"A STUDY ON METHYLENE BLUE CHROMOENDOSCOPY FOR THE EARLY DIAGNOSIS OF BARRETT'S METAPLASIA, DYSPLASIA AND EARLY ESOPHAGEAL ADENOCARCINOMA IN OUR INSTITUTE"

DISSERTATION SUBMITTED FOR

DM MEDICAL GASTROENTEROLOGY

BRANCH- IV

AUGUST 2014

THE TAMILNADUDR.M.G.R.MEDICAL

UNIVERSITY CHENNAI,

TAMILNADU

CERTIFICATE

This is to certify that this dissertation entitled **"A study on Methylene Blue Chromoendoscopy for the early diagnosis of Barrett's metaplasia, dysplasia and early oesophageal adenocarcinoma in our Institute"** submitted by **Dr. Mukundan Swaminathan** to the Faculty of Medical Gastroenterology, The TamilnaduDr.MGR Medical University, Guindy, Chennai-600032, in partial fulfillment of the requirement for the award of DM Degree, Branch IV (Medical Gastroenterology) is a bonafide work carried out by him under my direct supervision and guidance, during the academic year 2011 – 2014.

Prof. Dr. P. Ganesh, M.D., D.M
Professor and HOD/ Guide
Department of Medical Gastroenterology,
(DDHD@GPH, Annanagar),
Kilpauk Medical College
Chennai

Dr. P. Ramakrishnan, M.D., D.L.O
Dean,
Kilpauk Medical College,
Chennai

ACKNOWLEDGEMENTS

I am greatly indebted to my guide **Dr. P .Ganesh, M.D., D.M.,** Professor of Medical Gastroenterology, Department of Digestive Health and Diseases, Kilpauk Medical College, Chennai, for giving me the chance to undertake this dissertation work under his guidance. Also I express my deep sense of gratitude for his constant encouragement, directions, periodical discussions, rigorous reviews and precious suggestions that helped in the shaping of my dissertation.

I express my sincere gratitude to **Dr. S. Jeevan Kumar, M.D., D.M.,** Professor of Medical Gastroenterology, Department of Digestive Health and Diseases, Kilpauk Medical College, Chennai, for giving me permission to do this dissertation in Govt. Peripheral Hospital, Anna Nagar, Chennai-102 and also his kind encouragement and review of my work, besides providing me with all the required facilities.

I also thank **Dr. T. Rajkumar Solomon, M.D., D.M.,** Professor of Medical Gastroenterology, Department of Digestive Health and Diseases, Kilpauk Medical college, Chennai for his constant encouragement and suggestions for my study.

I am extremely grateful to **Dr. P. Ramakrishnan, M.D., D.L.O,** Dean, Kilpauk Medical College for granting me permission to do this dissertation in Kilpauk Medical College, Chennai.

I am very much thankful to **Dr. M. Saraswathi, M.D.,** Professor and HOD, Department of Pathology, Kilpauk Medical College, Chennai who has helped me a lot during my dissertation.

I am also extremely thankful to **Dr. R. Balamurali, M.D., D.M., Dr. G. Ramkumar, M.D., D.M.,** and **Dr. K. Muthukumaran, M.D., D.M.,** who guided me a lot.

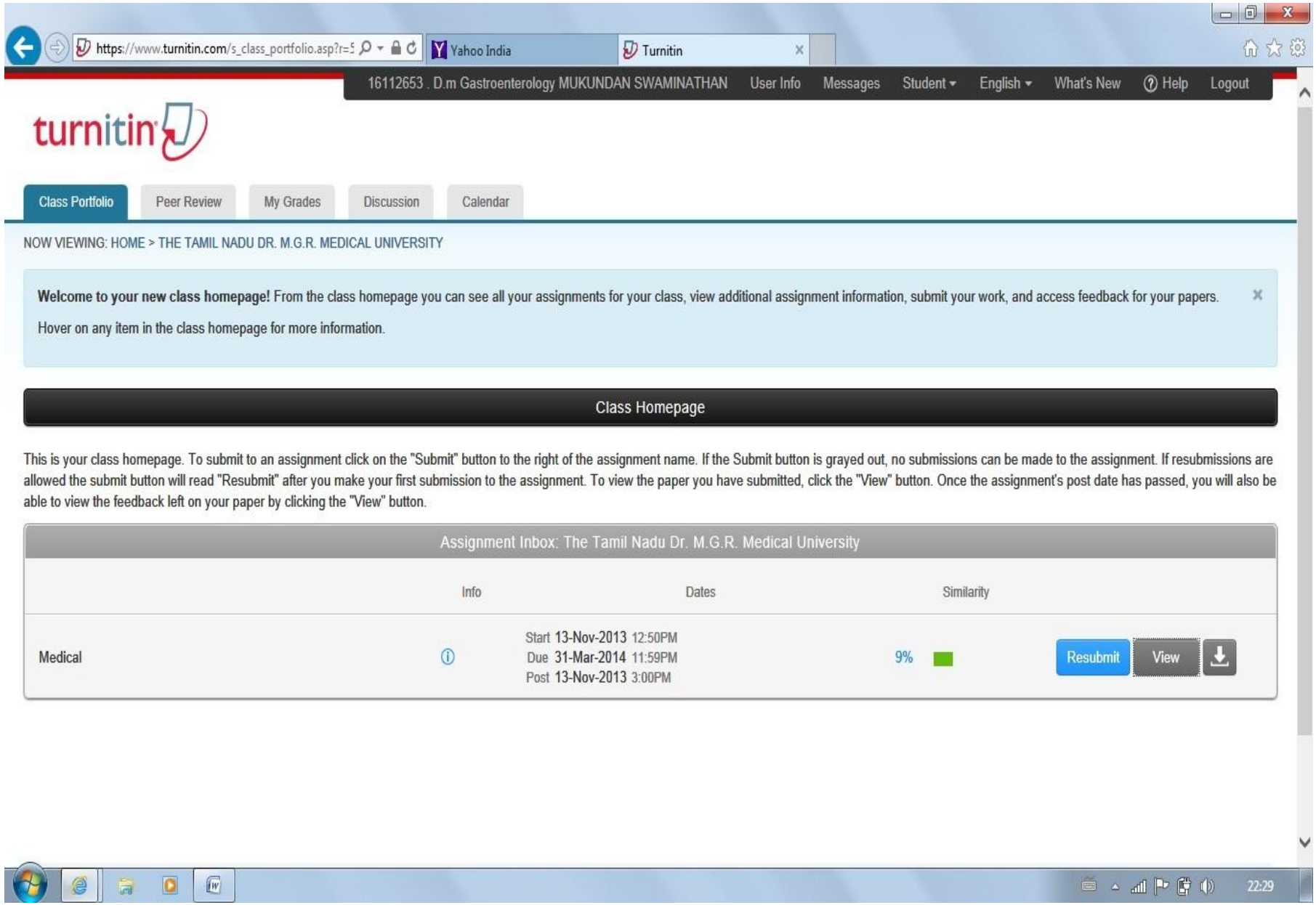
I am also very thankful to all my **Fellow Residents** who have helped me in this dissertation.

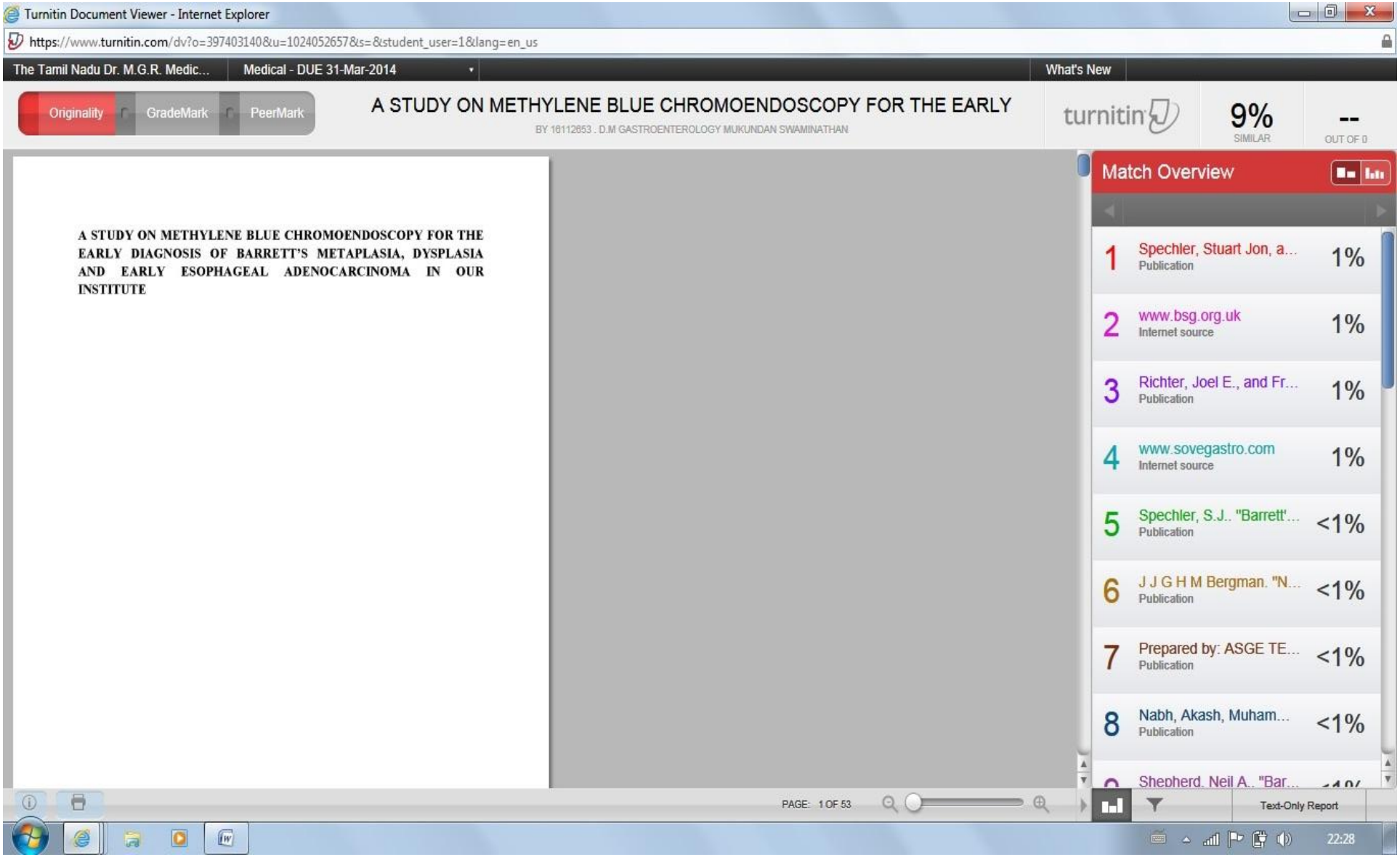
I am also thankful to **Dr. Balaji,** Assistant Professor, Department of Social and Preventive Medicine, SRM College, Chennai for his help in the statistical analysis of my dissertation work.

I thank all the patients who voluntarily participated in this study, without whom this study would not have seen the light of the day.

I also thank all the paramedical staff attached to Govt. Peripheral Hospital, Anna Nagar, Chennai who have helped me in doing this dissertation work.

Finally, I would like to thank my wife, **Dr. Vanathi Mukundan** without whose cooperation this work would not have been possible.


https://www.turnitin.com/s_class_portfolio.asp?r=5
Yahoo India
Turnitin
16112653 . D.m Gastroenterology MUKUNDAN SWAMINATHAN
User Info
Messages
Student
English
What's New
Help
Logout
turnitin
Class Portfolio
Peer Review
My Grades
Discussion
Calendar
NOW VIEWING: HOME > THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
Welcome to your new class homepage! From the class homepage you can see all your assignments for your class, view additional assignment information, submit your work, and access feedback for your papers.
Hover on any item in the class homepage for more information.
Class Homepage
This is your class homepage. To submit to an assignment click on the "Submit" button to the right of the assignment name. If the Submit button is grayed out, no submissions can be made to the assignment. If resubmissions are allowed the submit button will read "Resubmit" after you make your first submission to the assignment. To view the paper you have submitted, click the "View" button. Once the assignment's post date has passed, you will also be able to view the feedback left on your paper by clicking the "View" button.
Assignment Inbox: The Tamil Nadu Dr. M.G.R. Medical University
Info
Dates
Similarity
Medical
Start 13-Nov-2013 12:50PM
Due 31-Mar-2014 11:59PM
Post 13-Nov-2013 3:00PM
9%
Resubmit
View
22:29


Turnitin Document Viewer - Internet Explorer
https://www.turnitin.com/dv?o=397403140&u=1024052657&s=&student_user=1&lang=en_us
The Tamil Nadu Dr. M.G.R. Medic...
Medical - DUE 31-Mar-2014
What's New
Originality
GradeMark
PeerMark
A STUDY ON METHYLENE BLUE CHROMOENDOSCOPY FOR THE EARLY
BY 16112653 . D.M GASTROENTEROLOGY MUKUNDAN SWAMINATHAN
turnitin
9%
SIMILAR
--
OUT OF 0
A STUDY ON METHYLENE BLUE CHROMOENDOSCOPY FOR THE EARLY DIAGNOSIS OF BARRETT'S METAPLASIA, DYSPLASIA AND EARLY ESOPHAGEAL ADENOCARCINOMA IN OUR INSTITUTE
Match Overview
1 Spechler, Stuart Jon, a... Publication 1%
2 www.bsg.org.uk Internet source 1%
3 Richter, Joel E., and Fr... Publication 1%
4 www.sovegastro.com Internet source 1%
5 Spechler, S.J.. "Barrett'... Publication <1%
6 J J G H M Bergman. "N... Publication <1%
7 Prepared by: ASGE TE... Publication <1%
8 Nabh, Akash, Muham... Publication <1%
Shepherd, Neil A.. "Bar...
PAGE: 1 OF 53
Text-Only Report
22:28

CONTENTS

A STUDY ON METHYLENEBLUE CHROMOENDOSCOPY FOR THE EARLY DIAGNOSIS OF BARRETT'S METAPLASIA , DYSPLASIA AND ESOPHAGEAL ADENOCARCINOMA IN OUR INSTITUTE

INTRODUCTION

INTRODUCTION

Barrett's oesophagus is a condition in which an abnormal columnar epithelium that is predisposed to malignancy replaces the stratified squamous epithelium that normally lines the distal oesophagus. Barrett's oesophagus is a consequence of chronic gastro-oesophageal reflux disease. The prevalence is between 2 to 7% in the adult population. It is a risk factor for development of dysplasia and later adenocarcinoma. The risk of malignancy is approximately 0.5% per year increasing to 4-6% with high grade dysplasia. Majority of these individuals with metaplasia, dysplasia and early adenocarcinoma are asymptomatic.

