 10 patients, respectively (histologically in 7 patients). The kappa values for interobserver agreement regarding the diagnosis of esophagitis and BO were 0.67 (0.49–0.85) and 0.49 (0.17–0.81), respectively.
12	Freitas et al., 2008 Brazil	104	Prospective: To determine the prevalence of Barrett's in a Brazilian population older than 50 years	Age: BO in 7.75% in the male population and 3.8% in the general population.
13	Gerson et al., 2009 USA	126	Prospective: To determine the prevalence of BE in asymptomatic women.	Age: BO was found in 8 (6%). more likely to be older (mean age 60 years vs 49 years, respectively; P = .04).
14	Park et al., 2009 South Korea	25,536	Prospective: evaluate the prevalence of BO in the general Korean population by evaluating screening esophagogastroduodenoscopy	Age: BO with GORD 48 (22.3%). 60.1% with BO had reflux symptoms. male sex (OR: 1.82, 95% CI: 1.32-2.50), age ≥60 compared with an age <40 (OR: 1.81, 95% CI: 1.07-3.09).
15	Kubo et al., 2009 USA	320	Case control study: Collected information using validated questionnaires during direct in-person interviews. Analyses used multivariate unconditional logistic regression.	Alcohol: Ethanol not significantly associated with the risk of BO. although stratification by beverage type showed an inverse association for wine drinkers compared with non-drinkers (≥7 drinks of wine per week vs none: odds ratio, 0.44; 95%
16	Kuo et al., 2010 Taiwan	736	To investigate the frequency of and risk factors for BO in self-referred Taiwanese patients undergoing diagnostic endoscopy	GORD: HH (odds ratio [OR] = 4.7, 95% confidence interval [CI] = 1.3–17.7, P = 0.02) and GORD duration >5 years (OR = 4.2, 95% CI = 1.2–4.8, P = 0.03) were independent risk factors for the development of BO.
17	Chavalitdhamrong et al., 2011 USA	502	Prospective: Capsule endoscopy findings in patients with GORD symptoms and BO.	GORD: Reflux diagnosed via in 254 patients and 12 cases (2.4%) with suspected BO.
18	Mathew et al., (2011) India	46	To investigate the frequency and risk factors of BO in SAP with GORD prospective.	Age/ GORD/ HH: Risk factors for BO were age ≥ 45 years (OR: 2.63; CI: 1.03–6.71), hiatus hernia (OR: 3.95; CI: 1.24–12.56), and a history of eructation (OR: 3.41; CI: 1.19–9.78).
19	Juhasz et al., 2011 USA	47	Prospective: To determine the prevalence of BO in first-degree relatives of patients with oesophageal adenocarcinoma (OAC) and Barrett high-grade dysplasia (HGD).	Family history: BO was confirmed in 13 of 16 (27.7%). significantly high prevalence of BO in relatives of patients with ACO/HGD.
20	Steevens et al., 2011 Netherland	120,852	Prospective: to look for association between BO and overweight, cigarette smoking, and alcohol consumption	Smoking/ Obesity: cigarette smokers (women) were at increased risk of BE (RR = 1.33, 95% CI: 1.00–1.77)
21	Mussetto et al., 2013 Italy	18	Pilot study: capsule endoscopy. To evaluate the diagnostic yield of OAC in first-degree relatives of patients with BO	Family history: Prevalence of BO was 44%.
22	Balasubramanian et al., 2013 USA	1056	TO evaluate the association between cigarette smoking and presence of BO. Prospective cohort of patients with GORD.	Smoking: 474 subjects (44.9%) had a previous history of smoking. Anytime smokers were more likely to have BO (adjusted OR: 3.3; 95 CI: 1.7–6.3; p < 0.01).

23	Sharifi et al., 2014 Iran	736	Perspective to investigate the prevalence of and the risk factors for BE in an Iranian group of patients with reflux symptoms.	GORD and age: 283 had GORD and 34 patients BO BE patients being more likely to be older (Adjusted OR, 1.04; 95% CI, 1.02–1.06; P < 0.001) than others.
24	Preedy et al., 2016 UK	1772	Retrospective analysis of the NHS data base	124 of the 1772 (7%) had BO. < 50 years, 23 (3.6%) were identified as having BO.
25	Crews et al., 2016 USA	205	Prospective predictors erosive oesophagitis (EO) and Barrett's Oesophagus (BO). he risk of EE and BE associated with single and multiple risk factors (gender, age, GERD, Caucasian ethnicity, ever tobacco use, excess alcohol use, family history of BE or EAC, and central obesity) was analysed.	Male gender Obesity: 68 (33 %) of 205 subjects had EO and/or BO. Prevalence of BO was 7.8 % The odds of EO or BE were 3.7 times higher in subjects with three or four risk factors and 5.7 times higher in subjects with five or more risk factors
26	Braghetto and Csendes 2016, Chile	231	Prospective: to report the incidence of Barrett's oesophagus in patients submitted to sleeve.	Obesity: Erosive esophagitis was found in 38 (15.5 %), and BO in 3/231 cases (1.2 %).
27	D'Silva et al., 2018 India	675	To study the percentage of symptomatic and asymptomatic pathological OGD findings in obese patients	Obesity: reflux esophagitis (16.89%), Barrett's oesophagus (1.78%), gastric erosions (13.19%).

GORD: Gastroesophageal Reflux disease, BO: Barrett's Oesophagus, CBO: Circumferential Barrett's. OR: Odd's ratio. CI: Confidence Interval. MBO: Maximum Barrett's.

1.2.2 BO and progression to ACO

There is no dispute about the premalignant nature of BO (Lieberman and Sampliner, 2001; Holmberg *et al.*, 2017; Kang *et al.*, 2018; Reid *et al.*, 2010; Lepage *et al.*, 2013; Schneider and Corley, 2015; Cook *et al.*, 2018; Dias Pereira, Suspiro & Chaves, 2007; Rantanen, Oksala & Sand, 2016; Thomas *et al.*, 2007; Visrodia, Singh, Krishnamoorthi et al., 2016; Krishnamoorthi *et al.*, 2018). Moreover, it may be noted that although, there is some disagreement in the reported incidence of ACO in BO patients, ranging from 0.12% to 0.6% (de Jonge *et al.*, 2010; de Jonge *et al.*, 2014; Yousef *et al.*, 2008; Masclee *et al.*, 2014; Singh *et al.*, 2014) yet there is a general agreement that the incidence of BO is on the rise globally (Ladanchuk *et al.*, 2010; Reid *et al.*, 2010; Whiteman and Kendall, 2016; Falk, 2015; Dias Pereira, Suspiro & Chaves, 2007; Rana and Johnston, 2000; Bytzer *et al.*, 1999).

Progression to ACO is a stepwise process: starting with metaplastic change, through dysplasia, and finally ending in ACO (Jankowski *et al.*, 2018; Baruah and Buttar, 2015; Wattenberg, 1985; Fitzgerald, 2006; Jankowski *et al.*, 2000; Jankowski *et al.*, 2010; Flejou, 2005) in a genetically predisposed individual (Fitzgerald, 2006; Su *et al.*, 2012). The process appears complex and is shown in the **Figure 2** below.

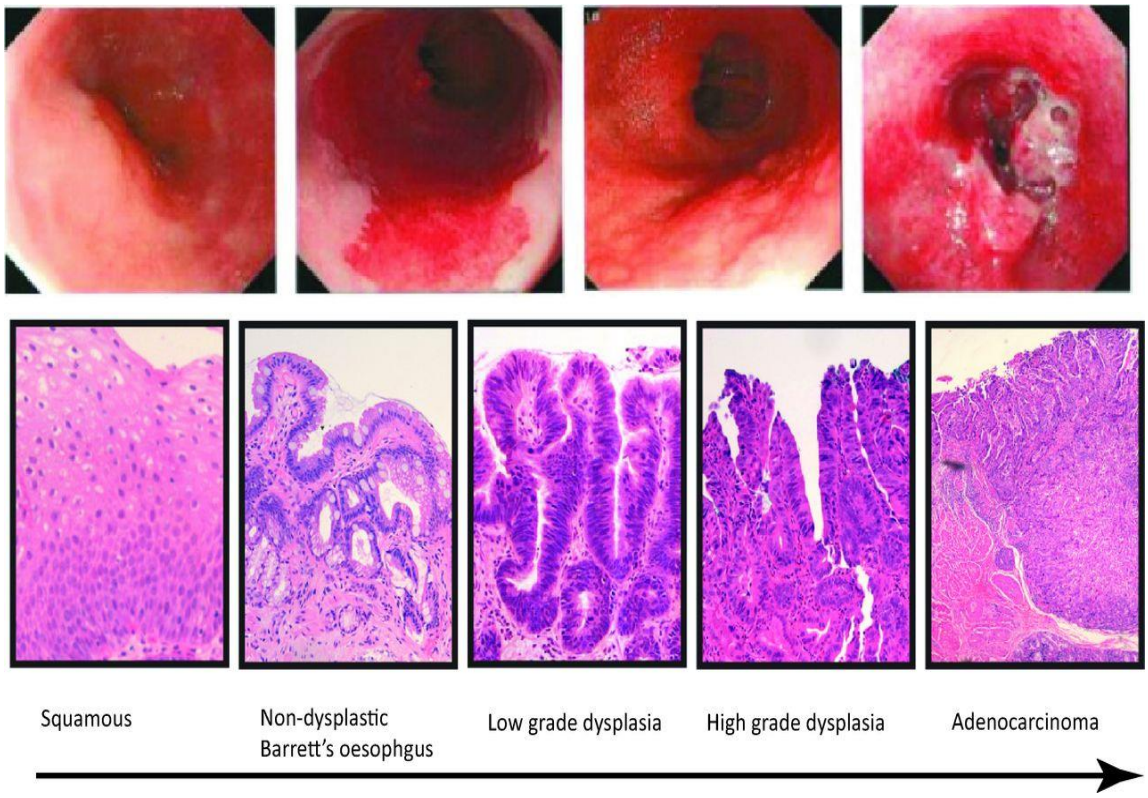

Figure 2: Stepwise progression of normal oesophageal squamous epithelium into dysplasia and then into ACO. It is noticeable that normal oesophagus is lined by well differentiated epithelium without luminal obstruction, whereas ACO is a mass lesion. The cells in dysplasia are clearly abnormal with dark nuclei but are attached to the basement membrane. ACO has haphazard cellular sheets with abnormal cells (Zeki and Fitzgerald, 2014).

1.2.3 Length of BO segment and Dysplasia in relation to ACO

Based on endoscopic length, BO has been sub-divided into short (≥ 1 cm and ≤ 3 cm), long segment (≥ 3 cm) (Sharma, Morales & Sampliner, 1998) and by some authors into a third category, termed as Ultra Short Segment BO (USSBO) (<1 cm) (Fléjou and Svrcek, 2007; Mueller, Werner & Stolte, 2004; Goldblum, 2003a; Matsuzaki *et al.*, 2011). It is noteworthy that in terms of prognosis, ACO is more common in Long Segment Barrett's Oesophagus (LSBO), as agreed by three well designed meta-analyses (Thomas *et al.*, 2007; Desai *et al.*, 2012; Chandrasekar *et al.*, 2019) and it is comprehensible as LSBO has more burden of metaplastic tissue, hence, more propensity towards dysplastic and or neoplastic proliferation. On the contrary, SSBO has

significantly lower annual neoplastic progression as concluded by a systematic review and meta-analysis which screened 486 studies (Chandrasekar *et al.*, 2019).

Attached to the above discussion and in quantitative terms the progression of segment length was assessed by Hamade and colleagues (2019) in a cohort study (n=1883). They reported a relatively lower annual progression rate for SSBO (n=822) as compared with LSBO (n=1061) [SSBO v LSSBO, 0.07%/year and 0.91%/year respectively, hazard ratio, 0.32; 95% CI, 0.18–0.57; P < .001). A slightly different methodology was adapted by an earlier study (Phol et al., 2016) and they reported the annual cancer transition rates for patients (n=1017) with long (56%), short (24%) and ultra-short (20%) Barrett's oesophagus as 0.22%, 0.03% and 0.01%, respectively. Although, both studies report slightly different rates, yet agree on the general conclusion by meta-analysis by Chandrasekar et al (2019) that there is a direct relationship between segment length and BO's progression to ACO. A relatively recent retrospective study (n=9121) by Fukuda et al., (2022) focusing on ultra-short segment BO reported an even lower rate of 0.0068%/year.

Looking at the above one may say that the difference in results may be partly explained by the difference in methodology although it may well be multifactorial and the old combination of GORD, male gender, smoking and other confounder(s) may well be playing some role. This is because there is indirect evidence from population-based studies that rise in ACO is associated with rise in GORD incidence (Lagergren *et al.*, 1999; Moayyedi and Axon, 2005; Arnold *et al.*, 2015; Gavin *et al.*, 2012; van Soest *et al.*, 2005). The significance of this finding is evident in the shorter surveillance interval for LSBO (Fitzgerald *et al.*, 2014).

A meta-analysis by Rubenstein & Taylor (2010) reported that once weekly symptom of GORD increases the odds of ACO by five folds (OR= 4.92, 95% CI= 3.9-6.2) and daily symptoms by seven folds (OR= 7.4, 95% CI= 4.94-11.1). The meta-analysis however only had only five

eligible studies with heterogeneous results and unclear thresholds, hence may not be accepted as an irrefutable evidence for this purpose.

Nonetheless, based on the evidence above, GORD has been implicated in the causation of BO (Lieberman and Sampliner, 2001; Cossentino and Wong, 2003; Crabb *et al.*, 1985; Anderson *et al.*, 2007), hence, it is possible to argue that low pH, by creating free radicals (Spechler, 2002; Ifeanyi, 2018), may play a role in the causation of ACO by promoting a hyper-proliferative environment for neoplastic cells (Guillem, 2005). How exactly this may lead to ACO is not clear but using biopsy samples from BO patients Abdel-Latif et al., (2015) noticed a higher activity of Nuclear Factor-kappaB (NF-κB), a regulator of oncogenes. This, in combination with free oxygen radicles, oxidative stress, tumour necrosis factor and activated tyrosine kinase may help neoplastic cells to flourish in pro-carcinogenic *milieu* (Zhang *et al.*, 2009; Hussain, Hofseth & Harris, 2003; Sihvo *et al.*, 2002; McCabe and Dlamini, 2005; Tselepis *et al.*, 2002).

The exact mechanism of progression to ACO is not clear but it is conceivable to suggest that GORD, a surrogate of persistently low pH (Katz *et al.*, 2007), may act independently or synergistically with longer segment BO to cause ACO. It is noteworthy that treatment with acid supressing medication has been reported to reduce the incidence of ACO, (Tan *et al.*, 2018), suggesting, albeit weakly, the direct role of GORD in the causation of ACO. Regardless of the sub-cellular mechanism, it is important to note that LSBO does not progress directly to ACO (Geboes and Van Eyken, 2000), but it rather follows a stepwise progression from dysplasia to neoplasia (Jankowski *et al.*, 2018; Jankowski *et al.*, 2010). It is thus important here to refer to the normal histology of oesophagus in the context of dysplasia briefly.

1.2.4 Dysplasia in Barrett's oesophagus

Oesophagus is lined by stratified squamous non keratinised epithelium (Gartner, 2015) and in BO the affected area of oesophagus (mainly distal) is lined by columnar epithelium of

intestinal type (CEIT) (Naini *et al.*, 2015). It is noteworthy that CEIT is normally found in stomach, small bowel, and colon (Kumar, Abbas & Aster, 2017). Normal histology of oesophagus is compared with IM in the figure below (**Figure 3**).

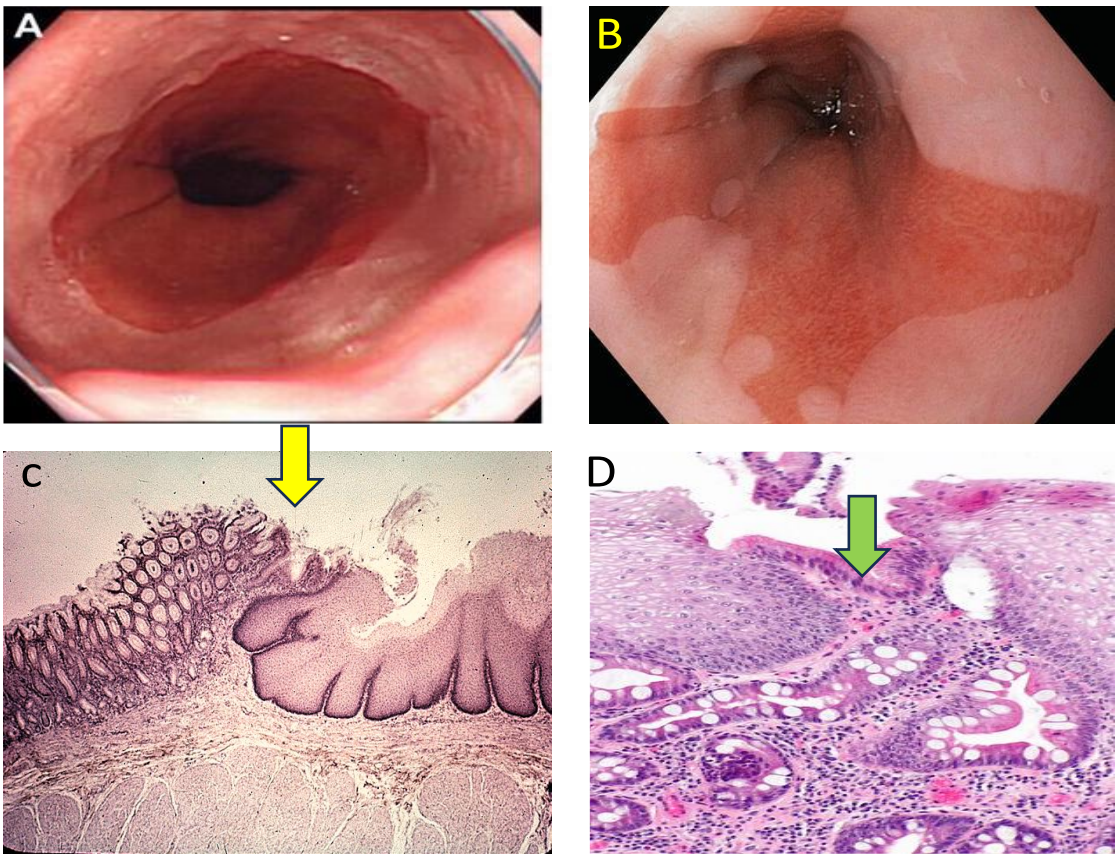

Figure 3: Endoscopic and histological comparison of Barrett's oesophagus showing normal squamo-columnar junction (C) (yellow arrow) and intestinal metaplasia (D). The epithelium in IM is composed of goblet cells interspersed between intermediate mucous cells (green arrow) courtesy google image.

Dysplasia in this context are cells which although, are cytogenetically abnormal yet have not detached from the oesophageal basement membrane (Odze, 2006) and with a potential to progress into neoplasia (National Cancer Institute, 2011). Based on cytological and structural atypia, dysplasia in BO is sub divided into Low (LGD) and High-Grade dysplasia (HGD) (Kerkhof *et al.*, 2007). In HGD, irregular crypts appear with cell crowding, budding and branching attaining a villiform configuration with marked increased in nucleus cytoplasmic ratio and higher numbers of mitotic figure (Odze, 2006). These changes are illustrated in **Figure 4** below.

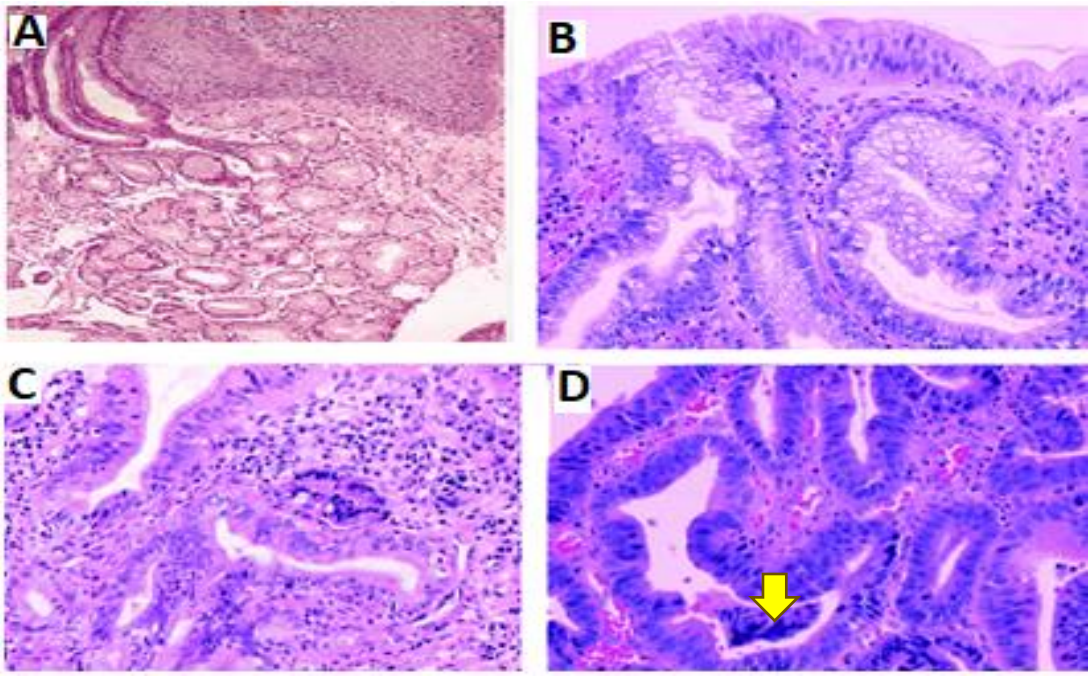

Figure 4: Transformation of normal Squamo-columnar junction (A) into BO (B) and subsequent LGD (C) and HGD (D).). HGD is characterized by marked increased in NCR and higher numbers of mitotic figures (yellow arrow) and this is in sharp contrast with normal epithelium. Adapted from Flejou, 2005.

In histopathological terms, detection of dysplasia needs a considerable amount of experience (Wel *et al.*, 2016). This is because interobserver variability has been reported among histopathologists (Goldblum, 2003b; Montgomery, 2005; Coco *et al.*, 2011). For this reason, at least two pathologists are required to diagnose dysplasia in BO (Curvers *et al.*, 2010; Kerkhof *et al.*, 2007; Goldblum, 2003b), a practice endorsed by the British Society of Gastroenterology (BSG) in their guidelines (Fitzgerald *et al.*, 2014). As a result, reporting dysplasia in BO specimens has been standardised with the passage of time (Kumarasinghe *et al.*, 2014).

A consensus developed by Bennett et al; (2015) endorsed the suggestion that at least two pathologists must agree on the diagnosis of any level of dysplasia. This, as suggested, will not only aim to rectify interobserver variability in the reporting system but may also help in risk stratification (Duits *et al.*, 2015). However, not every point in the management of BO is agreed

upon, and one of the major histopathological issues is the inclusion or exclusion of Intestinal Metaplasia (IM) in the definition of BO.

1.2.5 Definition of BO and related controversy between BSG and AGA

BO is codified by the International Classification of Diseases (ICD-9-CM 530.2) and is known as Barrett's oesophagitis or Columnar Lined Oesophagus/Esophagus (CLO/E). Additionally, it has other regional names, for example, it is known as Endo-brachyœsophage in French (Triboulet, 2006), Barrett-Ösophagus in German (Werner and Laßmann, 2012) and esófago de barrett in Spanish (Ramírez and Fluxá, 2015). However, the term "Barrett's Oesophagus" will be used extensively in this document as it is well known and recognised widely in Europe, the United States and the rest of the English speaking world. Similarly, in acronyms "O" will be used for "Oesophagus", the standard British spelling, to avoid confusion with North American usage of "E" which stems from a spelling variation, i.e., "Esophagus" (Brown, 2018).

An early definition by Spechler and Goyal (1986) suggested that BO was characteristic appearing pink mucosal endoscopic segment in oesophagus which was >3 cm, but later, with the emergence of Short Segment BO (SSBO) (Spechler *et al.*, 1994; Weston *et al.*, 1997) as a potential contender for the development of ACO, the definition was modified. Currently, the BSG defines BO as:

"*... an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥1cm) above the GOJ and confirmed histo-pathologically from oesophageal biopsies*" (Fitzgerald *et al.*, 2014).

This definition reflects the historical understanding of BO, where it was described as acquired metaplastic transformation of the stratified squamous epithelium of the oesophagus

into a simple columnar type of epithelium (Hassall, 1993) and was linked to repeated gastric acid exposure or gastroesophageal reflux disease (Spechler and Goyal, 1986; Jankowski *et al.*, 2010).

It is noteworthy that the ACG insists that IM is essential for the diagnosis of BO (Shaheen *et al.*, 2016) but conversely, it is not required by the BSG (Fitzgerald *et al.*, 2014). To see if IM eventually appears in IM negative BP, two studies have prospectively followed up IM negative BO cohorts (Khandwalla *et al.*, 2014; Gatenby *et al.*, 2008). In the study conducted by Gatenby et al., (2008) (n=1751), 90.8%patients, were evaluated and were IM negative at index endoscopy, but developed IM after 10 years of follow up. Following the above evidence, Khandwalla et al., (2014) in their prospective study (n=344) followed up IM negative patients for 2-3 years and 29% developed IM, thus agreeing with Gatenby et al., (2008). Hence, it is probably a matter of "when" and not "if" IM negative BO becomes IM positive BO.

Examining the evidence above, it appears that IM will appear in BO at some stage (Khandwalla *et al.*, 2014; Gatenby *et al.*, 2008), so it might not be necessary for a diagnosis of BO when BO is IM negative. Despite that, the area has divided opinions and to seek consensus, Bennett et al., (2015) conducted an extensive Delphi technique as an unanimity exercise to seek agreement on the international definition of BO, and it is defined as below.

"…by the presence of columnar mucosa in the oesophagus, and it should be stated whether IM is present above the gastroesophageal junction".

Considering the above, for the purpose of this thesis, the definition of BO as proposed by Bennett et al., (2015) will be followed, as it has been agreed by leading experts from all continents and encompasses and acknowledges the role of IM in BO.

1.2.6 Historical perspective, Diagnosis and Classification of BO and HH

The examination of body orifices was first performed by an Andalusian-Arab physician named Abu-al-Qasam Alzahrawi (936-1013 A.D), Latinised as Abulcasis (Saad, 2016; Spaner and Warnock, 1997; Cambra, 2016) and Giulio Cesare Aranzi (1530-1589) was the first to use a light source to visualise internal cavities (Ellison, 2015). This technique was further developed by Frankfurt-born Phillip Bozzini's (Engel, 2003) who used crude candle-powered *lichtleiter* in 1805. Following that, a versatile open tube and effective endoscope was developed by Des-ormeaux in 1865 (Davis, 1992). Rigid endoscopy was used in medical practice regularly as further refined by Adolf Kussmaul and Nitze around 1886 (Johnson *et al.*, 2009).

Further development happened almost a century later with the introduction of flexible gastrointestinal endoscopy by Basil Hirschowitz in the late 1950s (Gilger, 2001). Thereafter endoscopic technology evolved at a rapid pace at both diagnostic and therapeutic levels and procedures such as polypectomy (Berci, Panish & Morgenstern, 1973) and early cancer removal (Gotoda, 2007) emerged which were done entirely endoscopically, and the field continues to evolve as we write. The figure below shows the main historical milestones **(Figure 5)**

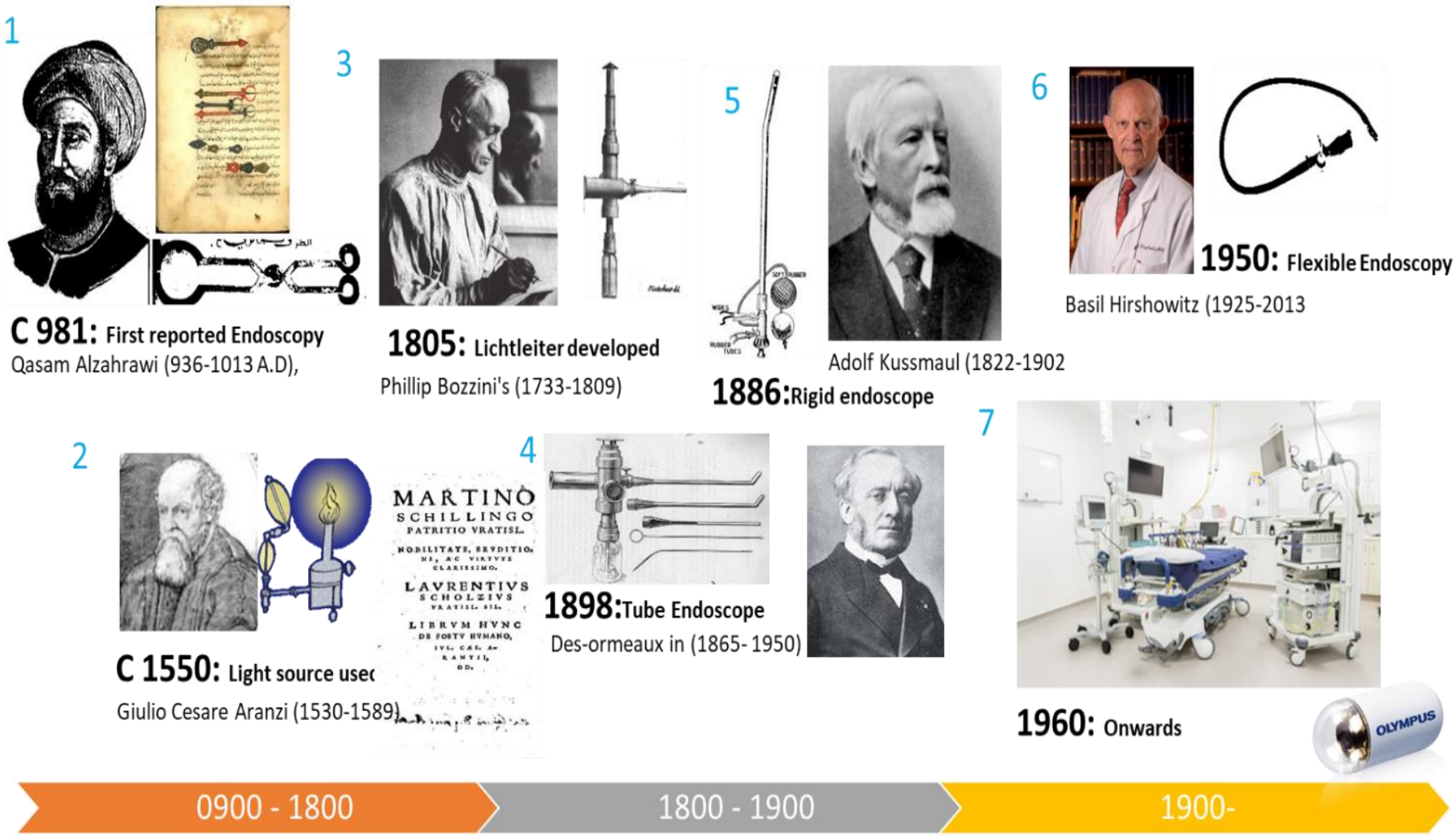

Figure 5: Approximate timeline of the major developments in endoscopy (Produced by the author).

1.2.7 Endoscopic examination of oesophagus

The length of BO is measured using Prague's Circumference and Maximal (C&M) criteria (Sharma *et al.*, 2006). In this method the length of both circumferential (C) and maximum (M) BO is dependent on the location of landmarks, such as the Gastro-oesophageal Junction (GOJ), and the Squamo-columnar Junction (or so called "Z" line). The circumferential Barrett's mucosa is measured in centimetres above the GOJ and maximum BO is the farthest extent of metaplastic mucosa, usually a tongue-like projection. BO may take several shapes, e.g., asteroid, flame-like, lotus-like (Akiyama *et al.*, 2010). Additionally, any BO islands should be recorded, and any additional recording of the lesion in or adjacent to the BO should also be noted (Epstein *et al.*, 2017). This is shown in **Figure 6** below.

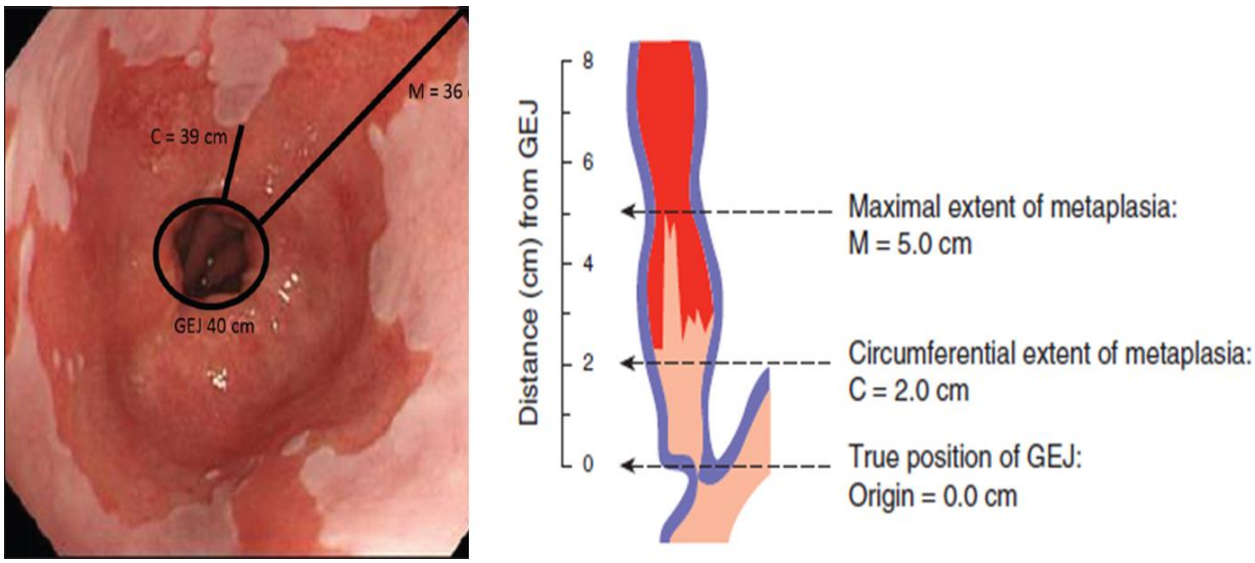

Figure 6: Prague Classification (CM) of BO adapted from (Shaheen, Nicholas J. et al., 2016; Schoofs, Bisschops & Prenen, 2017). All measurements are done in relation to GOJ (black circle) and incisors using the endoscopic shaft. Additionally, not shown here, if islands are presents, they are documented as well in the reporting.

Hiatus hernia (HH) refers to conditions in which elements of the abdominal cavity, most commonly the stomach, herniate through the oesophageal hiatus (OH) into the mediastinum

(Kahrilas et al., 2008). HH is classified into different types and **Figure 7** illustrates different types of HH in relation to normal anatomy.