Diagnosis is by endoscopy and biopsy confirmation of intestinal metaplasia. Routine white light endoscopy and biopsy identifies long segment Barrett's oesophagus with good accuracy. Short segment Barrett's, foci of dysplasia and early adenocarcinoma can easily be missed on routine white light endoscopy and biopsy. Identifying dysplasia and malignancy at an early stage is very important in decreasing the morbidity, mortality and improves treatment outcomes. Considering the increased risk of malignancy and better outcome with early diagnosis, various new techniques have been developed to improve the early detection.

Chromoendoscopy refers to the topical application of stains or dyes at the time of endoscopy in an effort to enhance tissue characterization, differentiation

or diagnosis. It enhances detection of dysplasia and early cancer of G.I tract, especially in patients with pre-malignant conditions and those with high risk of developing cancer. It is a valuable tool for early detection of Barrett's metaplasia, dysplasia and adenocarcinoma.

Among the various stains used methylene blue C.E is the most common technique used for identifying Barrett's epithelium. Various studies have highlighted the usefulness of methylene blue C.E in Barrett's metaplasia and dysplasia. However there are mixed reports from studies regarding the accuracy of this technique.

We conducted this study in our department to evaluate and compare the efficacy of methylene blue directed biopsy in early detection of Barrett's metaplasia, dysplasia and early adenocarcinoma in high risk population compared to random biopsy.

REVIEWOF LITERATURE

REVIEW OF LITERATURE

HISTORICAL PERSPECTIVE :

The term Barrett's oesophagus is coined after Norman Barrett, who first described the condition in 1950. He first described a case of chronic peptic ulcer in the mucosa of the distal oesophagus lined by epithelium[2]. It is also referred to as Barrett's syndrome or columnar lined lower oesophagus. The original initial description was related to congenital short oesophagus with intra thoracic gastric columnar lining. After three years, anatomical reason for the occurrence of columnar lining in the distal esophagus as an acquired condition seen in patients with chronic gastro-oesophageal reflux was provided by Allison[3]. Subsequently the association with gastro-oesophageal reflux was confirmed by several studies[4].

The development of a columnar lined oesophagus as an adaptive response to gastro-oesophageal reflux was demonstrated in animal studies subsequently in several studies[5]. As per histology the adaptive response includes, junctional type epithelium, gastric fundic type epithelium and a distinctive intestinal metaplasia[6]. Subsequent studies described the association of columnar lined oesophagus with risk of cancer[7]. Considering the malignant potential and the need to eliminate confusion between the type of epithelium, columnar lined oesophagus of 3cm length was needed to make a diagnosis[8]. Later studies

highlighted the fact that it was intestinal metaplasia that had malignant potential and not the fundic type epithelium.[9]Hence it is appropriate to make a diagnosis after endoscopic visualization and histological confirmation of intestinal metaplasia.[10]

DEFINITION :

"In 1998 the American college of gastroenterology defined Barrett's oesophagus as a change in the epithelium of the distal oesophagus of any length that can be detected at endoscopy and confirmed to have intestinal metaplasia by biopsy and excludes metaplasia of the cardia".[11]

"The British society of gastroenterology defines Barrett's oesophagus as any portion of the normal squamous lining replaced by macroscopically visible columnar epithelium and histologically confirmed intestinal metaplasia."

CLASSIFICATION OF BARRETT'S OESOPHAGUS :

Earlier studies recommended a minimum length of 3cm of columnar lined oesophagus from the GEJ for defining Barrett's oesophagus.[8] Subsequent studies revealed that even lesions (<3cm) with intestinal metaplasia were associated with malignant potential . Hence it was classified further into two types based on the length of columnar lined oesophagus. Barrett's oesophagus is categorized into two types, long segment and short segment. Long segment Barrett's also called traditional Barrett's oesophagus refers to

metaplasticcolumnar epithelium extending at least 3cm above the gastroesophageal junction (GEJ) and short segment < 3cm above the GEJ.[1]

Prague Criteria ForCategorizing Barrett's:

There has been significant inter and intra-observer variability when it comes to classifying long and short segment Barrett's oesophagus among endoscopist worldwide.[12]Several studies have shown that increase in length of columnar metaplasia is associated with a doubling of risk of adenocarcinoma.

Considering the increased malignant potential with increasing length of Barrett's metaplasia and significant inter-observer variability among endoscopist in identifying these lesions a validated, simple method to categorize Barrett's was required.

Hence the International working group on classification of oesophagitis came up with a new criteria in 2002. In Prague criteria C stands for circumferential extent and M stands for maximal extent of the suspected columnar metaplasia from the GEJ, identified as proximal extent of gastric mucosal folds (figure 1).[13]

The criteria was named Prague as it was presented first at Prague in September 2004. The criteria were found to be simple, reliable and easy to apply. However its clinical significance especially for identifying short segment's Barrett's remains inconclusive.

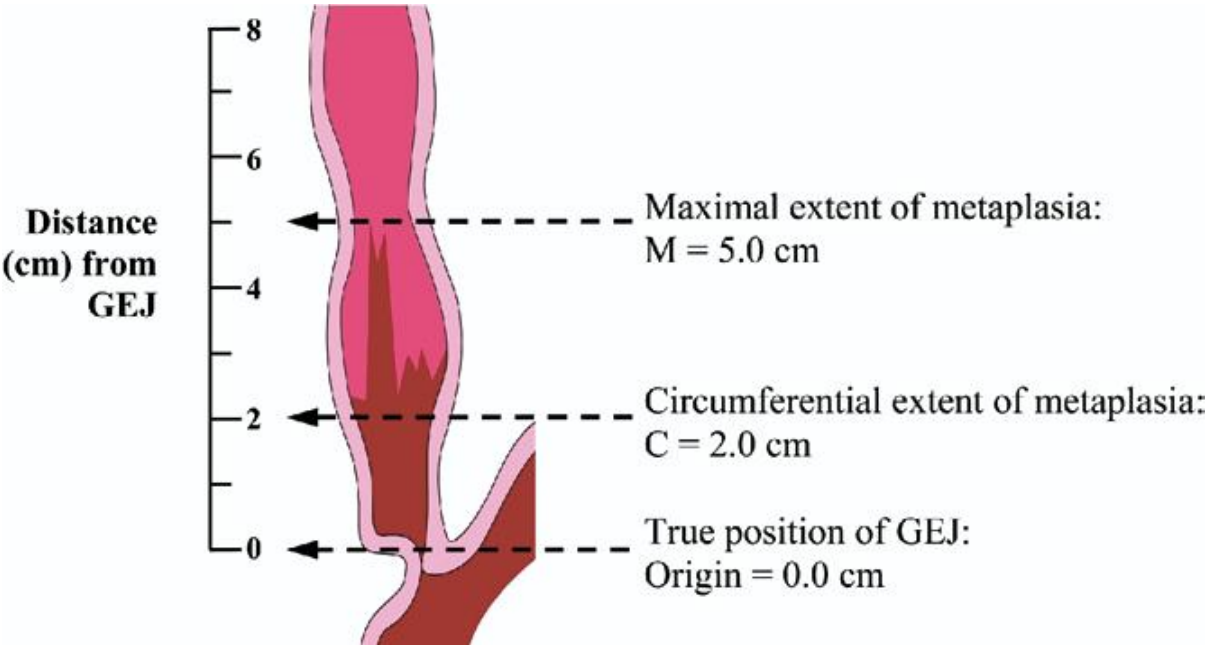


Figure 1: The Prague criteria (C and M criteria)

An alternative proposal was to use descriptive terms like oesophagus lined by columnar epithelium and to segregate based on the presence or absence of intestinal metaplasia, as per the modified Savary-Miller grading of oesophagitis. Using the above system grades range from 0 to 4, based on the extent of CLO and presence of intestinal metaplasia.[14]

EPIDEMIOLOGY :

The condition is commonly found in older individuals above the fifth decade during upper gastrointestinal endoscopy as a part of evaluation of chronic GERD.[15]The most common age group at diagnosis is the 6th to 7th decade, with a median age being approximately 55yrs. There is a sharp rise in the diagnosis of Barrett's metaplasia over the age of 40-50yrs.[16] In contrast the

prevalence is rare in children below the age of 10yrs and almost never seen below the age of 5yrs.[17]

The median incidence of Barrett's esophagus is 1.17%.[18]There is an increase in the incidence of Barrett's paralleling the increase in incidence of GERD. Among adults with symptoms of GERD lesions more than 3cm is found in 3% to 5 % and short segment in 10% to 20% during endoscopy.[1]Overall the prevalence is 1.6% to 6.8%.[19] In most series white Caucasian men are found to have the highest incidence of Barrett's metaplasia and the condition being uncommon in Asians and black Africans. Among men and women the prevalence is significantly more among men with an estimate of 65% affected being male population.

RISK FACTORS :

Gastro-esophageal reflux disease is the most important among various predisposing factors studied. Barrett's oesophagus arises as a result of chronic mucosal damage of the distal oesophagus due to chronic gastro-oesophageal acid reflux. This finding has been validated in several studies and meta-analysis.[20] Individuals with central obesity are strongly predisposed to GERD, Barrett's and its associated complications.[21]The proposed mechanism being, increase in intra-abdominal pressure leading predisposing to GERD.

Various studies have been conducted to study the association with lifestyle factors. Among the lifestyle factors cigarette smoking is found to increase the risk of Barrett's oesophagus modestly, whereas there seems to be no significant association with alcohol consumption.[22] Aspirin, various NSAIDs and Helicobacter pylori infection appear to decrease the risk of having these lesions.

RISK OF MALIGNANCY :

Barrett's metaplasia is a premalignant condition, predisposing to the development of adenocarcinoma. It has been found that 0.5% of individuals with simple Barrett's are likely to develop a malignant lesion in a calendar year.[23] It has also been found that around 4.3% and 0.9% of these individuals are likely to develop low-grade and high-grade dysplasia respectively in a year. A thorough analysis has found that the risk of developing malignancy in individuals with dysplasia ranges from 0.6% for low grade lesions and 4% to 6% in a year for high-grade lesions.[24]

PATHOGENESIS :

Barrett's oesophagus or columnar lined oesophagus is the end result of chronic severe gastro-oesophageal reflux disease. There are multiple physiological abnormalities in these individuals that puts them at the risk for severe gastro-oesophageal reflux disease. The proposed physiologic

mechanisms contributing to GERD in patients with Barrett's oesophagus are extreme lower oesophageal sphincter hypotension, ineffective oesophageal motility, hiatus hernia, gastric acid hyper secretion, duodenogastric reflux, decreased salivary secretion of epidermal growth factor (EGF) and decreased oesophageal pain sensitivity. The above physiological abnormalities either alone or in combination have potential consequences which ultimately lead to oesophageal mucosal injury and columnar metaplasia.

Transient lower oesophageal sphincter relaxation (tLESR):

tLESRs represent LES relaxation independent of swallowing. It is prolonged, associated with relaxation of crural diaphragm and not associated with oesophageal peristalsis.[25]60 to 70% of reflux episodes in GERD is secondary to this mechanism.[26]

Hypotensive lower oesophageal sphincter:

LES hypotension results in gastro-oesophageal reflux either strain-induced or free relux.[27] Strain induced reflux occurs when LES pressure is greater than 10mm hg, whereas free reflux usually occurs when LES pressure is less than 5mm hg. The reason for LES hypotension is obscure. Presence of hiatus hernia reduces the LES pressure due to loss of intrinsic crural diaphragmatic support.[27]Several studies have shown association of hypotensive LES with oesophagitis.

Hiatus hernia:

In patients with hiatus hernia the LES is displaced proximally into the chest, especially the high pressure zone.It impairs LES pressure mainly by reducing the LES pressure and to a certain extent by impairing the oesophageal acid clearance.[28,29] Hiatus hernia increases reflux episodes and is associated with complications like oesophagitis, stricturing and BE.[28]The incidence of hiatus hernia in patients with oesophagitis is 54% to 94%, and this association has been proven in two studies.[29,30]

Oesophageal acid clearance:

There are two mechanisms, namely

1. Volume clearance
2. Acid clearance

The normal oesophagus has two types of normal peristaltic waves (primary and secondary). Studies have shown that the normal oesophagus would be able to clear a 15 ml fluid bolus by means of primary peristalsis.[31]Peristaltic dysfunction is associated with increasing severity of oesophagitis. In a study done in Chicago it was found that oesophagealdysmotility was more prevalent in patients with severe oesophagitis, around 50%.[32]

Salivary secretion has been found to play a role in oesophageal acid clearance by clearing the remnant acid from the oesophagus after the peristaltic wave.[31] Stimulated salivation by sweeteners significantly reduces acid clearance time, whereas decreased salivation prolongs clearance.[33] Studies have shown an impaired oesophagosalivary reflux in these individuals.[34]

G**astric factors** :

The factors associated with GERD and its sequelae are gastric acid hyper secretion, duodenogastric reflux and delayed gastric emptying. Studies have found that when the frequency and duration of acid and bile reflux is high to an extent of pH <4, the severity of oesophageal injury is significantly high.[3536]

Further it has been shown in several studies that apart from acid, bile reflux also plays a significant role in oesophageal injury. In a study it was found that bile reflux, especially reflux occurring in the recumbent position was strongly associated with oesophageal mucosal injury and columnar lined oesophagus.[88]

COLUMNAR METAPLASIA :

Barrett's oesophagus or columnar metaplasia of the distal oesophagus occurs secondary to long standing GER. Columnar Metaplasia occurs as a result of the pathology described so far. The pathology is more pronounced in patients with long segment than short segment Barrett's oesophagus. But some studies

showed normal acid secretion in patients with long segment Barrett's and another study suggesting short segment Barrett's occurs in 5% of adults without association of GERD.[37,38] Columnar metaplasia occurs as a protective repair mechanism to chronic oesophageal injury.

The progenitor cell of origin for Barrett's metaplasia is not clearly known. The hypothesis put forward are

1. Abnormal differentiation of multipotent stem cells in the basal layer of oesophagus into columnar cells after GERD induced damage to squamous epithelium and exposure to gastric juice.

2. Differentiation of stem cells in ducts of oesophagealsubmucosal glands and bone marrow stem cells.[39]

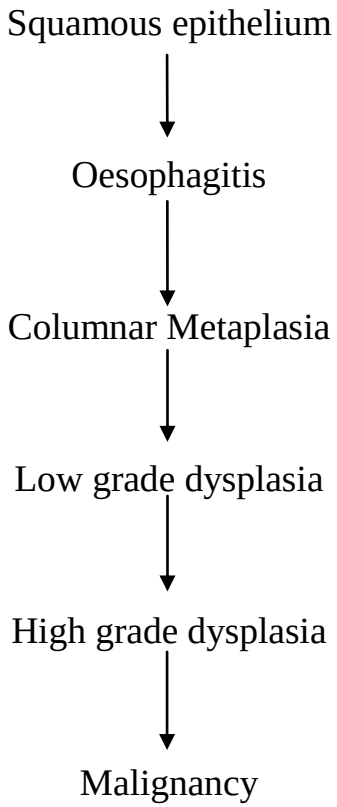
Varoius studies have shown the expression of certain genes is also important in the pathogenesis. The genes identified are Cdx genes and bone morphogenetic protein (BMP)-4, both of which are known to mediate differentiation of intestinal type columnar cells.[40] These genes are over-expressed in the squamous epithelium of patients with reflux oesophagitis.

CARCINOGENESIS :

Barrett's epithelial cells are more resistant to acid injury due to the property of mucin secretion and expression of tight-junction protein called claudin 18. However, it is predisposed to malignancy. Carcinogenesis occurs in

a stepwise manner through low-grade dysplasia, high-grade dysplasia and adenocarcinoma.

Progression to Malignancy



Carcinogenesis occurs as a result of accumulation of series of genetic and epigenetic alterations. These alterations include self-sufficiency in growth signals due to expression of oncogenes (cyclin D1, K-ras), growth factors (TGF-α), EGFR and insensitivity to anti-growth signals (TP53 and p16 inactivation).[41]Neovascularization and ability to invade and metastasize is achieved by expression of VEGF and MMPs.[22] Numerous genetic instability

have been detected in metaplastic cells at risk of cancer. Among them Aneuploidy detected by flow cytometry and FISH is a potential biomarker of neoplasia. [42]

CLINICAL FEATURES:

Barrett's oesophagus per se does not produce any characteristic clinical manifestations. Usually they will manifest features of chronic GERD. The clinical features of GERD are classified as oesophageal and extra-oesophageal. They are as listed below.

1. **Heart burn:**

   It is a classic symptom of GERD, described as burning sensation rising from the lower chest or stomach and radiating to the neck or throat. [43] It usually occurs postprandially and worsened by bending or supine posture. As a predominant symptom it has a specificity of (89%) and sensitivity of (38%) for GERD.[44]Heart burn for 2 or more days a week is usually diagnostic of GERD.

2. **Acid regurgitation:**

   Effortless regurgitation of acidic fluid especially after meals and worsened by supine posture and bending forward is highly suggestive of GERD.[44] Daily regurgitation is associated with LES hypotension

3. Less common symptoms are

    - Water brash,
    - Odynophagia,
    - Burping,
    - Hiccups, nausea, and vomiting,
    - Hematemesis and
    - Dysphagia.

4. **Extra-oesophageal symptoms :**

    Patients can present with noncardiac chest pain, asthma, reflux laryngitis, recurrent pneumonitis and dental erosions.[45] Numerous studies have shown that GER is the most common oesophageal cause of noncardiac chest pain.[46] GERD is seen in 34% to 89% of asthmatics. GERD should be considered in adult onset asthma without an atopic component.[47]It is one of the leading causes of chronic cough.

COMPLICATIONS OF GERD

Complications secondary to GERD have decreased significantly in the PPI era, especially non-cancer related complications. Some of the complications likely to occur and deserve attention are hemorrhagic oesophagitis, aspiration

pneumonia, and oesophageal rupture with severe oesophagitis, peptic stricture and Barrett's oesophagus. Upper Gastro Intestinal bleed is seen in 7-18%.[48] Peptic strictures are reported in 7% to 23% of untreated patients.[49]

COMPLICATIONS OF BARRETT'S OESOPHAGUS

Benign complications:

- Oesophagitis, Stricture formation, Ulceration and rarely Perforation.

  Oesophagitis: It has been shown in various studies 60 to 70% are found to have inflammation macroscopically, and on microscopy it is found in most patients. Inflammation is found in the more proximal segments. Persistent inflammation predisposes to stricture formation.

  Stricture: Various studies have shown that strictures occur in around 20-40% of individuals and is seen more often near the squamo-columnar junction.

  Ulceration: Ulceration in the columnarized segment has been reported to occur (2- 45%) in various studies. They can be asymptomatic or present with complications like bleeding (upto 50%) and rarely perforation.

Malignant complications:

- Low grade dysplasia

- High grade dysplasia and
- Malignancy – Barrett's predisposes to the development of adenocarcinoma of distal oesophagus.

The main concern with Barrett's metaplasia is its malignant potential. The overall incidence being 0.5% per year.[23] Low-grade and high-grade dysplasia develops at 4.3% and 0.9% per year respectively. A patient with Barrett's low grade and high-grade dysplasia have a 0.6% and 4 to 6% per year risk of malignancy.[24]

Since 1970's there has been a significant rise in the incidence of adenocarcinoma of the distal oesophagus. It has also been found in one of the studies that only 5% of individuals with malignancy were diagnosed to have BE, showing the ineffectiveness of available routine screening techniques (Dulai et al).[87] Dysphagia or development of alarm symptoms should alert to the possibility of malignancy.

DIAGNOSIS

There are 2 criteria for diagnosis of BE. They are endoscopy and histopathological examination.

ENDOSCOPY IN DIAGNOSIS : To make a diagnosis of columnar lined oesophagus on endoscopy one should first be aware of important anatomical landmarks, like the anatomical GEJ (proximal extent of gastric mucosal folds),

the Z line or squamo-columnar junction and appearance of columnar epithelium.[50]Endoscopically, columnar epithelium has a reddish colour and velvet like texture, which is readily distinguished from the pale and glossy squamous epithelium. **(Figure: 1)**

The diagnosis of long segment Barrett's can be done with reasonable accuracy, while lesions < 3 cm can be easily missed.[51] At endoscopy diagnosis is made by measuring the extent of columnar lining from GEJ proximally. As the columnar lining can be circumferential, tongue like projection or islands, the Prague criteria is used to describe the circumferential and maximum extent.[13] In a large scale endoscopic study the sensitivity and specificity for diagnosing CLO was 82% and 81% but significantly low for short segment disease.[52]

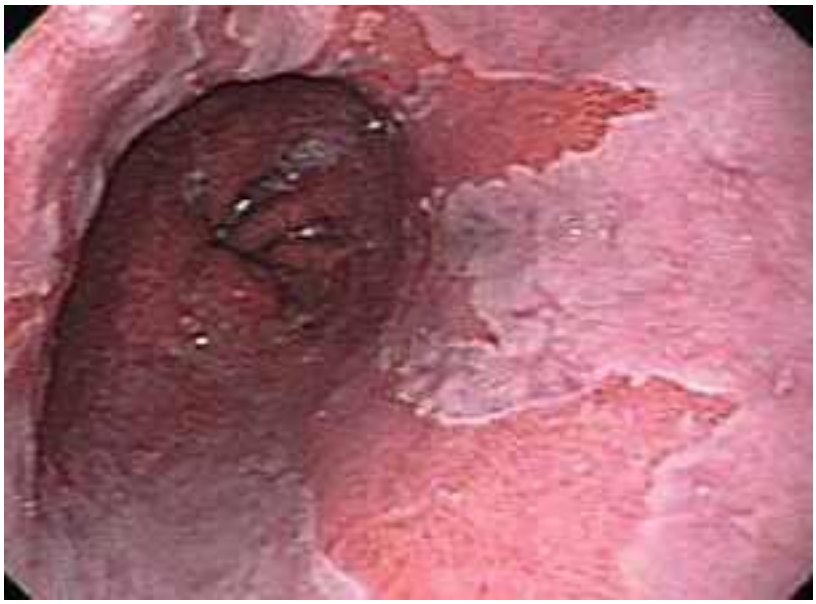


Figure 1: Shows the reddish, velvety columnar mucosa of Barrett's oesophagus

The next important role of endoscopy is to biopsy the columnar lined oesophagus. The most important role of oesophageal biopsy in patients with GERD is to determine the presence of Barrett's epithelium.[53]The protocols regarding site of biopsy, number of biopsies have been confusing. Studies have shown 4 quadrant biopsies at 2cm intervals may improve accuracy but data are lacking.[54]Overall routine white light endoscopy can identify long segment CLO with reasonable accuracy, with sensitivity dropping drastically for short segment CLO, stressing the need for alternative methods to endoscopically diagnose CLO.[52]

PATHOLOGY IN DIAGNOSIS :

Barrett's oesophagus occurs as a response to convert the compromised squamous epithelium to glandular epithelium which can resist acid induced tissue damage. The columnar lined epithelium can show three subtypes, namely cardiac type, fundic type and intestinal type.[55]Among these the intestinal type mucosa has characteristic villiform pattern with profound incomplete morphological and histochemical properties and is considered to be pathognomic of Barrett's metaplasia.[56]

Immunohistochemistry has demonstrated small intestinal type protein villin and cytokeratin histochemistry shows oesophageal specificity.[57,58] Lot of research has gone into identifying the type of epithelium required to confirm columnar metaplasia. It is now required to identify intestinal type of columnar

metaplasia with goblet cells and native oesophageal structures in juxtaposition in the biopsy specimen to make a definitive diagnosis of Barrett's oesophagus. **(Figure 2)**

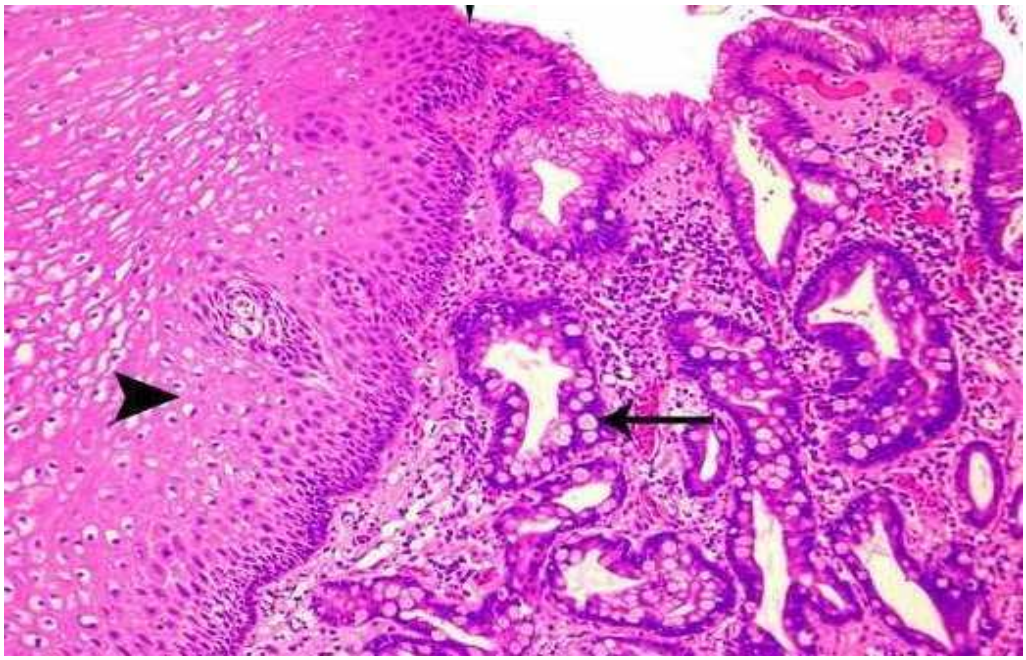


Figure 2 : Shows normal squamous epithelium (arrow head), juxtaposed with metaplastic columnar epithelium containing intestinal type goblet cells

Subsequently studies found that by using these criteria a definitive diagnosis can be made in only 10% to 15% of biopsies studied. In a multi-centre study conducted by United Kingdom Barrett's oesophagus registry only 15% of biopsies were found to have native oesophageal structures.[59]Hence the British Society of Gastroenterology guidelines suggests that "histological correlation of endoscopically visible columnarisation results in highest diagnostic accuracy".