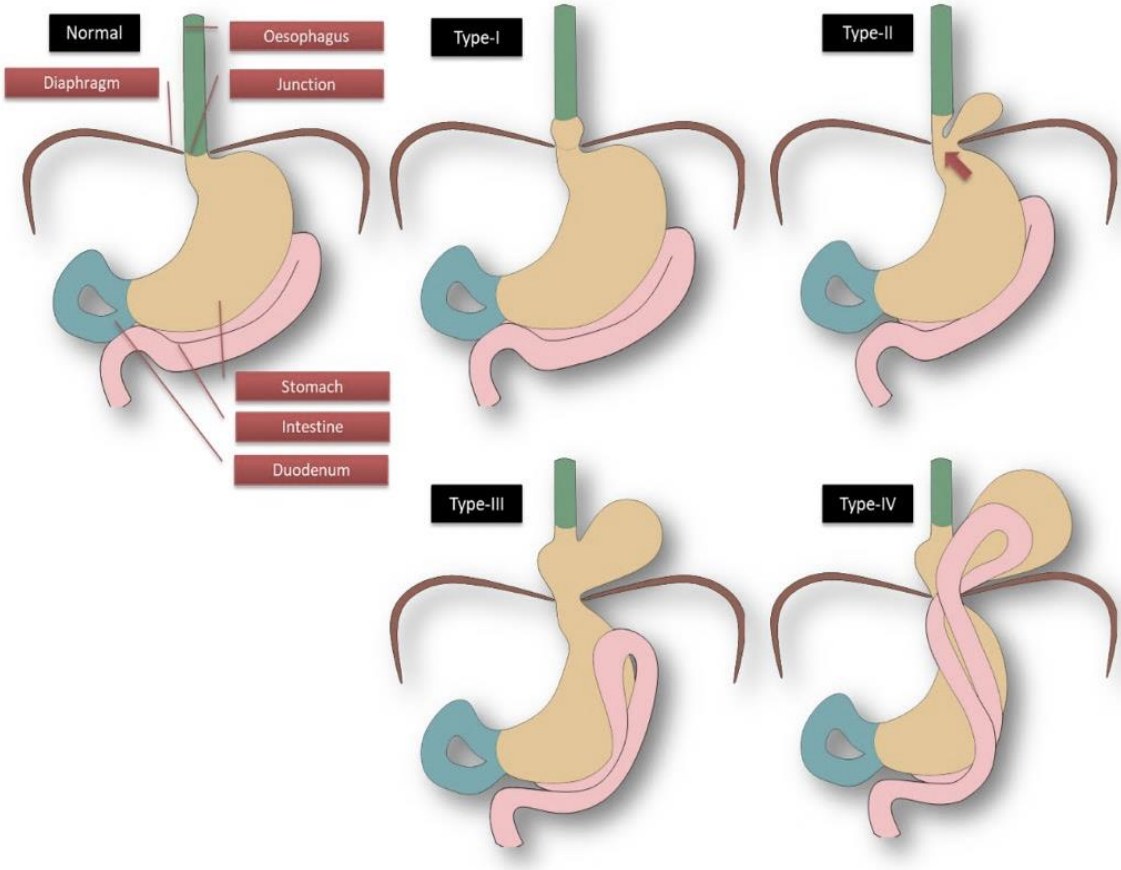

Figure 7 Hiatus hernia (types) compared with normal anatomy. Note the progressive invagination of gastric and intestinal parts into thoracic cavity. Modified by Dr A Khurshid from TrojanImaging.com

Endoscopic measurement of HH may be performed both during insertion (intubation) and during withdrawal (extubation). The former method involve involves first identifying the diaphragmatic impression and then withdrawing the scope gently until the point where the upper gastric fold appears along with Z line and the distance between theses points is measured (Wallner, 2009). The later method is inverse of the former method. Both views are illustrated in **Figure 8**.

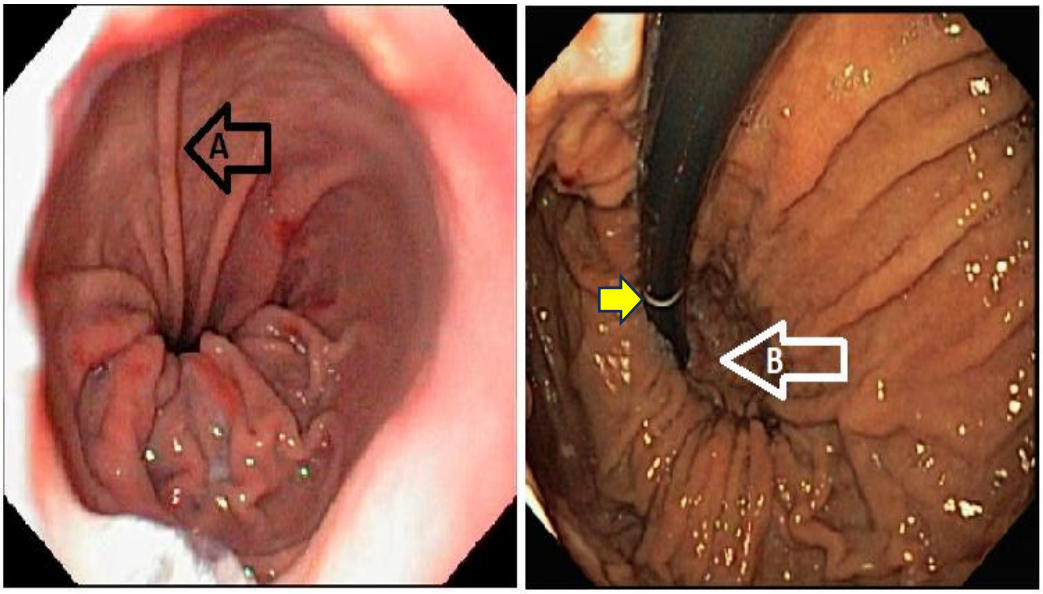

Figure 8: Hiatus hernia in Forward (arrow A) and retro flexion (arrow B) view. All measurements are done relative to incisors and white mark on the retroflexed endoscopic shaft (yellow arrow) marking 5 cm, act as a visual aid to measurements. Image courtesy www.google.com.

The Prague's C&M classification system has been validated (Vahabzadeh *et al.*, 2012), used in several studies and has acceptance among professional bodies (Knabe and Pohl, 2014; Brown and Sharma, 2016; Kinjo *et al.*, 2010; Anand, Wani & Sharma, 2008). Additionally, it is considered as one of the quality markers in endoscopic evaluation of BO (Vogt *et al.*, 2018; Gorrepati and Sharma, 2018; Choe *et al.*, 2016; Brown and Sharma, 2016). It may thus be argued that the Prague classification system is a valid and widely used system for the classification of BO, and it will be used in this MD for the purpose of BO measurement as well as the diagnosis of hiatus hernia which is explained next.

1.2.8 Epidemiology of Barrett's Oesophagus in the ethnic context

BO is characteristically found in middle-aged white males during an OGD typically done for reflux symptoms (Runge, Abrams & Shaheen, 2015; Cameron, 1997) and male gender has higher prevalence of BO compared to female (Ford *et al.*, 2005; Chang *et al.*, 2009; Kim *et al.*, 2007; de Jonge *et al.*, 2010; Dong *et al.*, 2013; Wang and Sampliner, 2008; Zavala-Gonzales *et al.*, 2014). There is a direct correlation of prevalence of BO with advancing age, as suggested by the metanalysis by Qumseya et al., (2019) (>50 years: 6.1%, 95% CI, 4.6%-8.1%).

BO is a global disease and, apart from in the US and Northern Europe, it has been reported in many other ethnicities such as Afro-Caribbeans (Abrams *et al.*, 2008), Hispanics (Keyashian *et al.*, 2013) Orientals (Tseng *et al.*, 2008), Indians (Dhawan *et al.*, 2001), Chinese (Rosaida and Goh, 2004) and Middle Eastern ethnicities (Gadour and Ayoola, 1999). However, it is rare in these ethnicities in comparison to its prevalence amongst Whites (Wang *et al.*, 2009; Abrams *et al.*, 2008; Corley *et al.*, 2009). Additionally, there have been reports of racial disparity in terms of reflux symptoms, prevalence, segment length and dysplastic patch, and progression of BO to ACO (Abrams, Fields, Lightdale & Neugut, 2008; Khoury *et al.*, 2012; El-Serag *et al.*, 2002; Kubo and Corley, 2004; Spechler *et al.*, 2002; Ali *et al.*, 2013; Rasool *et al.*, 2021).

In a comparative manner, Corley et al., (2009) analysed a community database (n=4,205), and BO was more common in whites (39/100,000) as compared to Hispanic (22/100,000) and Asian (16/100,000) populations. Although the study was retrospective, it still pointed at differences in prevalence of BO in relation to ethnicity and agreed with previous reports (Cameron *et al.*, 1990; Fan and Snyder, 2009; Ford *et al.*, 2005).

Although BO and ACO are less prevalent in the South Asian population (SAP) (Eusebi *et al.*, 2021; Ghoshal, Singh & Rai, 2021), yet they are on the rise (Coleman *et al.*, 2011; Post, Siersema

& Van Dekken, 2007; Hurschler *et al.*, 2003) and in parallel with western population as suggested by Tony et al., (2008) in a retrospectively analysis of 29,926 OGDs.

Since BO is the precursor lesion of ACO (Jankowski, Jankowski & Wormsley, 1993; Jankowski *et al.*, 2000; Yasuda *et al.*, 2014; Visrodia *et al.*, 2016) it is plausible to infer that ACO may also be on the rise in SAP. This is because the risk factors for BO, e.g., obesity, GORD and smoking, are also on the rise in population-based studies concerning SAP (Sharma *et al.*, 2008; Kalra and Unnikrishnan, 2012; Goel *et al.*, 2014). Among these factors GORD is the only factor which is strongly associated with BO (Taylor and Rubenstein, 2010), and there is evidence to suggest that GORD too is on the increase in Asian countries (Goh *et al.*, 2000; Sharma *et al.*, 2008). Hence, it is important to evaluate BO in the context of South Asian ethnicity.

Among SAP, BO has been reported in Indians, who have been found to have relatively higher prevalence as compared to Chinese and Malay populations (Rajendra, Kutty & Karim, 2004). Furthermore, in the Indian population *per se* there is a high variability in the reported prevalence, as it ranges from 2.3-23.6% (Wani *et al.*, 2014; Bamanikar *et al.*, 2011; Mathew *et al.*, 2011; Dutta, 2022; Punia *et al.*, 2006). This contrasts significantly with reported prevalence range (1.6-5.6%) in western studies (Ronkainen *et al.*, 2005; Rex *et al.*, 2003) as the reported range (2.3-23.6%) is different and wide in Indian studies.

Age has also been studied in relation to BO in SAP, and BO was reported to be a disease of young people (Punia *et al.*, 2006). This is in sharp contrast to the findings of a meta-analysis conducted by Qumseya et al., (2019) where increasing age was found to be associated with BO. This was explained by the low power (n=13) in the study by Punia et al., (2006).

Mathew et al., (2011) reported on BO length in Indian patients in their study (n=278) of patients with GORD and found that 46 (16.4%) had BO. The median lengths of CBO and MBO were 2 cm (1–10 cm) and 3 cm (2–11) respectively. To illustrate if there are differences in the

length between South Asians and Whites, Ford et al., (2005) examined the endoscopy data bases of two cities with multi-ethnic populations (n=1,005) and compared the lengths of BO. It was reported that there were 736 patients with LSBO (mean: 6.5 cm), 202 had SSBO, and 67 patients had no length recorded. Both LSBO and SSBO were more common amongst the WBP as compared to the SAP. Although high powered, the study was retrospective and may have been affected by selection bias.

Wani et al., (2014) also referred to the length but from the angle of SSBO and LSBO. According to the authors, the means length of SSBO was 1.86±0.68 cm whereas for LSBO it was reported to be 3.43±0.49 cm comparing them with studies involving Whites where relatively longer length has been reported (Cameron and Lomboy, 1992; Champion *et al.*, 1994; Desai *et al.*, 2012; Abdallah *et al.*, 2015). The study has objectively measured the length using standard criteria; however, it lacked direct data about WBP for comparison.

This point is important as if there is indeed a difference between the length of BO segment between WBP and SAP, then this may well be one factor to account for differences in progression to ACO. Nonetheless, there is a lack of research to compare the lengths in both WBP and SAP. Other factors which are also objective, and if different may affect the diagnosis and prognosis of BO, include the way biopsies are taken during GI endoscopy, and the measurement of oesophageal landmarks during both phases of endoscopy. This will be discussed in the next section.

1.2.9 Biopsy Techniques in Gastrointestinal Endoscopy

Collection of Biopsy (bio-life; opsia-to see) is a routine procedure during endoscopy to diagnose a variety of conditions ranging from simple inflammation to a graver diagnosis i.e., ACO. Surveillance guidelines for BO, for example, recommend that quadratic biopsies should be performed every one to two cm in the columnar segment, together with biopsies of any visible lesions (Abrams *et al.*, 2009; Spechler *et al.*, 2011) and this means that the number of biopsies collected is directly proportional to the length of BO segment.

Forceps are used to collect tissue biopsies and they are classified based on size, appearance, harbouring needle, and cup size. Figure 9 shows the shapes of commonly used different types of forceps.

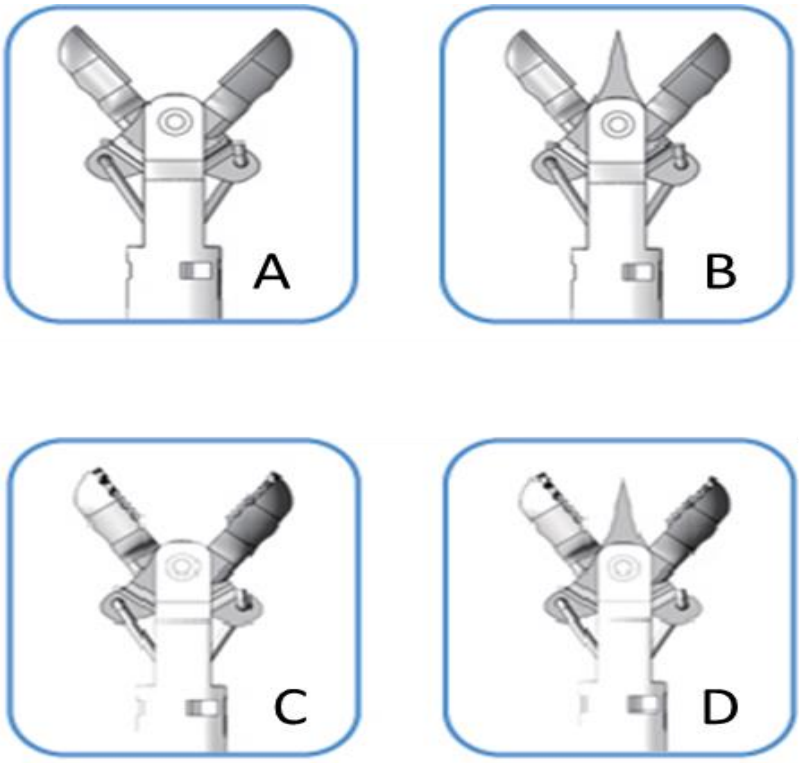

Figure 9: Standard gastrointestinal biopsy forceps. A: Plain cup forceps, B: Plain cup forceps with needle, C: Serrated forceps, D: Serrated forceps with needle. Image courtesy www.google.com.

1.2.9.1 Cost comparison of disposable and non-disposable forceps

Using non-disposable equipment pose the danger of transmission of infection (El-Demerdash *et al.*, 2019; Fireman, 2006; Chiaramonte *et al.*, 1983; Lee *et al.*, 1998; Kozarek *et al.*, 2001; Sautereau and Palazzo, 2001; Kinney *et al.*, 2002). On the flipside, using disposable equipment may negate the risk of infection transmission, but results in other issues, such as economic burden and environmental damage caused by the production and incineration of forceps (O'neale, 1992; O'Connor, 1993). Keeping in view the cost, earlier literature is heavily focused on the utility of disposable forceps (DF). Nonetheless, these studies have historical importance only as, it is a standard practice in almost all endoscopy units in the UK to use disposable forceps.

1.2.9.2 Comparing the histological quality in the context of defined GI pathology

Hookey et al., (2007) conducted a prospective equal arm randomised and blind study comparing the evaluation of histological specimens for detection of dysplasia in patients with ulcerative colitis (n=12), in specimens (n=468) collected through SBB and DBB. They noticed that DBB specimens were comparatively inadequate for the assessment of dysplasia when compared with SBB (OR=2.78, 95% CI 1.37 to 5.59; P=0.005). Similarly, Latorre et al., (2015) in a prospective cohort and blinded study, examined the histological orientation of biopsy specimens obtained through either SBB or DBB from the duodenum of patients (n=86) with suspected Coeliac Disease (CD) (47%), known CD (36%) and controls (17%). SBB yielded well oriented specimens in 66% of patients, and DBB returned well oriented specimens in 42% ($p<0.01$); matched pairs showed improved orientation with SBB (OR 3.1; 95% CI, 1.5-7.1; $P < .01$). The study was well designed and blinded, however they selectively excluded duodenal cap biopsy specimens, which are useful in the diagnosis of CD (Murch *et al.*, 2013)

Examining the above evidence, forceps may not have much effect on the diagnostic quality of specimens obtained from superficial mucosal areas, provided that the disease is not patchy, and specimens are obtained from the affected area. The issue may be rectified by taking multiple biopsies, as specific biopsy guidelines have been developed for the efficient detection of specific pathologies (Abrams *et al.*, 2009; Lebwohl *et al.*, 2011; Shinozaki *et al.*, 2017).

1.2.9.3 Comparison of time taken to obtain biopsies

Zaidman et al., (2006) reported that SBB took relatively longer time, but it is noteworthy that this study was based on a canine model where animals are completely sedated and easy to biopsy. Another study, using gastric biopsies, compared time taken between the two techniques, and reported reduced overall time for biopsies taken through DBB (Pappas *et al.*, 2021). There, thus is some evidence that DBB takes less time.

1.2.9.4 Comparisons of the histological quality of biopsy specimens

Padda et al., (2003) in their prospective randomised study (n=16) directly compared the histological quality of SBB (n=96) and DBB (n=196) biopsies. They reported relatively increased first specimen loss (25%, p=0.02) with DBB, and the loss was worse with non-spiked forceps (28.1% vs. 13.3%; p=0.01). The study was a well-designed, prospective but the histological criteria were not defined precisely in the study and the authors failed to state if the pathologist was blind to the type of biopsy collection.

Fantin and colleagues (2001) compared conventional forceps biopsies (n=510) with multi-bite forceps biopsies (n=520) and reported no significant differences between the histological quality between both types of biopsy collection. Chu et al., (Chu *et al.*, 2003), in contrast to the above two studies, compared histological quality in terms of: size, crush artefact, depth, adequacy, weight and overall rating in biopsies collected with forceps with

needles, and reported that forceps with needles take more biopsies per cycle and had better histological quality, although no effect was noticed in depth or squash artefact scores. It was a well-designed prospective study, and the pathologists were blinded, but the study only compared one region i.e., gastric biopsies.

Following this, Zaidman et al., (2006) studied multi-bite pelican forceps use in a collection of porcine specimens (n=2, biopsy = 36), comparing SBB, DBB and multi-bite forceps; they did not report major differences in histological quality. It may be noted that the pathologists were not blind to the techniques of biopsy collection. This finding was confirmed by a study (n=142) which also did not report any significant differences in histological quality (depth, crush artefacts, epithelial striping and overall diagnostic quality) between the specimens collected through SBB or DBB (Stern *et al.*, 2005). However, this was a conference abstract and full findings were never published. Similarly, Edery et al., (2018) also agreed with Zaidman et al., (2006), although they used canine specimens (n=12).

Looking at the above studies, it is evident that research in this area has evolved around the concept of specimen quality, and this has been assessed by comparing SBB with DBB by using different forceps (Fantin *et al.*, 2001; Chu *et al.*, 2003; Zaidman *et al.*, 2006). Since forceps have different designs, this factor *per se* may possibly have added a strong variable which may then have affected the results. Additionally, there is significant methodological inconsistency and variation in the studies cited above. It may thus be inferred that the exact clinical value of either taking DBB or SBB is not clear from the studies cited above. What is missing is a holistic clinical study which takes multi-regional samples, and examines histological adequacy, time taken to complete the biopsy cycles, and specimen loss. Such a study would give clear guidance to endoscopists and support the adoption of a standardised method of endoscopic sampling. Study one of this MD has addressed this particular question in a prospective manner to arrive

at a specific answer and will be detailed in relevant section below (Chapter 2). However, to take targeted biopsies correct measurements are needed which are taken in reference to certain landmarks and the next section explain the identification of these landmarks in detail.

1.2.10 Landmarks in endoscopy

Since the oesophagus is a mobile organ, loosely suspended from its origin in the mediastinum (Sinnatamby, 2011) none of its parts, including the GOJ, may be used as a primary reference point for accurate measurement(s) of BO length. It is therefore imperative that a fixed anatomical mark is used for measurements, relative to which other landmarks may be measured. The upper incisor teeth have traditionally been used in the OGD for the purpose of measurement (McClave, Boyce & Gottfried, 1987). This may be because incisors are fixed, visible to the naked eye and, more importantly, fall in the way of an inserted OGD scope.

One of the most measured landmarks relative to incisors is the GOJ, and the accurate measurement of both HH and BO are dependent on it. Although, studies have attempted to define the precise location of GOJ using endoscopic, radiologic, and histologic methods, yet its exact location is controversial and shows variation depending on the method used (Sato *et al.*, 2010). This is because there are many factors which may physiologically affect this as reference point, such as: primary and secondary oesophageal peristalsis and possibly physiological distension of the oesophagus with air (Pandolfino *et al.*, 2006; Pouderoux, Lin & Kahrilas, 1997; Shi *et al.*, 2002; Boesmans *et al.*, 2010). **Figure 10** shows the endoscopic view of the Z line: the meeting or transition point between oesophagus and stomach.

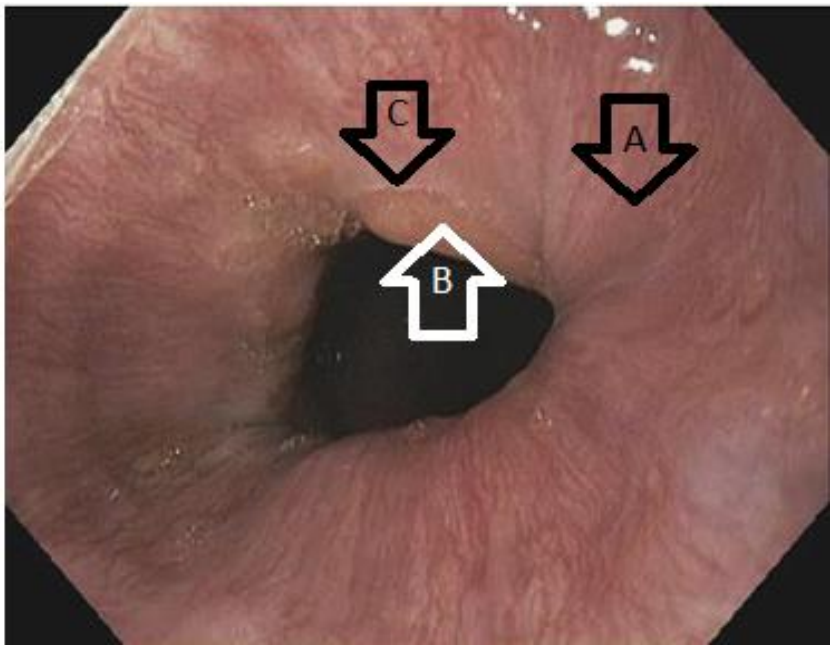

Figure 10: Squamo-columnar junction of normal oesophagus. Appearance of oesophageal mucosa (A), appearance of gastric mucosa (B), and Z line (C) as modified. from Naini et al., (2015).

It is important to state that when there is no hiatus hernia, the Z line almost coincides with the GOJ, but this is not a universal rule (Spechler *et al.*, 1994; McClave, Boyce & Gottfried, 1987; Nandurkar *et al.*, 1997; Johnston *et al.*, 1996) and there exist a disagreement if gastric longitudinal folds (GLF) or palisade vessels (PVs) should be considered as the distal most boundary of oesophagus. This dispute is examined in the light of evidence below.

1.2.10.1 GOJ as a landmark, the Western and the Japanese controversy

Apart from the histological GOJ, as explained above there are two endoscopic methods by which to define the GOJ: the Japanese and the western literature methods. In the former method, the PVs of the distal end of the oesophagus are considered as the GOJ (Aida *et al.*, 2011; Ogiya *et al.*, 2008; Ishimura, Amano & Kinoshita, 2009; Hoshihara and Kogure, 2006) whereas in the western literature method, the upper end of the GLF serves as the landmark for the beginning of the gastric lumen (Osawa *et al.*, 2009; Akiyama *et al.*, 2012; Amano *et al.*, 2006; Chandrasoma *et al.*, 2006; Huang, 2011). It is noteworthy that there are no comparative studies

to assert the superiority of one method over the other, but most studies quote the GOJ as the distal most landmark in the oesophagus (Nishimaki *et al.*, 1996; Nandurkar *et al.*, 1997; Gadour and Ayoola, 1999; Lagergren, 2006; Anand, Wani & Sharma, 2008; Choe *et al.*, 2016; Epstein *et al.*, 2017; Ishimura, Amano & Kinoshita, 2009; Akiyama *et al.*, 2012; Brown and Sharma, 2016; Hamade *et al.*, 2019; Kinjo *et al.*, 2010; Vogt *et al.*, 2018). Figure 11 below shows the endoscopic appearance of both landmarks (PVs and GLF) in a comparative fashion.

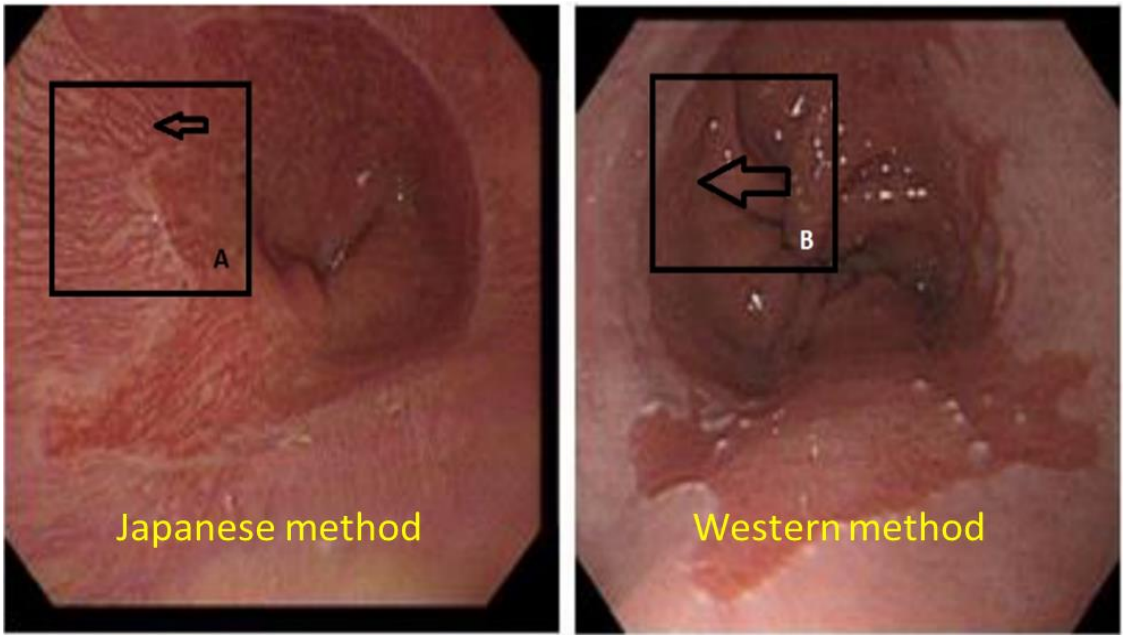

Figure 11: Comparative analysis of both gastric folds and palisade vessels. Box (A) shows. Japanese method i.e., converging PVs which end abruptly around the Z line. Box (B) shows. Western method i.e., converging gastric folds just distal to the Z line. Modified from Amano et al., (2006).

Amano et al., (2006) in a prospective observational study (n=88) asked endoscopists to measure the GOJ using C&M and then Japanese methods in the same patients, to assess the diagnostic consistency of BO. They reported that the former landmark was more suitable in relation to BO measurement. In contrast to this choice, Kumagai and colleagues (2012) supported the use of PVs as an endoscopic marker for the distal oesophagus by demonstrating that the density of PVs is pronounced at the SCJ, and hence serves as a specific marker for the GOJ. It may be noted that the density of PVs may be affected by BO, as intense GORD and

inflammation may affect the local vasculature. This point remains unsettled and has not gained universal acceptability among endoscopists outside Japan.

GLF, on the other hand, have been referred to extensively in the literature as a landmark for the GOJ. This was perhaps based on an earlier post-mortem study where it was noticed that gastric folds had a close relationship with the oesophageal muscular end and the beginning of the stomach pouch (Bombeck, Dillard & Nyhus, 1966). The authenticity of this study could be questioned as they used post-mortem specimens for the determination of the GOJ. This is because post-mortem changes in body may affect the anatomy and may not be compared with endoscopic examination of GOJ in patients. Nevertheless, in all western literature GOJ has been measured using GLF where applicable.

It is thus concluded that the definitive method for defining the GOJ is a disputed area. The studies presented above refer to histology, GLF and PVs as markers of the GOJ, yet there is no conclusive evidence that one particular method is superior to another. It is noteworthy that both BSG and ACG recommend GLF in their guidelines (Shaheen *et al.*, 2016; Fitzgerald *et al.*, 2014). Therefore, for the purpose of this MD, GLF will be used in the definition of the GOJ.

1.3 SECTION 2

1.3.1 Research Question and Aims of MD

The literature review above shows that there are several reported disputes surrounding the histological diagnosis of BO, the way biopsies should be taken and possible variations in length if measures in different phases of endoscopy but to sum up, there is no single study which has holistically examined the histological quality, time taken to collect tissue samples per cycle, and lost specimens during collection from multiple regions.

Although, there are several published studies covering these topics, they are either not blinded, assess the issue indirectly, or have deficiencies in their methodology. It is thus argued that a prospective, blind methodology should be used to design a study, using up-to-date forceps, to answer the question:

"Is there a significant difference in the histological quality or time taken to collect biopsies using single vs double bite biopsy methods?"

Secondly, no study has examined or specifically declared if their measurements were taken during a specific phase of endoscopy, i.e. intubation or extubation. This point is extremely important clinically, as the literature review above shows that there are cut-off marks for classifying long and short segment Barrett's, and in addition the length of BO plays an important role in the progression to ACO. It is thus important to design a prospective study which examines this area and attempts to answer the next research question:

"Is there a difference in the measurements of two endoscopic landmarks, i.e. GOJ and SCJ, and is there a difference in the length of hiatus hernia and BO, when measured in intubation vs extubation during diagnostic or surveillance endoscopy?"

Finally, and linked to the above discussion, there is evidence to suggest that there is ethnic disparity in patients with BO when analysed in terms of demographics and progression to ACO. Although, this disparity may be partly explained by study design, power, and selection

"Is there a difference in the length of BO between South Asian and White populations?"

bias, in objective terms there is very sparse research into whether the length of BO is different based on racial characteristics. To explore this area, a prospective study may examine the question:

This MD aims to answer the above research questions. Firstly, by comparing the microscopic quality of specimens collected during double bite biopsy and single bite biopsy in terms of: size, depth of tissue obtained, interpretability of the tissue microscopically, crush artefacts, epithelial striping and distortion of samples collected. Specifically, to answer the second research question we will assess the changes in length of four anatomical landmarks (BO, GOJ, HH, and SCJ) in upper GI endoscopy, in relation to the insertion or withdrawal of the endoscope. Finally, the MD also aims compare the lengths of BO in different ethnicities.

These aims, if met, will add to existing knowledge about the way biopsies are taken during diagnosis and surveillance of BO. In addition, new guidance may emerge to guide clinicians and researchers to standardise the way BO length is measured in different phases, i.e. insertion or withdrawal of scope, using Prague CM criteria. Furthermore, differences in

length of BO between WBP and SAP, if any, may add to current knowledge and may change the way we provide the surveillance programme. A summary is presented in Table 2

Table 2: Brief overview of the studies, their null hypotheses, and their aims in relation to the MD

	Null Hypothesis	Aims
Study No I (BITES)	"There are no significant differences in the histological quality, or time taken to collect biopsies, using the single or double bite biopsy method".	To assess the histological quality of specimens collected through single or double bite technique along with the time taken to complete the biopsy cycle and to record the incidence of lost or irretrievable biopsies during collection.
Study No II (SALAHADEEN)	"There are no differences in the measurements of two endoscopic landmarks (GOJ and SCJ), or in the lengths of HH and BO, when measured during intubation vs extubation"	To ascertain the position of two main endoscopic landmarks i.e., GOJ and SCJ from the incisors during intubation and extubation and to chart significant differences and then derive the lengths of BO and HH during intubation and extubation and to compare for significant differences.
Study No III(LUMBAEE)	"There is no difference in the length of BO and HH between South Asians and Whites"	To ascertain the lengths of HH and BO using Prague CM criteria in mixed ethnic sample and to evaluate differences in the lengths of HH and BO based on ethnicity.

2 CHAPTER II

Study 1: An investigation into biopsy technique and its effect on histological quality of gastrointestinal biopsies (BITES)

2.1 SECTION 1

Introduction

The literature review above shows that it is not clear if taking double bite endoscopic biopsies will affect the histological quality of the specimens (Muhammad *et al.*, 2022; Pappas *et al.*, 2021; Stern *et al.*, 2005; Frimberger *et al.*, 2000). Studies designed prior to BITES had methodological flaws and that is why they reported mixed results (Muhammad et al., 2022) and there is no clear prospective randomised human study to compare time taken and instances of specimen loss during collection of tissue samples using both methods i.e. SBB and DBB. Hence, a holistic prospective study, using specimens from upper as well lower gastrointestinal tract, was needed which examines all of these aspects, i.e. histological quality, time taken to collect specimens, and instances of lost or irretrievable specimens (specimen handling) and examines the histological quality of specimens using the same cohort of patients in one setting.

2.1.1 Aims and Methodology

Based on research question (No 1), the primary aim of the study was to assess and compare the microscopic quality of the specimens collected during upper and lower gastrointestinal endoscopic procedures by using two standard techniques: DBB and SBB. Another aim for the study was to quantify the number of times a specimen is lost or was difficult to retrieve (tease out) from the biopsy forceps. More importantly, it measured the time taken for the biopsy cycle, i.e., from the beginning of the insertion of forceps into the biopsy channel to the very end of the biopsy extraction from the forceps' cup. To achieve the

desired outcome, the objectives were: to assess the histological quality of the specimens obtained, and to compare DBB and SSBB for statistical significance. The study was feasible as the required population of patients was available within our trust where, across the three sites, eight fully functional endoscopy rooms are available.

2.1.2 Pilot Project

To assess the feasibility of the study, an initial smaller pilot project was conducted as such projects are known to helps in understanding and solving possible barriers prior to the initiation of a full project (Latorre et al., 2015; Wittes and Brittain, 1990; Gul and Ali, 2010). Additionally, the PP was used to finalise the protocol, calculate power requirements for the full study, and identify potential negative impacts (Eldridge *et al.*, 2016).

For this purpose, 10 SBB and 10 DBB specimens were collected and compared from patients (n=20). It may be noted that the pathologists (n=5) were not blinded at this stage. It is also pertinent to note that the data from this pilot project was not used in the final study. During the pilot phase availability of specimen in the forceps was recorded along with the ability to extract the specimen from the cusps of the forceps. On histological grounds size was sufficient if it was > 2 mm.

The primary outcome was histological adequacy was based on crush artifacts in the specimens. **Table 3** below shows the histological criteria of quality assessment used in the study.

Table 3 Histological parameters used to define the quality of specimens based on histology reports..

Criteria	Description
Size	2 mm or more
Depth	At least mucosa available for histological assessment
Assessment	Interpretable, just interpretable, and uninterpretable
Crush artefact	False distortion of tissue caused by iatrogenic compression of a tissue. (Y/N)
Epithelial Stripping	Epithelial layer detached from the rest of the tissue. (Y/N)
Fragmentation	Multiple bits of tissue in the slide. (Y/N)
Distortion	Resulting from even the compression of the tissue (Y/N)
Necrosis	Morphologic changes that follow cell death (Y/N)
Overall Issues with diagnosis	(Y/N)

It was a randomised prospective study in line with previous research in this area (Padda et al., 2003; Fantin et al., 2001; Zaidman et al., 2006). Additionally, the pathologists were blind to the types of biopsy specimens they were reporting on (Fantin et al., 2001; Hookey et al., 2007). To assess the feasibility of the study, an initial smaller pilot project (PP) was conducted (Latorre et al., 2015; Wittes and Brittain, 1990; Gul and Ali, 2010) and for this purpose, 10 SBB and 10 DBB specimens were collected and compared from patients (n=20). It may be noted that the pathologists (n=5) were not blinded at this stage. It is also pertinent to note that the data from this pilot project was not used in the study analysis.