The guidelines also recommend that the reporting of diagnostic biopsies be done as Biopsies diagnostic of CLO, Biopsies corroborative of endoscopic diagnosis, Biopsies in keeping with, but not specific for CLO and Biopsies with no evidence of CLO.

NEW ENDOSCOPIC MODALITIES :

Barrett's oesophagus is considered a premalignant condition. Regular endoscopic surveillance is recommended to diagnose early malignancy.[60] Barrett's mucosa is heterogenous in that areas of metaplasia, dysplasia and foci of early malignancy can occur simultaneously, making it difficult to distinguish with routine endoscopy and biopsy.[61] As discussed above routine white light endoscopy can easily miss short segment Barrett's, areas of dysplasia and early adenocarcinoma, thereby stressing the need for alternative methods to endoscopically diagnose CLO. New developments which have shown lot of promise are discussed below.[52]

CHROMOENDOSCOPY :

"Chromoendoscopy, or chromoscopy, refers to the topical application of stains or dyes at the time of endoscopy in an effort to enhance tissue localization,characterization, differentiation, or diagnosis".[62] It enhances detection of dysplasia, early cancer of G.I tract and has clinical application in a wide range of conditions including Barrett's oesophagus. The stains or dyes

used are classified based on their mechanism of action as absorptive, contrast and reactive stains. Absorptive stains are used in study of Barrett's oesophagus. Among absorptive stains, methylene blue is most commonly used in detection of Barrett's metaplasia, associated dysplasia and cancer.[63]

METHYLENE BLUE CHROMOENDOSCOPY :

Most commonly used in the diagnosis of BE and its complications.[63] The mechanism is absorption of Methylene blue and staining of epithelium of small bowel, colon and intestinal metaplasia of oesophagus dark blue (Canto et al).[64] Whereas dysplasia and carcinoma show heterogenous or absent staining.[65] Methylene blue directed biopsy has a sensitivity of (32 to 98%) and specificity of (23 to 100%).

PROCEDURE :

Materials required :

1. Methylene blue (liquid formulation) – 0.5% strength
2. Spray catheter – 7 Fr
3. Biopsy forceps

Technique :

- The patient first undergoes a white light endoscopy

- The area to be stained is rinsed using normal saline or N-acetyl cysteine vigorously to remove excess mucous attached to the mucosa
- Then a Spray catheter is introduced through the working channel
- 5 to 10ml of Methylene Blue 0.5% is sprayed across the area of interest starting from squamo-columnar junction
- After two to three minutes, the excess dye is washed using normal saline
- 10 minutes later, staining pattern is noted and targeted biopsies taken.

SPRAY CATHETER :

The most important step in doing chromoendoscopy is staining of the area of interest. Proper and uniform circumferential staining is required, so that targeted biopsies can be taken, thus improving the yield of the procedure. This cannot be achieved using a regular catheter or cannula. Hence the need for an ideal catheter.

The spray catheter has at its tip, numerous fine porous openings, which sprays the solution in the form of a fine uniform mist at a certain pressure, resulting in uniform homogenous staining, thus making the procedure simple and easy **(Figure 3 & 4).**

Dimensions :

1. Size : 7 Fr,

2. Catheter Length – 240 cm, Stylet length – 100cm,

3. Catheter tip – spray and

4. Minimum accessory channel – 2.8 mm

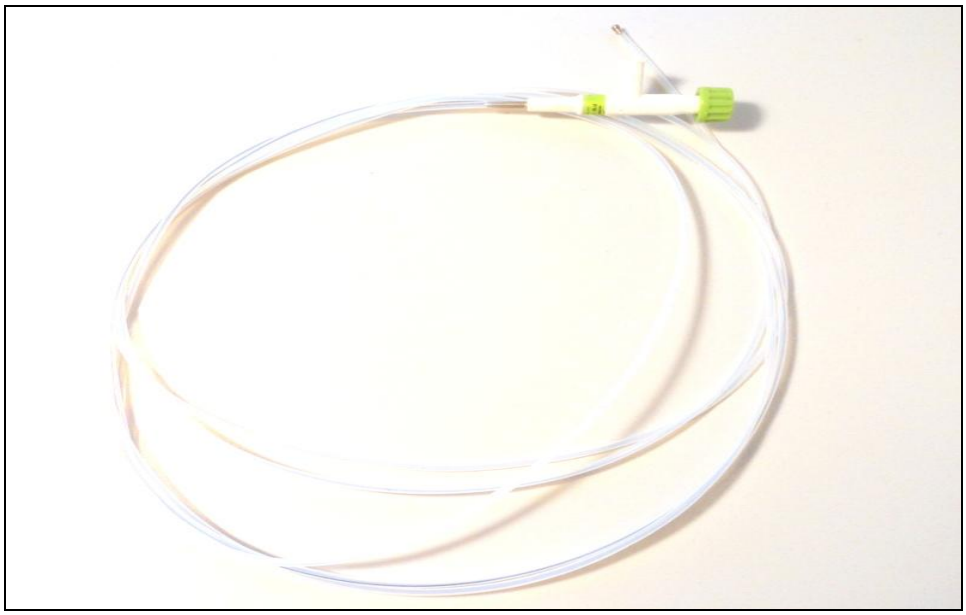


Figure 3 : Spray catheter used in our study

Figure 4 : Depicts fine,uniform and circular spraying of dye using spray catheter

Ragunath K, Krasner et al in a randomized control trial published in 2003 reported a statistically significant increased detection rate for Barrett's metaplasia using methylene blue chromoendoscopy directed biopsy in comparison to white light endoscopy and random biopsy.[66]

Similarly John David Horwhat et al in a randomized control trial published in 2008 found that using methylene blue chromoendoscopy lesser number of biopsies were required to diagnose Barrett's metaplasia and dysplasia. They also reported that methylene blue chromoendoscopy helped to define areas to target for biopsy.[85]Increased detection of dysplasia and cancer in Barrett's oesophagus has also been demonstrated in studies.[65]

The main disadvantage with methylene blue chromoendoscopy is the differences in staining technique, inter and intra-observer variability in interpreting staining pattern as reported by Meining A et al.[67] Overall methylene blue C.E has better detection rate and is inexpensive, relatively easy to perform with minimal side effects.

Various other new endoscopic modalities have been developed to improve detection of metaplasia, dysplasia and cancer. They will be discussed in brief as follows.

High Resolution Endoscopy (HRE): These are endoscopes with mechanically and electronically moveable lens at the distal tip of variable focal length, which

can be zoomed in and out at areas of interest without compromise of image quality. Sharma et al has described areas of high grade dysplasia to have irregular mucosal pattern on HRE.[68] Various studies have also shown the efficacy of HRE in detecting intestinal metaplasia.[69] Finally HRE when combined with chromoscopy increases the yield significantly.

Narrow Band Imaging (NBI):

The NBI system has a standard high definition mode and in addition an NBI mode where an interference filter is used to illuminate the area of interest using narrowed red, blue and green filters, with a relative increase in blue filter bandwidth. By the above mechanism, different images at different levels of mucosa are seen, with an increase in contrast between epithelium and underlying vasculature. The end result is image and mucosal characterization of high resolution without the need of chromoscopy.[70]

Autofluorescence Imaging (AFI):

In AFI certain molecules called fluorospore when excited or stimulated by ultraviolet light; emit fluorescent light spreadover a range of longer wavelengths from the green to thered spectrum. The composition of fluorospores in dysplastic and metaplastic epithelium is different and hence have different autofluorescence spectra compared to normal epithelium. Many studies have reported good results in distinguishing non-dysplastic from dysplastic and cancerous tissue in Barrett's oesophagus.[71] AFI results are

affected by tissue morphology and it samples only a small area, hence needs further validation.

Some of the other modalities which have shown promise are optical coherence tomography (OCT) and light scattering spectroscopy.

MANAGEMENT :

Management includes treatment per se and surveillance. The decision to treat, the type of treatment and the ideal surveillance strategies differ from one individual to another. It also depends on the extent of lesion and the presence or absence of dysplasia. Treatment of Barrett's oesophagus includes medical (acid suppression), endoscopic therapy and surgery.

A. Treatment of Non-dysplastic Barrett's:

1. **Acid suppression:** Treatment of GERD in patients with Barrett's oesophagus does not differ much from that in the general population, except that it is recommended to maintain therapy with a PPI even in the absence of symptoms. The reason for this approach is based on the evidence that persistent exposure to acid promotes carcinogenesis.[72]For individuals with no adequate clinical or endoscopic response it is recommended to increase the dose of PPI by four times or the maximum recommended dose. Both American college of gastroenterology and British society of gastroenterology recommend use of PPI at a dose that controls GERD symptoms and heals oesophagitis.

2. **Antireflux surgery:** The role of fundoplication in Barrett's oesophagus is similar to GERD in the general population at present. A meta-analysis conducted by Mayo clinic showed that competent fundoplication reduced the need for PPI and also reduced the risk of adenocarcinoma.[73]But a meta-analysis by Corey et al did not show statistical significance.[74] At present it is recommended not to do fundoplication for the sole purpose of cancer prevention.
3. **Endoscopic Ablation:** Endotherapy is a useful therapeutic tool which removes the metaplastic epithelium and leads to regeneration of squamous epithelium.[75]Endotherapy is of two types namely thermal and non-thermal. Among the various ablative modalities RFA gives the best results. The problem at present is the persistence of rests of glandular metaplasia underneath the neo-squamous epithelium.[76]At this juncture ablative therapy as a single modality is not recommended for non-dysplastic Barrett's.

B. Management of Low-grade Dysplasia:

Diagnosis of low-grade dysplasia in Barrett's CLO first needs to be confirmed with a repeat biopsy after 8 to 12 weeks of aggressive PPI therapy as presence of oesophagitis can result in false positive diagnosis.[77]If repeat biopsy confirms the diagnosis then management is similar to non-dysplastic Barrett's

CLO. Regular surveillance at 6month or 1 year interval until regression and then every 2 to 3 years is recommended.[78]

C. Management of High-grade Dysplasia:

Diagnosis of high grade dysplasia needs a repeat confirmation by an expert pathologist. Treatment should be individualized. Individualization is based on age, comorbidities and life expectancy. Treatment options include endotherapy and surgery. Young, healthy individual with verified high-grade dysplasia is best treated with esophagectomy,[79] whereas for an elderly, infirm individual with comorbidities, endotherapy is best suited.[80] For short segment CLO, Endoscopic mucosal resection (EMR) followed by PPI and for long segment Barrett's, EMR followed by RFA is recommended.[81]

SURVEILLANCE:

Barrett's oesophagus is a pre-malignant condition, with risk of cancer being 0.5% per year, with risk increasing to 0.6% with low grade dysplasia and 4% to 6% with high grade dysplasia. Considering the increased risk and good treatment outcomes with early detection of malignancy, it is important to have regular surveillance programs. Surveillance protocols differ according to whether an individual has non-dysplastic or dysplastic Barrett's oesophagus. The guidelines put forward by various societies are discussed below.

Non-dysplastic Barrett's:

In an individual with Barrett's metaplasia without dysplasia, verified on 2 consecutive endoscopy and biopsy, the American college of Gastroenterology guidelines recommends surveillance endoscopy and four quadrant biopsy at three year intervals.[82] The British Society of Gastroenterology guidelines on the other hand recommend surveillance endoscopy with four quadrant biopsy and biopsy of any suspicious lesion once in two years.[83,84] Among the two the American guidelines is the most widely accepted and followed.

Dysplastic Barrett's:

If low-grade dysplasia is identified on biopsy from CLO, both the American and British society of gastroenterology recommend a repeat endoscopy and quadrantic biopsy after 8 to 12 weeks of PPI therapy. The repeat biopsy needs careful evaluation by an experienced pathologist for evidence of dysplasia and any foci of invasive carcinoma. If the repeat endoscopy and biopsy is positive for low-grade dysplasia, then the American college of gastroenterology recommends surveillance endoscopy and quadrantic biopsy plus biopsy of any new lesion at one year interval,[82] while the British society recommends endoscopy and four quadrant biopsy every 6 months.[78]

AIM OF THE STUDY

AIM OF THE STUDY

- To evaluate and compare the efficacy of methylene blue chromoendoscopy inthe detection of Barrett's metaplasia, Dysplasia & early esophageal adenocarcinoma in high risk population compared to routine random biopsy.

MATERIALS AND METHODS

MATERIALS AND METHODS

This is a hospital based prospective cohort study, done at Department Of Digestive Health and Sciences, Government Peripheral hospital, Anna nagar, Chennai from April 2013 to February 2014. A total of 50 patients were selected for the study using the inclusion criteria.

INCLUSION CRITERIA:

1. Chronic Gastro-oesophageal reflux disease
2. Chronic smoking
3. Chronic Alcohol intake
4. Obesity

EXCLUSION CRITERIA:

1. Oesophageal candidiasis
2. Oesophageal varies
3. Hypersensitivity / allergy to drugs
4. Prior H/o oesophageal malignancy
5. H/o endoscopic therapy
6. NSAID intake
7. Pregnancy

METHODOLOGY:

50 patients were selected based on the inclusion and exclusion criteria

- A detailed history was taken and physical examination done for all the patients
- Complete blood count, renal parameters and random blood sugars were checked for all patients
- Written and informed consent was obtained from all the patients prior to the procedure
- White light video oesophago-gastroduodenoscopy was done and random four quadrant biopsy was taken from columnar appearing and suspicious lesions of the distal oesophagus

Technique of staining :

- Spray catheter is introduced through the working channel. The area to be stained is washed with normal saline.
- Then 0.5 % methylene blue, 5 ml to 10ml was sprayed over the areas of interest distal to proximal starting from the OGJ. A vigorous saline rinse was done to remove the excess dye.

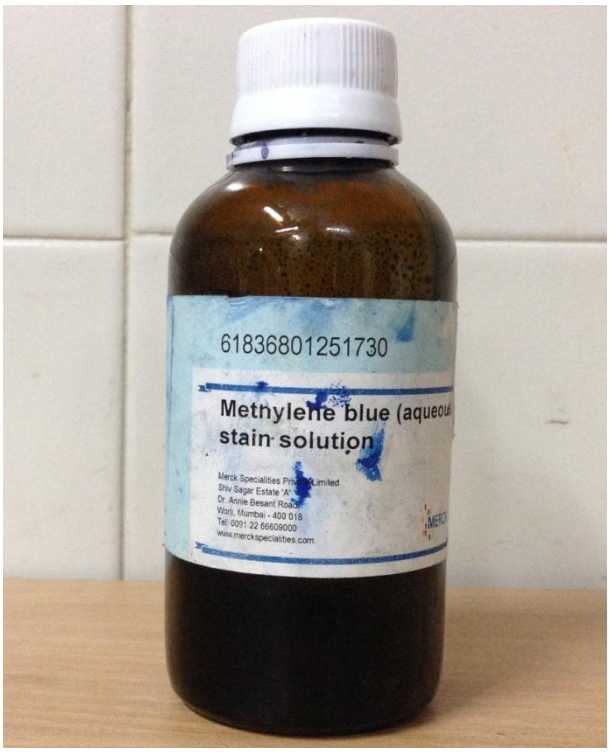
- After 10 minutes, a repeat VOGD was done, staining pattern was observed and targeted biopsies were taken as per staining pattern.

Biopsy material was sent for histopathological examination using routine Haematoxylin, eosin and Alcian blue staining to look for evidence of Barrett's metaplasia, dysplasia and adenocarcinoma.

- Results were assessed and compared for the detection of Barrett's metaplasia, dysplasia and adenocarcinoma.

Materials required :

1. Methylene blue (liquid formulation) – 0.5% strength
2. Spray catheter – 7 Fr, 240cm, minimal accessory channel of 2.8 mm
3. Biopsy forceps

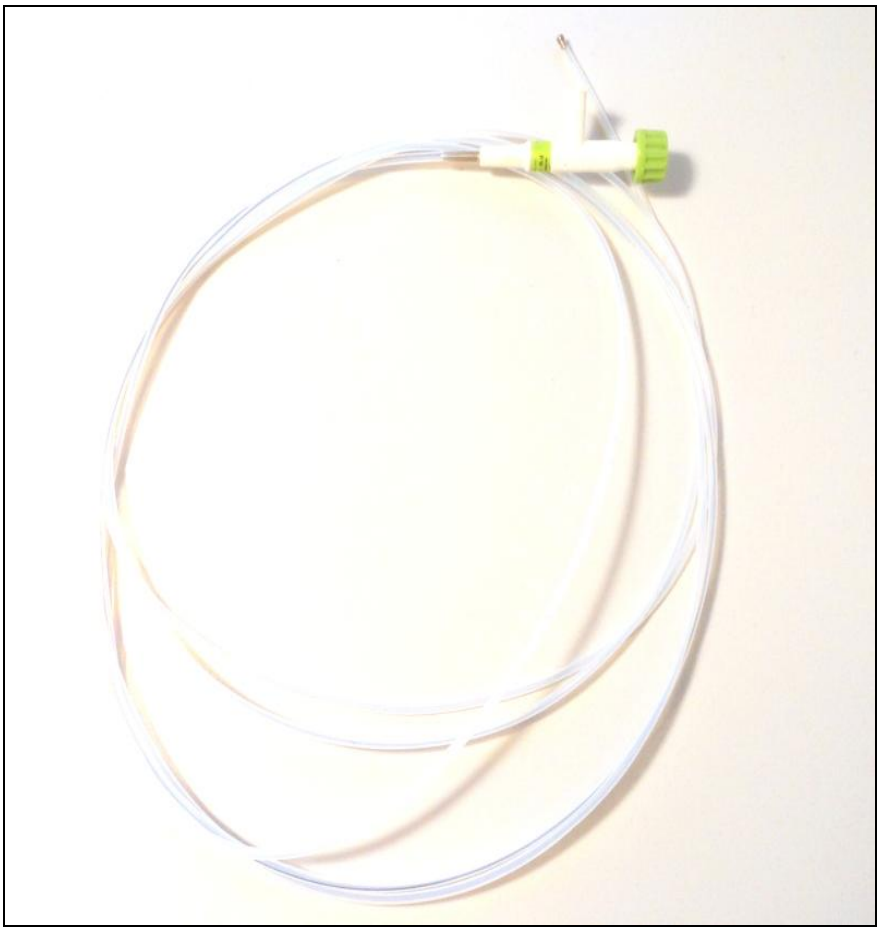


Methylene Blue (0.5%) from Merc specialities used in the study

SPRAY CATHETER USED IN THE STUDY

Dimensions :

1. Size : 7 Fr,
2. Catheter Length – 240 cm, Stylet length – 100cm,
3. Catheter tip – spray and
4. Minimum accessory channel – 2.8 mm



Spray catheter used in the study

RESULTS AND ANALYSIS

RESULTS AND STATISTICAL ANALYSIS

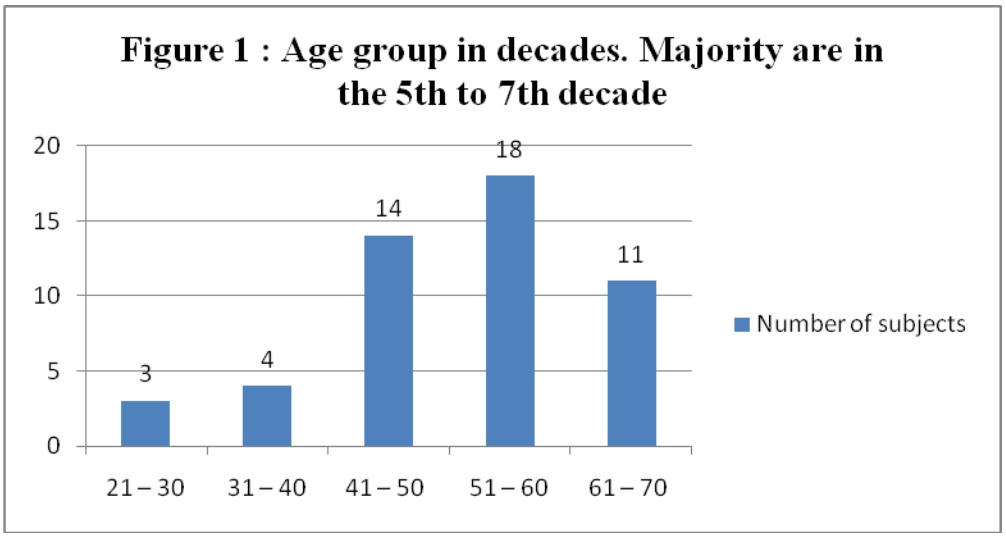
A total of 50 patients were included for the study based on inclusion criteria. All patients had atleast one feature of Chronic GERD

Statistical analysis was done using SPSS software (Version 19). Univariate and Multivariate analysis was done. Z test for proportion was used to compare histology results of the two study arms.

AGE DISTRIBUTION : Among the 50 patients included in our study, most of the patients were middle aged with 18 (36%) in the 6th decade followed by 28% in the 5th and 22% in the 7th decade. **(Table 1, Figure 1)**

Age groups	Number of subjects	Percentage
21 – 30	3	6
31 – 40	4	8
41 – 50	14	28
51 – 60	18	36
61 – 70	11	22
Total	50	100

Table 1: Shows the age distribution of subjects



GENDER DISTRIBUTION:

Among the 50 patients in our study 40 (80%) were males and 10 (20%) were females. (Table 2, Figure 2)

Table 2: Gender Distribution

Gender	Number of subjects	Percentage
Male	40	80
Female	10	20
Total	50	100

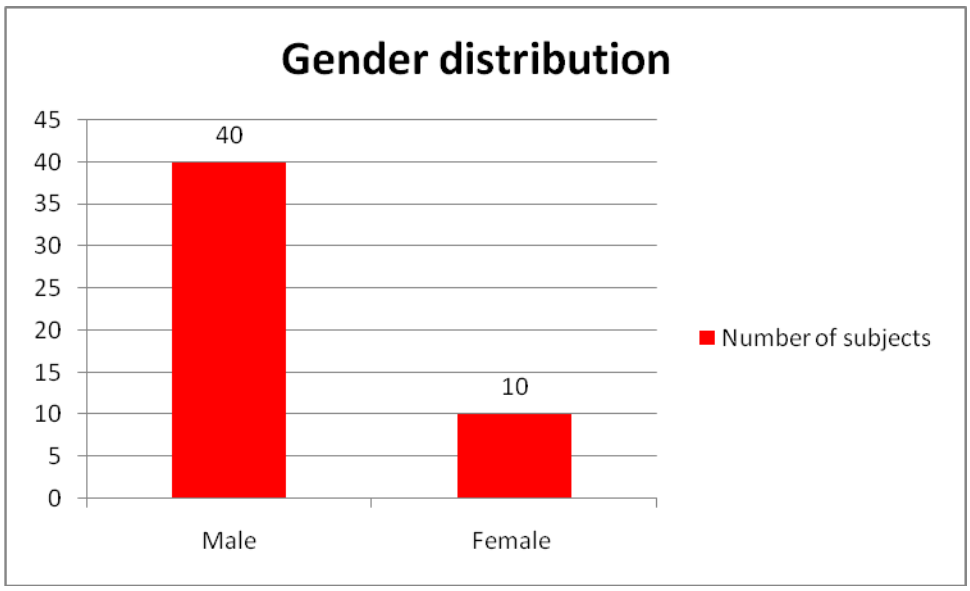


Figure 2: Depicts gender distribution. 40 (80%) were male patients

PRESENTING COMPLAINTS: In our study most of the patients presented with clinical features of GERD. Among which Heartburn (n=40), and Regurgitation (n=31) were the most common presentation. 11 (22%) also had nocturnal symptoms. All the patients had atleast 1 symptom of GERD, with many having more than two features of GERD. **(Table 3; Figure 3)**

Table 3: Shows presenting features of study population

Presentation	Number of subjects	Percentage
Heart burn	40	80%
Regurgitation	31	62%
Non-cardiac chest pain	8	16%
Vomiting	5	10%
Nocturnal symptoms	11	22%

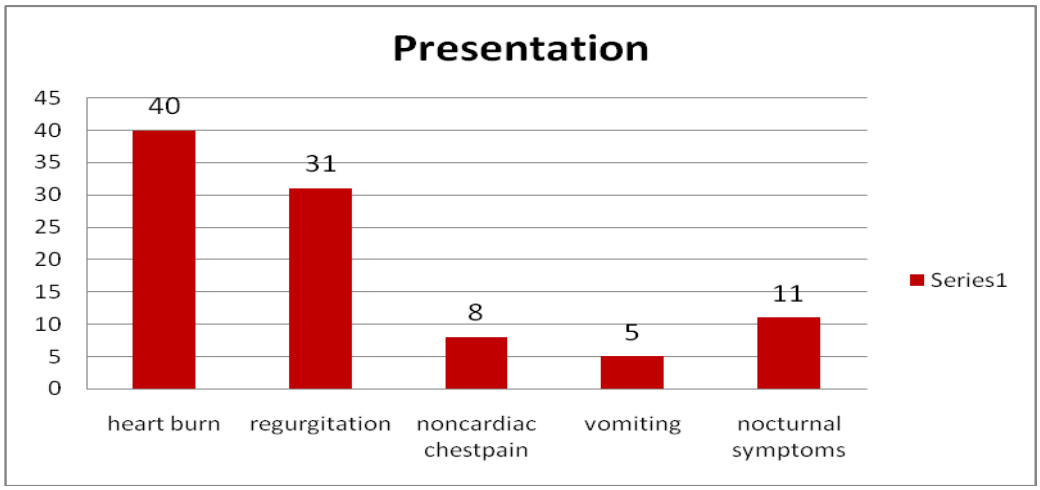


Figure 3: Shows the clinical presentation in the study population.