2.1.3 Participants and exclusion criteria

Patients (> 18 years) who were likely to have multiple biopsies taken were preferentially included. All patients below 18 years of age or those who were not able to consent were excluded from the study. Additionally, patients who were on anti-platelet and anti-coagulant medication were not included in the study, as although this is not a specific contraindication

to taking biopsies (Yuki *et al.*, 2017; Fujita *et al.*, 2015), such patients may suffer minor haemorrhage, and this could have potentially affected the study. **Table 4** below gives the details of the exclusion criteria. A consort diagram is attached as appendix 7.52 (page 227).

Table 4: Exclusion criteria used in the study and reason for exclusion.

Criteria	Reason/ Description
Age	below 18 years of age excluded
Not for biopsies	Indications clearly suggesting not for biopsy i.e., polyp check,
Capacity	Those who could not give consent were excluded
Therapeutic procedures	Banding, polypectomy, stent placement etc.
Anti platelets/ anti-coagulant	Patients with potential to increase intubation time i.e. bleeding were excluded.
Language	Patients who could not be consented because of language barrier for the study. Language line was available but for endoscopy and not for the study's consent.

2.1.3.1 Randomisation, Statistical Analysis and Ethics:

Randomisation was done by an independent statistician. This was done by randomly permuting blocks of size 4, using Microsoft Excel®. It may be noted that the endoscopists were not blind to the randomisation list although pathologists stayed blind till the very end of the study. Data was entered as the procedures were performed. It is possible that the data might well have been affected by selection bias as an important multi centre study AspECT was running at the same time and the available referrals for randomisation might have been mostly from reflux and or possible Barrett's oesophagus referrals.

From the pilot data, the percentage of single bite samples with crushing was estimated as 25%. To have 80% power to detect a relative risk of crushing with double bite of 2.0 with significance level 5%, using Fisher's exact test, required 66 samples in each arm (Dupont and

Plummer, 1990). To allow for an expected rate of 5% of samples providing no data (for example biopsy at wrong site; necrotic tissue only), 70 patients were recruited into each arm of the study. A further two patients were added in each arm to compensate for possible attrition rate (Dumville, Torgerson & Hewitt, 2006).

For statistical analysis, the Fisher exact test was performed with SPSS (SPSS, Inc., Chicago, Ill version 28) for Windows 10. Odds ratios (OR) including 95% confidence intervals (CI) were calculated to describe the relative risks of adverse results. Qualitative data was analysed using Fisher's exact test/ Chi Square (χ^2) for binary outcomes, and the exact Cochran-Armitage trend test for the ordinal outcomes. Normality was assessed by Kolmogorov–Smirnov test and a p value <0.05 was considered statistically significant for all statistical operations.

The Integrated Research Application System (IRAS) was used to apply for ethical approval for the study (IRAS ID: AB/121377/1) and permission was granted by the Leicestershire, Northamptonshire & Rutland Local Research Ethics Committee (Ref 08/H0406/21). The local NHS research and development department at UHL was involved through a site-specific application form linked to the IRAS form, and local approval was granted by UHL (UHL-10629). Furthermore, University of Central Lancashire (UCLan) ethics committee granted permission for the use of this study towards the MD project through their letter dated 24th April 2017 (STEMH 622). (Appendix No 2.1 A, 2.3, 2,3B)

2.2 SECTION 2

2.2.1 Results

2.2.1.1 Demographics

A total of 230 patients were initially screened; after applying exclusion criteria, 188 suitable patients were identified from the GI waiting list and approached for the study and finally 135 patients were enrolled in the study as detailed in the consort diagram (Appendix 5, 7.52). The age of the population (n=135) ranged from 20 to 91 years (M = 54.5, SD±15.8, IQR = 42-66) and was distributed normally (p=0.20), with skewness of 0.07 (SE = .20) and kurtosis of -.68 (SE = .41). The sample was predominantly male (54.1%) and the most prevalent age-group was between age 49 to 59 years (n=31), followed by < 39 years (n=28). **Table 5** below shows the demographic details of the population sample (Appendix No 3.1).

Table 5: Gender and ethnic distribution of the population in relation to age groups in the sample. The sample was WBP dominant and has relatively more males than females.

	Total	Gender			Ethnicity		
	n=135	Male	Female		WBP	SAP	
Age (M±SD)	54.5±15.8	57.2±17.8	51.2 ±13.1		57.1 ±15.9	47.1±13	
Grand Total	**135**	**73 (54.1%)**	**62 (49.9%)**		**100 (74.1%)**	**35 (25.9%)**	

*Independent sample *t*-test. M=Mean, SD = Standard Deviation.

The table above shows that the number of males, although fewer in comparison to females in the lower age groups, increases with increasing age bracket. Overall, the population was male and WBP dominant who had significantly higher ages as compared with females and SAP.

2.2.1.2 Histological comparison

Histologically assessed sample sizes ranged from 2 to 6 mm (Med = 2, IQR = 2-3) and this was not distributed normally ($p<0.01$), with skewness of 1.7 (SE = .20) and kurtosis of 3.65 (SE = .40). Comparison of the sizes for SBB and DBB revealed that, in the former category, the size ranged from 2 to 6 mm (Med = 2, IQR = 2-3) and this was not distributed normally ($p<0.01$), with skewness of 2.0 (SE = .28) and kurtosis of 5.4 (SE = .55), whereas size for DBB ranged from 2 to 6 mm (Med = 3, IQR = 2-3) and this was not distributed normally ($p<0.01$), with skewness of 1.3 (SE = .28) and kurtosis of 2.4 (SE = .28).

No significant difference was noted between SBB and DBB specimen size when analysed using MWU test: SBB (Mdn = 2, n =72, IQR= 2-3) and DBB (Mdn = 3, n =72, IQR= 2-3), U = 2368, z = -.99, p =.32, r = -.006. This suggests that, although DBB specimens appeared larger than SBB specimens, this difference was not significant histologically (Appendix No 3.1L). Crush artefacts were reported in three specimens: two specimens exhibited mild artefacts (SBB=1, DBB=1) and one specimen (SBB) exhibited moderate artefacts.

None of these finding was significant enough to affect the histological quality of the specimens; $\chi2$ (1, n=144) =1.0, p =.60, phi = .08. Other histological parameters, as assessed by the pathologists, are displayed in **Table 6.**

Table 6: Comparison of dfferent histological parameters against endoscopic and demgraphic factors

		Demographic parameter						Procedure and biopsy technique					
		Gender			Ethnicity			Procedure			Technique		
		Male 79 (54.9%)	Female 65 (45.1%)	P*	White 105 (72.9%)	S Asian 39 (27.1%)	P*	UGIPs 68 (47%)	LGIPs 76 (53%)	P*	SBB 72 (50%)	DBB 72 (50%)	P*
Depth	No	2 (1.4%)	--	0.16	1 (0.7 %)	1 (0.7 %)	0.46	1 (0.7 %)	1 (0.7 %)	0.93	2 (1.4%)	--	0.15
	Yes	77 (53%)	65 (46%)		104 (73%)	38 (26.8%)		67 (46%)	75 (52%)		70 (48.6%)	72 (50%)	
Ep-Strip	No	79 (55 %)	64 (44.5 %)	0.26	105 (73 %)	38 (26.4 %)	0.1	68 (47 %)	75 (52 %)	.34	71 (49.3 %)	72 (50 %)	0.31
	Yes	0	1 (0.7 %)		0	1 (0.7%)		0	1 (0.7%)		1 (0.7%)	0	
Fragmentation	No	75 (67 %)	63 (33.3 %)	0.55	99 (67 %)	39 (27 %)	0.12	66 (46 %)	72 (50 %)	0.48	66 (45.8%)	72 (50 %)	**0.01**
	Yes	4 (2.4%)	2 (1.8%)		6 (4.2%)	0		2 (2.9%)	4 (5.3.8%)		6 (8.3%)	0	
Necrosis	No	79 (54.9%)	65 (45.1%)	0	105 (72.9%)	39 (27.1%)	0	68 (47%)	76 (53%)	0	72 (50%)	72 (50%)	0
	Yes	0	0		0	0		0	0		0	0	
Size > 2mm	No	79 (54.9%)	65 (45.1%)	0	105 (72.9%)	39 (27.1%)	0	68 (47%)	76 (53%)	0	72 (50%)	72 (50%)	0
	Yes	0	0		0	0		0	0		0	0	
Crush Artefact	No	79 (55 %)	64 (44.5 %)	0.26	105 (73 %)	38 (26.4 %)	0.1	68 (47 %)	75 (52 %)	.34	71 (49.3 %)	72 (50 %)	0.31
	Yes	1 (0.7 %)	0		1 (0.7 %)	0		1 (0.7 %)	0		1 (0.7%)	0	
Distortion	No	79 (54.9%)	65 (45.1%)	0	105 (72.9%)	39 (27.1%)	0	68 (47%)	76 (53%)	0	72 (50%)	72 (50%)	0
	Yes	0	0		0	0		0	0		0	0	

*Chi Square test, Depth = does the specimen have sufficient depth?, Ep-Strp= epithelial stripping present?, Fragmentation= specimen fragmentation present?, Necrosis= necrosis present C. artefact= crush

It is evident from the above table that there is a significant difference in terms of fragmentation between SBB and DBB: $\chi 2$ (1, n=144) =6.26, p =0.01, phi = -.20. This suggests that SBB are significantly more prone to fragmentation than DBB although it may be noted that the number of specimens are 6. As a concluding remark, no effect of biopsy technique was observed on diagnosis, especially for BO (n=19 13.2%).

To see if there is any time difference (time per biopsy) between specific regions, oesophageal biopsies and duodenal biopsies were compared (both being tubular structures). In the SBB category, 17 cases were identified, out of which 12 were duodenal biopsies and the remaining were oesophageal biopsies. Similarly, in the DBB category, 25 cases were identified, out of which 17 were duodenal biopsies and the remaining were oesophageal biopsies. Time taken was calculated and is presented in **Table 7**

Table 7: Table depicting time taken: oesophageal and duodenal biopsies as per single and double bite

		Biopsy technique (n=42)				
Region	**Total**	**Single Bite Biopsy (n= 17)**		**Double Bite Biopsy (n= 25)**		**P**
Time taken	** T (Med IQR)	Med (IQR)	Min-Max (SD)	Med (IQR)	Min-Max	
Oesophagus (n=13)	27 (22-35)	50.5 (39-61)	35-63 (±11.7)	22.7 (19-28)	19-34 (±5.7)	**<0.01**
Duodenum (n=29)	24 (18-36)	36.9 (33.8-50)	33-72 (±3.8)	19.2 (17.6-21)	15-42 (±6.1)	**<0.01**

*** MWU Test, **Total time in seconds, Med= Median, M= Mean, IQR= Inter quartile range.**

The table above suggests that time taken to collect both duodenal and oesophageal biopsies was significantly different, as analysed with MWU test, and this means that DBB are

more efficient than SBB in terms of time taken. (Appendix No 3.1K). Next, the histological comparison will be drawn to evaluate the quality of collected specimens.

2.2.1.3 Comparing single and double bite biopsies

The total number of procedures (n=144) were divided into equal halves; half of the biopsies were taken using SBB technique (n=72) and the remaining half were taken as DBB. In addition to that, 39 (27%) SBB came from male participants and 33 (23%) from female participants. **Table 8** shows the comparison of age, ethnicity, and gender according to the biopsy technique.

Table 8: Comparison of Biopsy technique in relation to age, ethnicity and gender.			
		Biopsy technique	
	Total (n=144)	Single Bite (n=72)	Double Bite (n=72)
Age (M±SD)	54 ± 15.8	55.2 ±15.9	52.8±15.7
Gender			
Male	79 (54.9%)	39 (27.1%)	40 (27.8%)
Female	65 (45.1%)	33 (22.9%)	32 (22.2%)
Ethnicity			
WBP	105 (72.9%)	57 (39.6%)	48 (33.3%)
SAP	39 (27.1%)	15 (10.4%)	24 (16.5%)

The table above (**Table 8**) comparing procedures (n=144) and not the patients) illustrates that the sample is bisected in equal proportions and not biased in terms of biopsy technique in relation to the demographics of the study groups.

2.2.1.4 Description of indications for the procedure

Out of 144 procedures performed, the most common indication for the procedure was diarrhoea (n=50), followed by anaemia (n=34). There were 16 patients who had BO as their indication. Indications (n=135) were also analysed according to the genders and ethnicities of patients; there were relatively more males (n=10) with BO as compared to females (n=6). Although most patients (58%) had multiple indications, only the first indication was used as the main indication. **Table 9** illustrates the main indications as split by the gender and ethnicity of the patients.

Table 9: Gender and ethnic distribution of the population in relation to endoscopy indication. It may be noted that diarrhoea was the main indication which was followed by anaemia.

	Total	Gender			Ethnicity	
		Male	Female		WBP	SAP
	135	**73 (54.1%)**	**62 (49.9%)**		**100 (74.1%)**	**35 (25.9%)**
Diarrhoea	47 (34.8%)	21 (15.6%)	26 (19.3%)		33 (24.4%)	14 (10.4%)
Anaemia	28 (20.7%)	16 (11.9%)	12 (8.9%)		20 (14.8%)	8 (5.9%)
Barrett's Oesophagus	16 (11.9%)	10 (7.4%)	6 (4.4%)		14 (10.4%)	2 (1.5%)
IBD assessment	12 (8.9%)	9 (6.7%)	3 (2.2%)		8 (5.9%)	4 (3.0%)
Weight loss	3 (2.2%)	1 (0.7%)	2 (1.5%)		3 (2.2%)	0 (0.0%)
Dyspepsia	10 (7.4%)	2 (1.5%)	8 (5.9%)		6 (4.4%)	4 (3.0%)
Others	19 (14.1%)	14 (10.4%)	5 (3.7%)		16 (11.9%)	3 (2.2%)

*IBD: Inflammatory bowel disease. Others: Polyp, gastric ulcer, coeliac disease, gastritis, family history of cancer, reflux, dysphagia.

The table above shows that BO, as an indication was more common in WBP males. It may be noted that the above table presents data for patients (n=135) and not total number of procedure (n=144) as nine patient had dual procedures (Appendix 3.1 E). Procedures and biopsies lead to certain diagnosis or normal results which is explained next.

2.2.1.5 Description of procedures performed and diagnoses.

A total of 144 procedures were performed: there were 68 (47.2%) upper (UGIP) and 76 (52.8%) lower GI procedures (LGIP). Diagnosis/outcome in this study was recorded from the histological reports (n=144) and a clear majority (n=94) tissue samples obtained were normal histologically. The relative percentages of the main diagnoses are shown in the pie chart below (Figure 12)

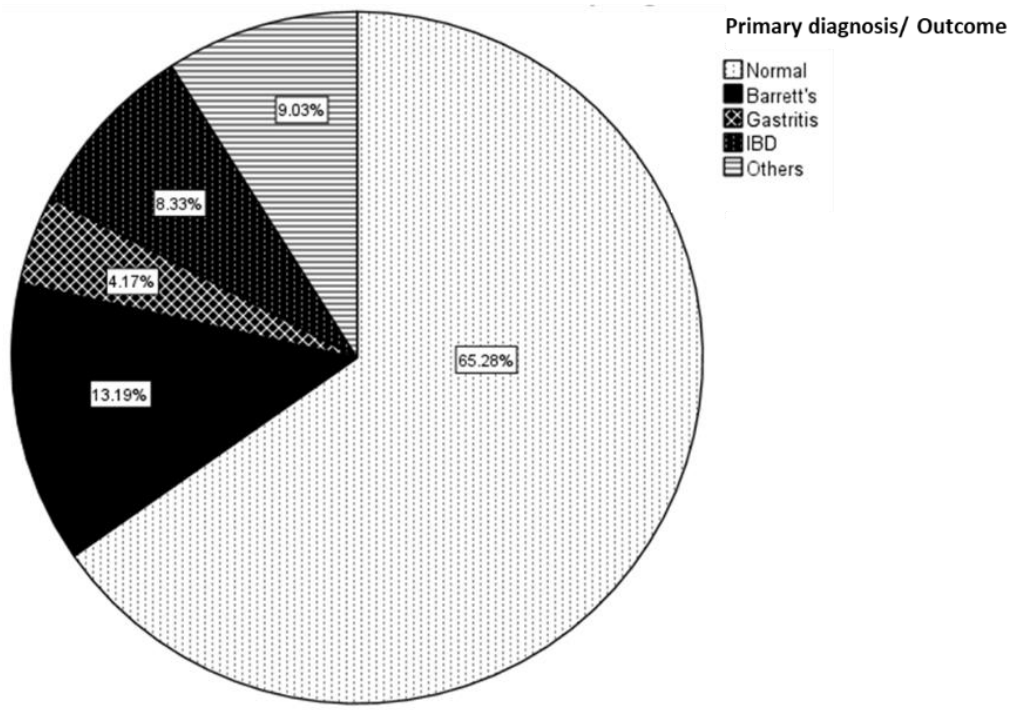

Figure 12: Pie chart depicting main diagnoses in the study population. It may be noted that majority of the specimens (65.28%) examined were normal histologically. The most common pathology encountered was Barrett's oesophagus (13.19%).

The pie chart above shows that the most common pathology diagnosed was BO (n=19) and then a miscellaneous group of other conditions (n=13), i.e., coeliac disease, reflux oesophagitis, adenomatous polyp and microscopic colitis.

Histologically recorded diagnosis was analysed according to the biopsy technique. Most of the samples were reported as normal but the predominant diagnosis in both groups was

BO. This was followed by and IBD and Gastritis. When compared according to biopsy technique i.e. SBB and DBB, the results are displayed in **Table 10.**

Table 10: Comprehensive analysis of biopsy collection according to site, procedure, and biopsy technique							
		Biopsies		Biopsy technique			
				Single Bite		Double bite	
	Total	n (%)	Med (IQR)	n (%)	Med (IQR)	n (%)	Med (IQR)
Procedure	144						
UGIPs	68 (47.2%)	316 (37.3%)	4 (4-6)	159 (18.6%)	4 (4-6)	157 (18.4%)	4 (4-4.5)
LGIPs	76 (52.7%)	537 (62.6%)	7 (4-10)	307 (35.8%)	8 (4-10)	230 (26.9%)	6 (3-10)
Regions							
Oeso'gus	29 (20%)	125 (14.6%)	4 (2-4)	75 (16%)	4 (2.7-6.5)	50 (12.9%)	4 (2-4)
Gastric	13 (9%)	33 (3.8%)	2 (2-2)	17 (3.6%)	2 (2-3.2)	16 (4.1%)	2 (2-2)
Duodenum	44 (30%)	167 (19.5%)	4 (4-4)	76 (16.3%)	4 (3-4)	91 (23.5%)	4 (4-4)
T-Ileum	15 (10%)	34 (3.9%)	2 (2-2)	21 (4.5%)	2 (2-3.7)	13 (3.3%)	2 (2-2)
Caecum	37 (25%)	76 (8.9%)	2 (2-2)	49 (10.5%)	2 (2-2)	27 (6.9%)	2 (2-2)
A-Colon	36 (25%)	65 (7.6%)	2 (1.2-2)	37 (7.9%)	2 (2-2)	28 (7.2%)	2 (1-2)
T-Colon	30 (20%)	52 (6.0%)	2 (1-2)	30 (6.4%)	2 (1-2)	22 (5.6%)	2 (1-2)
D-Colon	39 (27%)	72 (8.4%)	2 (1-2)	39 (8.3%)	2 (1-2)	33 (8.5%)	2 (1-2)
S- Colon	63 (43%)	114 (13.3%)	2 (1-2)	66 (14.1%)	2 (1-2)	48 (12.4%)	2 (2-2)
Rectum	59 (40%)	113 (13.2%)	2 (2-2)	54 (11.5%)	2 (1-2)	59 (15.2%)	2 (2-2)
G Total	144 (100%)	853 (100%)	6 (4-8)	466 (100%)	5 (4-9)	387 (100%)	4 (4-6)

The data displayed in the table above (**Table 10**) suggests that using both techniques biopsies were collected from different sites during the endoscopic procedure signifying the diversity in biopsy collection. Following the theme of biopsy collection, we will next examine the time taken to collect these biopsies.

2.2.1.6 Evaluation of biopsy collection

In UGIP the number of biopsies ranged from 2 to 16 (Med = 4, IQR= 4-6) and were collected from different sites depending on the pathology. No complications (i.e., major bleeding, admission to hospital, or other serious untoward outcomes) were detected during the study. In addition, no discrepancy was noted in the number of biopsies collected by the nurses and the number of biopsies received in the pathology lab. Furthermore, the study also analysed data for instances when biopsies were lost, or when nurses reported difficulty in extraction of the biopsy specimen from the cups of the spiked forceps. Additionally, out of 144 procedures, there were 13 (9.0%) instances where nurses reported a lost biopsy; there were 7 (4.8%) occurrences where biopsies were difficult to extract. These number were low and no meaningful statistics could be done. They are displayed in Appendix 6 (page 231). **Table 11** shows the relative frequencies and percentages of regions biopsied.

Table 11:Detailed log of procedures performed as per upper and lower GI endoscopy and number of biopsies collected during the study.

Procedure (n) and regions biopsied (n)		Biopsies (n)		Gender					Ethnicity			
				Male (n=73)		Female (n=62)			WBP (100)		SAP (35)	
	n (%)	n (%)	Med (IQR)	n (%)	Med (IQR)	n (%)	Med (IQR)		n (%)	Med (IQR)	n (%)	Med (IQR)
Procedure												
UGIP	68 (47.2%)	316 (37.3%)	4 (4-6)	165 (52.2%)	4 (4-6)	151 (47%)	4 (4-4)		254 (80%)	4 (4-6)	62 (20%)	4 (2-4)
LGIP	76 (52.7%)	537 (62.6%)	7 (4-10)	317 (59%)	8 (3-11)	220 (42%)	7 (4-10)		399 (74%)	7 (4-11)	138 (26%)	6 (2-10)
Regions												
Oesophagus	29 (20%)	125 (14.6%)	4 (2-4)	68 (14.1%)	4 (2-5)	57 (15.3%)	4 (3.2-4)		113 (17.3%)	4 (2-5)	12 (6%)	3 (2-4)
Gastric	13 (9%)	33 (3.8%)	2 (2-2)	25 (5.1%)	2 (2-3)	8 (2.1%)	2 (2-2)		29 (4.4%)	2 (2-2)	4 (2%)	2 (2-2)
Duodenum	44 (30%)	167 (19.5%)	4 (4-4)	84 (17.4%)	4 (4-4)	83 (22.3%)	4 (4-4)		121 (18.5%)	4 (4-4)	46 (23%)	4 (4-4)
T-Ileum	15 (10%)	34 (3.9%)	2 (2-2)	23 (4.7%)	2 (2-3)	11 (2.9%)	2 (1.7-2)		26 (3.9%)	2 (2-3)	8 (4%)	2 (2-2)
Caecum	37 (25%)	76 (8.9%)	2 (2-2)	45 (9.3%)	2 (2-2)	31 (8.3%)	2 (1-2)		55 (8.4%)	2 (2-2)	21 (10.5%)	2 (2-2)
A-Colon¥	36 (25%)	65 (7.6%)	2 (1.2-2)	36 (7.4%)	2 (2-2)	29 (7.8%)	2 (1-2)		46 (7%)	2 (1-2)	19 (9.5%)	2 (2-2)
T-Colon¢	30 (20%)	52 (6.0%)	2 (1-2)	29 (6%)	2 (1-2)	23 (6.1%)	2 (1-2)		40 (6.1%)	2 (1-2)	12 (6%)	2 (1-2)
D-Colon§	39 (27%)	72 (8.4%)	2 (1-2)	42 (8.7%)	2 (2-2)	30 (8%)	2 (1-2)		52 (7.9%)	2 (1-2)	20 (10%)	2 (2-2)
S- Colon¤	63 (43%)	114 (13.3%)	2 (1-2)	68 (14.1%)	2 (2-2)	46 (12.3%)	2 (1-2)		85 (13%)	2 (1-2)	29 (14.5%)	2 (1-2)
Rectum	59 (40%)	113 (13.2%)	2 (2-2)	62 (12.8%)	2 (2-2)	51 (13.7%)	2 (1-2)		84 (12.8%)	2 (2-2)	29 (14.5%)	2 (2-2)
G Total	144 (100%)	853 (100%)	4 (4-8)	482 (100%)	5 (4-9)	371 (100%)	4 (4-8)		653 (100%)	5 (4-9)	200 (100%)	4 (2-8)

¢ Transverse colon, § Descending colon, ¤Sigmoid colon, ¥ Ascending colon.

It is evident for the above table (**Table 11**) that specimens were collected from a diverse anatomical location in both upper and lower GI tract.

2.2.1.7 Time taken to collect biopsies.

The average time (AT) was defined as the total time taken divided by the number of biopsies taken to collect SBBs ranged from 26 to 72 seconds (Med = 36.5, IQR = 32.8-50) and was distributed normally (p=0.2), with skewness of .99 (SE = .44) and kurtosis of -.08 (SE = .85). Likewise, time taken to collect DBBs ranged from 14 to 42 seconds (Med = 19.5, IQR = 17.7-23.2) and was not distributed normally (p<0.01), with skewness of 2.1 (SE = .42) and kurtosis of 5.5 (SE = .82). The box plot below compares the biopsy techniques according to the time taken (**Figure 12**).

Figure 12: Whisker chart comparing single bit and double bite biopsy and time taken to complete this. It is clear that the AT to collect DBBs is significantly less as compared with single bite. This is shown by the fact that compare Mdn for SBB was 36.5 and 19.5 for DBB. (p<0.01) MWU test.

It is evident that DBB is more efficient in collection of biopsy specimens than SBB, according to time taken. MWU test was used to check the significance and it showed: SBB (Mdn = 175, n = 72, IQR=17-23) and DBB (Mdn = 77, n =72, IQR= 17.7-23.2), U = 31, z = -6.1, p <0.01,

r = -.1. This suggests that DBB takes less time (compare Mdns: 36.5 vs 19.5 for SBB and DBB respectively) and that the difference is statistically significant (Appendix No 3.1J).

2.3 SECTION 3

2.3.1 Discussion

The "BITES" study showed a significant difference in the time taken to collect tissue samples during endoscopic procedures and was able to demonstrate that single bite biopsies take longer than double bite biopsies. This is the first UK based study which has approached this area with a holistic design, using a multi-ethnic cohort, collecting samples from a diverse set of endoscopic regions and comparing samples from patients with different conditions.

The study met its aims by conducting a prospective and blind study (pathologist only) aimed to compare SBB and DBB techniques in terms of histological comparison and time taken. Additionally, the study also met the aim to record the incidence of lost or irretrievable biopsies during collection. It is important to differentiate BITES from previous research which compared the performance of forceps in relation to biopsy technique (Edery *et al.*, 2018; Chu *et al.*, 2003). It is notable that none of our participants dropped out of the study, thus the impact of attrition bias was not applicable (Dumville et al., 2006; Jüni et al., 2001). Discussion will therefore cover unique aspects of the conduct of the study, the population involved, biopsy collection and comparisons with the previous research.

2.3.1.1 Study Design

The study used a partly blind (pathologists were blind) and randomised design in accordance with previous research (Padda, Shah & Ramirez, 2003; Fantin *et al.*, 2001; Chu *et al.*, 2003; Hookey *et al.*, 2007; Latorre et al., 2015) and examined human specimens through a standard consent process for comparison, as opposed to previously conducted research which had used canine or feline samples (Edery *et al.*, 2018; Cartwright *et al.*, 2016; Goutal-Landry *et al.*, 2013; Ruiz *et al.*, 2016). This said, two authors used partly blind designs, but they evaluated

comparisons of single and double bite, and our study came close to their choice of design (Hookey *et al.*, 2007; Latorre et al., 2015). It is worth noting that biopsies in these studies were compared in the context of a defined pathology, i.e. UC by Hookey et al., (2007) and CD by Latorre et al., (2015), whereas BITES examined general aspects of histopathology.

2.3.1.2 Study population, procedures performed and regions biopsied.

BITES was based on a multi-ethnic population and was the first study of its kind, as previous human studies examining the histological background of specimens had either not included ethnic minorities or were not clear if they had included them (Fantin *et al.*, 2001; Hookey *et al.*, 2007; Stern *et al.*, 2005). The power of the study (n=144) is good in comparison with similar studies. In comparison to our study a much smaller power was observed in Hookey et al., (2007) whereas a relatively high power (n=86) was observed in Latorre et al., (2015) and a comparably similar power was seen in Frimberger et al., (2000). However, the superiority of BITES is that it meticulously calculated power through conducting a pilot trial which is a unique feature of this study in relation to other studies assessing this area of endoscopic biopsy practice.

The mean age of patients in BITES (54.5 ±15.8 years) is slightly higher than the mean age (49±18.9 years) in Latorre et al., (2015). This age difference may be explained by the fact that Latorre and colleagues (2015) mainly enrolled patients with coeliac disease (CD), whereas BITES accepted patients from a general endoscopy waiting list. Rubio-Tapia *et al* (2012) reported on the average age of CD (45 years) and this may explain the discrepancy of lower age in Latorre et al., (2015) vs. BITES.

The study reported biopsies from diverse regions, collected through both upper and lower GI endoscopies. Previous studies were either clearly uni-regional (e.g. duodenal (Latorre *et al.*, 2015)), bi-regional (e.g. oesophageal and gastric (Padda *et al.*, 2003)), or multi-regional but only collecting from the lower GI tract (e.g. Hookey *et al.*, 2007). In contrast to all of these studies, BITES improved on the previous designs by including specimens from all accessible parts of the GI tract during routine endoscopy.

BITES examined the collection process of biopsy specimens, and the reported number of biopsies in this study (n=853) is more than previously reported figures in the majority of the previous studies (Bersentes *et al.*, 1998; Chu *et al.*, 2003; Frimberger *et al.*, 2000; Zaidman *et al.*, 2006; Edery *et al.*, 2018; Stern *et al.*, 2005; Hookey *et al.*, 2007; Latorre *et al.*, 2015) and comes close to the study (n=1030) by Fantin et al., (2001). Areas in which BITES demonstrates comparative superiority over Fantan et al., (2001) are the use of a single type of forceps and collection from multi-regions.

It may thus be argued that BITES has approached the process of taking biopsies in a holistic way, improving on previous designs by using one type of forceps to collect human samples from all accessible regions, using both types of endoscopic procedures, and above all addressing the issue of study power in a methodical fashion.

2.3.1.3 Time, Biopsy discrepancy, loss and complication(s)

In BITES the time taken to obtain individual biopsies varied considerably. Fantin et al., (2001) has also made a passing comment on the time saving with DBB, but has not mentioned any methodology or estimation of time measurements in their study. Zaidman *et al.*, (2006) measured time while collecting biopsies and reported a mean time of 8.5 seconds per DBB, as

compared with 13.3 seconds with SBB. This is a contracted estimate in comparison to time reported by BITES, which found mean times of 36.5 seconds for SBB and 19.5 seconds for DBB.

This may be explained by the fact that the study by Zaidman *et al.*, (2006) involved porcine subjects (all sedated), whereas our study was based on patients (not all of whom were sedated) and secondly, Zaidman *et al.*, (2006) used colonic samples. It may be noted that taking samples from sedated pigs may be easier, whereas it is a lot more difficult from an un-sedated and anxious patient, hence leading to the calculated discrepancy.

Worthy of note, two studies were similar in terms of methodology to BITES and yet they reported contrasting results. Hookey et al., (2007) (n=12) examined the differences between the two techniques and reported that DBB was more prone to biopsy loss (SBB: n=8 (3.4%), DBB: n= 14 (6.0%)), although it was not significant statistically [OR 1.8 (95% CI 0.69 to 5.04; P=0.27)]. In contrast to this, Latorre and colleagues (2015) (n=86) reported significant differences between specimen loss with the two techniques (SBB n=2 (2%) vs DBB n=19 (22%), p=0.01).

Comparing these contrasting reports with BITES, one may notice that Latorre and colleagues (2015) compared biopsy loss in a specific region, i.e. duodenum only, and BITES was reporting biopsy loss from all endoscopic regions in a combined fashion; Hookey et al., (2007) was reporting their biopsy loss (non-significant) from colonic areas. With this in view, BITES compared biopsy loss according to the region, and no significant difference was found in any region including duodenum. It may be inferred that inconsistency may have come from the discrepancy in the powers of the studies, as Latorre et al., (2015) collected and analysed 242 biopsies from the duodenum (SB=158, DBB=84) and BITES only analysed 37 biopsies (SBB= 21 and DBB=24). There is thus a possibility that BITES may not have the sufficient power to comment on this area. Nonetheless, this point is clinically important, as the duodenum is a

commonly biopsied area in relation to iron deficiency anaemia (Howard *et al.*, 2002; Goddard *et al.*, 2011; Lopez *et al.*, 2016; Stonelake *et al.*, 2019).

Concluding on this point, it may be inferred that BITES, after disregarding the evidence in methodologically different studies (Frimberger *et al.*, 2000; Fantin *et al.*, 2001; Padda, Shah & Ramirez, 2003), is in agreement with Hookey et al., (2007) but in variance with Latorre and colleagues (2015), hence may have general applicability for taking biopsies (DBB= SBB) but may lack specific applicability, e.g. taking samples in the duodenal area. As a final comment, It may be asserted that when taking very small number of biopsies it is does not matter if one takes it with SSB or DBB and in duodenum usually four to six biopsies are taken hence one may follow guidance from Latorre and colleagues (2015).

2.3.1.4 Histological analysis of specimens

2.3.1.4.1 Size of specimen

Reporting on inadequacy of specimens, in contrast to BITES, Fantin and colleague (2001) in their study reported 26 (5%) of their single and 20 (3.9%) of their multi-bite specimens inadequate (<2mm), but this difference may be explained by the fact that they were using a different type of forceps, and forceps type is known to affect sample size (Dolwani *et al.*, 2002; Goutal-Landry *et al.*, 2013; Woods *et al.*, 1999). In contrast to Fantin and colleagues (2001), Ruiz et al., (2016) in their feline and canine study, reported a mean size of 2.5 mm, which is close to our study's mean (2.67 mm).

In a slightly different manner, Gonzalez et al., (2010) reported that 19.4% of their SBB and 16.1% of their DBB specimens were not adequate (p=.11), but the definition of adequacy of sample in this study was based on multiple factors, and size was just one of them, hence this assessment is not comparable to our study. Hookey et al., (2007) also reported that their SBB

specimens were significantly larger than their DBB specimens (SBB=4 mm, DBB=3.5, $p<0.01$) and it is noteworthy that they used spiked forcipes for all specimens.

2.3.1.4.2 Epithelial stripling, sample necrosis and sample fragmentation

Our study reported only one instance of epithelial striping (ES) (i.e. isolation of superficial epithelial cells from the underlying lamina propria) in a specimen (SBB). Although reported previously in a different context (Trapecar et al., 2017; Squier and Hall, 1985; Schulzke et al., 1986), this is the first time that a study has reported on a comparison of ES between SBB and DBB specimens. Similarly, our study reported significantly more fragmentation with SBB (n=6, 6.3%) as opposed to DBB (where no fragmentation was noticed). This is in sharp contrast to Woods *et al.*, (1999): in their study who did not report no difference but they were comparing forceps and not biopsy techniques. Hence, the difference with our study may be explained by the observation that Woods and colleagues (1999) were comparing different types of biopsy (n=12) forceps, whereas our study was referring to biopsy technique and used only one type of forceps .

BITES did report minor necrosis and crush artefacts in few specimens, but these were not significant enough to affect the histological quality for the purpose of diagnosis. Variable numbers of crush artefacts have been reported by other studies and yielded different results from ours. Fantin et al., (2001) reported one crush artefact (non-significant) in their study. Similarly, another study did not report any significant crush artefacts (Goutal-Landry *et al.*, 2013). Woods *et al.*, (1999) and Padda *et al.*, (2003) also reported crush artefacts in their comparative study of different forceps and reported no significant difference. Ruiz *et al.*, (2016) in contrast to Woods et al., (1999) and Padda et al., (2003) reported relatively higher number of crush artefacts (8/42) using similar technique but non spiked forceps. It is evident

that our study is in accordance with the majority of the reported studies, and the discrepancy with Ruiz *et al.*, (2016) may be explained by the use of spiked forceps in our study.

2.3.1.4.3 Effect on diagnostic quality of BO

BITES used only one type of biopsy forceps in collecting all specimens and reported 100% endoscopic and histopathological correlation, and this is 50% higher than previous reports by Thota and colleagues (2017) but given that they based their findings on 151 BO cases as compared to 19 cases in BITES Thota et al., (2017) have a higher statistical power to make any claims regarding the effect on the diagnostic quality. Additionally, their study was retrospective and compared HGD in BO in Endo Mucosal Resection (EMR) specimens, which may also explain the discrepancy. This is because EMR collects a sheet of tissue (more surface area to detect changes) and not a “pinch” of tissue as BITES did.

BO specimens in BITES were dysplasia and ACO free, and IM was reported in 5 (26%) specimens. Comparing this with published literature, a previous meta-analysis reported that the incidence of LGD in BO was 0.54% [0.54%, 95% CI, 0.32-0.76; 24 studies], but it may be noted that the total number of BO cases in BITES was 19, which is not sufficient for commenting on the incidence of dysplasia in BO. The incidence of IM in BITES correlated well with that in previous reports, albeit towards the higher end (Pera, 2003).

Considering the effect of biopsy technique on diagnosis, Latorre and colleagues (2015) (n=86) reported that DBB has a detrimental effect on the diagnostic quality of specimens, which is in clear contrast to BITES. The difference may be explained by the site and pathology in their study, as they examined their slides with coeliac disease (CD) in view, whereas BITES examined multiple pathologies including normal specimens. Keeping this in mind, Latorre and colleagues (2015) did not randomise their SBB and DBB specimens, and as a result exclusion criteria were not clear, and the study may well have suffered selection and reporting bias.

Nonetheless, the study was otherwise well designed and a repeat study with a randomised design may settle this question.

2.4 SECTION 4

2.4.1 Limitations of the study and recommendations

The findings of this study must be seen in light of few limitations. The first is the design of the study, as although the study improved on several aspects of designs by previous authors, it was addressing general aspects of histological standards during routine biopsies. The study thus lacks specific applicability, e.g. in assessing histological differences in duodenal specimens in CD, or oesophageal specimens in BO, and hence it was not possible for the study to conclusively comment on site specific histological differences.

The second limitation concerns the extraction of specimens with needles, which may have caused some observed histological anomalies. The third limitation is related to the population selection. Although multi-ethnic in comparison to the previously published studies (Frimberger *et al.*, 2000; Fantin *et al.*, 2001; Padda, Shah & Ramirez, 2003), the population may still have suffered selection bias as it was a single centre study. One way to address this limitation may well be to recruit patients from multiple regional centres as this may increase number of SAP in the study.

The fourth limitation in this study may arise from the sampling and reporting of the specimens, as 75% of the reports were done by one pathologist, and 90% of the specimens were collected by one endoscopist. This may have a positive as well as a negative effect on the study, as on the one hand it may have reduced inter-observer variability, but on the other hand it may have introduced “observer’s bias”. This could have been improved if all specimens had been reviewed by two pathologists, independently of each other.

The final limitation is associated with the lack of data about patients’ sedation status, as this was not recorded, and future studies in this area should keep that in mind, as sedated

patients are easier to biopsy than anxious patients who are in distress. It is also assumed that biopsy cycle (hence time to collect biopsy) may be short in a sedated patient but this needs to be examined in prospective analysis.

2.4.2 Summary and recommendations and future implications

BITES is a multi-ethnic holistic study comparing biopsy techniques at all levels, i.e., biopsy collection and histological assessment. The study did not find any significant histological differences between SBB and DBB biopsies but did report significant differences in the time taken to collect single bite biopsies (SBB>DBB), hence depicting the efficiency of DBB. The aim of the study was to compare these parameters in general terms, and although sub-analysis was done in order to compare site specific differences, it is accepted that power for individual regions might not be sufficient.

BITES is a holistic study and has examined the way biopsies are taken with a fresh pair of eyes and in light of previous research has improved design, years after the study by Fantin *et al.*, (2001). BITES is expected to change practice in terms of the way endoscopists take biopsies, and although the study does not promote one method as being particularly favourable and urge endoscopists to follow it, nonetheless suggests that DBB are efficient in terms of time and may save endoscopists time and reduce intubation time for patients.

3 CHAPTER III

Study 2: Study Assessing LAndmark Height Alteration During Endoscopic EvaluatioN (SALAHADEEN)

Introduction

The diagnosis of oesophageal pathologies such as HH, and more importantly BO, is dependent on the precise location of the GOJ (Armstrong, 2004; Roman and Kahrilas, 2014) and it is important to ascertain its exact anatomical position. This, as anticipated, will aid in the correct assessment of BO length (Sharma et al., 2006), which is used to guide clinicians regarding the prognosis and endoscopic follow up of BO (Fitzgerald *et al.*, 2014). Ascertaining the precise location of GOJ is important for another reason as well and that is its role as reference point in the classification of BO into long (≥ 3 cm) and short (≥ 1 cm and ≤ 3 cm) (Sharma, Morales & Sampliner, 1998). Length of BO segment is a key parameter in the progression of BO to ACO (Rastogi and Sharma, 2006; Pohl *et al.*, 2016; Rudolph *et al.*, 2000). That is why long segment BO will need a shorter interval for the surveillance of dysplasia/ACO (Fitzgerald *et al.*, 2014).

Keeping the above in mind, it has been established that surveillance of BO with the correct intervals helps in the detection of dysplastic elements in BO (Garside *et al.*, 2006; Sonnenberg, Soni & Sampliner, 2002; Armstrong, 2008; Mansour, El-Serag & Anandasabapathy, 2017; de Jonge *et al.*, 2014; De Looze, 2000), the precursor lesions to ACO (Headrick *et al.*, 2002; Spechler, 2013). To date, there have not been any studies which have specifically compared landmark measurements in both intubation and extubation (to answer research question no. 2). The study presented below was designed to assess landmark height alteration during endoscopic evaluation, and its effect on the diagnoses of HH and BO.

3.1 SECTION 1

3.1.1 Aims, Methodology and Design

The primary aim of the study was to assess the position of three anatomical landmarks, i.e. GOJ, Diaphragmatic indentation (DI), and Squamo-columnar junction (SCJ) during intubation and extubation phase of endoscopy. An additional aim of the study was to see the effect of change in the position of landmarks, if any, on the length and diagnosis of both HH and BO. To achieve the desired outcome, the objectives were to measure these landmarks in a pre-agreed standardised way (Sharma et al., 2006) and to compare them for statistical significance.

This was a prospective observational study and to assess the feasibility and associated risk of the study, an initial smaller pilot project was conducted to ascertain related issues and possible barriers prior to the launch of the full project (Turner, 2005). All procedures were done by experienced and independent endoscopists, who were certified according to the standards of the joint advisory group (JAG) of the UK (Valori, 2019) for upper GI endoscopy.

Two kinds of endoscopes were used during the study, i.e. Fujinon® (Video Gastroscope EG-530FP) and Olympus® (GIF-HQ290 Evis Video-gastroscope) and all measurements were relative to the incisors. SCJ (Z line), the meeting or transition point between oesophagus and stomach mucosa, was identified by the sharp demarcation between the two mucosae, which were visually distinct entities. Furthermore, the level of diaphragmatic crura was identified by an indentation, as it appeared as an internal pinch of indentation and it is understood that this level is displaced proximally, leading to the formation of HH.

It should be noted that all extubation measurements were taken on nearly deflated gastric as deflated stomach may affect the position of the GOJ (Kahrilas, Kim & Pandolfino, 2008). BO if present (salmon pink oesophageal mucosa), was measured using Prague CM classification

as recommended by the international working group for the classification of oesophagitis (Sharma *et al.*, 2006) In cases where both HH and BO were present in the same patient, the endoscopist determined the GOJ, relying on their experience, by first carefully demarcating the diaphragmatic indentation as the distal margin of HH. The scope was then withdrawn gently and, keeping the mucosal views, proximal gastric folds and possible lower oesophageal "sphincter pinch" as the proximal margin of the HH were noted.

Participants for this study were identified from the UGI waiting list which was available from the endoscopy department. All patients who could consent and were >18 years were selected. It may be noted that no upper age limit was set, as long as the patient could consent. Indications such as chronic liver disease, and patients who clearly needed therapeutic interventions were filtered out at this stage.

3.1.1.1 Statistics and Ethics

Using an online *a priori* calculator sample size for this study was determined. To calculate this, Student's t-Test (two-tailed hypothesis, p=<0.05) and anticipated effect size (Cohen's d) of 0.25 was used. With these values in view and keeping desired statistical power level to 0.8, a minimum sample size of 253 was calculated. For statistical tests and methods used, please refer to chapter 2, in relation to study no one. The Integrated Research Application System (IRAS) was used (IRAS ID: H0402), and permission was granted by the Leicestershire, Northamptonshire & Rutland Local Research Ethics Committee (Ref 09/H0402/54). The local NHS research and development department at UHL was also involved (UHL-10749). Furthermore, the UCLan ethics committee granted permission for the use of this study towards the MD project through their letter dated 24th April 2017 (STEMH 622) (Appendix 2.3).

3.2 SECTION 2

3.2.1 Results

3.2.1.1 Demographics

A total of 415 patients identified from the GI waiting list were approached for the study. Based on exclusion criteria 156 patients were excluded and 259 patients were finally selected for the study. The consort diagram is presented in the appendix (7.53, page 228). The ages of the population (n=259) ranged from 18 to 95 years (M = 58.9, SD±17.2, IQR = 47-73) and were not distributed normally (p<.01), with skewness of -.30 (SE = .15) and kurtosis of -.68 (SE = .41). The most prevalent age group was > 70 years (n=72, 28.2%), followed by age group 60-70 years (n=58, 18.1%). The sample had a female predominance and on ethnic grounds, it was a mixed sample and had patients from south Asian (i.e., Indian, Pakistani and Bangladeshi) background. The table below shows the demographic details of the population sample (**Table 12).**

Table 12 Gender and ethnic distribution of the population in relation to age groups in the sample.

Age (years)		Ethnicity		Gender					
				Males			Females		
	N=259	WBP (n=228)	SAP (n=31)	Total (n=121)	WBP (n=104)	SAP (n=17)	Total (n=138)	WBP (n=124)	SAP (n=14)
M±SD	58.9±17.2	60 ±17.2	50.7±14.3	58.8±17.4	60.2±17.5	49.8±14.3	59±17.1,	59.8±17.1	51.7±14.9
Min-Max	18-95	18-95	26-75	21-95	21-95	29-75	18-93	18-93	26-76
IQR	47-73	49-74	40-62	48-74	50-72	37-61	47-72	48-73	40-62
Median	61	61	51	61	62	50	60	60	52
Grand Total	259 (100%)			121 (46.7%)			138 (53.3%)		

*MWU test. **χ2 test. M=Mean, SD = Standard Deviation.

3.2.1.2 Assessment of Landmarks

All procedures (n=259) were completed to the level of at least the second part of the duodenum. The dose of midazolam used ranged from 1.5 to 3.5 mg (Mdn = 2.5, IQR = 2.5-3) and it was not distributed normally (p<.01), with skewness of -.59 (SE = .25) and kurtosis of .74 (SE = .50), and the doses of Xylocaine for the procedures ranged from 50 to 100 mcg (Mdn = 70, IQR = 60-70). Agreed upon oesophageal landmarks were measured during the study: both in intubation and extubation.

Since height and weight and BMI may affect the landmarks and possibly HH, it is important to give a brief overview of these parameters in relation to the study population.

3.2.1.3 Body Mass Index of the study population

The BMIs ranged from 14 to 44 Kg/ m^2 (M = 27.4, SD±0.40, IQR = 27-31) with skewness of .31 (SE = .15) and kurtosis of -.37 (SE = .30). KS test was significant (p<0.01), suggesting that the data was not distributed normally. The **figure 13** below compares weight, height and BMI of both populations.

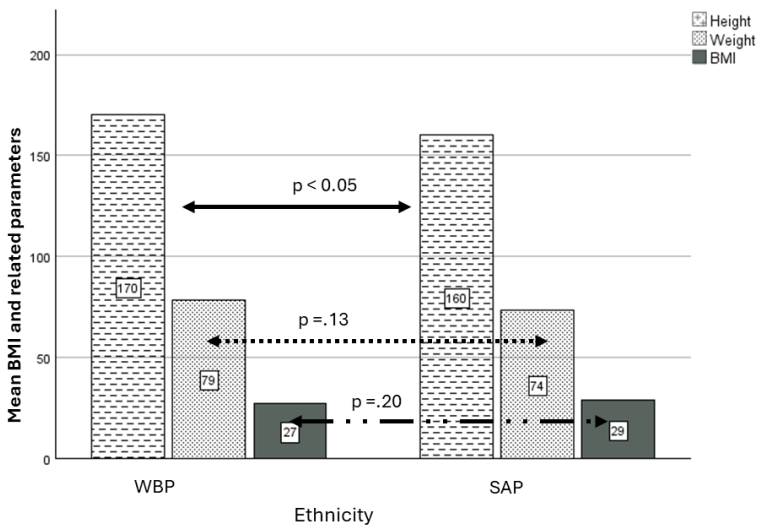

Figure 13 Bar chart comparing weight, height, and BMI of WBP and SAP.

The bar chart above (**figure 13**) shows that there is a significant difference between the height of WBP and SAP ($p<0.01$) but no significant difference in BMI and weights. This means that WBP is taller in our sample, but BMI is similar. We will now examine individual landmarks and diagnoses i.e. BO and HH.

3.2.1.3.1 Landmarks GOJ and DI

GOJ measurements (n=259) in intubation ranged from 32 to 50 cm (Mdn = 40, IQR = 38-42) and were not distributed normally ($p<.01$), with skewness of .36 (SE = .15) and kurtosis of .70 (SE = .30). Similarly, during extubation in 258 (99.9%) procedures; they ranged from 30 to 50 cm (Mdn = 40, IQR = 38-42) and were not distributed normally ($p<.01$), with skewness of .05 (SE = .15) and kurtosis of .33 (SE = .30). Using Wilcoxon Signed-Ranks test (WSRT), both phases of endoscopy were compared in relation to the location of GOJ from incisors: intubation (Mdn = 40, M =40 ±2.8, n =259, IQR=38-42) and extubation (Mdn = 40, M =40 ±2.9, n =258, IQR=38-42), z = -3.9, $p<.01$). This means that there is a significant difference between GOJ measurements during intubation and extubation.

Similarly, DI was recorded in 244 (94.3%) procedures during intubation (Male=115, Females 128). The recordings ranged from 32 to 50 cm (Mdn = 40, IQR = 39-43) and were not distributed normally ($p<.01$), with skewness of .38 (SE = .15) and kurtosis of .60 (SE = .30). DI measurements were also recorded during extubation in 243 (93.8%) procedures. They ranged from 34 to 52 cm (Mdn = 40, IQR = 39-42) and were not distributed normally ($p<.01$), with skewness of .31 (SE = .15) and kurtosis of .45 (SE = .31).

Using Wilcoxon Signed-Ranks test (WSRT), both phases of endoscopy were compared in relation to the location of DI from the incisors: intubation (Mdn = 40, M =40.8 ±2.8, n =243, IQR=39-43) and extubation (Mdn = 40, M =40.7 ±2.8, n =243, IQR=39-42), z = -1.7, $p=.07$). This

denotes that DI on insertion was located at same distance from incisors in both phases of endoscopic test.

This was further analysed, and sub analysis for gender was done; the bar chart below compares the intubation and extubation phases of DI measurements in relation to gender (Figure 13).

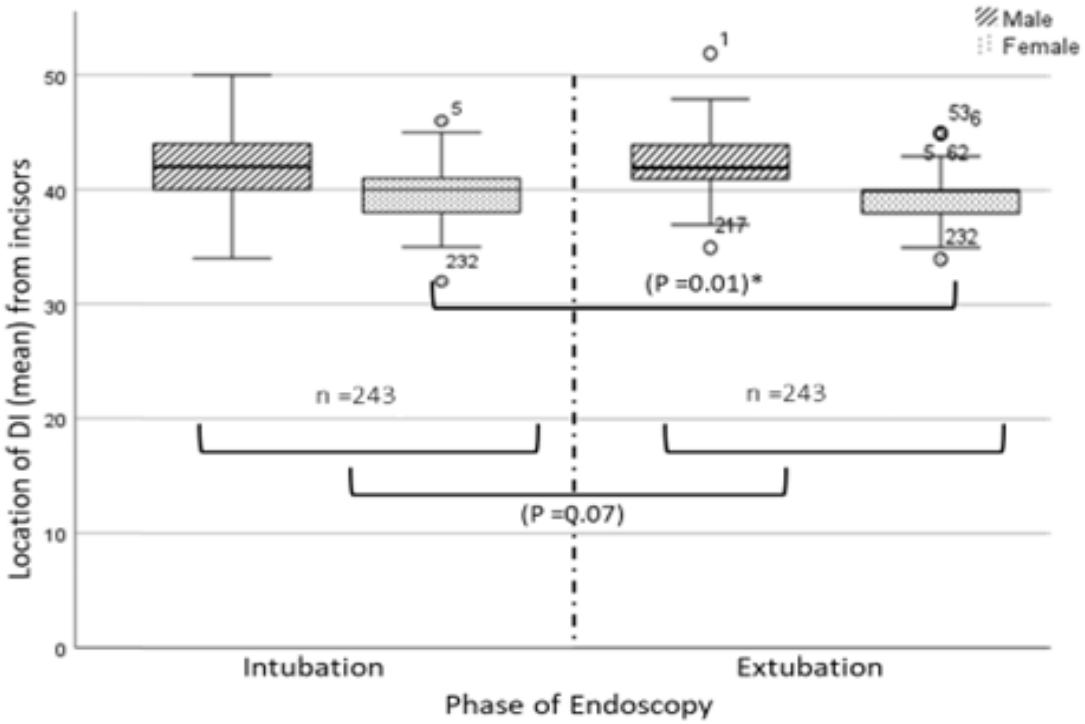

Figure 14: Comparison of genders in relation to distance of DI from incisors during the intubation and extubation phases of endoscopy. Please note that there a significant difference in DI was related to female gender only (P=0.01, Wilcox S-R test) and no difference was noted when DI was compared between intubation (Mdn = 40, M =40.8 ±2.8, n =243, IQR=3943-) and extubation(Mdn = 40, M =40.7 ±2.8, n =243, IQR=39-42) (P=0.07) MWU test.

The chart above shows that the significant difference in DI was related to female gender only. Similarly, when analysed based on ethnicity, no significant proximal/ distal displacement of DI was noted during extubation (p>0.05).

3.2.1.3.2 GOJ in relation to the height of patients

The position of oesophageal landmarks i.e. GOJ and DI may well be related to the length of oesophagus which in turns may well be relate to the heights of participants. This ranged from 150 to 198 cm (Mdn = 168) and were not distributed normally (p<.01), with skewness of .28 (SE = .15) and kurtosis of .66 (SE = .30). Bar chart below (**Figure 14**) shows the height of patients.

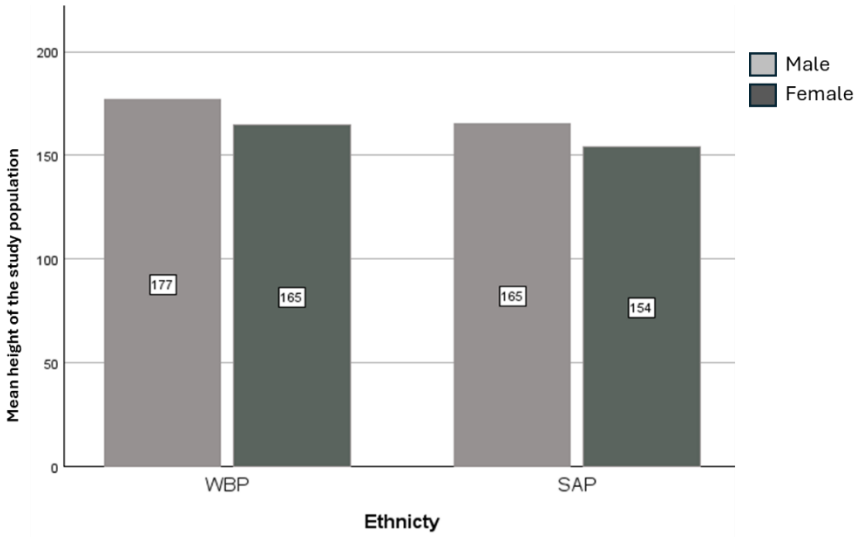

Figure 15: Comparison of ethnicity in relation to GOJ and height of patients.

It is clear from the bar char above (**Figure 14**) that males are taller than females, that this trend is significant (P< 0.05) and same in both ethnicities. Equally, WBP was taller as compared to SAP. The height of participant and position of GOJ in intubation was analysed and a significant difference was noted intubation GOJ (Mdn = 40, n =259) and height (Mdn = 168, n =259), z = -13.9, p<0.01). This means that in relation to incisors the GOJ was distally placed in WBP patients.

3.2.1.3.3 Landmarks : Maximum Barrett's and Circumferential Barrett's

MBO or SCJ junction were recorded in 237 (91%) procedures during intubation (Male=112, Females =125). It ranged from 28 to 49 cm (Mdn = 37, IQR = 35-39) and it was not distributed normally (p<.01), with skewness of .25 (SE = .15) and kurtosis of .97 (SE = .31). Both phases of endoscopy were compared in relation to the location of MBO from incisors: Intubation (Mdn = 37, M =37.4±3.3, n =237, IQR=35-39) and extubation (Mdn = 37, M =37.3 ±3.3, n =237, IQR=35-39), z = -1.1, p=.26).

Similarly, CBO were recorded in 237 (91%) procedures during intubation (Male=112, Females =125) and recorded in 235 (Male=111, Females =124) procedure during extubating. In intubation phase it ranged from 19 to 50 cm (Mdn = 38, IQR = 37-41) and it was not distributed normally (p<.01), with skewness of .50 (SE = .15) and kurtosis of .64 (SE = .31). Similarly, in extubation phase it ranged from 31 to 49 cm (Mdn = 38, IQR = 36-40) and it was not distributed normally (p<.01), with skewness of .23 (SE = .15) and kurtosis of .12 (SE = .31).

Both phases of endoscopy were compared in relation to the location of CBO from incisors: Intubation (Mdn = 38, M =38.6±3.1, n =237, IQR=37-41) and extubation (Mdn = 38, M =38.3 ±3.0, n =235, IQR=38-42), z = -1.1, p<.01). The differences between the location of CBO is significant in both phases of endoscopy and by examining the ranks table it is clear that 104 measurements observed reduction on extubating whereas, 66 showed increase and no change was observed in 84 measurements. This denotes that CBO on intubation was located distal in comparison to extubating. This was further analysed and sub analysis for gender and ethnicity. **Figure 15** below compares the intubation and extubation phases of GOJ measurement in relation to gender.

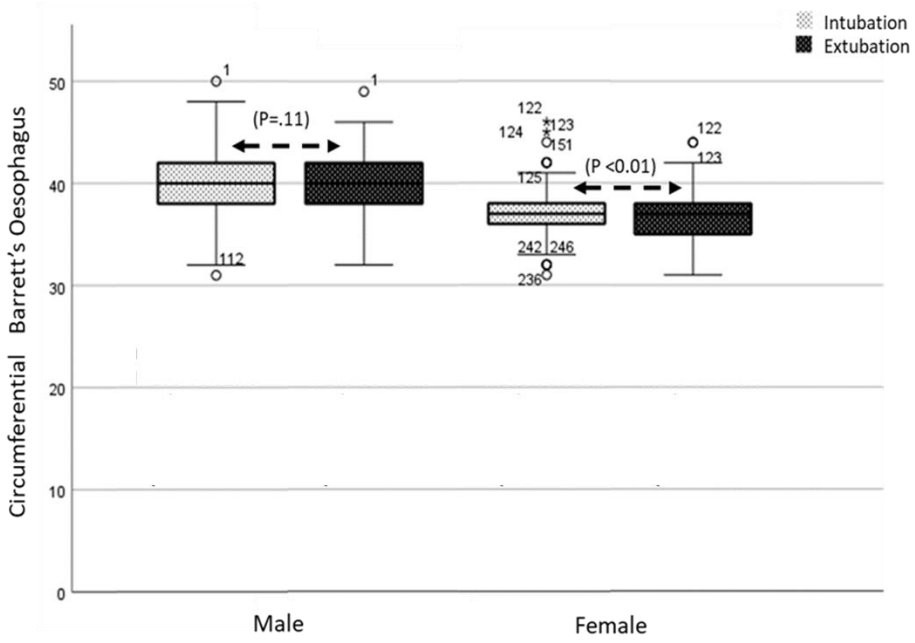

Figure 16: Comparison of CBO in both Intubation and extubation in relation to gender. MWU test. both phases of OGD were compared, a significant difference was noted in the location of MBO in the female gender only (<0.01). There was no significant difference note

The comparative whisker chart shows that CBO was distally located on intubation. When both phases of OGD were compared, a significant difference was noted in the location of CBO in the female gender only. This means that CBO moved proximally amongst females on extubation. Similarly, values were compared for ethnicity as well and are presented elsewhere in the MD (Chapter no 4). To summarise the data, the table below compares all of the landmarks (Table 13).

Table 13: Comparison of location of GOJ, DI, SCJ and CBO in both phases of endoscopy

	Intubation Phase of OGD (Mdn, IQR)						Extubation Phase of OGD (Mdn, IQR)				
	Total	Gender		Ethnicity			Total	Gender		Ethnicity	
		Male	Female	WBP	SAP			Male	Female	WBP	SAP
GOJ	40* (38-42)	42 (40-43)	39* (37-40)	42* (40-43)	39* (37-40)		40* (38-42)	41 (40-43)	38* (37-40)	41 (40-43)	38* (37-40)
DI	40 (39-43)	42 (40-44)	40* (38-41)	42 (40-44)	40 (38-41)		40 (39-44)	42 (41-44)	40* (38-40)	42 (41-44)	40 (38-40)
SCJ or MBO	37 (35-39)	39 (37-41)	36* (35-38)	39 (37-41)	36 (35-38)		37 (35-39)	39 (37-41)	36 (37-34)	39 (37-41)	36 (34-37)
CBO	38* (37-41)	40 (38-42)	37* (36-38)	40* (38-42)	37* (36-38)		38* (36-40)	40 (38-42)	37* (35-38)	40* (38-42)	37* (35-38)

* Significant relationship. GOJ= gastroesophageal junction, DI= Diaphragmatic indentation, SCJ= squamo-columnar junction, CBO= circumferential Barrett's, MBO= maximum Barrett's. WBP= White British population SAP= South Asians population.

It is clear from the summary table above that GOJ and CBO were located significantly distally on intubation, and DI and SCJ/MBO were equidistant from the incisors during both phases of endoscopy. Furthermore, sub analysis shows that, in relation to gender, all parameters were significantly proximally located in females, and no change was observed in males, suggesting that changes in the location of landmarks are gender dependant. In terms of ethnicity, only GOJ and CBO were significantly distally located during the insertion phase of the endoscopic procedure in both ethnicities. In the next section, the derived diagnoses (i.e. BO and HH) will be explored in both phases of the endoscopic procedures.

3.2.2 Hiatus Hernia and Barrett's Oesophagus

3.2.2.1 Diagnosis 1: Hiatus Hernia

HH was measured in 244 cases and was detected in 137 (56.1%) on insertion. The missing cases (n=15) were where either GOJ or DI was not measured, hence the values of HH could not be derived. Of the detected cases of HH, 58 (23.8%) were male and 79 (57.7%) were female. Similarly, from an ethnicity point of view, HH was detected in 126 (51.6%) WBP and 11 (4.5%) SAP. The length of HH was not distributed normally ($p<.01$), with skewness of 2.8 (SE = .20) and kurtosis of 9.3 (SE = .20). **Table 14** presents the descriptive statistics of HH in both phases in relation to gender and ethnicity.

Table 14: Comparing the diagnosis of hiatus hernia based on ethnicity and gender

	Intubation Phase					Extubation Phase				
	Total	Gender		Ethnicity		Total	Gender		Ethnicity	
		Male	Female	WBP	SAP		Male	Female	WBP	SAP
M±SD	1.48±.87	1.46±.78	1.50±.94	1.54±.94	1.0±.22	1.44±.92	1.54±1.0	1.43±.82	1.48±.95	1.0±0.0
L'gth (Mdn, IQR)	1 (1-2)	1 (1-1.2)	1 (1-2)	1 (1-2)	1 (1-1)	1 (1-2)	1 (1-1.2)	1 (1-2)	1 (1-2)	1 (1-1)
Age (Mdn, IQR)	60.9 (49-76)	59.7 (49-74)	79 (48-77)	62 (49-77)	50 (47-58)	60 (47-71)	59.5 (42-71)	61 (47.2-72)	61 (46-73)	55 (47-62)
HH (n)	137 (56.1%)	58 (23.8%)	79 (57.7%)	126 (51.6%)	11 (4.5%)	174 (71.6%)	74 (30.5%)	100 (41.2%)	154 (63.4%)	20 (8.2%)

L'gth= Length, Mdn= Median, IQR= Inter quartile range, HH=hiatus hernia, WBP= White British population SAP= South Asians population.

It may be noted from the above table that, although there was no difference between the length of HH according to gender (p=.94), there was a significant difference between the lengths of HH according to ethnicity: White (Mdn = 1, n = 126, IQR=1-2) and Asians (Mdn = 1, n =11, IQR= 1-1), U = 1087, z = -2.6, p <.01, r = -.01. This means that HH was significantly longer in White participants (Appendix 3.2Ca).

3.2.2.1.1 Relationship of Body Mass Index to the HH

Body Mass Index (BMI) is a risk factor of HH and to see if the increased length of HH in WBP could be explained by the difference in the BMI, a comparison was drawn between the BMIs of the ethnicities. The BMI of the entire population ranged from 14 to 44 (Mean 27.4 ± SD=.4) and it was not distributed normally in both genders (P<0.05). Using MWU test, a significant no difference was noted in the BMI of WBP (Mdn = 27, n =259) and SAP (Mdn = 28, n =259), z = -1.48, p<0.13). This means that there was no difference of BMI between the ethnicities.

In the extubation phase, there is also a progressive increase in the number of HH cases detected with increasing age, although this was also not significant (p=.50). Furthermore, in this phase a significant difference was noted in the diagnosis of HH according to gender ($\chi2$ (1, n=259) =6.62, p =.01, phi = .16), but not ethnicity ($\chi2$ (1, n=259) =0, p =.98, phi = -.001). This means that significantly more HH was detected in females. Furthermore, there was a significant difference between the lengths of HH according to ethnicity: White (Mdn = 1, n = 154, IQR=1-2) and Asians (Mdn = 1, n =20, IQR= 1-1), U = 1087, z = -2.6, p <.01, r = -.01. This means that, similar to intubation, HH was significantly longer in WBP in extubation.

Comparing the intubation and extubation phases of endoscopy, it is interesting to note that, in comparison to insertion (n=137), significant amount of HH (n=174) was detected during extubation, and this difference was significant: $\chi2$ (1, n=259) =92.8, p =<.01, phi = .68. This

change, as explained above, was mainly seen in HH in female patients. Similarly, when the length of HH was analysed using Wilcoxon Signed Rank test, a significant difference was noted in the length of HH during both phases of endoscopy: intubation (Mdn = 1, M =1.44 ±.92, n =137, IQR=1-2) and extubation (Mdn = 1, M =1.48 ±.87, n =175, IQR=1-2), z = -2.0 p=.03). This is shown in the bar chart below **(Figure 16).**

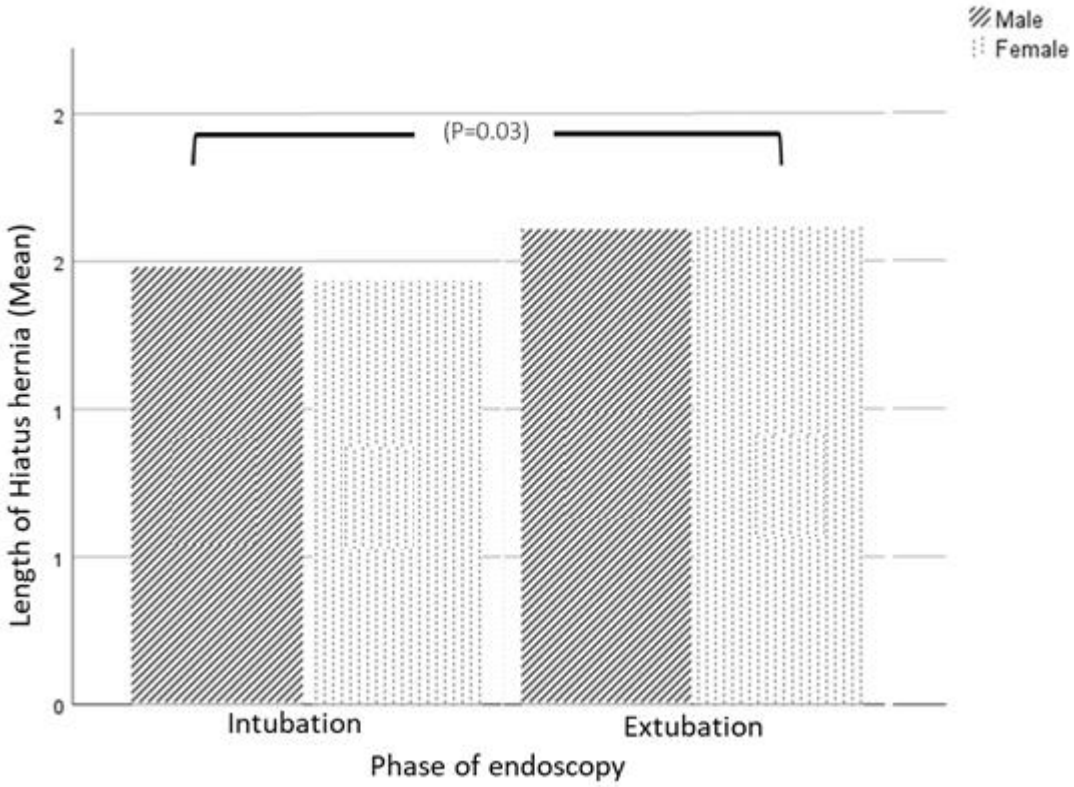

Figure 17: Comparison of genders in relation to the diagnosis of HH. It may be noted that there is a significant difference in the length of HH during both phases of endoscopy: intubation (Mdn = 1, M =1.44 ±.92, n =137, IQR=1-2) and extubation (Mdn = 1, M =1.48 ±

3.2.2.2 Subdivisions of Hiatus Hernia

HH was further divided into small (<3 cm) and large (≥3cm) hernia. The lengths of large HH (>3cm) on intubation ranged from 3 to 6 cm (Mdn = 3, IQR = 3-4) and were not distributed normally (p<.01), with skewness of 1.3 (SE = .59) and kurtosis of .50 (SE = 1.1). Correspondingly, the lengths on extubation ranged from 3 to 6 cm (Mdn = 3, IQR = 3-4) and were not distributed normally (p<.01), with skewness of 1.7 (SE = .59) and kurtosis of 2.2 (SE = .99). The gender distribution and lengths of clinically significant HH (i.e., large HH) are given below in a bar chart in both phases of endoscopy (**Figure 17).**

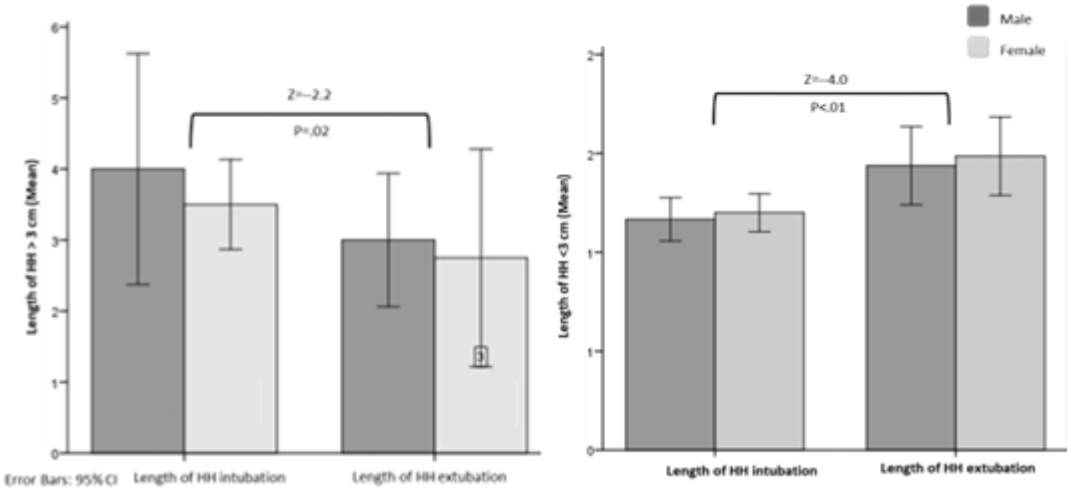

Figure 18: Comparison of genders in relation to the diagnosis of HH in large (left) and small HH (right). It may be noted that there is a significant increase in the number of small HH on extubation. The bar chart above shows a significant decrease (p<.01) in the

The bar chart above shows a significant decrease in the length of large HH (> 3 cm) in relation to both genders on extubation (z = -2.2 p=.02) whereas small HH increased during extubation phase of endoscopy, and this was significant (z = -4.0 p<.01) (Appendix 3.2Cb).