RISK FACTORS:

In our study all 50 patients had chronic GERD. Among the other risk factors smoking was seen in 28 (56%), Alcohol intake was seen in 12 (24%) and Obesity in 8 (16%). Patients either had a single or combination of risk factors. **(Table 4; Figure 4)**

Table 4 : Shows the risk factors seen in the study population

Risk Factors	Number of Subjects	Percentage
Chronic GERD	50	100%
Obesity	8	16%
Smoking	28	56%
Alcohol	12	24%

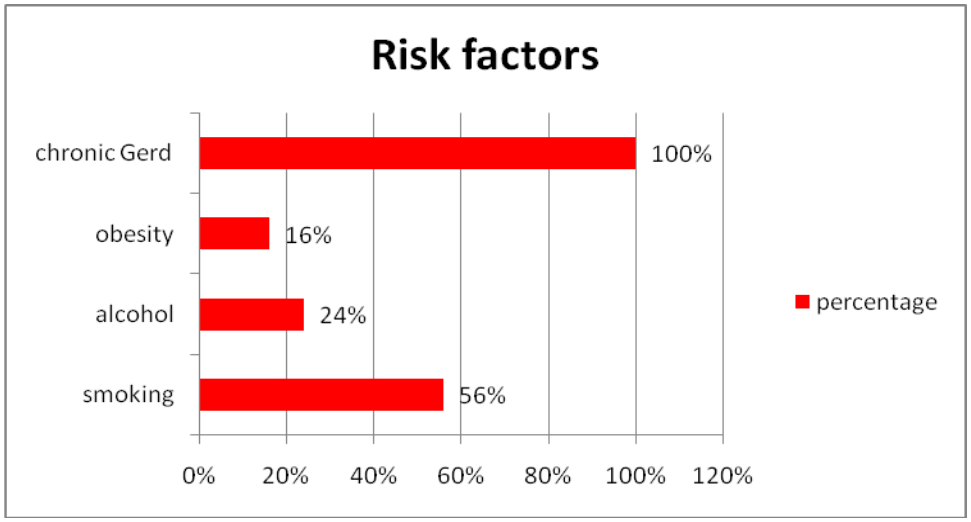


Figure 4: Depicts the risk factors and their prevalence in the study population

METHYLENE BLUE STAINING PATTERN:

In our study the presence of homogenous dark blue staining was considered uniform pattern and heterogenous staining was classified as patchy staining pattern. Out of the 50 patients studied 11(22%) had uniform staining pattern , 35 (70%) had patchy staining and 4 had absent staining. **(Figure 5, 6& 7).**

Table5 : Shows the staining pattern and their frequency

Staining pattern	Number of subjects	Percentage
Uniform staining	11	22%
Patchy staining	35	70%
Absent	4	8%

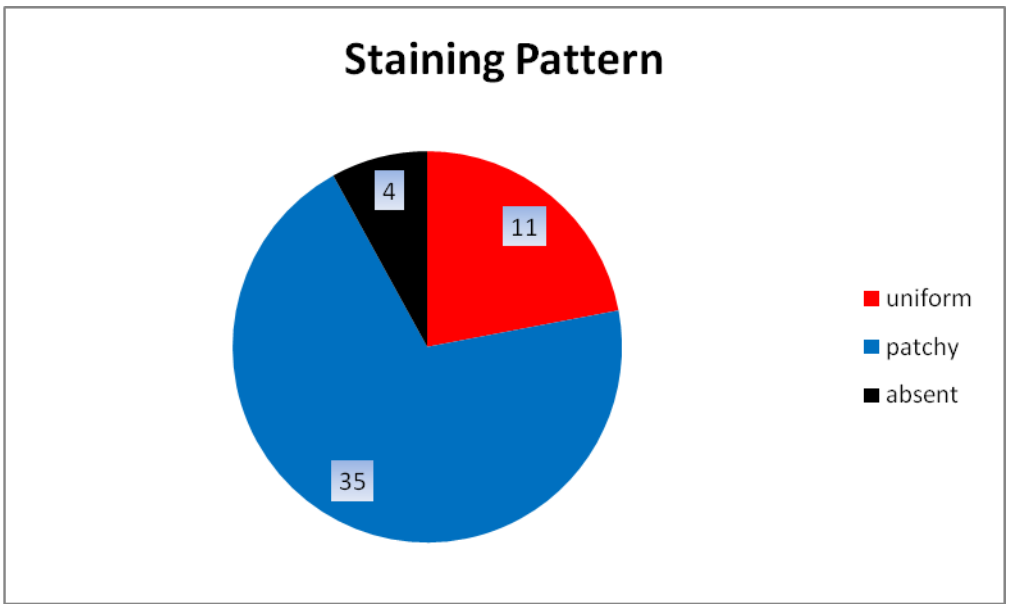


Figure 5 : Depicts the staining pattern in the study population

DIFFERENT STAINING PATTERNS

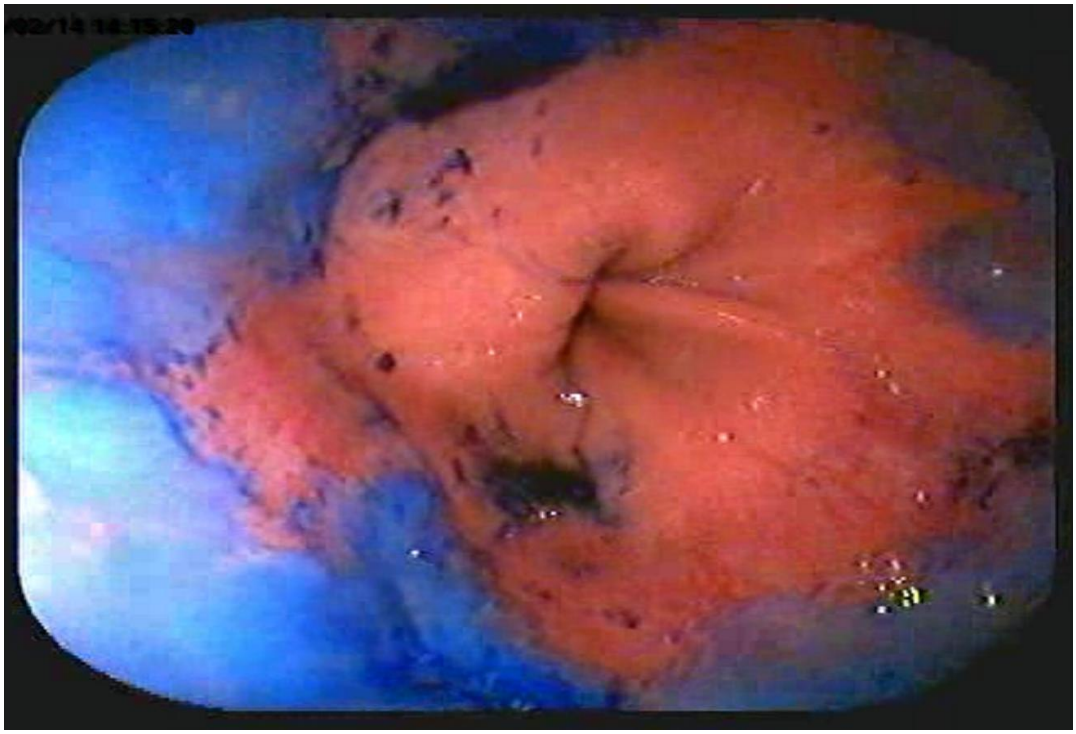


Figure 6: Depicts uniform staining pattern in a patient with Barrett's

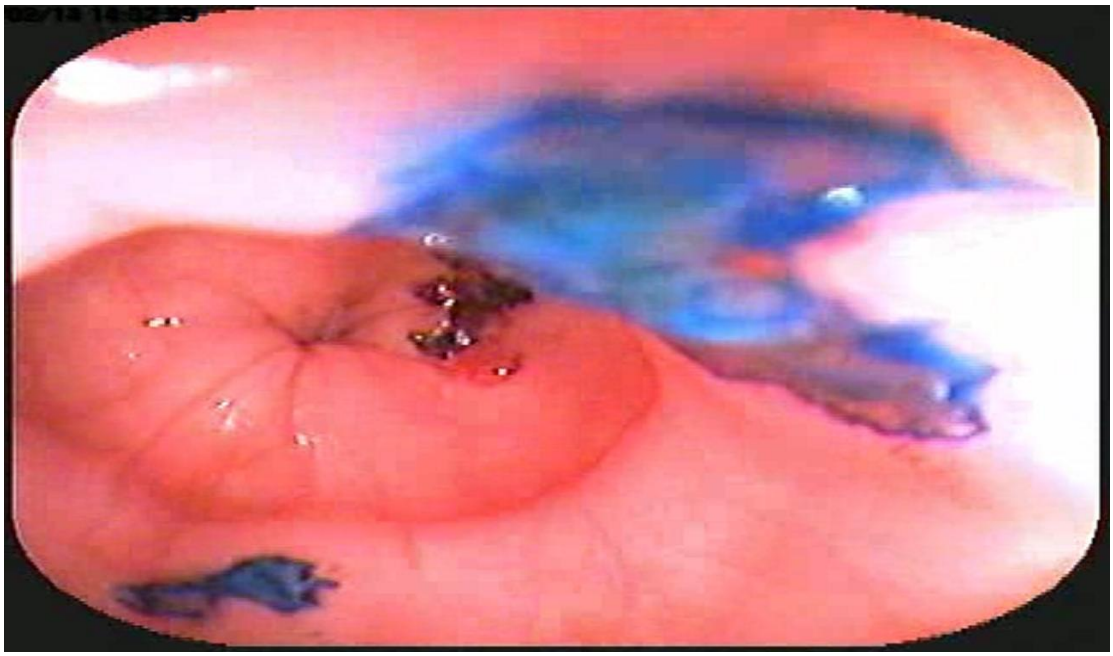


Figure 7 : Depicts patchy staining

NUMBER OF BIOPSIES :

In our study, a total of 189 biopsies were taken from areas of interest in the random biopsy arm and 139 biopsies in the methylene blue chromoendoscopy arm. The average number of biopsies taken in the random biopsy arm was 4 and number of biopsies taken in the MBDB arm was 3.

The reason for decreased number of biopsies required in the MBDB arm can be explained by the targeting of the biopsies to the well stained areas highlighted by methylene blue. **(Table 6; Figure 8)**

Table 6: Shows the total and average number of biopsies in each arm

Biopsy type	Total number	Average number
Random biopsy	189	3.78
MBDB	139	2.78

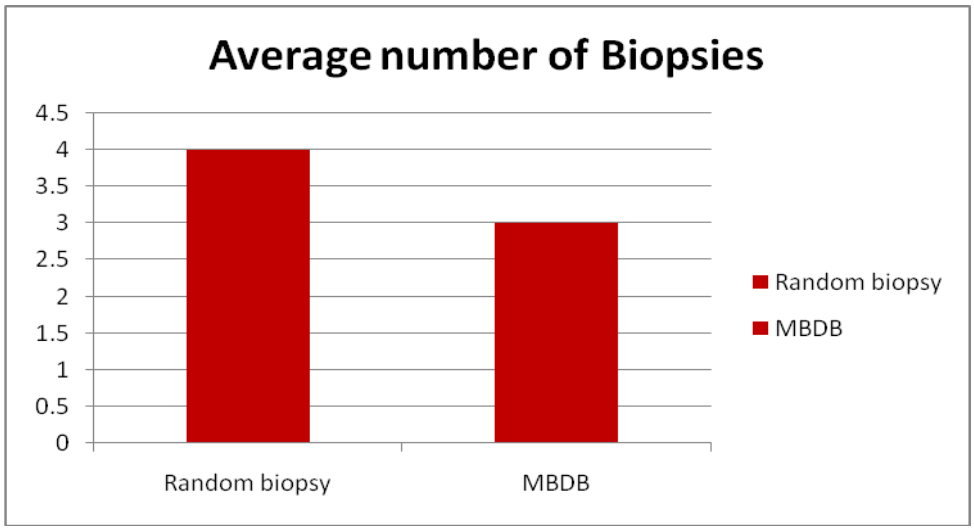


Figure 8 : Shows the average number of biopsies taken in each arm

Correlation between Staining pattern and Study end points:

Among 50 patients, 5 patients were diagnosed to have Barrett's metaplasia in the methylene blue chromoendoscopy arm. Out of these 5 patients 4 had uniform staining and 1 had patchy staining pattern. (Figure 6)

Out of the 50 patients 2 patients were diagnosed to have low-grade dysplasia. Out of these 2 patients 1had uniform and 1 had patchy staining. **(Figure 9)**

Patients with Barrett's metaplasia were more likely to have uniform staining. However the above findings did not have any statistical significance.

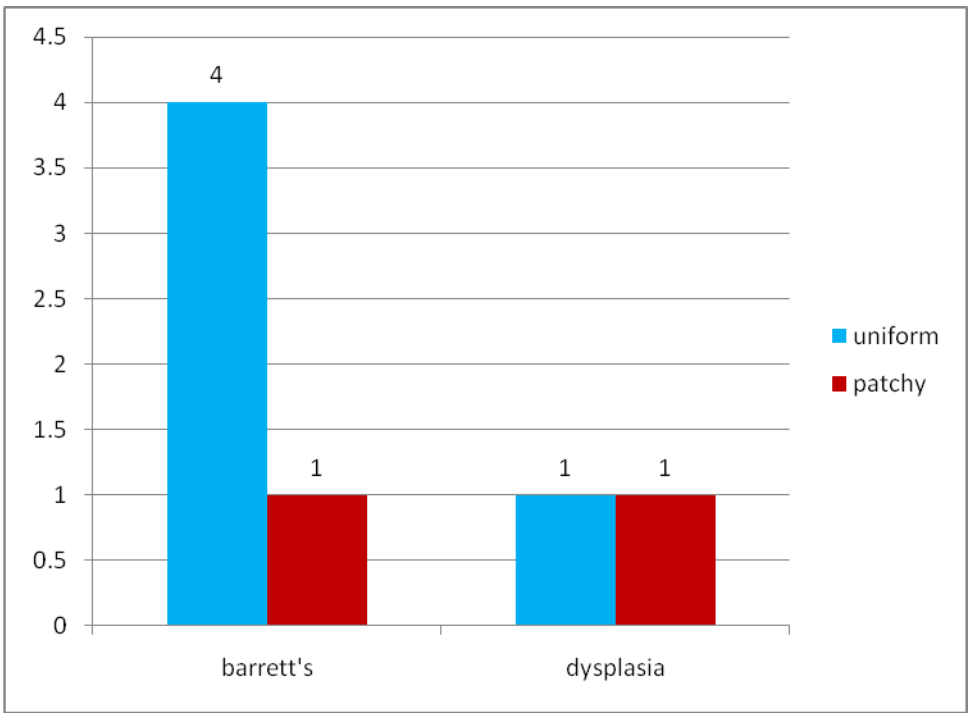


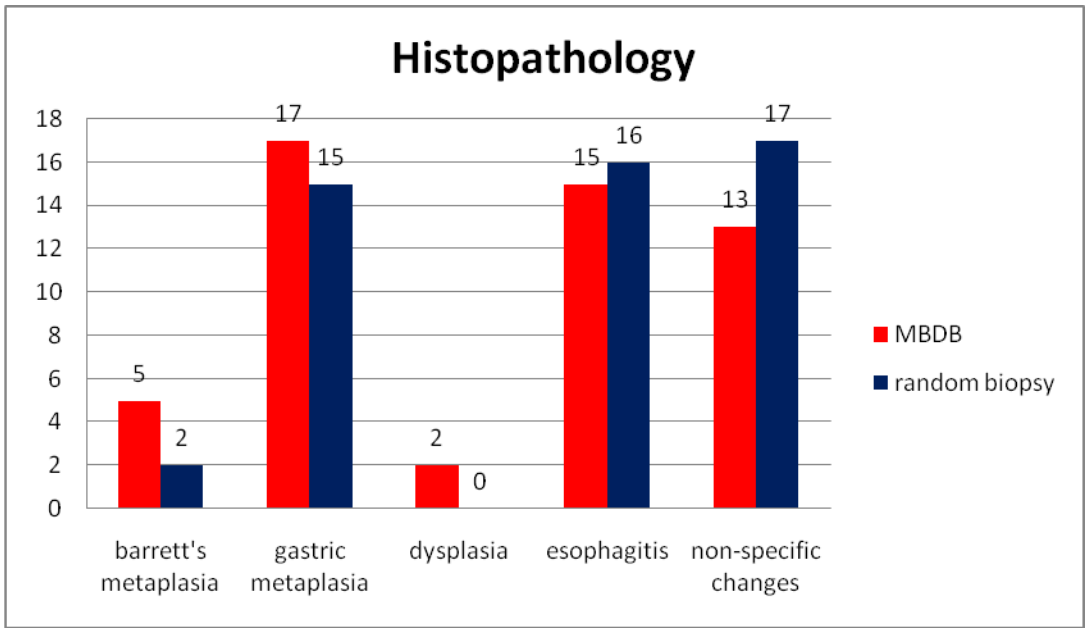
Figure 9: Shows staining pattern in patients with Barrett's & dysplasia

HISTOPATHOLOGY:

In our study overall 5 (10%)patients were diagnosed to have Barrett's metaplasia using methylene blue chromoendoscopy, whereas only 2 (6%) patients were diagnosed to have Barrett's using random biopsy. 3 out 5 with Barrett's were found to have non-specific changes in the Random Biopsy group. The 2 arms of the study were comparable for detection of gastric metaplasia and Oesophagitis.