The summary results for both phases of endoscopy in relation to the diagnosis of HH are compared in the table below (Table 17).

Table 15: Comparison of Hiatus Hernia in both phases of endoscopy

		Intubation Phase					Extubation Phase				
		Total	Small HH (<3 cm) (n=123)		Large HH (>3 cm) (n=14)		Total	Small HH (<3 cm)		Large HH (>3 cm)	
		N=259	Gender		Gender		N=259	Gender		Gender	
			Male	Female	Male	Female		Male	Female	Male	Female
HH (n)		137 (52.8%)	52 (38%)	71 (51.8%)	6 (4.4%)	8 (5.8%)	175 (67%)	65 (37.5%)	90 (51.4%)	9 (5.1%)	11 (6.3%)
Length of HH	Mean ±SD	1.44±0.92	1.1±0.3	1.4±0.9	4±1.5	3.5±0.7	1.48±0.87	1.2±0.4	1.2±0.4	3.2±0.4	3.7±1.1
	Median (IQR)	1 (1-2)	1 (1-1)	1 (1-1)	3 (3-6)	3 (3-4)	1 (1-2)	1 (1-1)	1 (1-1)	3 (3-3)	3 (3-5)
Age of patients	Mean ±SD	60.9±16.3	58.5±16.3	60.9±16.3	70.8±11.3	69.3±15.8	58.6±16.9	54.8±17.2	58.3±16.3	74.5±10.4	70.7±11.2
	Median (IQR)	61 (49-74)	58 (48-73)	61 (48-76)	70.8 (63-81)	69.5 (55-84)	60 (47-71)	58 (40-69)	60 (47-70)	79 (67-83)	72 (60-80)

HH=hiatus hernia, SD: Standard deviation, IQR =Inter quartile range

In summary, it is clear from the table that an increase in HH diagnosis was noted on extubation as compared to intubation.

3.2.2.3 Diagnosis 2: Barrett's Oesophagus

Out of the 259 patients, complete BO related data was available for 237 patients, and it was diagnosed in 228 (88%) cases on intubation (ranging from 1 to 6 cm, MDN = 1, IQR = 1-2), whereas 230 (88.8%) patients were found to have BO on extubation. The lengths of MBO on insertion ranged from 1 to 12 cm (M: 2.91±2.9), whereas on extubation they ranged from 1 to 11 cm (M: 2.47±1.6). Similarly, CBO ranged from 0 to 11 cm (M: 1.45±1) and 0 to 9 cm (M: 1.41±1) on intubation and extubation respectively. The figure below compares the lengths of both types of BO segments (Figure 18).

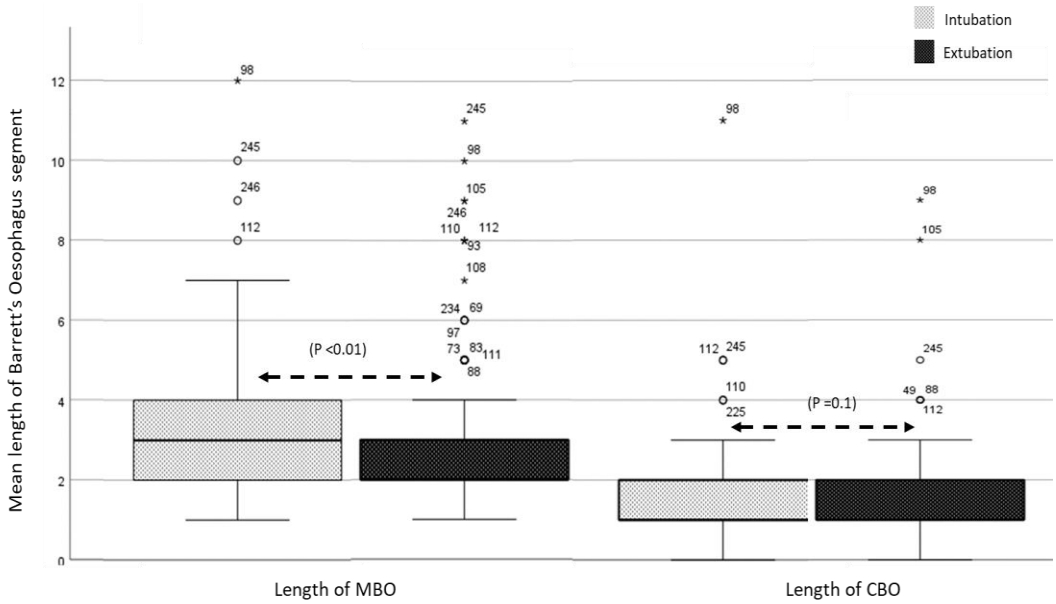

Figure 19: Box plot comparing the lengths of both types of BO segments. NB: MBO exhibits a significant decrease in its length. MWU test. It may be noted that there is a significant decrease in the length of MBO on extubation (p<0.01).

It may be noted that there is a significant decrease in the length of MBO on extubation (p<0.01), but no such decrease was noted in the length of CBO. This suggests that the maximum length of BO is reduced on extubation. For a detailed comparison the table below exhibits the lengths of both segments in relation to gender (Table 16) Appendix 3.2Bc.

Table 16 Comparison of length of Maximum and circumferential BO in both phases of endoscopy

	Length of Maximum Barrett's Oesophagus						Length of Circumferential Barrett's Oesophagus					
	Intubation			Extubation			Intubation			Extubation		
	T (n=237)	M (n=112)	F (n=125)	T (n=237)	M (n=112)	F (n=125)	T (n=237)	M (n=112)	F (n=125)	T (n=237)	M (n=112)	F (n=125)
M±SD	2.91±3.3	38.92±1.6	36.19±2.2	37.32±3.3	38.94±3.3	35.87±2.6	1.4±3.1	40.23±3.1	37.70±2.4	38.37±3.0	40.03±2.8	36.88±2.3
Median	2	39	36	37	39	36	1	40	37	38.	40	37
Mode	2	37	36	37	40	37	1	38	37	38	40	37
Skewness (SE)	1.7 (.16)	-.05 (.22)	.10 (.21)	.06(.15)	-.24 (.22)	-.15 (.21)	3.8 (.15)	.15 (.22)	.53 (.21)	.23 (.15)	-.06 (22)	.12 (.21)
Kurtosis (SE)	5.7 (.32)	1.16 (.45)	1.90 (.43)	1.16 (.45)	.93 (45)	1.74 (.43)	30.3 (.31)	.76 (.45)	1.77 (.43)	1.16 (.45)	.57(.45)	.55 (.43)
Max-Min	1-12	28-49	28-45	26-49	28-49	26-44	0-11	31-50	31-46	31-49	32-49	31-44
IQR	2-4	37-41	35-38	35-39	37-41	34-37	1-2	38-42	36-38	36-40	38-42	35-38

T=Total, M=Males, F=Females, SD=Standard Deviation, SE=Standard error. All values are in centimetres.

It may be noted from the above table that the spread and distribution of the data from both genders is relatively similar but the positions of both landmarks (i.e. CBO and MBO) are located proximally in females when compared to males.

It is noteworthy that there was no significant difference between the diagnoses of BO on insertion (n=228) and extubation (n=230), but when examined according to the type of BO (i.e. SSBO or LSBO) the numbers of diagnosed cases changed. In subgroup analysis there were 108 (47.4%) SSBO cases (2 cm or less) and 120 (52.6%) LSBO cases (> 2 cm) on intubation, whereas on extubation there were 156 SSBO cases and 74 LSBO. This means that there were 48 (20.4%) more cases of SSBO and 46 (42%) fewer cases of LSBO but this is understandable as intubation shortens the oesophagus and contracts the BO segment. In the next section, after concluding the results, the significance of these findings will be discussed.

3.3 SECTION 3

3.3.1 Discussion

Introduction

SALAHADEEN is the only study of its kind which has examined oesophageal landmarks in both phases of endoscopy and has shown that there is a significant difference in the measurements of certain landmarks. The study was therefore able to achieve its main aim and was successful in answering the research question. In terms of clinical impact, this study asks for standardisation of landmark measurements, as not only is HH underdiagnosed if measured in intubation, but also the length of BO may be underestimated.

A slightly different study has also measured landmarks in both phases, but it may be noted that the study did not correlate this with BO and/or HH (Kaplan *et al.*, 2016). In relation to HH SALAHADEEN has implications for day-to-day clinical practice as, if the diagnosis of HH is missed, it will lead to unnecessary referrals of patients for pH manometry, whereas correct diagnosis may lead to advice and counselling about lifestyle measures (Matsunaga *et al.*, 2021) which may help with symptoms of reflux (Murao *et al.*, 2011). Overdiagnosis of HH, on the other hand, may lead to unnecessary prescriptions of medication, restrictions in lifestyle, surgery and associated anxiety for patients (Hopper, 2015; Roman and Kahrilas, 2014). Standardisation of HH measurement will correctly diagnose HH in patients with reflux symptoms.

Our study has shown that, although the diagnosis of BO is not different when measured between intubation and extubation, the length of BO is different in the two phases of endoscopy. Since the premalignant burden of metaplastic tissue (i.e. length of BO) is directly proportional to the development of high grade dysplasia and subsequent oesophageal adenocarcinoma (OAC) (Krishnamoorthi *et al.*, 2018; Rudolph *et al.*, 2000; Anaparthy and Sharma, 2014) it is of the utmost importance to standardise its measurement.

3.3.1.1 Demographics

Although the power (n=259) in SALAHADEEN compares well with the few previous studies examining similar parameters, such as HH and BO (Avidan *et al.*, 2002a; Che *et al.*, 2013; Di Pietro *et al.*, 2015; Anagnostopoulos *et al.*, 2007; Avidan *et al.*, 2002b; Naini *et al.*, 2015b; Cooper *et al.*, 2009), it is accepted that this is a wide subject area and wide variation has been noted in the power of studies examining both BO and HH. Sharma et al., (2006), for example, measured landmarks in 29 patients in order to develop and validate Prague C&M criteria. This, in comparison to our study, is a low powered study, but if one examines the purpose of the study it is evident that the power was sufficient.

In terms of ethnicity profile, SALAHADEEN was a unique multi-ethnic British study and this, in comparison to the majority of previous research, is a distinctive point. Although Ford and colleagues (2005) previously compared BO between the South Asian Population (SAP) and White British Population (WBP) (n=20,310), the method and aims of this study differed from those in SALAHADEEN. Similarly, Gladman et al. (2006) included SAP in their retrospective audit, but the aim of their study was to assess the surveillance efficiency of BO over 17 years. Several other British studies have looked at HH, reflux and BO using both SAP and WBP, but wide variation has been noted in power, methodology and the aims of the researchers (Freeman *et al.*, 2017; Sagar *et al.*, 1995; Mandal, Playford & Wicks, 2003; Rajendra and Ho, 2005; Mohammed et al., 2005; Cooper *et al.*, 2006). Detailed analysis of these studies is not necessary here; it is sufficient to say that SALAHADEEN is the first British study to use a multi-ethnic population in a prospective manner for the assessment of landmarks.

3.3.2 Comparing SALAHADEEN and Kaplan et al., (2016)

Kaplan et al., (2016), a Turkish study, examined 116 patients who underwent diagnostic gastroscopy with the aim of assessing the difference in landmark locations, while comparing readings during intubation and extubation. Although the authors did not explicitly mention if they were using Prague C&M criteria (Sharma *et al.*, 2006) for the measurement of landmarks, they did define the method by which they identified their landmarks in both intubation and extubation.

There are several similarities between the two studies, such as: prospective methodology, defining landmarks, and taking measurements in both phases of endoscopy. This said, there are major differences between the studies. For example, Kaplan et al., (2016) excluded patients with BO and/or reflux symptoms, and since both BO and GORD are related to HH (Andrici *et al.*, 2013; van Herwaarden, Samsom & Smout, 2004), may well have excluded cases of HH. Furthermore, they used consecutive sampling in their study. Both of these points are in sharp contrast to SALAHADEEN, where patients were selected from a general list and BO patients were included. DI, GOJ and SCJ, Kaplan et al., (2016) agreed with SALAHADEEN on the point that DI was located at the same distance on both intubation and withdrawal.

However, they noted that GOJ in extubation (M: 38.62 cm) was more distal when compared to the insertion values (M: 38.21 cm) ($t = 0.048$, $p < 0.05$), and similar results were presented for SCJ or Z line, which also moved distally in extubation. This is in sharp contrast to our study, where GOJ was more proximal on extubation, and no significant difference was noted in the location of SCJ. Next, we will discuss how these differences could be explained.

First and foremost is the population selection. GORD and BO were preferentially excluded in the Turkish study and as explained earlier, this may have excluded HH as well. It is also important to mention that our data was analysed in the context of height of the individuals

as well and the discrepancy in the GOJ position between ethnicities and gender is well explained by the results that females in SALAHADEEN were shorter than males and so were SAP, who were shorted than the WBP counterparts. This said it is previously reported that both males and females in Turkey are shorter as compared to USA and Western Europe (Özer, 2008).

Hence, in comparison to SALAHADEEN, the Turkish study had predominantly competent GOJ and our study had lax GOJs. Lax GOJ has a tendency to move proximally, and this is the main patho-physiological mechanism of HH.

It is noteworthy that the Turkish study described GOJ as the line where the distal oesophagus opened out to become the stomach, whereas SALAHADEEN specifically considered the proximal convergence of the gastric folds as the GOJ. It is evident that the former definition is a vague statement, and open to subjectivity when measurements are done in a patient who might well be anxious, moving and stressed at the end of endoscopy. We also note that they collected extubation data on completely deflated stomachs, whereas our data was collected with 20% deflated stomachs and it is natural to assume that any air in the stomach may move GOJ proximally.

The combined impact of: differences in distribution of the data, population selection, power of the study (2,259 vs 116), gender bias, exclusion of HH, deflation level of stomach, and ambiguity in definition of GOJ may all have affected the movement of GOJ during extubation in the Turkish study. We think that, in terms of design, selection criteria, and data analysis SALAHADEEN has a clear edge over the study by Kaplan and colleagues (2016).

3.4 Hiatus Hernia and SALAHADEEN

The prevalence of HH in our study was 56.1%, which falls with the parameters of previous reports (Weston, 1996) where a highly variable prevalence (10 to 80%) of HH has been suggested. It may be noted that the exact prevalence of HH is not known and is affected by

multiple factors such as: BMI (Che *et al.*, 2013), presence of BO (Cameron, 1999), GORD (Cram and de Caestecker, 2011), gender (Panzuto *et al.*, 2004), smoking (Sontag *et al.*, 1991) and alcohol (Masuda *et al.*, 2018). In our study, the proximal movement of GOJ has a direct impact on the number of HH cases, as we detected 71% HH on extubation; It is thus suggested that all HH should be measured in extubation (using Prague criteria).

Secondly, it is recommended that the stomach should be fully deflated, to avoid any possibility of air moving the GOJ. Gastric distention is known to cause lower oesophageal sphincter relaxation, as shown in a study using manometry (Kahrilas *et al.*, 2000), and (using the EndoFLIP balloon method) it was observed that GOJ in HH has lower pressure and increased distensibility (Lottrup *et al.*, 2016). Thirdly, it should be clearly documented in the endoscopy report if the HH was measured on extubation, and the distention level of the stomach should also be recorded. As a final point, in out study WBP were found to have longer HH and this difference was not explained by the BMI as there was no significant difference between SAP and WBP in terms of BMI. This said, it is also important to note that in high powered published national data WBP is known to have higher BMIs as compared to SAP (Health Survey England, 2022). This means that our power was low for this point and this point may well be explained by the higher BMI of the WBP.

3.4.1 Barrett's Oesophagus and SALAHADEEN

SALAHADEEN was successful in ascertaining the landmarks associated with BO in a prospective manner and was able to compare them in both phases of endoscopic examination in a pre-agreed way. The significant finding that the positions of MBO and CBO moved proximally in females may be explained by the fact that GOJ moved proximally on extubation in females, and since both MBO and CBO are measured in relation to GOJ (Sharma et al., 2006), it is an expected finding.

As explained earlier, in Kaplan et al., (2016) the stomach was completely deflated; in SALAHADEEN it was just close to complete deflation (15-20%). It is possible that the semi distended stomach may have caused the GOJ to move proximally. The other important finding from the study is the change in the length of BO, where LSBO was found to shorten. One explanation is the possible use of IV Midazolam, which may have affected muscle contraction in the oesophagus. IV Midazolam is known to affect smooth muscle contraction in vessels, as evidenced in both animal and human models (Tomita, Matsuura & Ichinohe, 2013; Matsuura, 2017; Molliex *et al.*, 1993; Gelissen *et al.*, 1996).

It is thus possible that segmental oesophageal relaxation might have stretched the oesophagus and increased the MBO. Nonetheless, it is not clear how much this effect is clinically relevant in oesophageal musculature. It may be suggested, as a starting point, that *in vitro* studies be designed to see the effect of Midazolam (used in 96% of the procedures) on oesophageal musculature.

Although it is clear from the results that there was no significance difference in the overall diagnosed cases in both intubation (n=228) and extubation (n=230), 20.4% new cases of SSBO appeared on extubation, with a similar reduction in LSBO. Since segment length is related to cancer progression (Pohl *et al.*, 2016; Rudolph *et al.*, 2000; Gatenby and Soon, 2014;

Behrens *et al.*, 2015; Kuipers and Spaander, 2018) and a surrogate marker for more frequent surveillance (De Looze, 2000; Sonnenberg, Soni & Sampliner, 2002; Kastelein *et al.*, 2015; van Sandick *et al.*, 1998) one may assume that, in the long run, surveillance may be affected if measurements are taken in extubation. It is, therefore suggested that measurement should be taken in intubation.

In summary, SALAHADEEN has demonstrated that there are differences in landmark positions when measured in both phases of endoscopy. Additionally, the length of BO is affected, possibly by oesophageal contraction, but how relevant this is clinically is not clear and needs more research. The relatively distal position of GOJ to incisors in males is explained by the height

In the next section, study limitations will be discussed along with future implications.

3.5 SECTION 4

3.5.1 Study limitations and future implications

SALAHADEEN has opened up a new discussion regarding the standardisation of measurements of oesophageal landmarks. It is also important to note that previous research into the diagnosis, prognosis and treatment of Barrett's oesophagus has not specifically mentioned if the readings were taken in intubation or extubation, although one may assume them to have been in extubation (as it is more convenient to take measurements during this phase), and this was suggested by SALAHADEEN and Kaplan and colleagues (2016).

The first limitation of the study is the specific applicability of the study, as the data had both HH and BO patients. Keeping incisors (the fixed landmark) in view, all other landmarks are relative to each other, and since HH in its most common type (type 1) is the proximal displacement of the stomach into the thoracic cavity, may have affected the measurement.

A more rational design thus, would have been to exclude patients with HH from the study of BO and *vice versa*. However, this does not mean that SALAHADEEN is not clinically relevant, as HH and BO are concomitant pathologies and are frequently found in the same patients (Avidan et al., 2002, Cameron 1999). That said, designing a study which examines BO without HH may well serve as an improvement on the design of SALAHADEEN.

Secondly, although multiple endoscopists (n=4) collected the data, there was no quality assurance for individual endoscopists. This could have been improved by either video recording for later measurements by another independent endoscopist, or the presence of another endoscopist in the room. Thirdly, it could have been agreed that endoscopic biopsies would be taken at the very end of the procedure, to ensure that possible oesophageal contraction as a result of the exposure of sub-mucosal musculature did not affect the position of landmarks. It

may be noted that, as a general principle (although not part of any guidelines), biopsies are taken after measurements are recorded. Fourthly, apart from Kaplan et al., (2016) there is no research with which to compare our study findings.

Fifthly, one type of endoscope could have been used in the whole study for maximal uniformity of modifiable variables. Sixthly, complete social, smoking, alcohol and dietary information could have been obtained for individual patients, as these parameters tend to affect GORD, which in turn may affect both HH and BO and finally, the study should be interpreted in light of the fact that SALAHADEEN was a WBP and female gender biased study. The low percentage of SAP and relative lack of male gender may have been improved by effective recruitment by using leaflets and social media such as including a YouTube® video link explaining the purpose of study, and the benefits for patients and community (Culshaw, 2020). This could be further improved if the link was presented in ethnic languages as well (Muhammad, Reeves & Jeanes, 2019). Finally, height and weight for individual patients could have been charted and incorporated in the statistical analysis as the location of GOJ, and therefore related landmarks may well be affected by individual height and or BMI.

3.5.2 Future implications for research and conclusion

SALAHADEEN has touched upon a new area of knowledge and suggests measurement of oesophageal landmarks in intubation. This has two purposes: firstly, it will increase the sensitivity of HH detection and secondly, will classify BO into SSBO and LSBO in a standardised fashion. Given the tendency for the LSBO to change into SSBO, hence may change surveillance intervals, it is recommended that BO measurements should be done in intubation.

It may be noted that, although SALAHADEEN showed a difference in the number of diagnosed HH cases, it did not change the number of diagnosed BO cases when analysed according to the phase of endoscopy. Keeping this in view, it is suggested that future research should specifically mention the phase of endoscopy in which the measurements are taken. Furthermore, the length of BO should be revisited and (as well as SSBO, LSBO and ultrashort BO) a new term "borderline BO" should be introduced. This is because the length of BO dictates the surveillance interval (Fitzgerald *et al.*, 2014; Shaheen *et al.*, 2016) as it has a direct relationship with progression to HGD or ACO (Pohl *et al.*, 2016; Weston *et al.*, 1997; Aly, 2017).

It is anticipated that prospective research in these four categories may re-classify BO into the categories of non-surveillance, wide and close interval surveillance. This may not only rationalise the ethos of the whole programme, but also offer economic benefits to the health system and individual patients as endoscopy, although safe, is not an entirely risk-free procedure (Cha *et al.*, 2021; Behrens *et al.*, 2019; Attard, Grima & Thomson, 2018).

In conclusion, SALAHADEEN was a prospective study which has met its aim and has demonstrated that oesophageal landmarks change position during both phases of endoscopy and as result of that both HH and BO length may change. However, this was a gender and ethnicity biased study, although to some extent the issue of the ethnicity data may be partly

rectified by combining the BO data of BITES and SALAHADEEN to assess ethnic differences in the length of BO between WBP and SAP; this is presented as the third study (Chapter IV).

4 CHAPTER IV

Study 3: Comparison of segment Length in Columnar lined oesophagus between South Asian and White populations using Prague's criteria, a pilot project (LUMBAEE).

Introduction

Barrett's Oesophagus is a global disease (Marques de Sá *et al.*, 2020) and relatively more prevalent in Whites as compared to other communities (Corley *et al.*, 2009). Parallel rising trends in the incidence of BO (Rajendra, 2011; van Soest *et al.*, 2005; Post, Siersema & Van Dekken, 2007) and ACO (Lagergren, 2005) have been noted worldwide; this is not surprising, as BO is the precursor lesion of ACO (Reid *et al.*, 2010). It is noteworthy that prospective endoscopic and histopathological research in BO is relatively objective and has established a strong propensity for LSBO with HGD to develop into ACO (Pohl *et al.*, 2016; Rastogi *et al.*, 2008; Yousef *et al.*, 2008). Nonetheless, there exist paucity of objective, prospective and translational research comparing SAP and WBP in relation to certain parameter in BO such as length of BO and dysplasia detection.

Such comparison is possible with a degree of objectivity, as the length of the oesophagus is objectively measurable according to the Prague CM criteria (Sharma et al., 2006) which is a reliable and validated method (Vahabzadeh *et al.*, 2012). Nevertheless, there is a lack of research to compare the lengths in both WBP and SAP in a prospective manner; previous research in this area examined this point retrospectively (Ford et al., 2005).

4.1 SECTION 1

4.1.1 Aims and Methodology and Design

Data from the previous two multi-ethnic studies (BITES and SALAHADEEN) generated 403 patients and there were 249 BO patients in both studies combined. These patients could be compared for segment length in term of their ethnicity, as a pilot project. The overarching aim of this project was to compare the location of GOJ in the context of ethnicity. To achieve this aim, all patients with BO in SALAHADEEN and BITES (n=249) were combined. During the data collection for the aforementioned studies, GOJ and lengths of BO had already been measured according to the Prague criteria (Sharma et al., 2006) and this has been explained in the relevant section (Page no 79). The parameters (GOJ and lengths of BO) in this combined data set were then analysed for statistical significance comparing SAP and WBP, and the results of the analysis were interpreted in the light of previous research. The methodology of collection of data may be seen in the previously explained sections (pages no 39-42and 75-76).

4.1.2 Results

4.1.2.1 Demographics

A total of 249 cases of BO were identified using both sets of data, i.e., Landmarks and biopsy data. The ages of the population (n=249) ranged from 18 to 95 years (M = 58.2, SD±17.3, IQR = 25-75) with skewness of -.26 (SE = .15) and kurtosis of -.70 (SE = .30). Comparing the age groups, the most prevalent age group was >70 (n=65, 26.1%), followed by age group >60 but < 70 (n=51, 20.5%), and the least prevalent group was age <20 (n=6, 2.4%). The histogram below shows the ages of the population (**Figure 19)**.

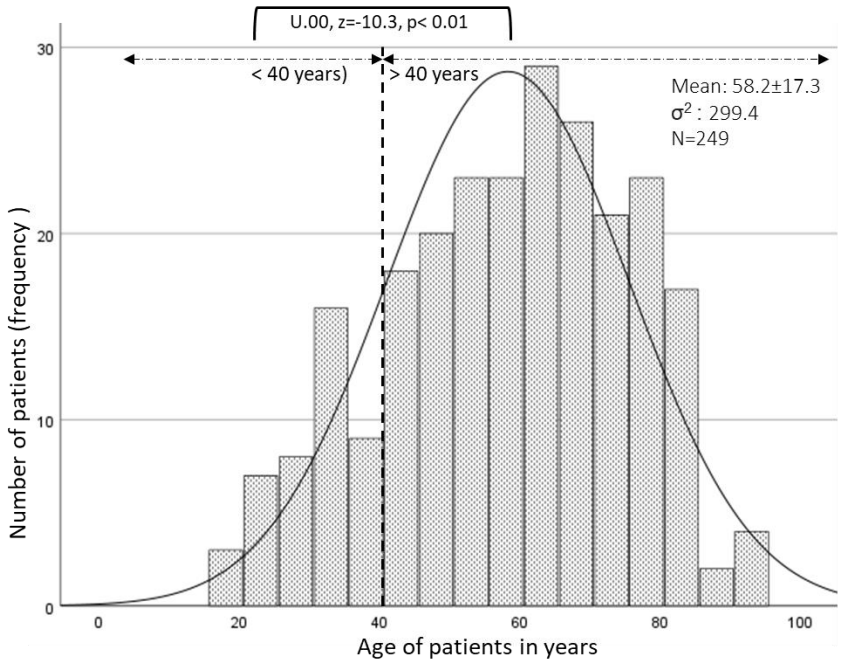

Figure 20: Ages of study population and relationship of increasing age.

It is clear from the histogram above that the cut-off point is 40 years and above, as the majority (78.6%) of the data lies to its right. This means that majority of the patients diagnosed with BO in this dataset were above 40 years and this was significant (U = .00, z = -10.3, p <0.01).

4.1.2.2 Gender of the study population

The numbers of males and females in the study population (n=249) were 117 (47%) and 135 (53%) respectively. Comparing the ages, the males ages ranged from 21 to 95 years (M = 58, SD±17.5) with skewness of -.31 (SE = .22) and kurtosis of -.82 (SE = .44), whereas the female ages ranged from 18 to 93 years (M = 58.4, SD±17.1) with skewness of -.22 (SE = .21) and kurtosis of -.57 (SE = .41). **Figure 20** compares the population based on gender and ethnicity.

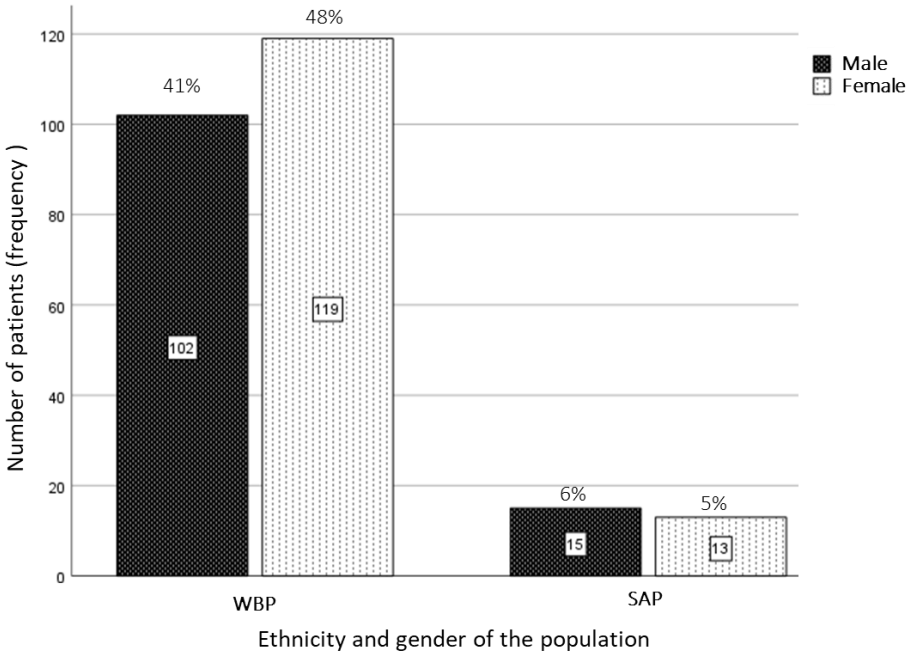

Figure 21: Bar chart comparing WBP and SAP groups in terms of frequency and percentages. It is clear that the population was mainly white British female dominant.

The chart above shows that the population was predominantly WBP, but there were relatively more females in the WBP group as compared to SAP. Age was further compared based on ethnicity and gender and the table below shows the detailed analysis of age and ethnicity (Table 17)

Table 17: Gender and ethnic distribution of the population in relation to age groups in the sample.

Age		Ethnicity		Gender					
				Males			Females		
	N=249	WBP (221)	SAP (28)	Total (117)	WBP (102)	SAP (15)	Total (132)	WBP (119)	SAP (13)
M±SD	58.2±17.3,	59.0 ±17.4	52.1±14	58.0±17.5	58.9±17.8	51.0±14.6	58.4 ±17.1,	59.0±17.3*	52.6±14.6*
Range	18-95	18-95	26-75	21-95	21-95	29-75	18-93	18-93	26-74
IQR	46-72	47-73	43-62	45.4-73	47-75	42-63	47-71.5	47-72	44-63
Age Groups (%)									
< 20	6 (2.4%)	6 (2.7%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0%)	5 (3.8%)	5 (3.8%)	0 (0%)
21-30	17 (6.8%)	12 (4.8%)	5 (2.0%)	13 (11.1%)	10 (8.5%)	3 (2.6%)	4 (3.0%)	2 (1.5%)	2 (1.5%)
31-40	28 (11.2%)	28(11.2%)	0 (0.0%)	13 (11.1%)	13 (11.1%)	0 (0%)	15 (11.4%)	15 (11.4%)	0 (0%)
41-50	41 (16.5%)	32 (12.9%)	9 (3.6%)	15 (12.8%)	9 (7.7%)	6 (5.1%)	26 (19.7%)	23 (17.4%)	3 (2.3%)
51-60	41 (16.5%)	36 (14.5%)	5 (2.0%)	22 (18.8%)	19 (16.2%)	3 (2.6%)	19 (14.4%)	17 (12.9%)	2 (1.5%)
61-70	51 (20.5%)	45 (18.1%)	6 (2.4%)	21 (17.9%)	20 (17.0%)	1 (0.9%)	30 (22.7%)	25 (18.9%)	5 (3.8%)
70+	65 (26.1%)	62 (24.9%)	3 (1.2%)	32 (27.4%)	30 (25.6%)	2 (1.7%)	33 (25.0%)	32 (0.8%)	1 (1.7%)
Total	249 (100%)	221 (88.8%)	28 (11.2%)	117 (100%)	102 (87.2%)	15 (12.8%)	132 (100%)	119 (87.2%)	13 (12.8%)
Total	**249 (100%)**			**117 (47.0%)**			**132 (53.0%)**		

WBP: White British Population, SAP: South Asian Population.

Looking at the above table, it may be noted that the number of cases of BO start increasing after age 40, a trend noted in both genders. In ethnic terms as described earlier, there is a significant difference between the ages of SAP and WBP which means that BO affects younger people in SAP. It is noteworthy that there was a significance difference in ages between ethnicities but not based on genders. The relevant statistical tests are shown in the appendix below (appendix no 3.3A).

4.1.2.3 GOJ and position of circumferential and maximum BO

The position gastro-oesophageal junction (GOJ) was measured in all BO patients (n=249), using the incisors as the reference point, and it ranged from 20 to 37 cm (M = 39.6, SD±2.04, IQR = 38-41, σ^2=8.5) with skewness of .20 (SE = .15) and kurtosis of .13 (SE = .30). The data was not distributed normally in either gender or in WBP (p<0.01), whereas it was normally distributed in SAP (p=.12) and shown in bar chart below (**Figure 21).**

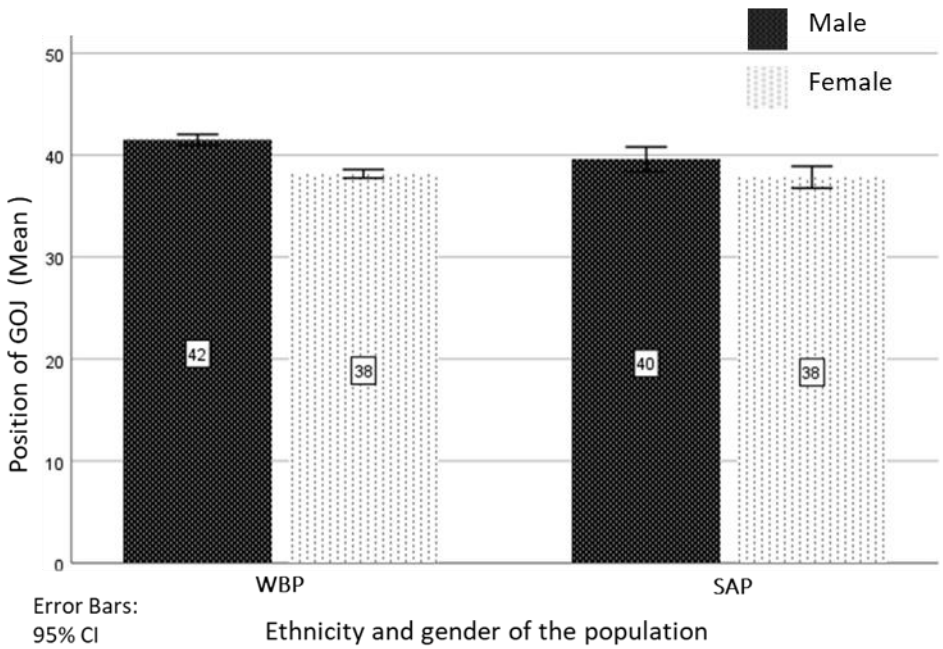

Figure 22: Bar chart comparing GOJ in White British and South Asian populations.

The bar chart evidently shows that GOJ of females and SAPs is located more proximally as compared with rest of the population. With this in mind, the GOJs were compared, and significant differences were observed in gender (Male (Median = 41, n = 117, IQR=40-43) and female (Median = 38, n = 132, IQR=37-40), U = 2856, z = -8.62, p <0.01)). But no such difference was observed in ethnicity (WBP (Median = 40, n = 221, IQR=38-42) and SAP (Median = 39, n = 28, IQR=38-40), U = 2579.5, z = -1.44, p =.15)) (Appendix n 3.3 D and E). This means that GOJ was located proximal in females but at equidistance from incisors when compared between ethnicities. The Position of Circumferential (PCBO), Maximum Barrett's Oesophagus (PMBO) and GOJ are shown in **Table 18.**

Table 18; GOJ, CBO and MBO in relation to ethnicity in the study population

	GOJ			Position of Barrett's Oesophagus					
				PCBO			PMBO		
		WBP (221)	SAP (28)		WBP (220)	SAP (28)		WBP (221)	SAP (28)
M±SD	39.6±2.9	39.7±2.9	38.7±2.1	38.0±3.0	38.1±3.0	37.6±.2.2	37.0 ±3.2	37.0±3.3	36.8±2.3
Median	40	40	30	38	38	38	37	37	37
Mode	38	38	40	38	38	39	37	37	36
Variance	8.5	8.9	4.6	9.0	9.5	5.2	10.4	11.0	5.3
Skewness	.20	.19	-.73	.23	.24	-.58	.07	.08	-.38
SE Skewness	.15	.16	.44	.15	.16	.44	.15	.16	.44
Kurtosis	.13	.01	.12	.24	.16	-.14	.70	.62	-.74
SE Kurtosis	.30	.16	.85	.30	.32	.85	.30	.32	.85
Minimum	33	33	34	31	18	33	26	26	32
Maximum	50	50	38	49	31	41	49	49	40
25th Percentile	38	38	38	36	36	36	37	35	35
75th Percentile	41	42	40	40	40	39	39	39	39

GOJ: Gastro-oesophageal junction, PCBO: Position of Circumferential Barrett's oesophagus, PMBO: Position of Maximum Barrett's oesophagus

Examining the table above, it may be noted that the positions of all landmarks are proximally located in SAP when compared with WBP and, in terms of statistical significance, both CBO and MBO no difference was observed (appendix no 3.3E). This means that both CBO and MBO were located at semi-distance from incisors when compared in terms of ethnicities. Next, we will examine the lengths of CBO and MBO in the ethnic context and will present the relationship with age and gender.

4.1.2.4 Short and long segment BO

Based on the length of segment, BO was divided into short (≥ 1 cm and ≤ 3 cm) and long (≥ 3 cm) segment (Sharma, Morales & Sampliner, 1998). There were 159 (63.9%) cases of SSBO and 90 cases (36.1%) of LSBO in the population (n=249). Figure 22 displays the population in terms of ethnicity and gender, and both segments are compared.

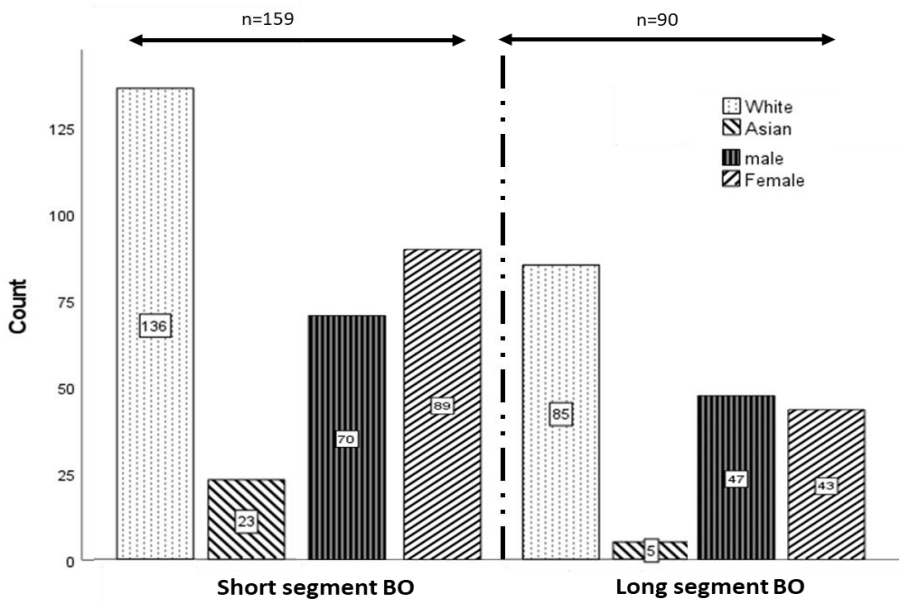

Figure 23: Bar chart comparing LSBO and SSBO as per gender and ethnicity. Please note that short segment BO is more prevalent (n=159) than long segment BO (n=90).

It is evident from the bar chart above that SSBO (n=159, 83.8%) is more prevalent than LSBO (n=90, 36.2%), Furthermore, SSBO was more common in females (n=89, 67%) as

compared to males. The diagnosis of BO was compared in both ethnicities and WBP was diagnosed comparatively more with BO and this was a significant difference: X^2 (1, N = 84) = 4.57, p = .03. This means that WBP has significantly more BO (both SSBO and LSBO) as compared to SAP. In relation to gender, no such difference was observed (p> 0.05) (appendix 3.3F) which means that there was no difference in the diagnosis of BO when analysed according to the gender.

4.1.2.5 Length of segment, CBO and MBO

Both CBO and MBO were derived from the GOJ using Prague CM criteria. The mean lengths of MBO (n=249) ranged from 1 to 11 cm (M = 2.57, SD±1.6, IQR = 2-3) with skewness of 2.16 (SE = .15) and kurtosis of 6.5 (SE = .30). Similarly, the lengths of CBO segment ranged from 0 to 9 cm (M = 1.55, SD±1.1, IQR = 1-2) with skewness of 2.6 (SE = .15) and kurtosis of 11.9 (SE = .30); CBO and MBO were not distributed normally (p<0.01). **Figure 23** below compares MBO in relation to ethnicity and gender below.

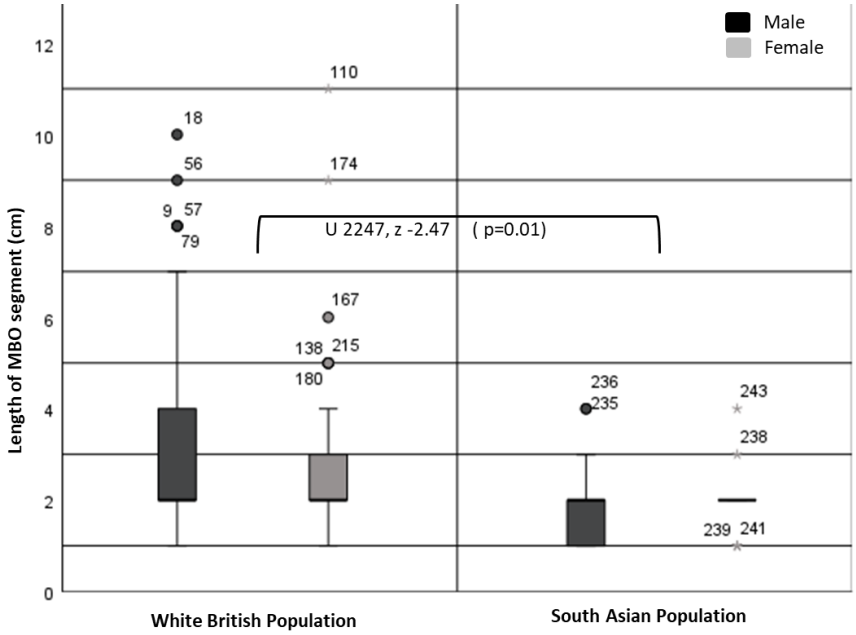

Figure 24: Comparing length of MBO between SAP and WBP.

The box plot diagram above shows lower values for SAP as compared to WBP and this difference is noted from the perspective of gender as well. The detailed comparison of BO segments is displayed in the Table 19.

Table 19: MBO in relation to gender and ethnicity in the study population

MBO		Ethnicity		Gender					
				Males			Females		
	n=249	WBP (221)	SAP (28)	Total (117)	WBP (102)	SAP (15)	Total (132)	WBP (119)	SAP (13)
M±SD	2.5±1.6	2.6±1.6	1.93±0.9	2.7±1.7	2.8±1.8	1.8±1.0	2.4 ±1.4	2.46±1.4	2.0±0.8
Median	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Mode	2.0	2.0	2.0	2.0	2.0	1.0	2.0	2.0	2.0
Variance	2.6	2.7	0.8	3.1	3.3	1.1	2.0	2.1	.66
Skewness	2.1	2.1	1.0	1.7	1.7	1.1	2.6	2.6	1.0
SE Skewness	.15	.16	.44	.22	.23	.58	.21	.22	.61
Kurtosis	6.5	6.0	0.50	3.6	3.2	.32	11.9	11.2	2.2
SE Kurtosis	.30	.32	0.85	.44	.47	1.1	.41	.44	1.1
Minimum	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Maximum	11	11	4.0	10	10	4.0	11	11	4.0
25th Percentile	2.0	2.0	1.0	2.0	2.0	1.0	2.0	2.0	2.0
75th Percentile	3.0	3.0	2.0	3.5	4.0	2.0	3.0	3.0	3.0

Looking at the above table, it may be noted that SAP have shorter MBO as compared to WBP, and this was true for SAP males on sub-group analysis. To assess for significance, both segments were compared and significant differences were observed in both MBO (WBP (Median = 2, n = 221, IQR=2-3) and SAP (Median = 2, n = 28, IQR=1-2), U = 2247, z = -2.4, p =0.01)) and CBO (WBP (Median = 1, n = 219, IQR=1-2) and SAP (Median = 1, n = 28, IQR=1-1), U = 2407, z = -2.0, p <0.01)) (appendix 3.3 E).

In summary, the above examined data shows that it was a female dominant population. The majority (78.6%) of the data represents patients aged 40 and above. Additionally, the data was WBP dominant, with only 28 (11.2%) SAP patients. In addition, the oesophageal lengths of SAP patients, as measured directly from the position of the GOJ, were shorter when compared with the WBP patients. Looking at the data, SSBO was more prevalent than LSBO. Furthermore, both types of BO, i.e., SSBO and LSBO, were more common in females than in males. It is also important to note that SAP has shorter LMBO as compared to WBP.

4.2 SECTION 3

4.2.1 Discussion

LUMBAEE was a prospective endoscopic study which examined the segment length of BO in the multi-ethnic population of Leicestershire, UK. Although several other studies have also examined this question, they were either not specific for the purpose of comparison of BO length (Whiteman and Kendall, 2016; Fass *et al.*, 2001; Coleman *et al.*, 2011; Gatenby and Soon, 2014; Abrams *et al.*, 2008), or they lacked SAP data even if they did have ethnic data (Weston *et al.*, 1997; Aly, 2017; Rajendra, Kutty & Karim, 2004; Chang *et al.*, 2009; Corley *et al.*, 2009). LUMBAEE specifically addressed this issue by having a reasonable power (n=249), prospective methodology, and by measuring the length using Prague CM criteria (Sharma *et al.*, 2006) in a standardised fashion, using a multi-ethnic British population.

LUMBAEE is thus a relatively high-powered study and demonstrated that both segments are more prevalent and are longer in WBP in comparison to SAP. This point, as described later, has implications in terms of progression of BO into OAC and surveillance intervals for BO. In addition, this pilot study demands more prospective research to look for causes of shorter BO in SAP population, by comparing dietary habits, BMI, tobacco and alcohol consumption in both populations.

Two studies reported similar data characteristics as our study. Both of them specifically used multi ethnic data with an SAP population in contrasting manner and may be compared with LUMBAEE in terms of methodology and population demographic characteristics (Ford *et al.*, 2005; Mathew *et al.*, 2011). Ford et al., (2005) examined the endoscopy data bases of two British cities with multi-ethnic populations (n=1,005) and compared the lengths of BO. It was reported that there were 736 patients with LSBO (mean: 6.5 cm), 202 had SSBO, and 67

patients had no length recorded. Both LSBO and SSBO were more common amongst the WBP as compared to the SAP. Although high powered, the study was retrospective and may have been affected by selection bias.

We will first analyse the demographics of the study population and compare it with reported similar studies, and then discuss the strengths of our study in answering the research question objectively. Finally, we will concentrate on a few limitations of the study and discuss if further research is needed and how that should be performed.

4.2.1.1 Demographics differences of LUMBAEE

The mean age in our study (58.2 years) is less than the previously reported ages in several studies (Drewitz, Sampliner & Garewal, 1997; Paraf *et al.*, 1995; Nguyen *et al.*, 2009; Sharma *et al.*, 1998; Gopal *et al.*, 2003; Menke-Pluymers *et al.*, 1992) and this difference deserves some explanation. Looking at the data, the disparity may be explained by the variation of methodologies adapted by the studies and our population. For example, Drewitz et al., (1997) reported a mean age (MA) of 62 for BO, which is 4 years older than our age, but it is worth noting that their age range was 30-85 years and ours was 18-95. Similarly, Gopal et al., (2003) reported MA of 67 years, but their prospective cohort had patients with adenocarcinoma and dysplasia, which is associated with higher MA (in comparison to non-dysplastic BO as in our study (Guardino *et al.*, 2006).

It is interesting to note that two previous Leicestershire based studies examined BO in patients and used the same hospital data base as LUMBAEE (Moayyedi *et al.*, 2008; Macdonald, Wicks & Playford, 2000). Considering their age as benchmark, the MAs in these studies were reported to be 63 and 66.6 years respectively, which is higher than our reported MA. It may be noted that there was a major difference in the method of selection of patients, as Macdonald et al., (2000) only selected longer segment BO (> 3 cm), hence biased by segment type, and the

latter study (which was high powered (n=1737)) retrieved complete records of BO patients but retrospectively. LUMBAEE may be distinguished from these studies based on methodology, as it used the waiting list for endoscopy prospectively (n=249), where patients were consented to be included in the study, and exclusion of non-consenting patients (n=26, gender unknown) might have skewed the results.

There are a few studies where the reported MA is similar to that in LUMBAEE (El-Serag *et al.*, 2016; Laitakari, Laippala & Isolauri, 1995; Hage *et al.*, 2005; Hillman *et al.*, 2004; Di Caro *et al.*, 2016; Masci *et al.*, 2011; Hamade *et al.*, 2019) and among them Hamade et al., (2019) needs attention. The authors in this prospective study (n=1,883) examined a cohort of only SSBO patients and reported a MA of 57.3 years, which is similar to the reported MA in LUMBAEE (58.2 years). It may be noted that, like our population which was predominantly SSBO, the authors only examined SSBO.

It is thus accepted that the age variation in LUMBAEE is explained by the above factors, and since LUMBAEE has used exactly the same multi-ethnic population as two previously reported studies (Moayyedi *et al.*, 2008; Macdonald, Wicks & Playford, 2000) it may be assumed that LUMBAEE was biased based on patient selection and methodology.

4.2.1.2 Comparison of BO segment

In our cohort, there were relatively more SSBO as compared to LSBO (63% vs 36%) and this is in relative agreement with previous two reports (Yamasaki *et al.*, 2019; Shimizu *et al.*, 2018), but in sharp contrast to previous other reports (Hamade *et al.*, 2019; Weston *et al.*, 1997; Clark *et al.*, 1997; Benipal *et al.*, 2001; Zentilin *et al.*, 2002; Öberg *et al.*, 1998; Pohl *et al.*, 2016). However, it may be noted that the reported presence of SSBO and LSBO in a given population depends on certain factors, such as presence of ACO or high-grade dysplasia. This may be observed in the study (n=1,017) by Pohl et al., (2016) who reported more LSBO in their study population where

LSBO as compared with SSBO (56% vs 24% respectively). Looking closely, it is evident that the authors explored the association of ACO retrospectively with segment length. This point is important, as it is the LSBO and not SSBO which is closely associated with ACO (Rudolph *et al.*, 2000) and that is why naturally and proportionately there was comparatively more LSBO in their study population.

In contrast to this, Shimizu and colleagues (2018) reported proportionately more SSBO (LSBO: 21%, SSBO: 79%) in their retrospective study. Here, only those patients where BO could be resected endoscopically were included. This means that patients with un-resectable lesions (i.e. longer segments) were excluded. Keeping this in mind, although LUMBAEE was a prospective study where patients were selected from the general waiting list, it still had more SSBO. One explanation may well be the exclusion criteria, whereby patients who were already enrolled in other departmental studies such as AspECT (Jankowski *et al.*, 2018) may have been selectively excluded. AspECT, in their study, reported relatively higher numbers of LSBO and this may (albeit partly) explain the reported high number of SSBO in our study.

Prior to LUMBAEE, two studies have measured the lengths of Barrett's segments in SAP. Mathew et al., (2011) examined patients with GORD in an Indian population in a prospective manner and compared BO patients (n=71) in their population (n=278) in terms of risk factors including segment length. The study not only lacked WBP, but also lacked other SAP (i.e. Pakistani and Bangladeshi) data altogether, as it was conducted in mainland India. LUMBAEE was a multi-ethnic study which compared Indian as well as other SAP with WBP and came close to the findings of Ford et al., (2005) who examined the data for both SAP and WBP data; the two studies are compared below.

First and foremost, a key difference between Ford et al., (2005) and our study is the methodology adapted by the authors. They retrospectively analysed the OGD records of two

multi-ethnic cities (Bradford and Birmingham), retrieved the reports, captured the data and analysed it; whereas, in LUMBAEE, a GI waiting list was used to prospectively capture the multi-ethnic data from three hospitals in Leicestershire. There are certain characteristics in the SAP data which are different among these geographic area. One such difference is the predominance of Gujarati Indians in Leicester area, whereas in Bradford there is a predominance of Pakistanis. How exactly this may affect the results in LUMBAEE is not clear, but the Indian subcontinent is comprised of a diverse set of different populations (Basu *et al.*, 2003) with different linguistic (Abbi, 2012) and genetic backgrounds (Xing *et al.*, 2010). Nonetheless, SAP was defined as people from the Indian sub-continent in both studies. Furthermore, BO was defined similarly in both studies.

Analysing the data presented, Ford et al., (2005), in their retrospective search, captured 20,412 (F: 10,762; M: 9,650) patients who underwent OGDs, with a mean age of 56 years. The combined number of WBP and SAP BO patients identified from this cohort was 924. When analysed according to segment length, they had 196 (21.3%) SSBO and 728 (78.7%) LSBO, and this is the inverse of our finding. Similarly, the numbers of LSBO and SSBO in their population were 684 and 172 in WBP respectively, compared to 44 and 24 in SAP respectively. It is evident that the study has higher power than LUMBAEE.

With the above demographics in mind, Ford et al., (2005) reported that SSBO was more common in WBP than in SAP, with a univariate odds ratio of 2.78 (95 percent confidence interval (CI): 1.81, 4.47), and our study agrees with their finding. They also reported that patients with LSBO were more likely to be male (OR = 2.51, 95 percent CI: 2.03, 3.12) and LUMBAEE agrees with this.

Although, in racial terms, both SAP and WBP speak Indo-European language suggesting their common origin but they are genetically different and this may explain differences in

disease processes in these population (Chambers *et al.*, 2009; Jordan-Yu *et al.*, 2021; Peeraully and Tan, 2012; Wulan, Westerterp & Plasqui, 2010). In relation to BO and GORD, clear differences have been documented in the reported literature (Abrams, Fields, Lightdale & Neugut, 2008; Rajendra, Kutty & Karim, 2004a; Rajendra and Alahuddin, 2004; Ho, Kang & Seow, 1998; Rosaida and Goh, 2004). Additionally, Ford et al., (2005) suggested that the risk of developing LSBO in WBP was greater when compared with SAP (OR = 6.03, 95 percent CI: 3.56, 10.22).

It is accepted that this area is complex and needs detailed research involving dietary diaries. In the context of LUMBAEE this point is important, as length seems to be significantly different between the two populations at index endoscopy. It is also established that, apart from genetic differences, there also exist dietary differences between the two populations. Therefore, it may be appropriate for a future study to examine differences in the dietary patterns of the two populations, using a prospective cohort, to see if there is a link between diet and the progression of BO to ACO.

4.3 SECTION 4

4.3.1 Limitations and future implications

The findings of this study must be seen in the light of a few limitations. The first is the design of the study. Although LUMBAEE improved on several aspects of the designs used by previous authors, the power of the SAP was relatively low in the final analysis. However, it may be asserted that, a reasonable number of patients was recruited prospectively although this may still have missed patients who are undiagnosed or who do not fall under current surveillance guidelines.

LUMBAEE needs careful interpretation in light of the fact that it was a predominantly female population. This is because there are not only differences in prevalence of BO between the genders, but also the segment length and possibly the progression to ACO (Falk *et al.*, 2005). Additionally, the study lacked associated factor data, such as smoking, which is known to be an associated risk factor (Cook *et al.*, 2012) and the lack of this information may have affected interpretation of the results. Similarly: diet, consumption of alcohol, socioeconomic data, and religious beliefs may well have affected the results.

Finally, H pylori is suggested to reduce the prevalence of BO (Fischbach *et al.*, 2012) and there are racial differences in the prevalence of H Pylori (Huerta-Franco, Banderas & Allsworth, 2018) with particularly high prevalence noted in SAP (Kharel *et al.*, 2020). Since H pylori is more common in SAP than WBP, if gastric urase tests and/or biopsies had been performed, the racial discrepancies might have been explained.

4.4 Summary and Recommendations

LUMBAEE may be treated as a pilot study which analysed a multi-ethnic population from Leicestershire and detected significant differences in the lengths of BO when compared by ethnicity. It is accepted that the study could have been improved by collecting data about

demographic and socioeconomic factors, supplemented by dietary factors. One way to conduct such holistic research would be to undertake a prospective, larger (higher powered) study from BO surveillance groups, collecting data about risk factors (e.g., BMI, smoking, Townsend Index, use of PPI, diet, Hy pylori and religious beliefs), with a follow-up period of at least 5 years. Patients should also be asked to fill in a reflux questionnaire, HRQoL questionnaire, and Townsend index, for complete assessment of symptoms and effect on health related quality of life. We suggest that biopsies should also be collected from the stomach for Urease tests or histopathological analysis.

The data may then be analysed in terms of BO length, progression to dysplasia and ACO, and comparative analysis may be presented in terms of ethnicity. This approach is feasible as surveillance is an ongoing programme with definitive protocols and outcomes for dysplasia and/or neoplasia. Secondly, Leicester has a large cohort of BO patients within a surveillance programme and, being a multi-ethnic city, offers an opportunity to conduct this project. The results of such a study may determine future surveillance intervals for different ethnicities.

5 CHAPTER V

5.1 Conclusion

5.1.1 Scope of the MD

The MD assessed several debatable areas in relation to Barrett's oesophagus, by undertaking a focused but structured literature search, and testing three research questions in clinical studies. These findings were disseminated through three original articles and two review articles, which were published in the Scandinavian Journal of Endoscopy. In this section, a brief overview of the progress made will be given, with special reference to the pre and post MD gaps in knowledge and if the MD has met its aims. Since the first chapter started with reference to a few controversies, a brief overview of the controversies will be presented, and the role of this MD will be examined in the light of previous evidence. Before we discuss the disagreements, it is important to refer to certain agreements in general terms and specifically assert that the MD has not changed any aspect of this area of knowledge in relation to BO. This is because the MD did not aim to visit these areas.

There is no dispute about the metaplastic and premalignant nature of BO (Holmberg *et al.*, 2017; Kang *et al.*, 2018; Lepage *et al.*, 2013; Cook *et al.*, 2018; Rantanen, Oksala & Sand, 2016; Visrodia, Singh, Krishnamoorthi, Ahlquist, Wang, Iyer & Katzka, 2016; Krishnamoorthi *et al.*, 2018; Tan *et al.*, 2020; Gharahkhani *et al.*, 2016). Furthermore, it is also established that the progression to ACO is a stepwise process: starting with metaplastic change, through dysplasia, and finally ending in ACO (Jankowski *et al.*, 2018; Baruah and Buttar, 2015; Wattenberg, 1985; Fitzgerald, 2006; Jankowski *et al.*, 2000; Jankowski *et al.*, 2010; Flejou, 2005) in a genetically predisposed individual (Fitzgerald, 2006; Su *et al.*, 2012).

In relation to surveillance of BO, authors have raised questions about its economics and the health-related quality of life effects of surveillance (Amadi and Gatenby, 2017; Sharma and

Sidorenko, 2005; Armstrong, 2008). However, it remains an accepted norm amongst all major gastroenterology societies (Fitzgerald *et al.*, 2014; Tan, Di Pietro & Fitzgerald, 2017; Shaheen *et al.*, 2016; Whiteman *et al.*, 2015; Fock *et al.*, 2016) and new methods (e.g. biomarkers, cyto-sponge, narrow band imaging) are evolving to accomplish this task (Hajelssedig *et al.*, 2021; Pilonis *et al.*, 2022; Ross-Innes *et al.*, 2017; Konda and Souza, 2018; Di Pietro *et al.*, 2015; Maes, Sharma & Bisschops, 2016; Waterhouse *et al.*, 2018; Tan, Di Pietro & Fitzgerald, 2017; Maitra and Martin, 2020).

The definition of BO remains a controversial point between the BSG and ACG: specifically about the inclusion of IM in the diagnosis of BO (Ghaus *et al.*, 2016; Codipilly *et al.*, 2022; Zhang *et al.*, 2021; Kusano *et al.*, 2022) However, after a consensus exercise by Bennett et al., (2015) the issue seems to be close to resolution, as the majority of BO expertise worldwide supports the stance taken by BSG. Finally, the disagreement between western and Japanese methods about the endoscopic identification of GOJ is difficult to settle, as there is no clear evidence by which either method can assert its superiority (Kusano *et al.*, 2022; Amano et al., 2006) However, the majority of the literature has reported the western method for the assessment of GOJ, and Japanese literature follows the Palisade Vessels (Kurahashi *et al.*, 2020; Emura *et al.*, 2022; Sugano *et al.*, 2022). The clinical implications of one choice over the other are not clear, and more research is needed to assess the diagnostic and prognostic implications.

5.1.2 Reflection on Individual Studies

Study I (BITES) in the MD was able to holistically assess the SBB and DBB biopsy samples, using prospective methodology in a clinical study, to reach a few conclusions (e.g. there is no difference between SBB and DBB when assessed histo-pathologically in terms of size, orientation, crush artefacts, fragmentation and epithelial striping) and meet its main aim. This was in accordance with previous research, as suggested by a detailed recent review (Muhammad *et al.*, 2022).

BITES was also able to comment on the fact that there is a time difference between SBB and DBB (SBB > DBB), and that extraction with a needle does not affect the quality of specimens. The study thus reinforced the message that, wherever possible, specimens should be taken as DBB, especially if large numbers of biopsies are being taken.

Study II (SALAHADEEN) has raised a few questions, especially with its similar methodology but contrasting results to the study by Kaplan et al., (2016). However, assessing both studies with a "fine tooth comb", it is clear that there are subtle but important methodological differences which may have affected the outcome. SALAHADEEN, by deriving the diagnosis of HH from the landmarks in both phases of endoscopy, was able to show that the number of HH cases changes (depending upon the phase), especially around the borderline (2-3 cm length) HH. This has clinical implications in terms of onward referral for oesophageal physiology tests.

SALAHADEEN has also presented the intubation and extubation data of BO and has detected that slight proximal movement of the landmarks may also change the type of BO. This again is in the borderline area (2-3 cm length), but it is important in the sense that length of BO is a significant factor in determining the surveillance interval of BO (Fitzgerald *et al.*, 2014). Nonetheless, it is accepted that this point needs more prospective high-powered clinical research.

Study III (LUMBAEE), based on prospective, objective and well powered methodology, was able to give a clear opinion on the difference of length of Barrett's segments, comparing SAP and WBP. This was an improvement on previous research methodologies, where there were deficiencies in terms of SAP or even WBP data. However, it is accepted that progression to ACO is complex and multifactorial process, it is suggested that more prospective research with long term follow up is done, by inducting patients with BO from both ethnicities.

Being a pilot project, LUMBAEE has improved on the previous research conducted by Ford et al., (2005), but has not conclusively linked this difference with the low prevalence of ACO in SAP. Naturally, to prove such an association multi centre studies recruiting large number of patients with long term follow up will be needed. Such research needs funding and may well include an index endoscopy in patients with GORD. Hence, it is suggested that more research is needed, and this may have direct relevance to the future surveillance intervals of BO in different ethnicities. The MD thus has addressed important areas in the diagnosis and surveillance of BO. The recommendations in the MD need careful examination in view of the limitations and emerging literature.

5.1.3 How could one redesign / improve studies in the MD)

Both studies in this MD could be improved on several aspects including protocol registration, power calculation, selection of patients, sample reporting and recording of data and presentation of data.

I think both studies (BITES and SALAHADEEN) would benefit from pre-registration of study protocol. This is because registration of study protocol offers number of advantages. Firstly, it creates a publicly accessible record of the trial, which promotes openness and accountability and reduces the risk of selective reporting of results, ensuring that all pre-specified outcomes are reported regardless of the findings. It is needless to say that registered trials are more likely to avoid duplication and to publish their results, including negative or null findings, which contributes to a more balanced understanding of the evidence. Additionally, it encourages thorough planning and methodological rigor before the trial begins and improves ethical standards.

In relation to power calculation, from example in BITES, the primary end points such as crush artifacts, orientation, histological size, interpretability etc. could be entered into a

scoring system (0-5, 0 being “not interpretable” and 5 being “completely interpretable”). This means that such a scoring system quantifies these primary endpoints on a standardised scale. Each endpoint would have specific criteria and scores assigned based on their characteristics. This would lead to a more objective level of interpretability and presentation rather than a subjective impression of end point(s).

Expanding on the idea of improving patient selection for both studies one may resort to the general practitioners rather than general endoscopy list. It is understood that primary care is often the first point of contact for patients presenting with symptoms that may warrant further investigation through endoscopy and possible biopsies. This is to say, patients who present with specific symptoms i.e. weight loss, positive coeliac serology, demanding possible biopsies can be identified early, and possibly invited for the study. In addition, the sample bias could be further reduced by asking for funding for the language interpreters to avoid exclusion of certain ethnic / linguistic minorities.

Data recording could also be improved in both studies. Applying this approach, landmark measurement in SALAHADEEN and specimen reporting in BITES may involve having a second endoscopist /additional pathologist independently review the landmarks/ samples to eliminate interobserver bias and validate the results, thereby enhancing objectivity. Thus, by introducing a second reading, discrepancies between pathologists / endoscopist may be identified and resolved, ensuring that the final interpretation of the samples is more accurate and reliable. Consequently, this dual-review system fortifies the integrity of the data, minimises potential biases, and ultimately contributes to the scientific rigor and credibility of the clinical outcomes.

In relation to data collection, one may add that the study protocol should have included funding for measuring body mass index (BMI) on the day of endoscopy and not retrospective

population of data from the health record. This is because BMI, as a concept, is subject to change depending on diet and energy expenditure. Additionally, it will add transparency to the whole process as data will be prospective and not retrospective to possibly fit the research hypothesis. Lastly, presentation could be improved by avoiding too much statistical details and making the result section "slick and crisp" for the readers.

5.1.4 What has been learnt?

The MD has been a learning process including time management, enhancing communication with the university, learning new research skills, learning how to communicate with publishers and learning to presentation data, especially after *viva voce* examination.

The first learning experience in the MD was facing multiple changes in supervision during project. What I learn there is to stay flexible and open to new ideas and perspectives. This is important as each supervisor brings different expertise, insights, and management styles that can enrich the research process. I, thus, was able to develop generic skills in adaptability, effective communication, and motivation to continue despite hurdles. Additionally, I was able to foster a range of professional skills and perspectives that are beneficial for my growth as a researcher and as a clinician.

The second experience was learning from involvement with two studies converging on endoscopic practice. This was an interesting learning experience, exposing me to a wider range of topics and methodologies, expanding my understanding and expertise such as time management and prioritisation. This had aided to broaden my knowledge base, enhanced my methodological and analytical abilities, improved and problem-solving skills. This comprehensive skill set prepares me for a successful research career.

The third learning point is the general principle of data presentation which particularly came to surface during *viva voce* examination. I have learnt the importance of clarity and

relevance in conveying research findings in academic communication. Improving data presentation, for example, involves focusing exclusively on presenting data that directly relates to the research questions or hypotheses, thereby avoiding the inclusion of unrelated information that can obscure the main message.

I have learnt that each data point and statistical test should serve a clear purpose: either supporting or refuting the core arguments of the study. Thus, by selecting only the most pertinent data and employing appropriate statistical tests to validate the findings, I will be able to create more compelling and concise presentations. This approach not only enhances the comprehensibility and impact of the research but also ensures that the interpretation of the data and conclusions drawn by me are objective and robust.

Communication with publisher is the fourth learning point where clarity in condensed information i.e. submission of scientific data for peer review was in question. I learned to appreciate the reviewers' perspective on the importance of clarity and focus on scientific writing. I developed the skill of critically evaluating my work to identify areas of redundancy and irrelevance. This self-evaluation is crucial for maintaining high standards in future research publications.

Connected to this (post *viva voce*) several issues with spellings, sentence structure, presenting data, prioritisation of information in scientific presentation(s), formatting of the research thesis i.e. carefully checking the page numbers and, above all, adding necessary information for example, BMI related data emerged. It is understood that these all are minor but very important learning points. For example, a thorough proof reading and planning of data presentation could have avoided most of these issues.

Overall, this experience improved my ability to present research findings clearly and concisely, taught me the importance of focusing on key points, and enhanced my general

scientific communication skills, that is to say, I learned the importance of balancing the depth of information with brevity.

As a concluding remark, the final two words "*Tamam Shud*" (copied as an image) are added from the book *"Rubayat of Omar Khayyam"* by the English poet and prose writer Edward FitzGerald (1809 –1883), which in English means "The End".

(THE END)

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7 APPENDICES:

7.1 Appendix No 1: Individual Study Related Documents

7.2 Appendix 1.1A: Consent Procedure

University Hospitals of Leicester NHS
NHS Trust

Centre Number: ABC 123

Study Number: XYZ 123

Patient Identification Number for trial: CZ-12-34-5A-ST

CONSENT FORM

Research Study into the comparison between the two methods of taking biopsies (small pieces of human tissue) during endoscopy (tube camera test)

Name of Researcher: Dr Humayun Muhammad

Please initial box

1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from [company name] or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

☐

4. I agree to take part in the above study.

Mr A B C

_____ _____ _____

Name of Patient Date Signature

Dr XYZ

_____ _____ _____

Name of Person taking consent Date Signature

(When different from researcher)

Professor J Jankowski.

_____ _____ _____

Researcher Date Signature

1 for patient; 1 for researcher; 1 with hospital notes

7.3 Appendix 1.1B: Patient Information sheet

University Hospitals of Leicester NHS
NHS Trust

INFORMATION FOR:

Research Study into the comparison between the two methods of taking biopsies (small pieces of human tissue) during endoscopy (tube camera test)

You are being invited to take part in a research study being organised and funded by the University Hospitals of Leicester NHS Trust.