Figure 10 : Depicts Histological Correlation between the 2 study arms.

MBDB – Methylene Blue Directed Biopsy



Z TEST FOR PROPORTIONS

a. **Barrett's :** 6% of subjects were diagnosed with Barrett's in white light endoscopy - random biopsy, whereas 10% of subjects were diagnosed with Barrett's in methylene blue chromoendoscopy, but the difference is not statistically significant; (Z is -0.7372, p value – 0.459)
b. **Dysplasia :** 0% of subjects were diagnosed with Dysplastic changes in white light endoscopy - random biopsy, whereas 4% of subjects were diagnosed with dysplastic changes in methylene blue chromoendoscopy, but the difference is not statistically significant; (Z is – 1.4286, p value – 0.153)

DISCUSSION

DISCUSSION

Barrett's oesophagus represents an adaptive response of the mucosal lining of the distal oesophagus to the injurious effect of acid refluxing from the stomach over a prolonged period of time. Various studies have come up with different definitions for Barrett's. At present the definition which is accepted and followed is the ACGE definition in 1998. ACGE definition requires endoscopically proven change in the epithelial type and histological confirmation of intestinal metaplasia.[11]

The condition derives its importance because of its malignant potential. BE predisposes to the development of adenocarcinoma and this risk is found to correlate directly with the extent of lesion and the presence of dysplastic foci.[12] Since 1970's there has been a significant rise in the incidence of adenocarcinoma of the distal oesophagus. It has also been found in one of the studies that only 5% of individuals with malignancy were diagnosed to have BE, showing the ineffectiveness of available routine screening techniques (Dulai et al).[87]

Hence, it is important to make an early and definitive diagnosis of Barrett's oesophagus in high-risk groups. Routine white light endoscopy and biopsy is the commonly used screening technique. The diagnosis of lesions lesions>3cm can be done with reasonable accuracy, but easily misses smaller

lesions and dysplastic foci (Sharma et al).[51]Hence the need for alternative methods to endoscopically diagnose CLO.

In our study we have compared the efficacy of routine endoscopy and biopsy with methylene blue chromoendoscopy for detection of Barrett's oesophagus and its complications.

AGE GROUP :

In most of the studies in literature the most common age group at diagnosis is 6th and 7th decades, with a median age being approximately 55years. Studies have also found a significant increase in diagnosis above the 5th decade. (Bonelli L et al)[16]

In our study 43(86%) out of 50 patients were above the 5th decade, with 36% found in the 6th decade. Out of the 5 patients diagnosed to have Barrett's oesophagus 1 patient was in the 6th decade, 2 each in the 5th and 7th decade. The age distribution in our study is similar to other studies in literature.

GENDER :

Most studies of the studies done in patients having chronic GERD for diagnosis of BE have found a male predominance. In most of the studies 65 -75 % of the patients are male (Cameron AJ et al).[87]In a study by Van Blankenstein et al[88] a male to female ratio of four is to one was observed.

In our study 40 (80%) patients were male. This predominance of male sex in our study is in accordance with most studies in literature.

PREDISPOSING FACTORS :

Among predisposing factors studied, chronic gastro-oesophageal reflux is the most important. There appears to be linear correlation between increase in GERD prevalence and Barrett's. This finding has been validated in many studies and meta-analysis (Singh P; Taylor RH et al).[20] Among other factors central obesity is strongly associated (Hampel et al)[21] and smoking increases the risk modestly.[22]

In our study all 50 patients had features of Chronic GERD. Chronic smoking was present in 28(56%), Alcohol consumption in 12(24%) and obesity in 8(16%). Out of the 5 patients with Barrett's all had features of GERD, 3 patients were obese and 3 had smoking and alcohol consumption.

The result for GERD in our study is comparable to studies in literature (Singh P et al). The relationship for other predisposing factors does not correlate well with other studies.

STAINING PATTERN :

There was controversy regarding the staining pattern after methylene blue chromoendoscopy among various studies. ASGE guidelines for staining is currently used and also followed in our study. Persistent dark blue staining is

considered positive for metaplasia (Canto et al)[64] and heterogenous or absent staining suggestive of dysplasia or malignancy .[65]

In our study 11 out of 50 patients had uniform dark blue staining and 35 patients had patchy staining. Out of 5 patients with BE in our study, 4 patients had uniform staining and 1 had patchy staining. Out of 2 patients with dysplasia 1 each had uniform and patchy staining. The staining pattern for Barrett's oesophagus in our study is in accordance with studies in literature (Ragunath K, Krasner et al).[66]

NUMBER OF BIOPSIES :

Most studies on the efficacy of MBCE in the diagnosis of barrett's have shown that the number of biopsies required in the chromoendoscopy arm was significantly less compared to the routine endoscopy and random biopsy arm.

In a randomized control trial by John David Howard et al published in 2008 it was found that using methylene blue chromoendoscopy lesser number of biopsies were required to diagnose Barrett's metaplasia and dysplasia.

In our study, the total number of biopsies required were 189 and 139 in the random biopsy and MBDB arm respectively. The average number of biopsies required were 4 and 3 in random biopsy and MBDB arm respectively. This is in accordance with most studies in literature.

PREVALENCE :

The prevalence of BE worldwide is not exactly known because around one-third of these patients are asymptomatic(Gerson et al).[86] Overall prevalence in the western population ranges from 2 to 7%, with a slightly decreased prevalence in the Asians.(Ronkainen J et al)[19]

In a study by Punia RS et al[89] in the Indian population the prevalence was found to be 23.6%, out of 55 patients with Chronic GERD. This high prevalence could attributed to the inclusion of gastric metaplasia n making a diagnosis.

In our study the 6% detection rate of BE in random biopsy arm is similar to the overall prevalence worldwide, while the 10% detection rate in MBDB arm is higher than worldwide prevalence. This increase in detection rate in the MBDB arm is attributed to well targeted biopsies taken from dark blue stained areas.

Detection of Barrett's Oesophagus and Dysplasia:

Most studies on the efficiency of methylene blue chromoendoscopy in the diagnosis of Barrett's have shown a significantly better rate of detection for chromoendoscopy.

Ragunath K, Krasner et al in a randomized control trial published in 2003 reported a statistically significant increased detection rate for Barrett's

metaplasia using methylene blue chromoendoscopy directed biopsy in comparison to white light endoscopy and random biopsy.[66]

SimilarlyJohn David Horwhat et al in a randomized control trial published in 2008 found that using methylene blue chromoendoscopy lesser number of biopsies were required to diagnose Barrett's metaplasia and dysplasia.

In our study on histopathological examination Barrett's oesophagus was detected in 2 (6%) of patients on random biopsy arm, while 5(10%) were diagnosed in the methylene blue chromoendoscopy arm. The increased detection rate in the MBDB arm is attributed to targeted biopsies taken from dark blue stained areas. MBDB arm detected more cases and the results were in accordance with literature[(66,85)] (Z is 0.7372, P – 0.459)

In our study low grade dysplasia was not detected in any of the patients in the random biopsy arm, while 2 (6%) of biopsies in MBDB arm were positive for these lesions. Again MBDB detected cases were routine biopsy was negative, and the results are are in accordance with literature (John David Horwhat et al)[85] (Z is -1.4296, P – 0.153).

CONCLUSION

CONCLUSION

- This study is the first of its kind to be done in South India.
- In our study Methylene Blue Chromoendoscopy and biopsy diagnosed Barrett's metaplasia to a higher percentage than white light endoscopy and routine biopsy in patients with chronic gastro-oesophageal reflux disease.
- Further uniform staining pattern also suggested that the patient was more likely to have Barrett's metaplasia when compared to patchy staining.
- This procedure is very useful and can be done and reproduced in any centre without requirement of any specialized equipment. Hence Chromoendoscopy with Methylene blue is a useful tool for early detection of Barrett's oesophagus and thereby suggest appropriate treatment and surveillance for oesophageal malignancy.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Spechler SJ: Barrett's esophagus. *N Engl J Med* 2002; 346:836-842.
2. Barrett NR: Chronic peptic ulcer of the oesophagus and "oesophagitis.". *Br J Surg* 1950; 38:175-182.
3. Allison PR, Johnstone AS. The oesophagus lined with gastric mucous membrane. Thorax 1953; 8: 87–101. III
4. Moersch R, Ellis FH, McDonald JR. Pathologic changes occurring in severerefluxoesophagitis. SurgGynecolObstet 1959; 108: 476–484. IV
5. Bremner CG, Lynch VP, Ellis FH. Barrett's esophagus: congenital or acquired? An experimental study of esophageal mucosal regeneration in the dog. Surgery 1970; 68: 209–216. IIb
6. Paull A, Trier JS, Dalton MD, Camp RC, Loeb P, Goyal RP. The histological spectrum of Barrett's oesophagus. N Engl J Med 1976; 295: 476–480. III
7. Naef AP, Savary M. Ozzello L. Columnar-lined lower esophagus: an acquired lesion with malignant predisposition: report on 140 cases of Barrett's esophagus with 12 adenocarcinomas. J ThoracCardiovasc Surgery 1975; 70: 826–834. IIb
8. Skinner DB, Walther BC, Riddell RH, Schmidt H, Iascone C, DeMeesterTR.Barrett's esophagus: comparison of benign and malignant cases. Ann Surg 1983; 198: 554–565. III

9. Reid BJ, Haggitt RC, Rubin LE, Rabinovitch PS. Barrett's esophagus: correlation between flow cytometry and histology in detection of patients at risk for adenocarcinoma. Gastroenterology 1987; 93: 1–11. IIb
10. Spechler SJ &Goyal RK. The columnar-lined esophagus, intestinal metaplasia and Norman Barrett. Gastroenterology 1996; 110: 614–621.III
11. Sampliner RE, for the Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus. *Am J Gastroenterol*. 2002;97:1888–95.
12. Dekel R, Wakelin DE, Wendel C, Green C, Sampliner RE, Garewal HS, Martinez P, Fass R. Progression or regression of Barrett's esophagus—is it all in the eye of the beholder? Am J Gastroenterol 2003;98:2612–2615.
13. Sharma P, Dent J, Armstrong D, et al: The development and validation of an endoscopic grading system for Barrett's esophagus: The Prague C & M criteria. *Gastroenterology* 2006; 131:1392-1399.
14. Savary M, Miller G L'oesophage. Manuel et Atlas d'Endoscopie. Solothurn: VerlagGassmann, 1977
15. Cameron AJ: Epidemiology of columnar-lined esophagus and adenocarcinoma. *GastroenterolClin North Am* 1997; 26:487-494
16. BonelliL,& GOSPE. Barrett's esophagus: Results of a multicentric survey. Endoscopy 1993; 25 (suppl) 652–654. III

17. Hassall E: Esophageal metaplasia: Definition and prevalence in childhood. *GastrointestEndosc* 2006; 64:676-677

18. Prach AT, MacDonald TA, Hopwood DA, Johnston DA. Increasing incidence of Barrett's oesophagus: education, enthusiasm or epidemiology? The Lancet 1997; 350: 933. III

19. Ronkainen J, Aro P, Storskrubb T, et al: Prevalence of Barrett's esophagus in the general population: An endoscopic study. Gastroenterology 2005; 129:1825-1831

20. Singh P, Taylor RH, Colin-Jones DG. Esophageal motor dysfunction and acid exposure in reflux esophagitis are more severe if Barrett's metaplasia is present. American J Gastroenterol 1994; 89: 3: 349–356.IIb

21. Hampel H, Abraham NS, El-Serag HB: Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med* 2005; 143:199-211.

22. Souza RF, Spechler SJ: Concepts in the prevention of adenocarcinoma of the distal esophagus and proximal stomach. *CACancer J Clin* 2005; 55:334-351.

23. Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS: Is there publication bias in the reporting of cancer risk in Barrett's oesophagus?. *Gastroenterology* 2000; 119:333-338.

24. Spechler SJ: Dysplasia in Barrett's esophagus: Limitations of current management strategies. *Am J Gastroenterol* 2005; 100:927-935.