Before you decide if you would like to take part it is important for you to read this information carefully and make sure you understand the purpose of the study and your role in it.

If you would like to talk to someone or you have any other questions please don't hesitate to contact:

Dr Humayun Muhammad

Specialist Registrar

Department of Digestive Diseases

University Hospitals of Leicester

NHS trust Leicester

LE5 4PW

Tel: 07921574021

Why is the study being done?

Biopsies are taken during endoscopy tests for diagnostic reasons. There are two methods of taking biopsies.

In the first method the forceps are introduced into the camera tube (endoscope) each time a biopsy is taken. In the second method two biopsies are taken in one go.

There is some unreliable experience that biopsies collected in the second way might not be as good as in the first method. However there is no scientific proof to back this up.

The aim of the study is to compare the quality of the biopsies taken in these two ways and to determine whether one method provides a more reliable result over the other.

If we do not find any significant difference in the quality of the specimens taken using both methods we can reduce the length of time it takes to complete the test.

Why have I been chosen?

You have been invited to take part in the study because your clinician has referred you for an endoscopy (camera test) to collect biopsies for examination.

Do I have to take part?

No. If you don't take part in the study the way your camera test is carried out and the way the specimens are taken will not change from the standard practice.

If you do decide to take part you will be asked to sign a consent form.

You will still be able to withdraw at any time and without giving a reason. If you do change your mind your decision not to take part will not affect the standard of care you receive.

What do I have to do if I decide to take part?

You won't have to do anything different to what you have already been told will happen in your camera test.

On arrival the study will be explained to you again and you will be asked to sign a consent form.

Your biopsies will be taken using one of the two methods and sent for microscopic examination.

No extra specimens will be collected. Whether you take part in the study or not the number of specimens taken and the length of time it will take will be the same. The pathologist (the doctor who analyses the biopsies) will not know which way the specimens were collected.

There are no restrictions relating to your lifestyle or diet other than what is required for the camera test itself. If you have specific questions about the camera test please contact the department and they will answer any questions you may have.

Sometimes during the course of a research project new information becomes available. If this happens your research doctor will tell you about it and discuss whether you want to continue with the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. They will explain the reasons for this and arrange for your care to continue.

Are there any risks?

There are no risks other than those related to the camera test itself. They should have already been explained to you but if you want to discuss it again please don't hesitate to contact the doctor who referred you for the test.

Both of these biopsy methods are standard ways of taking biopsies during endoscopy. However, as with any camera test, if the specimens collected are poor and cannot be examined you might have to undergo the camera test again.

What are the benefits of taking part?

If we can prove that there is no significant difference between the quality of biopsy specimens collected using the two methods, we can change our practice to using the quicker method and therefore reduce the amount of time the procedure takes.

Will my taking part in this study be kept confidential?

If you decide to take part all information which is collected about you during the study will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

Will the results of the study be published?

The results are likely to be published in a medical journal but the identity of the patients who took part will not be disclosed. We will inform your GP of the outcome of the study and will write to you as well.

Has the study been approved?

The Research and Ethics Committee of the University Hospitals of Leicester has approved and granted permission after consulting the regional committee. All research that involves NHS patients or staff, information from NHS medical records or which uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

7.4 Appendix 1.2

7.5 Appendix 1.2A: Patient Information sheet

PATIENT INFORMATION SHEET

SALAHADEEN Study

(Study Assessing LAndmark Height Alteration During Endoscopic EvaluatioN)

Dear Sir/Madam

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the study?

We are currently conducting a study called the SALAHADEEN study, within the University Hospitals of Leicester NHS Trust, on Landmark Measurements (this is the measuring of the distance of the gastro-oesophageal junction or any lesions from the incisor by using marks on the gastroscope) taken during gastroscopy procedure. As part of the normal procedure, these measurements are usually taken either during insertion or withdrawal of the scope. In our study we will take these measurements on both occasions.

What is the purpose of the study?

We want to establish if there is a difference between these measurements and therefore hope to develop a standardized method in the future.

Version 4.0 12/05/2009

Who has reviewed the study?

The study has been reviewed by educational supervisor, Research & Development department in the UHL NHS Trust, and Leicestershire, Northamptonshire & Rutland Research Ethics Committee.

Why have I been chosen?

You have been chosen because you are aged 18 or over and are due to have a diagnostic gastroscopy within the trust at either the Leicester Royal, Leicester General or Glenfield Hospital. We are inviting over 250 patients to participate.

What will happen to me if I take part?

If you agree to go into the study during your diagnostic gastroscopy you will have your endoscopy as per usual practise then we will take measurements on both insertion and withdrawal of the scope. This should add no more than 1minute to the actual procedure. No tissue sample will be taken for the study

What do I have to do?

You don't have to do anything at the moment. On the day of your procedure the endoscopist will go through the consent for your endoscopy as per usual practise and then will ask you if you're willing to participate in this study, you will be required to sign a separate consent form for this. You will be given opportunity to ask any question or explanation you require.

What are the adverse effects of participating in the study?

There is a potential that there may be a slight increase in discomfort as the procedure may take up to a minute longer than normal.

What are the possible benefits of taking part?

It is only hoped that the measurements will be more accurate and improve treatment.

Will my taking part in this study be kept confidential?

All information collected will be kept strictly confidential.

What will happen to the results of the research study?

Results of the trial are likely to be published in medical journals, used for scientific presentations and may also be forwarded to health authorities worldwide. The confidentiality of all patients will be maintained. You will not be identified in any reports or publications resulting from the study.

The results of the study may be used by the researchers to change standard techniques for the measuring of landmarks.

If after participation in the study you would like to be informed of the overall findings, please leave your contact details and you will be sent a brief summary when available.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign a consent form prior to the procedure. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What if I have more questions or haven't understood something?

On the day of your procedure you can ask the doctors and nurses who are looking after you, before or after that you can get in touch with us via the above contact detail on the first page.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (Telephone No. 0116 204 7864) or contact us via above email . If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Thank you again for considering taking part in this study.

7.6 Appendix 1.2B: Consent Procedure

Version 4.0 12/05/2009

SALAHADEEN STUDY (patient consent form)

Patient Details (address label)

Patient Statement and Signature *To be completed by the patient*

Please initial the boxes below if you agree.

1. I have read and received a copy of the SALAHADEEN study Patient Information Sheet (version 4.0 dated 12/05/09) and I fully understand what is involved in taking part in this trial and have had an opportunity to ask questions, and all of my questions have been answered. ☐

2. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason, without my medical care or legal rights being affected. ☐

3. I understand that I will not be identified in any reports or publications resulting from the study. ☐

4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by the individuals from the research team, from regulatory authorities or from the NHS trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my record. ☐

My signature confirms that I have had an opportunity to ask questions, and all of my questions have been answered. I freely agree to participate in this study. You will be given a signed and dated copy of this consent form to take away with you.

Signature:	_____	Name *(print)*:	_____	Date Signed:	/ /

Investigator Statement and Signature *To be completed by the person taking consent*

I have discussed this clinical research study with the patient and/or his or her authorised representative, using a language that is understandable and appropriate. I believe that I have fully informed the participant of the nature of this study and its possible benefits and risks and I believe the participant understood this explanation.

Signature:	_____	Name *(print)*:	_____	Date Signed:	/ /

7.7 Appendix No 2 Ethical Approvals

7.8 Appendix 2.1 Study 1

7.9 Appendix 2.1A: Patient UHL Approval (BITES)

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH & DEVELOPMENT

Director: **Professor D Rowbotham**
Assistant Director: **John Hampton**
R&D Manager: **Carolyn Burden**

Research & Development Office
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

Direct Dial: (0116) 258 8351
Fax No: (0116) 258 4226

10/02/2009

Professor Janusz Jankowski
Leicester Royal Infirmary
Level 4 Windsor Building
Leicester
LE1 5WW

Dear Professor Janusz Jankowski

Ref: UHL 10629
Title: Randomized blind qualitative comparison of the histological specimens from single and double bitebiopsies taken during routine endoscopic procedure in the endoscopy department of UniversityHospitals of Leicester.
Project Status: Project Approved
End Date: 15/11/2009

I am pleased to confirm that with effect from the date of this letter, the above study now has Trust Research & Development permission to commence at University Hospitals of Leicester NHS Trust.

All documents received by this office have been reviewed and form part of the approval. The documents received and approved are as follows:

Document Name	Version Number	Date
Protocol	2	12.10.08
CF	2	12.10.08
PIS	3	01.12.08
Invitation Letter	3	01.12.08

Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study at this trust.

We are aware that undertaking research in the NHS comes with a range of regulatory responsibilities. Attached to this letter is a reminder of your responsibilities during the course of the research. Please ensure that you and the research team are familiar with and understand the roles and responsibilities both collectively and individually.

You are required to submit an annual progress report to the R&D Office and to the Research Ethics Committee. We will remind you when this is due.

The R&D Office is keen to support research, researchers and to facilitate approval. If you have any questions regarding this or other research you wish to undertake in the Trust, please contact this office.

We wish you every success with your research.

Yours sincerely

Carolyn Burden
R&D Manager

Encs: .Researcher Information Sheet.

7.10 Appendix 2.2

7.11 Appendix 2.2A: Patient IUHL Approval (SALAHADEEN)

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH & DEVELOPMENT

Director: **Professor D Rowbotham**
Assistant Director: **John Hampton**
R&D Manager: **Carolyn Maloney**

Research & Development Office
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

Direct Dial: (0116) 258 8351
Fax No: (0116) 258 4226

29/06/2009

Dr Othman Saraj
University Hospitals of Leicester NHS Trust
Digestive Disease Centre
Leicester Royal Infirmary
Infirmary Square, Leicester
LE1 5WW

Dear Dr Othman Saraj

Ref: UHL 10749
Title: Study Assessing LAndmark Height Alteration During Endoscopic EvaluatioN
Project Status: Project Approved
End Date: 30/09/2009

I am pleased to confirm that with effect from the date of this letter, the above study now has Trust Research & Development permission to commence at University Hospitals of Leicester NHS Trust.

All documents received by this office have been reviewed and form part of the approval. The documents received and approved are as follows:

Document Name	Version Number	Date
Protocol	2.0	02.04.09
Data Collection Sheet	3.0	02.05.09
PIS	4.0	12.05.09
CF	4.0	12.05.09

Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study at this trust.

We are aware that undertaking research in the NHS comes with a range of regulatory responsibilities. Attached to this letter is a reminder of your responsibilities during the course of the research. Please ensure that you and the research team are familiar with and understand the roles and responsibilities both collectively and individually.

You are required to submit an annual progress report to the R&D Office and to the Research Ethics Committee. We will remind you when this is due.

The R&D Office is keen to support research, researchers and to facilitate approval. If you have any questions regarding this or other research you wish to undertake in the Trust, please contact this office.

We wish you every success with your research.

Yours sincerely

Carolyn Maloney
R&D Manager

Encs: .Researcher Information Sheet.

7.12 Appendix 2.3

7.13 2.3A University Ethics approval letter

24 April 2017

Prof Janusz Jankowski / Dr Humayun Muhammad
School of Medicine
University of Central Lancashire

Dear Janusz / Humayun

Re: STEMH Ethics Committee Application
Unique Reference Number: STEMH 622

The STEMH ethics committee has granted approval for anonymised data from NREC studies (Ref UHL 10617 / REC Ref 08/H0402/110 & Ref UHL 10749 / REC Ref 09/H0402/54) to be used in your MD project 'Investigation of Mucosal Landmarks, Health Related Quality of Life and Biopsy Techniques in Barrett's Oesophagus'. Approval is granted up to the end of project date*.

It is your responsibility to ensure that

- the project is carried out in line with the information provided in the forms you have submitted
- you regularly re-consider the ethical issues that may be raised in analysing your data
- any proposed amendments/changes to the project are raised with, and approved, by Committee
- you notify roffice@uclan.ac.uk if the end date changes or the project does not start
- serious adverse events that occur from the project are reported to Committee
- a closure report is submitted to complete the ethics governance procedures (Existing paperwork can be used for this purposes e.g. funder's end of grant report; abstract for student award or NRES final report. If none of these are available use e-Ethics Closure Report Proforma).

Yours sincerely

Dr Ambreen Chohan
Chair
STEMH Ethics Committee

* for research degree students this will be the final lapse date

NB - Ethical approval is contingent on any health and safety checklists having been completed, and necessary approvals as a result of gained.

7.14 Appendix 2.3B: NHS No objection letter for the MD research

RESEARCH & INNOVATION

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH & INNOVATION

Research & Innovation Office
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

Director: **Professor Nigel Brunskill**
Deputy Director: **Dr David Hetmanski**
Head of Research Operations: **Carolyn Maloney**

Direct Dial: (0116) 258 8351
Fax No: (0116) 258 4226

Date: 31st January 2020

Dr Humayun Muhammad
MD research student
University of Central Lancashire
Fylde Rd,
Preston
PR1 2HE

Dear Dr Muhammad,

RE: UHL 10617 REC Ref 08/H0402/110
Randomized blind qualitative comparison of the histological specimens from single and double bite biopsies taken during routine endoscopic procedure in the endoscopy department of University Hospitals of Leicester
CI: Prof J Jankowski

RE: UHL 10749 REC Ref 09/H0402/54
Study Assessing Landmark Height Alteration During Endoscopic EvaluatioN (SALAHADEEN Study)
CI: Dr Othman Saraj Academic Supervisor: Prof J Jankowski

As you are aware from your time here the policy of the Trust is to encourage researchers to publish research findings.

In line with that policy, I can confirm that the Trust has no objection to you to fully utilise the research data generated in the above studies for further analysis, research and dissemination.

If you require any further information or clarification please do not hesitate to contact me.

Kind regards,

Dr David Hetmanski
Deputy Director Research & Innovation

7.15 Appendix No 3: Statistics

7.16 Appendix 3.1 Study 1

7.17 3.1 Aa: Age and ethnicity of population

Descriptive

Ethnicity	Gender				Statistic	Std. Error
White	Male	Age	Mean		59.58	2.317
			95% Confidence Interval for Mean	Lower Bound	54.94	
				Upper Bound	64.22	
			5% Trimmed Mean		59.83	
			Median		62.00	
			Variance		306.070	
			Std. Deviation		17.495	
			Minimum		21	
			Maximum		91	
			Range		70	
			Interquartile Range		29	
			Skewness		-.270	.316
			Kurtosis		-.897	.623
	Female	Age	Mean		53.17	1.960
			95% Confidence Interval for Mean	Lower Bound	49.22	
				Upper Bound	57.11	
			5% Trimmed Mean		53.00	
			Median		52.00	
			Variance		184.482	
			Std. Deviation		13.582	
			Minimum		29	
			Maximum		81	
			Range		52	
			Interquartile Range		19	
			Skewness		.276	.343
			Kurtosis		-.562	.674
Asian	Male	Age	Mean		46.73	3.012
			95% Confidence Interval for Mean	Lower Bound	40.46	
				Upper Bound	52.99	
			5% Trimmed Mean		46.39	
			Median		45.50	
			Variance		199.541	
			Std. Deviation		14.126	
			Minimum		27	

			Maximum	73	
			Range	46	
			Interquartile Range	27	
			Skewness	.145	.491
			Kurtosis	-1.297	.953
	Female	Age	Mean	47.47	2.827
			95% Confidence Interval for Mean — Lower Bound	41.48	
			95% Confidence Interval for Mean — Upper Bound	53.46	
			5% Trimmed Mean	47.97	
			Median	50.00	
			Variance	135.890	
			Std. Deviation	11.657	
			Minimum	20	
			Maximum	66	
			Range	46	
			Interquartile Range	16	
			Skewness	-.827	.550
			Kurtosis	.576	1.063

Tests of Normality

Ethnicity	Gender		Kolmogorov-Smirnov[a] Statistic	df	Sig.	Shapiro-Wilk Statistic	df	Sig.
White	Male	Age	.101	57	.200*	.966	57	.111
	Female	Age	.101	48	.200*	.968	48	.213
Asian	Male	Age	.134	22	.200*	.933	22	.145
	Female	Age	.148	17	.200*	.947	17	.411

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

7.18 3.1 Ab: Gender and Ethnicity

Crosstab

			Ethnicity		
			White	Asian	Total
Age Group drived from SPSS by divifng them intodifferent age groups	Less than 39 years	Count	17	11	28
		% within Age Group drived from SPSS by divifng them intodifferent age groups	60.7%	39.3%	100.0%
		% within Ethnicity	17.0%	31.4%	20.7%
		% of Total	12.6%	8.1%	20.7%
	40 - 48 years	Count	18	6	24
		% within Age Group drived from SPSS by divifng them intodifferent age groups	75.0%	25.0%	100.0%
		% within Ethnicity	18.0%	17.1%	17.8%
		% of Total	13.3%	4.4%	17.8%
	49 - 59 years	Count	19	12	31
		% within Age Group drived from SPSS by divifng them intodifferent age groups	61.3%	38.7%	100.0%
		% within Ethnicity	19.0%	34.3%	23.0%
		% of Total	14.1%	8.9%	23.0%
	60 - 67 years	Count	20	5	25
		% within Age Group drived from SPSS by divifng them intodifferent age groups	80.0%	20.0%	100.0%
		% within Ethnicity	20.0%	14.3%	18.5%
		% of Total	14.8%	3.7%	18.5%
	68+ years	Count	26	1	27
		% within Age Group drived from SPSS by divifng them intodifferent age groups	96.3%	3.7%	100.0%
		% within Ethnicity	26.0%	2.9%	20.0%
		% of Total	19.3%	0.7%	20.0%
Total		Count	100	35	135
		% within Age Group drived from SPSS by divifng them intodifferent age groups	74.1%	25.9%	100.0%
		% within Ethnicity	100.0%	100.0%	100.0%
		% of Total	74.1%	25.9%	100.0%

	% within Age Group drived from SPSS by divifng them intodifferent age groups	74.1%	25.9%	100.0%
	% within Ethnicity	100.0%	100.0%	100.0%
	% of Total	74.1%	25.9%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	12.651[a]	4	.013
Likelihood Ratio	15.048	4	.005
Linear-by-Linear Association	8.266	1	.004
N of Valid Cases	135		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 6.22.

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	.306	.013
	Cramer's V	.306	.013
N of Valid Cases		135	

7.19 3.1 Ac: Gender Distribution Age groups

Crosstab

			Gender		
			Male	Female	Total
Age Group drived from SPSS by divifng them intodifferent age groups	Less than 39 years	Count	13	15	28
		% within Age Group drived from SPSS by divifng them intodifferent age groups	46.4%	53.6%	100.0%
		% within Gender	17.8%	24.2%	20.7%
		% of Total	9.6%	11.1%	20.7%
	40 - 48 years	Count	12	12	24
		% within Age Group drived from SPSS by divifng them intodifferent age groups	50.0%	50.0%	100.0%
		% within Gender	16.4%	19.4%	17.8%
		% of Total	8.9%	8.9%	17.8%
	49 - 59 years	Count	11	20	31
		% within Age Group drived from SPSS by divifng them intodifferent age groups	35.5%	64.5%	100.0%
		% within Gender	15.1%	32.3%	23.0%
		% of Total	8.1%	14.8%	23.0%
	60 - 67 years	Count	15	10	25
		% within Age Group drived from SPSS by divifng them intodifferent age groups	60.0%	40.0%	100.0%
		% within Gender	20.5%	16.1%	18.5%
		% of Total	11.1%	7.4%	18.5%
	68+ years	Count	22	5	27
		% within Age Group drived from SPSS by divifng them intodifferent age groups	81.5%	18.5%	100.0%
		% within Gender	30.1%	8.1%	20.0%
		% of Total	16.3%	3.7%	20.0%
Total		Count	73	62	135
		% within Age Group drived from SPSS by divifng them intodifferent age groups	54.1%	45.9%	100.0%
		% within Gender	100.0%	100.0%	100.0%

% of Total	54.1%	45.9%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	13.654[a]	4	.008
Likelihood Ratio	14.458	4	.006
Linear-by-Linear Association	6.895	1	.009
N of Valid Cases	135		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 11.02.

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	.318	.008
	Cramer's V	.318	.008
N of Valid Cases		135	

7.20 3.1B: t test comparing ages of different ethnicities

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means							
						Significance				95% Confidence Interval of the Difference	
		F	Sig.	t	df	One-Sided p	Two-Sided p	Mean Difference	Std. Error Difference	Lower	Upper
Age	Equal variances assumed	3.218	.075	3.344	142	<.001	.001	9.596	2.870	3.924	15.269
	Equal variances not assumed			3.691	83.933	<.001	<.001	9.596	2.600	4.426	14.767

7.21 3.1C: t test comparing ages of different genders

Group Statistics

	Gender	N	Mean	Std. Deviation	Std. Error Mean
Age	Male	79	56.00	17.524	1.972
	Female	65	51.68	13.260	1.645

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means							
						Significance				95% Confidence Interval of the Difference	
		F	Sig.	t	df	One-Sided p	Two-Sided p	Mean Difference	Std. Error Difference	Lower	Upper
Age	Equal variances assumed	10.369	.002	1.640	142	.052	.103	4.323	2.637	-.889	9.535
	Equal variances not assumed			1.684	141.071	.047	.094	4.323	2.567	-.753	9.399

7.22 3.1D: χ2 test comparing ethnicity and gender

Ethnicity * Gender Crosstabulation

			Gender		
			Male	Female	Total
Ethnicity	White	Count	57	48	105
		% within Ethnicity	54.3%	45.7%	100.0%
		% within Gender	72.2%	73.8%	72.9%
		% of Total	39.6%	33.3%	72.9%
	Asian	Count	22	17	39
		% within Ethnicity	56.4%	43.6%	100.0%
		% within Gender	27.8%	26.2%	27.1%
		% of Total	15.3%	11.8%	27.1%
Total		Count	79	65	144
		% within Ethnicity	54.9%	45.1%	100.0%
		% within Gender	100.0%	100.0%	100.0%
		% of Total	54.9%	45.1%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.052[a]	1	.820		
Continuity Correction[b]	.002	1	.969		
Likelihood Ratio	.052	1	.820		
Fisher's Exact Test				.853	.485
Linear-by-Linear Association	.051	1	.821		
N of Valid Cases	144				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 17.60.

b. Computed only for a 2x2 table

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	-.019	.820
	Cramer's V	.019	.820
N of Valid Cases		144	

7.23 3.1E: χ2 test comparing ethnicity and gender with procedure type

Crosstab

			Gender		
			Male	Female	Total
Procedure type i.e. upper Gi endoscopy or lower Gi endoscopy	Upper GI	Count	35	33	68
		% within Procedure type i.e. upper Gi endoscopy or lower Gi endoscopy	51.5%	48.5%	100.0%
		% within Gender	44.3%	50.8%	47.2%
		% of Total	24.3%	22.9%	47.2%
	Lower GI	Count	44	32	76
		% within Procedure type i.e. upper Gi endoscopy or lower Gi endoscopy	57.9%	42.1%	100.0%
		% within Gender	55.7%	49.2%	52.8%
		% of Total	30.6%	22.2%	52.8%
Total		Count	79	65	144
		% within Procedure type i.e. upper Gi endoscopy or lower Gi endoscopy	54.9%	45.1%	100.0%
		% within Gender	100.0%	100.0%	100.0%
		% of Total	54.9%	45.1%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.598[a]	1	.439		
Continuity Correction[b]	.367	1	.545		
Likelihood Ratio	.598	1	.439		
Fisher's Exact Test				.503	.272
Linear-by-Linear Association	.594	1	.441		
N of Valid Cases	144				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 30.69.

b. Computed only for a 2x2 table

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	-.064	.439
	Cramer's V	.064	.439
N of Valid Cases		144	

Crosstab

			Ethnicity		
			White	Asian	Total
Procedure type i.e. upper Gi endoscopy or lower Gi endoscopy	Upper GI	Count	51	17	68
		% within Procedure type i.e. upper Gi endoscopy or lower Gi endoscopy	75.0%	25.0%	100.0%
		% within Ethnicity	48.6%	43.6%	47.2%
		% of Total	35.4%	11.8%	47.2%
	Lower GI	Count	54	22	76
		% within Procedure type i.e. upper Gi endoscopy or lower Gi endoscopy	71.1%	28.9%	100.0%
		% within Ethnicity	51.4%	56.4%	52.8%
		% of Total	37.5%	15.3%	52.8%
Total		Count	105	39	144

	% within Procedure type i.e. upper Gi endoscopy or lower Gi endoscopy	72.9%	27.1%	100.0%
	% within Ethnicity	100.0%	100.0%	100.0%
	% of Total	72.9%	27.1%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.283[a]	1	.595		
Continuity Correction[b]	.119	1	.731		
Likelihood Ratio	.284	1	.594		
Fisher's Exact Test				.708	.366
Linear-by-Linear Association	.281	1	.596		
N of Valid Cases	144				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 18.42.
b. Computed only for a 2x2 table

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	.044	.595
	Cramer's V	.044	.595
N of Valid Cases		144	

7.24 3.1F: Independent sample t test by age and procedure

Group Statistics

	Procedure type i.e. upper Gi endoscopy or lower Gi endoscopy	N	Mean	Std. Deviation	Std. Error Mean
Age	Upper GI	68	55.94	16.113	1.954
	Lower GI	76	52.36	15.498	1.778

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means							
						Significance				95% Confidence Interval of the Difference	
		F	Sig.	t	df	One-Sided p	Two-Sided p	Mean Difference	Std. Error Difference	Lower	Upper
Age	Equal variances assumed	.168	.682	1.360	142	.088	.176	3.586	2.636	-1.625	8.797
	Equal variances not assumed			1.357	138.840	.088	.177	3.586	2.642	-1.637	8.809

Independent Samples Effect Sizes

		Standardizer[a]	Point Estimate	95% Confidence Interval	
				Lower	Upper
Age	Cohen's d	15.791	.227	-.102	.555
	Hedges' correction	15.875	.226	-.101	.552
	Glass's delta	15.498	.231	-.099	.560

a. The denominator used in estimating the effect sizes.
Cohen's d uses the pooled standard deviation.
Hedges' correction uses the pooled standard deviation, plus a correction factor.
Glass's delta uses the sample standard deviation of the control group.

7.25 3.1G: MWU test comparing n of biopsies with procedure type

Ranks

	Procedure type i.e. upper Gi endoscopy or lower Gi endoscopy	N	Mean Rank	Sum of Ranks
Total number of biopsies taken	Upper GI	68	59.69	4059.00
	Lower GI	76	83.96	6381.00
	Total	144		

Test Statistics[a]

	Total number of biopsies taken
Mann-Whitney U	1713.000
Wilcoxon W	4059.000
Z	-3.545
Asymp. Sig. (2-tailed)	<.001

a. Grouping Variable: Procedure type i.e. upper Gi endoscopy or lower Gi endoscopy

7.26 3.1H: χ2 test comparing biopsy method with ethnicity and gender

Crosstab

			Gender		
			Male	Female	Total
Bite for biopsy (Biopsy techniques) was it single or double bite	Single bite	Count	39	33	72
		% within Bite for biopsy (Biopsy techniques) was it single or double bite	54.2%	45.8%	100.0%
		% within Gender	49.4%	50.8%	50.0%
		% of Total	27.1%	22.9%	50.0%
	Double bite	Count	40	32	72
		% within Bite for biopsy (Biopsy techniques) was it single or double bite	55.6%	44.4%	100.0%
		% within Gender	50.6%	49.2%	50.0%
		% of Total	27.8%	22.2%	50.0%
Total		Count	79	65	144
		% within Bite for biopsy (Biopsy techniques) was it single or double bite	54.9%	45.1%	100.0%
		% within Gender	100.0%	100.0%	100.0%
		% of Total	54.9%	45.1%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.028[a]	1	.867		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.028	1	.867		
Fisher's Exact Test				1.000	.500
Linear-by-Linear Association	.028	1	.867		

N of Valid Cases	144				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 32.50.
b. Computed only for a 2x2 table

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	-.014	.867
	Cramer's V	.014	.867
N of Valid Cases		144	

Crosstab

			Ethnicity		
			White	Asian	Total
Bite for biopsy (Biopsy techniques) was it single or double bite	Single bite	Count	57	15	72
		% within Bite for biopsy (Biopsy techniques) was it single or double bite	79.2%	20.8%	100.0%
		% within Ethnicity	54.3%	38.5%	50.0%
		% of Total	39.6%	10.4%	50.0%
	Double bite	Count	48	24	72
		% within Bite for biopsy (Biopsy techniques) was it single or double bite	66.7%	33.3%	100.0%
		% within Ethnicity	45.7%	61.5%	50.0%
		% of Total	33.3%	16.7%	50.0%
Total		Count	105	39	144
		% within Bite for biopsy (Biopsy techniques) was it single or double bite	72.9%	27.1%	100.0%
		% within Ethnicity	100.0%	100.0%	100.0%
		% of Total	72.9%	27.1%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.848[a]	1	.091		
Continuity Correction[b]	2.251	1	.134		
Likelihood Ratio	2.868	1	.090		
Fisher's Exact Test				.133	.067
Linear-by-Linear Association	2.829	1	.093		
N of Valid Cases	144				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 19.50.
b. Computed only for a 2x2 table

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	.141	.091
	Cramer's V	.141	.091
N of Valid Cases		144	

7.273.1 I: Independent sample t test by age and number of biopsies

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means	
		F	Sig.	t	df
Age	Equal variances assumed	.028	.867	.920	142
	Equal variances not assumed			.920	141.972

Independent Samples Test

		t-test for Equality of Means			
		Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower
Age	Equal variances assumed	.359	2.431	2.641	-2.790
	Equal variances not assumed	.359	2.431	2.641	-2.790

Procedure type i.e. upper Gi endoscopy or lower Gi endoscopy			Levene's Test for Equality of Variances		t-test for Equality of Means							
							Significance				95% Confidence Interval of the Difference	
			F	Sig.	t	df	One-Sided p	Two-Sided p	Mean Difference	Std. Error Difference	Lower	Upper
Upper GI	Age	Equal variances assumed	3.671	.060	1.810	66	.037	.075	6.985	3.858	-.718	14.689
		Equal variances not assumed			1.771	56.134	.041	.082	6.985	3.944	-.915	14.886
Lower GI	Age	Equal variances assumed	1.946	.167	-.289	74	.387	.774	-1.036	3.589	-8.187	6.114
		Equal variances not assumed			-.283	63.321	.389	.778	-1.036	3.663	-8.355	6.283

7.28 3.1J: MWU test comparing biopsy method with Time (T) and (t)

Ranks

	Bite for biopsy (Biopsy techniques) was it single or double bite	N	Mean Rank	Sum of Ranks
Time taken in seconds from first to final Bx is taken	Single bite	28	43.25	1211.00
	Double bite	31	18.03	559.00
	Total	59		
total time taken divided by biopsy, dervide from division by total time /number of biopsies	Single bite	28	44.39	1243.00
	Double bite	31	17.00	527.00
	Total	59		

Test Statistics[a]

	Time taken in seconds from first to final Bx is taken	total time taken divided by biopsy, dervide from division by total time /number of biopsies
Mann-Whitney U	63.000	31.000
Wilcoxon W	559.000	527.000
Z	-5.632	-6.120
Asymp. Sig. (2-tailed)	<.001	<.001

a. Grouping Variable: Bite for biopsy (Biopsy techniques) was it single or double bite

7.29 3.1K: MWU Time in relation to oesophagus and duodenum biopsies

Test Statistics[a]

Oesophagus Site from which Bx were taken YN?		total time taken divided by biopsy, dervide from division by total time /number of biopsies
	Mann-Whitney U	5.000
	Wilcoxon W	83.000
	Z	-3.755
	Asymp. Sig. (2-tailed)	<.001
	Exact Sig. [2*(1-tailed Sig.)]	<.001[b]

a. Grouping Variable: Bite for biopsy (Biopsy techniques) was it single or double bite
b. Not corrected for ties.

Test Statistics[a]

Duodenum Site from which Bx were taken YN?		total time taken divided by biopsy, dervide from division by total time /number of biopsies
Yes	Mann-Whitney U	15.000
	Wilcoxon W	268.000
	Z	-5.165
	Asymp. Sig. (2-tailed)	<.001

a. Grouping Variable: Bite for biopsy (Biopsy techniques) was it single or double bite
b. Not corrected for ties.

7.30 3.1L: MWU Time in relation to biopsy size and technique

Ranks

	Bite for biopsy (Biopsy techniques) was it single or double bite	N	Mean Rank	Sum of Ranks
Specimen size from histology report	Single bite	72	69.40	4996.50
	Double bite	72	75.60	5443.50
	Total	144		

Test Statistics[a]

	Specimen size from histology report
Mann-Whitney U	2368.500
Wilcoxon W	4996.500
Z	-.990
Asymp. Sig. (2-tailed)	.322

a. Grouping Variable: Bite for biopsy (Biopsy techniques) was it single or double bite

7.31 Appendix 3.2 Study 2

7.32 Appendix 3.2 A: Patients' demographics

7.33 Appendix 3.2 Aa:

Statistics

Age

N	Valid	259
	Missing	0
Mean		58.93
Std. Error of Mean		1.070
Median		61.00
Mode		61[a]
Std. Deviation		17.222
Variance		296.595
Skewness		-.306
Std. Error of Skewness		.151
Kurtosis		-.685
Std. Error of Kurtosis		.302
Minimum		18
Maximum		95
Sum		15262
Percentiles	25	47.00
	50	61.00
	75	73.00

a. Multiple modes exist. The smallest value is shown

Gender * Ethnicty Crosstabulation

			Ethnicty		
			White	Asian	Total
Gender	male	Count	104	17	121
		% of Total	40.2%	6.6%	46.7%
	Female	Count	124	14	138
		% of Total	47.9%	5.4%	53.3%
Total		Count	228	31	259
		% of Total	88.0%	12.0%	100.0%

Appendix 3.2 Ab:

Crosstab

			Ethnicty		
			White	Asian	Total
age groups	< 20	Count	3	0	3
		% of Total	1.2%	0.0%	1.2%
	21 to 30	Count	9	5	14
		% of Total	3.5%	1.9%	5.4%
	31 to 40	Count	23	3	26
		% of Total	8.9%	1.2%	10.0%
	41 to 50	Count	31	7	38
		% of Total	12.0%	2.7%	14.7%
	51 to 60	Count	41	6	47
		% of Total	15.8%	2.3%	18.1%
	60 to 70	Count	51	7	58
		% of Total	19.7%	2.7%	22.4%
	> 70	Count	70	3	73
		% of Total	27.0%	1.2%	28.2%
Total		Count	228	31	259
		% of Total	88.0%	12.0%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	13.714[a]	6	.033
Likelihood Ratio	12.947	6	.044
Linear-by-Linear Association	7.133	1	.008
N of Valid Cases	259		

a. 5 cells (35.7%) have expected count less than 5. The minimum expected count is .36.

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	.230	.033
	Cramer's V	.230	.033
N of Valid Cases		259	

7.34 Appendix 3.2 Ac:

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles 25th	50th (Median)	75th
Insertion for OGJ	259	40.04	2.895	32	50	38.00	40.00	42.00
Extubation for OGJ	258	39.68	2.960	30	50	38.00	40.00	42.00

Ranks

		N	Mean Rank	Sum of Ranks
Extubation for OGJ - Insertion for OGJ	Negative Ranks	112[a]	90.66	10154.00
	Positive Ranks	62[b]	81.79	5071.00
	Ties	84[c]		
	Total	258		

a. Extubation for OGJ < Insertion for OGJ

b. Extubation for OGJ > Insertion for OGJ

c. Extubation for OGJ = Insertion for OGJ

Test Statistics[a]

	Extubation for OGJ - Insertion for OGJ
Z	-3.917[b]
Asymp. Sig. (2-tailed)	.000

a. Wilcoxon Signed Ranks Test

b. Based on positive ranks.

Frequencies

		N
Extubation for OGJ - Insertion for OGJ	Negative Differences[a]	112
	Positive Differences[b]	62

	Ties[c]	84
	Total	258

a. Extubation for OGJ < Insertion for OGJ
b. Extubation for OGJ > Insertion for OGJ
c. Extubation for OGJ = Insertion for OGJ

Test Statistics[a]

	Extubation for OGJ - Insertion for OGJ
Z	-3.715
Asymp. Sig. (2-tailed)	.000

a. Sign Test

7.35 Appendix 3.2 Ad:

Ranks

	Gender	N	Mean Rank	Sum of Ranks
Insertion for OGJ	male	121	168.33	20368.50
	Female	138	96.39	13301.50
	Total	259		

Test Statistics[a]

	Insertion for OGJ
Mann-Whitney U	3710.500
Wilcoxon W	13301.500
Z	-7.777
Asymp. Sig. (2-tailed)	.000

a. Grouping Variable: Gender

7.36 Appendix 3.2Ba: Comparison of gender in relation to Maximum BO

Statistics

Gender			Insertion Maximum BO	Ex Maximum BO
male	N	Valid	112	112
		Missing	9	9
	Mean		38.92	38.94
	Std. Error of Mean		.321	.303
	Median		39.00	39.00
	Mode		37	40
	Std. Deviation		3.394	3.206
	Variance		11.516	10.275
	Skewness		-.054	-.245
	Std. Error of Skewness		.228	.228
	Kurtosis		1.166	.939
	Std. Error of Kurtosis		.453	.453
	Range		21	21
	Minimum		28	28
	Maximum		49	49
	Sum		4359	4361
	Percentiles	25	37.00	37.00
		50	39.00	39.00
		75	41.00	41.00
Female	N	Valid	125	125
		Missing	13	13
	Mean		36.19	35.87
	Std. Error of Mean		.238	.239
	Median		36.00	36.00
	Mode		36	37
	Std. Deviation		2.666	2.676
	Variance		7.108	7.161
	Skewness		.102	-.153
	Std. Error of Skewness		.217	.217
	Kurtosis		1.901	1.746
	Std. Error of Kurtosis		.430	.430
	Range		17	18
	Minimum		28	26
	Maximum		45	44

Sum		4524	4484
Percentiles	25	35.00	34.00
	50	36.00	36.00
	75	38.00	37.00

7.37 Appendix 3.2Bb: Comparing gender and MBO

Ranks

Gender			N	Mean Rank	Sum of Ranks
male	Ex Maximum BO - Insertion Maximum BO	Negative Ranks	32[a]	37.50	1200.00
		Positive Ranks	38[b]	33.82	1285.00
		Ties	42[c]		
		Total	112		
Female	Ex Maximum BO - Insertion Maximum BO	Negative Ranks	53[a]	44.75	2372.00
		Positive Ranks	32[b]	40.09	1283.00
		Ties	40[c]		
		Total	125		

a. Ex Maximum BO < Insertion Maximum BO
b. Ex Maximum BO > Insertion Maximum BO
c. Ex Maximum BO = Insertion Maximum BO

Test Statistics[a]

Gender		Ex Maximum BO - Insertion Maximum BO
male	Z	-.256[b]
	Asymp. Sig. (2-tailed)	.798
Female	Z	-2.483[c]
	Asymp. Sig. (2-tailed)	.013

a. Wilcoxon Signed Ranks Test
b. Based on negative ranks.
c. Based on positive ranks.

Frequencies

Gender			N
male	Ex Maximum BO - Insertion Maximum BO	Negative Differences[a]	32
		Positive Differences[b]	38
		Ties[c]	42
		Total	112
Female	Ex Maximum BO - Insertion Maximum BO	Negative Differences[a]	53
		Positive Differences[b]	32
		Ties[c]	40
		Total	125

a. Ex Maximum BO < Insertion Maximum BO

b. Ex Maximum BO > Insertion Maximum BO

c. Ex Maximum BO = Insertion Maximum BO

Test Statistics[a]

Gender		Ex Maximum BO - Insertion Maximum BO
male	Z	-.598
	Asymp. Sig. (2-tailed)	.550
Female	Z	-2.169
	Asymp. Sig. (2-tailed)	.030

a. Sign Test

7.38 Appendix 3.2Bc: Comparing gender and CBO length

Ranks

		N	Mean Rank	Sum of Ranks
Length of circumfrential Barrett's oesophagus extubation - Length circumfrential Barrett's oesophagus insertion	Negative Ranks	60[a]	50.30	3018.00
	Positive Ranks	41[b]	52.02	2133.00
	Ties	125[c]		
	Total	226		

a. Length of circumfrential Barrett's oesophagus extubation < Length circumfrential Barrett's oesophagus insertion

b. Length of circumferential Barrett's oesophagus extubation > Length circumferential Barrett's oesophagus insertion
c. Length of circumferential Barrett's oesophagus extubation = Length circumferential Barrett's oesophagus insertion

Test Statistics[a]

	Length of circumferential Barrett's oesophagus extubation - Length circumferential Barrett's oesophagus insertion
Z	-1.601[b]
Asymp. Sig. (2-tailed)	.109

a. Wilcoxon Signed Ranks Test
b. Based on positive ranks.

Ranks

Gender			N	Mean Rank	Sum of Ranks
male	Length of circumferential Barrett's oesophagus extubation - Length circumferential Barrett's oesophagus insertion	Negative Ranks	28[a]	25.46	713.00
		Positive Ranks	25[b]	28.72	718.00
		Ties	51[c]		
		Total	104		
Female	Length of circumferential Barrett's oesophagus extubation - Length circumferential Barrett's oesophagus insertion	Negative Ranks	32[a]	25.25	808.00
		Positive Ranks	16[b]	23.00	368.00
		Ties	74[c]		
		Total	122		

a. Length of circumferential Barrett's oesophagus extubation < Length circumferential Barrett's oesophagus insertion

b. Length of circumferential Barrett's oesophagus extubation > Length circumferential Barrett's oesophagus insertion
c. Length of circumferential Barrett's oesophagus extubation = Length circumferential Barrett's oesophagus insertion

Test Statistics[a]

Gender		Length of circumfrential Barrett's oesophagus extubation - Length circumferential Barrett's oesophagus insertion
male	Z	-.024[b]
	Asymp. Sig. (2-tailed)	.981
Female	Z	-2.421[c]
	Asymp. Sig. (2-tailed)	.015

a. Wilcoxon Signed Ranks Test
b. Based on negative ranks.
c. Based on positive ranks.

7.39 Appendix 3.2Ca: Comparing ethnicity and hiatus hernia

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Length of hiatus hernia on extubation	175	1.48	.877	1	6
Ethnicity	259	1.12	.325	1	2

Ranks

	Ethnicity	N	Mean Rank	Sum of Ranks
Length of hiatus hernia on extubation	White	155	90.98	14102.50
	Asian	20	64.88	1297.50
	Total	175		

	Length of hiatus hernia on extubation
Mann-Whitney U	1087.500
Wilcoxon W	1297.500
Z	-2.667
Asymp. Sig. (2-tailed)	.008

a. Grouping Variable: Ethnicity

7.40 Appendix 3.2Cb: Comparing type of HH on phases of endoscopy

Ranks

Type of HH on exunation			N	Mean Rank	Sum of Ranks
< 3 cm	Lenght of hiatus hernia on extubation - Lenght of hiatus hernia on intubation	Negative Ranks	15[a]	19.33	290.00
		Positive Ranks	20[b]	17.00	340.00
		Ties	77[c]		
		Total	112		
> 3 cm	Lenght of hiatus hernia on extubation - Lenght of hiatus hernia on intubation	Negative Ranks	3[a]	9.83	29.50
		Positive Ranks	14[b]	8.82	123.50
		Ties	3[c]		
		Total	20		

a. Lenght of hiatus hernia on extubation < Lenght of hiatus hernia on intubation
b. Lenght of hiatus hernia on extubation > Lenght of hiatus hernia on intubation
c. Lenght of hiatus hernia on extubation = Lenght of hiatus hernia on intubation

Test Statistics[a]

Type of HH on exunation		Lenght of hiatus hernia on extubation - Lenght of hiatus hernia on intubation
< 3 cm	Z	-.458[b]
	Asymp. Sig. (2-tailed)	.647
> 3 cm	Z	-2.279[b]
	Asymp. Sig. (2-tailed)	.023

a. Wilcoxon Signed Ranks Test
b. Based on negative ranks.

7.41 Appendix 3.3 Study 3

7.42 Appendix 3.3A Endoscopic variables as per gender

Statistics[a]

		Age	Extubation for OGJ	Extubation for circumferential BO	Ex Maximum BO	Length of Maximum Barrett's oesophagus extubation	Length of circumferential Barrett's oesophagus extubation
N	Valid	117	117	117	117	117	117
	Missing	0	0	0	0	0	0
Mean		58.04	41.26	39.62	38.52	2.74	1.65
Std. Error of Mean		1.621	.250	.272	.298	.165	.121
Median		60.00	41.00	40.00	39.00	2.00	1.00
Mode		52[b]	41	40	40	2	1
Std. Deviation		17.537	2.705	2.947	3.229	1.787	1.309
Variance		307.541	7.317	8.687	10.424	3.192	1.712
Skewness		-.311	.001	-.026	-.137	1.779	2.861
Std. Error of Skewness		.224	.224	.224	.224	.224	.224
Kurtosis		-.824	.448	.413	.728	3.679	12.146
Std. Error of Kurtosis		.444	.444	.444	.444	.444	.444
Range		74	16	17	21	9	9
Minimum		21	34	32	28	1	0
Maximum		95	50	49	49	10	9
Sum		6791	4828	4635	4507	321	193
Percentiles	25	45.50	40.00	38.00	37.00	2.00	1.00
	50	60.00	41.00	40.00	39.00	2.00	1.00
	75	73.00	43.00	42.00	40.00	3.50	2.00

a. Gender = male

b. Multiple modes exist. The smallest value is shown

Statistics[a]

		Age	Extubation for OGJ	Extubaion for circumfrentioa l BO	Ex Maximum BO	Length of Maximum Barrett's oesophagus extubation	Length of circumfrential Barrett's oesophagus extubation
N	Valid	132	132	131	132	132	130
	Missing	0	0	1	0	0	2
Mean		58.41	38.14	36.69	35.73	2.42	1.46
Std. Error of Mean		1.493	.197	.204	.227	.125	.080
Median		60.00	38.00	37.00	36.00	2.00	1.00
Mode		41[b]	38	37	37	2	1
Std. Deviation		17.159	2.259	2.337	2.607	1.431	.908
Variance		294.427	5.101	5.460	6.795	2.046	.824
Skewness		-.223	-.085	-.109	-.339	2.680	1.537
Std. Error of Skewness		.211	.211	.212	.211	.211	.212
Kurtosis		-.579	.162	.240	1.354	11.930	2.366
Std. Error of Kurtosis		.419	.419	.420	.419	.419	.422
Range		75	12	13	18	10	5
Minimum		18	33	31	26	1	0
Maximum		93	45	44	44	11	5
Sum		7710	5035	4807	4716	319	190
Percentiles	25	47.00	37.00	35.00	34.00	2.00	1.00
	50	60.00	38.00	37.00	36.00	2.00	1.00
	75	71.50	40.00	38.00	37.00	3.00	2.00

a. Gender = Female

b. Multiple modes exist. The smallest value is shown

7.43 Appendix 3.3B: Tests of normality of data Gender

Tests of Normality[a]

	Kolmogorov-Smirnov[b]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.077	117	.083	.964	117	.003
Extubation for OGJ	.119	117	<.001	.978	117	.055
Extubaion for circumfrentioal BO	.090	117	.020	.983	117	.145
Ex Maximum BO	.103	117	.004	.978	117	.055
Length of Maximum Barrett's oesophagus extubation	.260	117	<.001	.798	117	<.001
Length of circumfrential Barrett's oesophagus extubation	.280	117	<.001	.688	117	<.001

a. Gender = male

b. Lilliefors Significance Correction

Tests of Normality[a]

	Kolmogorov-Smirnov[b]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.071	130	.193	.983	130	.098
Extubation for OGJ	.114	130	<.001	.974	130	.014
Extubaion for circumfrentioal BO	.117	130	<.001	.977	130	.027
Ex Maximum BO	.114	130	<.001	.971	130	.007
Length of Maximum Barrett's oesophagus extubation	.287	130	<.001	.735	130	<.001
Length of circumfrential Barrett's oesophagus extubation	.379	130	<.001	.725	130	<.001

a. Gender = Female

b. Lilliefors Significance Correction

7.44 Appendix 3.3C Endoscopic variables as per Ethnicity

Statistics[a]

		Age	Extubation for OGJ	Extubaion for circumfrentioa l BO	Ex Maximum BO	Length of Maximum Barrett's oesophagus extubation	Length of circumfrential Barrett's oesophagus extubation
N	Valid	221	221	220	221	221	219
	Missing	0	0	1	0	0	2
Mean		59.00	39.71	38.13	37.06	2.65	1.60
Std. Error of Mean		1.177	.201	.209	.224	.112	.078
Median		61.00	40.00	38.00	37.00	2.00	1.00
Mode		61	38	38	37	2	1
Std. Deviation		17.497	2.995	3.093	3.328	1.663	1.155
Variance		306.150	8.968	9.567	11.078	2.764	1.333
Skewness		-.302	.198	.244	.084	2.118	2.618
Std. Error of Skewness		.164	.164	.164	.164	.164	.164
Kurtosis		-.707	.019	.165	.626	6.092	11.373
Std. Error of Kurtosis		.326	.326	.327	.326	.326	.327
Range		77	17	18	23	10	9
Minimum		18	33	31	26	1	0
Maximum		95	50	49	49	11	9
Sum		13040	8777	8389	8191	586	350
Percentiles	25	47.00	38.00	36.00	35.00	2.00	1.00
	50	61.00	40.00	38.00	37.00	2.00	1.00
	75	73.00	42.00	40.00	39.00	3.00	2.00

a. Ethnicty = White

Statistics[a]

		Age	Extubation for OGJ	Extubaion for circumfrentioa l BO	Ex Maximum BO	Length of Maximum Barrett's oesophagus extubation	Length of circumfrential Barrett's oesophagus extubation
N	Valid	28	28	28	28	28	28
	Missing	0	0	0	0	0	0
Mean		52.18	38.79	37.61	36.86	1.93	1.18
Std. Error of Mean		2.756	.409	.434	.439	.178	.127
Median		52.50	39.00	38.00	37.00	2.00	1.00
Mode		26[b]	40	39	36	2	1
Std. Deviation		14.583	2.166	2.299	2.321	.940	.670
Variance		212.671	4.693	5.284	5.386	.884	.448
Skewness		-.382	-.739	-.582	-.388	1.014	1.375
Std. Error of Skewness		.441	.441	.441	.441	.441	.441
Kurtosis		-.740	.122	-.144	-.745	.505	2.908
Std. Error of Kurtosis		.858	.858	.858	.858	.858	.858
Range		49	8	8	8	3	3
Minimum		26	34	33	32	1	0
Maximum		75	42	41	40	4	3
Sum		1461	1086	1053	1032	54	33
Percentiles	25	43.00	38.00	36.25	35.25	1.00	1.00
	50	52.50	39.00	38.00	37.00	2.00	1.00
	75	62.75	40.00	39.00	39.00	2.00	1.00

a. Ethnicty = Asian

b. Multiple modes exist. The smallest value is shown

7.45 Appendix 3.3B: Tests of normality of data Ethnicity

Tests of Normality[a]

	Kolmogorov-Smirnov[b]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.068	219	.016	.975	219	<.001
Extubation for OGJ	.082	219	.001	.985	219	.024
Extubaion for circumfrentioal BO	.096	219	<.001	.985	219	.025
Ex Maximum BO	.078	219	.002	.988	219	.055
Length of Maximum Barrett's oesophagus extubation	.266	219	<.001	.772	219	<.001
Length of circumfrential Barrett's oesophagus extubation	.314	219	<.001	.702	219	<.001

a. Ethnicty = White

b. Lilliefors Significance Correction

Tests of Normality[a]

	Kolmogorov-Smirnov[b]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.114	28	.200*	.946	28	.161
Extubation for OGJ	.147	28	.128	.930	28	.061
Extubaion for circumfrentioal BO	.146	28	.132	.931	28	.064
Ex Maximum BO	.153	28	.091	.940	28	.111
Length of Maximum Barrett's oesophagus extubation	.291	28	<.001	.792	28	<.001
Length of circumfrential Barrett's oesophagus extubation	.427	28	<.001	.669	28	<.001

*. This is a lower bound of the true significance.

a. Ethnicty = Asian

b. Lilliefors Significance Correction

7.46 Appendix 3.3 C: T test for comparison of age as per gender

T-Test

Group Statistics

	Gender	N	Mean	Std. Deviation	Std. Error Mean
Age	male	117	58.04	17.537	1.621
	Female	132	58.41	17.159	1.493

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means							
						Significance				95% Confidence Interval of the Difference	
		F	Sig.	t	df	One-Sided p	Two-Sided p	Mean Difference	Std. Error Difference	Lower	Upper
Age	Equal variances assumed	.038	.846	-.166	247	.434	.868	-.366	2.201	-4.702	3.970
	Equal variances not assumed			-.166	242.056	.434	.868	-.366	2.204	-4.708	3.976

Independent Samples Effect Sizes

				95% Confidence Interval	
		Standardizer[a]	Point Estimate	Lower	Upper
Age	Cohen's d	17.337	-.021	-.270	.228
	Hedges' correction	17.390	-.021	-.269	.227
	Glass's delta	17.159	-.021	-.270	.228

Appendix 3.3A: T test for comparison of age as per gender

7.47 Appendix 3.3D: MWU test for comparison of gender

Ranks

	Gender	N	Mean Rank	Sum of Ranks
Extubation for OGJ	male	117	166.59	19490.50
	Female	132	88.14	11634.50
	Total	249		
Extubaion for circumfrentioal BO	male	117	161.93	18945.50
	Female	131	91.07	11930.50
	Total	248		
Ex Maximum BO	male	117	159.10	18614.50
	Female	132	94.78	12510.50
	Total	249		
Length of Maximum Barrett's oesophagus extubation	male	117	130.27	15241.50
	Female	132	120.33	15883.50
	Total	249		
Length of circumfrential Barrett's oesophagus extubation	male	117	128.67	15054.00
	Female	130	119.80	15574.00
	Total	247		

Test Statistics[a]

	Extubation for OGJ	Extubaion for circumfrentio al BO	Ex Maximum BO	Length of Maximum Barrett's oesophagus extubation	Length of circumfrential Barrett's oesophagus extubation
Mann-Whitney U	2856.500	3284.500	3732.500	7105.500	7059.000
Wilcoxon W	11634.500	11930.500	12510.500	15883.500	15574.000
Z	-8.626	-7.808	-7.069	-1.141	-1.101
Asymp. Sig. (2-tailed)	<.001	<.001	<.001	.254	.271

a. Grouping Variable: Gender

7.48 Appendix 3.3E: MWU test for comparison of ethnicity

Ranks

	Ethnicity	N	Mean Rank	Sum of Ranks
Extubation for OGJ	White	221	127.33	28139.50
	Asian	28	106.63	2985.50
	Total	249		
Extubaion for circumfrentioal BO	White	220	125.51	27612.00
	Asian	28	116.57	3264.00
	Total	248		
Ex Maximum BO	White	221	125.26	27683.50
	Asian	28	122.91	3441.50
	Total	249		
Length of Maximum Barrett's oesophagus extubation	White	221	128.83	28472.00
	Asian	28	94.75	2653.00
	Total	249		
Length of circumfrential Barrett's oesophagus extubation	White	219	127.01	27814.50
	Asian	28	100.48	2813.50
	Total	247		
Age	White	221	128.38	28372.00
	Asian	28	98.32	2753.00
	Total	249		

Test Statistics[a]

	Extubation for OGJ	Extubaion for circumfrentioal BO	Ex Maximum BO	Length of Maximum Barrett's oesophagus extubation	Length of circumfrential Barrett's oesophagus extubation	Age
Mann-Whitney U	2579.500	2858.000	3035.500	2247.000	2407.500	2347.000
Wilcoxon W	2985.500	3264.000	3441.500	2653.000	2813.500	2753.000
Z	-1.441	-.624	-.164	-2.476	-2.092	-2.081
Asymp. Sig. (2-tailed)	.150	.532	.870	.013	.036	.037

a. Grouping Variable: Ethnicty

7.49 Appendix 3.3F: MWU test for comparison of ethnicity

Crosstab

			Type of Ext Barrett's Short segment	Long segment	Total
Ethnicity	White	Count	136	85	221
		% within Ethnicty	61.5%	38.5%	100.0%
		% within Type of Ext Barrett's	85.5%	94.4%	88.8%
		% of Total	54.6%	34.1%	88.8%
		Residual	-5.1	5.1	
	Asian	Count	23	5	28
		% within Ethnicty	82.1%	17.9%	100.0%
		% within Type of Ext Barrett's	14.5%	5.6%	11.2%
		% of Total	9.2%	2.0%	11.2%
		Residual	5.1	-5.1	
Total		Count	159	90	249
		% within Ethnicty	63.9%	36.1%	100.0%
		% within Type of Ext Barrett's	100.0%	100.0%	100.0%
		% of Total	63.9%	36.1%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.571[a]	1	.033		
Continuity Correction[b]	3.722	1	.054		
Likelihood Ratio	5.043	1	.025		
Fisher's Exact Test				.037	.023

Linear-by-Linear Association	4.553	1	.033		
N of Valid Cases	249				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 10.12.
b. Computed only for a 2x2 table

Crosstab

			Type of Ext Barrett's		
			Short segment	Long segment	Total
Gender	male	Count	70	47	117
		% within Gender	59.8%	40.2%	100.0%
		% within Type of Ext Barrett's	44.0%	52.2%	47.0%
		% of Total	28.1%	18.9%	47.0%
		Residual	-4.7	4.7	
	Female	Count	89	43	132
		% within Gender	67.4%	32.6%	100.0%
		% within Type of Ext Barrett's	56.0%	47.8%	53.0%
		% of Total	35.7%	17.3%	53.0%
		Residual	4.7	-4.7	
Total		Count	159	90	249
		% within Gender	63.9%	36.1%	100.0%
		% within Type of Ext Barrett's	100.0%	100.0%	100.0%
		% of Total	63.9%	36.1%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.550[a]	1	.213		
Continuity Correction[b]	1.239	1	.266		
Likelihood Ratio	1.550	1	.213		
Fisher's Exact Test				.236	.133

Linear-by-Linear Association	1.544	1	.214		
N of Valid Cases	249				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 42.29.
b. Computed only for a 2x2 table

7.50 Appendix 3.3F: MWU test for comparison of ethnicity

Ranks

	Ethnicty	N	Mean Rank	Sum of Ranks
Extubation for OGJ	White	221	127.33	28139.50
	Asian	28	106.63	2985.50
	Total	249		
Extubaion for circumfrentioal BO	White	220	125.51	27612.00
	Asian	28	116.57	3264.00
	Total	248		
Ex Maximum BO	White	221	125.26	27683.50
	Asian	28	122.91	3441.50
	Total	249		
Length of Maximum Barrett's oesophagus extubation	White	221	128.83	28472.00
	Asian	28	94.75	2653.00
	Total	249		
Length of circumfrential Barrett's oesophagus extubation	White	219	127.01	27814.50
	Asian	28	100.48	2813.50
	Total	247		
Age	White	221	128.38	28372.00
	Asian	28	98.32	2753.00
	Total	249		

Test Statistics[a]

	Extubation for OGJ	Extubaion for circumfrentio al BO	Ex Maximum BO	Length of Maximum Barrett's oesophagus extubation	Length of circumfrential Barrett's oesophagus extubation	Age
Mann-Whitney U	2579.500	2858.000	3035.500	2247.000	2407.500	2347.000
Wilcoxon W	2985.500	3264.000	3441.500	2653.000	2813.500	2753.000
Z	-1.441	-.624	-.164	-2.476	-2.092	-2.081
Asymp. Sig. (2-tailed)	.150	.532	.870	.013	.036	.037

a. Grouping Variable: Ethnicty

7.51 Appendix 4 Table of main studies in relation to ethnicity and BO

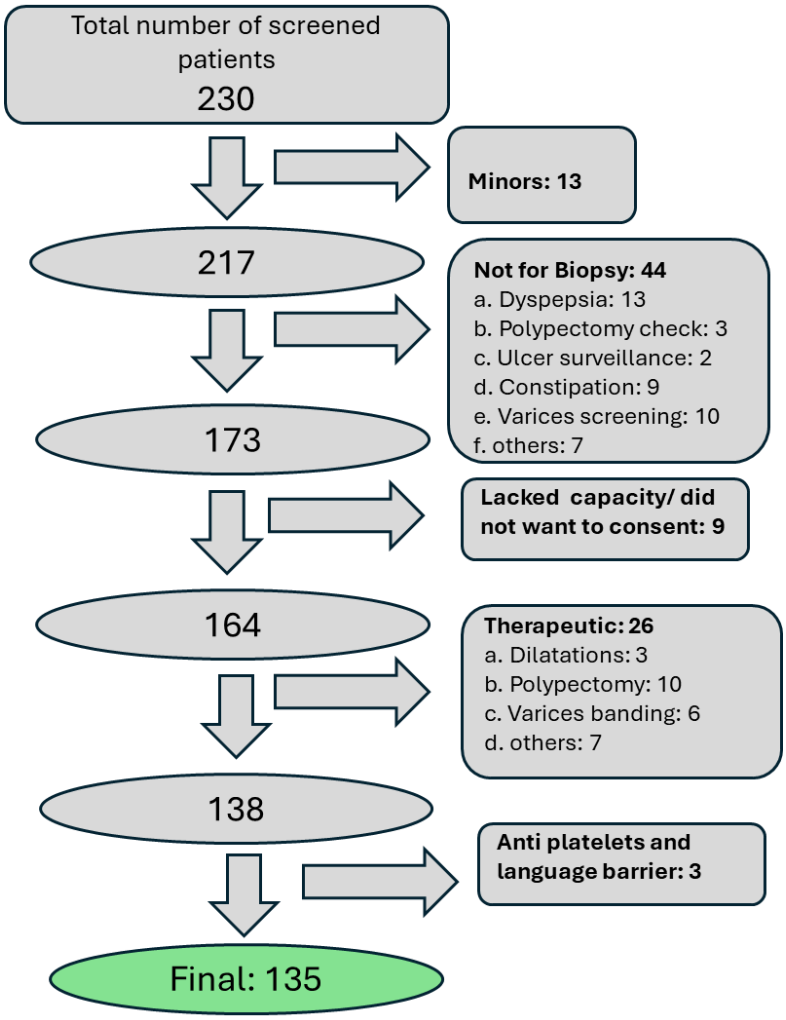
Table 20: Studies concerning Barrett's oesophagus in South Asin population, in chronological order.

No	Author, year, Country	number	Description and methods	Results and comments
1	(ABBAS *et al.*, 1995) Pakistan	29	To demonstrate the presence of Helicobacter pylori in the metaplastic epithelium of BO.	H pylori in 38% of BO based on antral biopsies. The positivity of BO for H. pylori correlated with the presence of H. pylori antral gastritis. Retrospective study, case selection bias.
2	(Dhawan *et al.*, 2001) India	271	To determine Prevalence of SSBO association with GORD. Prospective analysis.	Prevalence 6% (CI 5.03-6.97). Increasing age and oesophagitis was associated but smoking and alcohol were not with BO.
3	(Gupta *et al.*, 2001) India	169	Retrospective comparison of squamous cell carcinoma (SCC) with ACO in terms of outcome.	SCC (n=100) vs ACO (n=69): SCC more resectable than ACO with more 5 years survival rate. Noe of the ACO was associated with BO. Retrospective collection and quality biased
4	(Spechler *et al.*, 2002) US	2.989	To explore the racial differences in the frequency of GORD and its complications.	Complication: White patients (12.3%), black patients (2.8%), West Asian patients (4.8%) and none of East Asian patients seen. BO 1% in SAP and less aggressive in SAP.
5	(Rajendra, Kutty & Karim, 2004) Malaysia	1,985	Prospective Endoscopic study to determine prevalence of GORD and risks of BO in SAP.	Prevalence of GORD in SAP 2.3%. SAP ethnicity and HH associated with BO as compared to chinses and Malaysians. Prevalence over estimated as m88% of GORD was mild.
6	(Alidina *et al.*, 2004) Pakistan	263	Retrospective data and factors associated with oesophageal cancer in Pakistan.	Squamous CC (81%) was more common than ACO (19%) suggesting < BO. Retrospective and indirect inference. The study was conducted in private setup hence data biased.
7	(Rajendra *et al.*, 2005). Malaysia	119	To investigate whether certain HLA types in SAP are associated with BO using PCR.	HLA-B7 allele was present in 17%, SAP. Genes may be playing some role in SAP in relation to BO. Objective methodology and multi-ethnic study but larger power required.
8	(Ang *et al.*, 2005) Singapore	690	Comparison of the clinical, demographic and psychiatric profiles among patients with GORD	14.8% Indians had Reflux, majority had NERD in younger age and erosive oesophagitis. BO was 1.7%. Patients on PPI were excluded who are likely to be known to have GORD/BO.
9	(Punia *et al.*, 2006) India	55	Retrospective study to determine the relative age of occurrence and incidence of dysplasia	13 had BO, 8 males 5 females 6/13 IM. 77% below age 40. No dysplasia detected in cases. Although BO is reported in younger patient in SAP, the power of the study is low.
10	(Rajendra *et al.*, 2007) Australia	188	Prospective study OGD on GORD patients to assess for association of H Pylori with BO.	H Pylori protective for LSBO and GORD. SAP: highest Prevalence of H Pylori (75%) and corpus atrophy. No information about the PPI was given which may affect GORD.

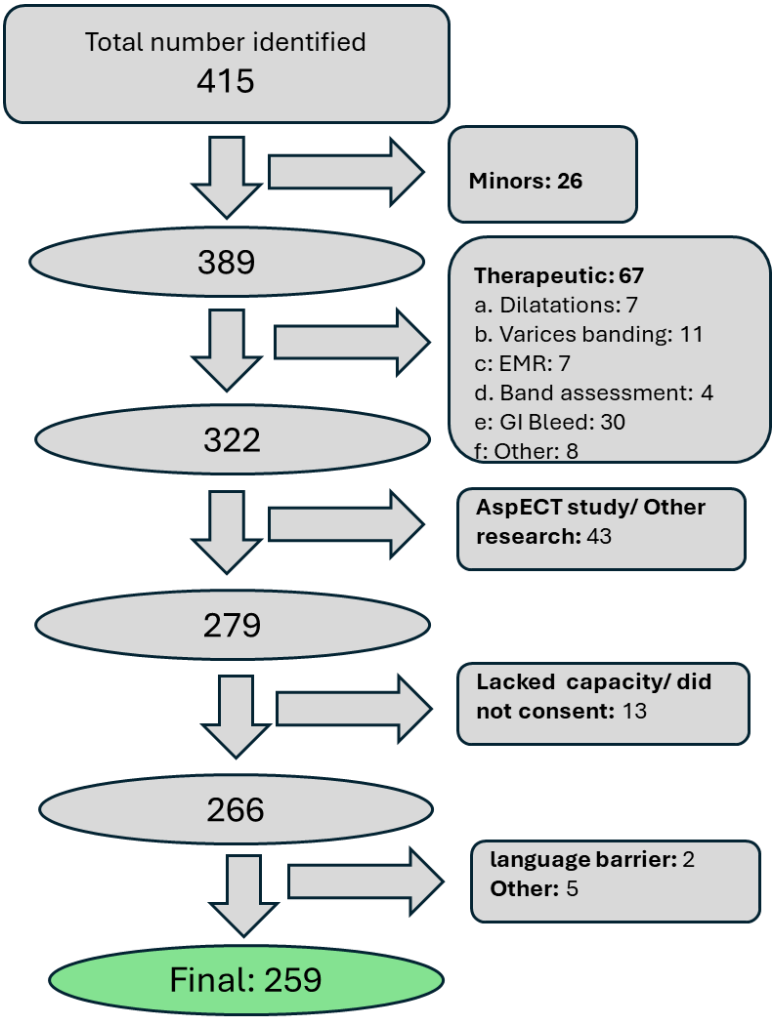
11	(Navarathne *et al.*, 2010) Sri Lanka	1,150	To study inter-relationships of endoscopic findings around GOJ in symptomatic GORD.	HH, BO and GORD was 14.3% , 9.5%, and 13.3% respectively. In 165 endoscopic BO only 48 positive histology. BO associated with age, male gender, higher BMI, presence of HH.
12	(Bamanikar *et al.*, 2011) India	77	To compare prevalence of BO in patients with BMI > 30 and BMI < 30.	BO 9.5% in patients with > 30 and 6.7% in patients with BMI <30 suggesting obesity might not predispose to BO. Selection bias may have affected the study.
13	(Abid, Siddiqui & Jafri, 2011) Pakistan	272	To evaluate functional upper GI symptoms for organic causes.	Symptomatic (Dyspepsia) Rome III 5/ 191 patient had BO. Dyspepsia is not strongly associated with BO and the study may have suffered selection bias.
14	(Padmavathy, Siddaraju & Sistla, 2011) India	8	To examine the role of Role of brush cytology in the diagnosis of Barrett's oesophagus.	Brush cytology good in picking BO. Low powered and pathologist was not blind. More high-powered studies are needed to explore this area.
15	Mathew et al., (2011) India	46	To investigate the frequency and risk factors of BO SAP with GORD prospective.	46 (16.54%) had BO and risks were HH, age but BMI not a risk factor. The median CBO 2 cm (1-10) and MBO was 3 (2–11) cm in both groups. Study lacked WBP data.
16	(Wani *et al.*, 2014) India	378	To assess prevalence of BO with prospective endoscopic and histology.	BO on endoscopy was found in 56 (14.8%) out of which 9 (2.3%) had IM. Reflux and length of BO associated with IM. However, authors excluded patients below the age of 25 years.
17	(Pasricha *et al.*, 2015) US	5521	Treatment efficacy, and safety outcomes by sex and race for RFA for BO.	136 Asians and they reported less dyspepsia, although tend to stricture more. No difference in efficacy was noticed between races. Private healthcare, selection bias.
18	(Hewett *et al.*, 2015) UK	460	To determine (retrospective) the odds of having IM by ethnic origin and age and gender	SAP (n=45) were 70% less likely to have IM. No difference was documented between the length of BO according to ethnicity. Retrospective and may have suffered sampling bias.
19	(Sonnenberg *et al.*, 2017) US	596,479	interaction of ethnicity and H-pylori infection in the occurrence of BO in multi-ethnic sample.	Retrospective Indian (0.39, 0.32–0.47), H pylori protective, (0.39, 0.32–0.47). A low prevalence of H. pylori was associated high prevalence of BO (R2 = 0.82, P < 0.001),
20	(Kinra *et al.*, 2018) India	59	Retrospective study examining dysplasia in BO with immunohistochemical markers	Agreement was poor to differentiate LGD and indefinite dysplasia (k 0.06; 95% CI −0.089 to 0.145). pathologist blinded but experience may be different.

SCC: Squamous cell carcinoma, H Pylori: Helicobacter pylori, HLA Human Leukocyte antigen, SAP: South Asian population, WBP: White British population. IM Intestinal metaplasia, LGD Low grade dysplasia.

7.52 Appendix 5 Consort diagram of exclusion criteria for BITES



7.53 Appendix 6 Consort diagram of exclusion criteria for SALAHADEEN



7.54 Appendix 7 Consort diagram of exclusion criteria for SALAHADEEN

Table 21: Table depicting biopsy collection, loss and discrepancy as per single and double bite

		Biopsy technique (n=144)				
		Single Bite (n=72)		Double Bite (n=72)		
Parameter	n= 144	UGIPs (n=31)	LGIPs (n=41)	UGIPs(n37=)	LGIPs (n=35)	
Biopsy loss	13 (9.0%)	6 (8.3%)	7 (9.7%)	3 (4.2%)	4 (5.6%)	
Biopsy extraction	7 (4.8%)	5 (7.5%)	2 (3.3%)	6 (9.1%)	2 (3%)	
Discrepancy*	0	0	0	0	0	
Complication(s)	0	0	0	0	0	

***Discrepency in tissue identification**