25. Holloway RH, Penagini R, Ireland AC: Criteria for objective definition of transient lower esophageal sphincter relaxation. *Am J Physiol* 1995; 268:G128-G133.

26. Dent J, Holloway RH, Toouli J, Dodds WJ: Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastroesophageal reflux. *Gut* 1988; 29:1020-1028.

27. Dodds WJ, Dent J, Hogan WJ, et al: Mechanisms of gastro-esophageal reflux in normal human subjects. *N Engl J Med* 1982; 307:1547-1552.

28. Mattioli S, D'Ovidio F, Pilotti V, et al: Hiatus hernia and intrathoracic migration of the esophagogastric junction in gastroesophageal reflux disease. *Dig Dis Sci* 2003; 48:1823

29. Koek GH, Sifrim D, Lerut T, et al: Multivariate analysis of the association of acid and duodeno-gastro-oesophageal reflux exposure with the presence of oesophagitis, the severity of oesophagitis and Barrett's oesophagus. *Gut* 2008; 57:1056-1064.

30. Sontag SJ, Schnell TG, Miller TQ, et al: The importance of hiatal hernia in reflux esophagitis compared with lower esophageal sphincter pressure or smoking. *J ClinGastroenterol* 1991; 13:628

31. Helm JF, Dodds WJ, Pek LR, et al: Effect of esophageal emptying and saliva on clearance of acid from the esophagus. *N Engl J Med* 1984; 310:284.

32. Kahrilas PJ, Dodds WJ, Hogan WJ, et al: Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1986; 91:897

33. Helm JF, Dodds WJ, Hogan WJ, et al: Acid neutralizing capacity of human saliva. *Gastroenterology* 1987; 83:69

34. Helm JF, Dodds WJ, Ricdel DR, et al: Determinants of esophageal acid clearance in normal subjects. *Gastroenterology* 1983; 86:607

35. Stein HJ, Barlow AP, DeMeester TR, Hinder RA: Complications of gastroesophageal reflux disease. *Ann Surg* 1992; 216:35

36. Vaezi MF, Richter JE: Role of acid and duodenogastro-esophageal reflux in gastro-esophageal disease. *Gastroenterology* 1996; 111:1192.

37. Hirschowitz BI: Gastric acid and pepsin secretion in patients with Barrett's esophagus and appropriate controls. *Dig Dis Sci*1996;41:1384-1391

38. Rex DK, Cummings OW, Shaw M, et al: Screening for Barrett's oesophagus in colonoscopy patients with and without heartburn. *Gastroenterology* 2003; 125:1670-1677.

39. Sarosi G, Brown G, Jaiswal K, et al: Bone marrow progenitor cells contribute to esophageal regeneration and metaplasia in a rat model of Barrett's esophagus. *Dis Esophagus* 2008; 21:43-50.

40. Souza RF, Krishnan K, Spechler SJ: Acid, bile and CDX: The ABCs of making Barrett's metaplasia. Am J PhysiolGastrointest Liver Physiol2008; 295:G211-G218.

41. Hanahan D, Weinberg RA: The hallmarks of cancer. Cell 2000; 100:57-70

42. Fritcher EG, Brankley SM, Kipp BR, et al: A comparison of conventional cytology, DNA ploidy analysis, and fluorescence in situ hybridization for the detection of dysplasia and adenocarcinoma in patients with Barrett's esophagus. *Hum Pathol* 2008; 39:1128-1135.

43. Carlsson R, Dent J, Bolling-Sternevold E, et al: The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease. *Scand J Gastroenterol*1998;33:1023

44. Klauser AG, Schindlebeck NE, Muller-Lissner SA: Symptoms of gastro-oesophageal reflux disease. *Lancet* 1990; 335:205.

45. Extraesophageal presentations of gastroesophageal reflux disease. *Am J Gastroenterol* 2000; 25:S1.

46. Richter JE: Approach to the patient with non-cardiac chest pain.In: Yamada T, ed. *Textbook of gastroenterology*, ed 2. Philadelphia: JB Lippincott; 1995:648

47. Irwin RS, Curley FJ, French CL: Difficult-to-control asthma: contributing factors and outcome of a systemic protocol. Chest 1993;103:1662

48. DaCosta N, Guillaume C, Merle C, et al: Bleeding reflux esophagitis: A prospective 1-year study in a university hospital. *Am J Gastroenterol* 2001; 96:47.

49. Richter JE: Peptic strictures of the esophagus. *GastroenterolClin North Am* 1999; 28:875.

50. Delvaux M, Korman LY. Minimal standard terminology. *Endoscopy* 2000;32:159–88. IV

51. Sharma P, Morales TG, Sampliner RE. Short segment Barrett's oesophagus—the need for standardization of the definition and of endoscopic criteria. *Am.J.Gastroenterol.* 1998;93:1033–6. III

52. Eloubeidi MA, Provenzale D. Does this patient have Barrett's oesophagus? The utility of predicting Barrett's esophagus at the index endoscopy. *Am J Gastroenterol.* 1999;94:937–43. IIb

53. DeVault KR, Castell DO: Updated guidelines for the diagnosis And treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2005; 100:190.

54. Stein JH, et al. Esophageal cancer: screening and surveillance. Results of a consensus conference held at the VIIth World Congress of the International Society for Diseases of the Esophagus. *Dis Oesophagus*1996;9suppl 1:3–19. IV

55. Paull A, Trier JS, Dalton MD, Camp RC, Loeb P, Goyal RK. The histologic spectrum of Barrett's esophagus. *N Engl J Med* 1976;295:476–80. III

56. Spechler SJ. The columnar-lined esophagus. History, terminology, and clinical issues. *GastroenterolClin North Am* 1997;26:455–66. IV

57. MacLennan AJ, Orringer MB, Beer DG. Identification of intestinal-type Barrett's metaplasia by using the intestine-specific protein villin and esophageal brush cytology. *MolCarcinog*1999;24:137–43. III

58. Boch JA, Shields HM, Antonioli DA, Zwas F, Sawhney RA, Trier JS. Distribution of cytokeratin markers in Barrett's specialized columnar epithelium. *Gastroenterology* 1997;112:760–5. III

59. Biddlestone LR, Bailey TA, Whittles CE, Shepherd NA. The clinical and molecular pathology of Barrett's oesophagus. In Kirkham N, Lemoine NR, eds. *Progress in Pathology*. London: Greenwich Medical media, 2000, in press. III

60. Sampliner RE. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus. The Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol 1998;93:1028–32.

61. Riddell RH. Early detection of neoplasia of the esophagus and gastroesophageal junction. Am J Gastroenterol 1996;91:853–63.

62. Fennerty MB. Tissue staining. GastrointestEndoscClin N Am 1994;4:297.

63. Canto MI. Chromoendoscopy and magnifying endoscopy for Barrett's esophagus. ClinGastroenterolHepatol 2005;3:S12-5.

64. Canto MI, Setrakian S, Willis J, et al. Methylene blue–directed biopsies improve detection of intestinal metaplasia and dysplasia in Barrett's esophagus. GastrointestEndosc 2000;51:560-8.

65. Canto MI, Setrakian S, Willis JE, et al. Methylene blue staining of dysplastic and nondysplastic Barrett's esophagus: an in vivo and ex vivo study. Endoscopy 2001;33:391-400.
66. Ragunath K, Krasner N, Raman VS, et al. A randomized, prospective cross-over trial comparing methylene blue-directed biopsy and conventional random biopsy for detecting intestinal metaplasia and dysplasia in Barrett's esophagus. Endoscopy 2003;35:998-1003.
67. Meining A, Rosch T, Kiesslich R, et al. Inter- and intra-observer variability of magnification chromoendoscopy for detecting specialized intestinal metaplasia at the gastroesophageal junction. Endoscopy 2004;36:160-4.
68. Sharma P, Weston AP, Topalovski M, et al. Magnification chromoendoscopy for the detection of intestinal metaplasia and dysplasia in Barrett's oesophagus. Gut 2003;52:24–7.
69. Guelrud M, Herrera I, Essenfeld H, et al. Enhanced magnification endoscopy: a new technique to identify specialized intestinal metaplasia in Barrett's esophagus. GastrointestEndosc 2001;53:559–65.
70. Kara MA, Bergman JJ, Fockens P, et al. Narrow band imaging for mucosal pattern recognition in Barrett's esophagus. Presented at Digestive Disease Week [abstract]. Gastroenterology 2004;126:A50.

71. Georgakoudi I, Jacobson BC, Van Dam J, et al. Fluorescence, reflectance, and light-scattering spectroscopy for evaluating dysplasia in patients with Barrett's esophagus. Gastroenterology 2001;120:1620–9.

72. Feagins LA, Zhang HY, Hormi-Carver K, et al: Acid has antiproliferative effects in nonneoplastic Barrett's epithelial cells. *Am J Gastroenterol* 2007; 102:10-20.

73. Bammer T, Hinder RA, Klaus A et. Rationale for surgical therapy of Barrett's esophagus. Mayo Clinic Proc. 2001; 76:335–342. 11a

74. Corey KE, Schmitz SM, Shaheen NJ. Does a surgical antireflux procedure decrease the incidence of esophageal adenocarcinoma in Barrett's esophagus? A meta-analysis. Amer J Gastroenterol,2003;98:2390–2395.11a

75. Barham CP, Jones RZ, Biddlestone LR et al. Photothermal laser ablation of Barrett's oesophagus: endoscopic and histological evidence of squamous re-epithelialisation. Gut 197; 41: 281–4. IIb

76. Van den Boogert J, van Hillegersberg R, Siersena PD et al. Endoscopic ablation therapy for Barrett's esophagus: a review. Am J Gastroenterol 1999; 94: 1153–1159.III

77. Ouata-Lascar R, Fitzgerald RC, Triadafilopoulos G Differentiation and proliferation in Barrett's esophagus and the effects of acid suppression.Gastroenterology 1999;117:327–335. Grade IIb

78. Dent J, Bremner CG, Collen MJ et al. Working party report to the World Congresses of Gastroenterology, Sydney 1990: Barrett's Oesophagus. J GastroenterolHepatol 1991; 6: 1–22. IV.

79. Clark GWB, Ireland GWB, DeMeester TR. Dysplasia in Barrett's esophagus: Diagnosis, surveillance and treatment. Dig Dis 1996; 14: 213–227. III

80. Soehendra H, Binmoeller KF, Bohnacker S, et al. Endoscopic snaremucosectomy in the esophagus without any additional equipment: a simple technique for resection of flat early cancer. Endoscopy 1997; 29: 380–383. III.

81. Bremner RM, Mason RJ, Bremner CG, et al. Ultrasonic epithelial ablation of the lower esophagus without stricture formation. A new technique for Barrett's ablation. SurgEndosc 1998; 12: 342–346. IV.

82. Wang KK, Sampliner RE: Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008; 103:788-797.

83. Provenzale D, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. Am.J.Gastroenterol. 1999, 94, 2043–2053. (III)

84. Boyer J, Robaszkiewicz M. Guidelines of the French Society of Digestive Endoscopy: monitoring of Barrett's esophagus. The Council of the

French Society of Digestive Endoscopy. Endoscopy 2000, 32, 498–9. (IV)

85. John David Horwhat, Corinne L Maydonovitch, Fernando Ramos, Ramon Colina, Erich Gaertner, + et al.The American Journal of Gastroenterology 103, 546-554 doi:10.1111/j.1572-0241.2007.01601.

86. Gerson LB, Shetler K, Triadafilopoulos G. Prevalence of Barrett's oesophagus in asymptomatic individuals. Gastroenterology 2002;123:461-7.

87. Dulai GS, Guha S, Kahn KL, Gornbein J, Weinstein WM. Preoperative prevalence of Barrett's esophagus in esophageal adenocarcinoma: a systematic review. Gastroenterology 2002;122:26-33.

88. Gillan P, Keeling P, Byrne PJ. Implications of Duodenogastric Reflux in the Pathogenesis of Barrett's Oesophagus. Br J Surg (1988); 75: 540–543. IIb

89. Punia RS, Arya S, Mohan H, Duseja A, Bal A. Spectrum of clinico-pathologi-cal changes in Barrett oesophagus. J Assoc Physicians India. 2006;54:187–189

ANNEXURES

PROFORMA

Name : Age/ Sex : DDHD No:

HISTORY:

Heart Burn : Chest Pain : Regurgitation : Reflux :

Belching: Water brash : Odynophagia:

Nausea/ Vomiting : Dysphagia : Hiccughs : Early Satiety :

Cough : Wheeze : Nocturnal symptoms :

PAST HISTORY

DM: SHTN: PTB : IHD : Previous Surgery : Previous endoscopic Therapy : Drug / NSAID intake :

PERSONAL HISTORY:Smoking : Alcohol intake :

Tobacco : Caffine : Sleep pattern : Diet :

FAMILY HISTORY : G.I Malignancy, Chronic GERD

GENERAL EXAMINATION:

SensoriuPallor: Icterus :Cyanosis : Clubbing :Pedaledema:

Lymphadenopathy :

Other Signs :

Height : Weight : BMI:

Pulse : Blood pressure : Temp :

SYSTEMIC EXAMINATION:

CVS : RS : P/A : CNS :

INVESTIGATIONS:

Hb : ESR : TC : DC : Platelets :

BT : CT: Rbs : Urea : Creatinine :

ECG : Chest X-Ray :

VOGD Report :

Methylene Blue Chromoendoscopy :

HPE Report :

MASTER CHART

S. NO	DDHD No	Age	Sex	Heartburn	Regugitation	NCCP	Vomiting	Nocturnal symptoms	Smoking	Alcohol	Obesity	White Light endoscopy	MBCE	RB	MBDB
1	3440/12	39	1	1	1	2	2	1	1	1	2	1	1	2	2
2	6611/13	44	1	1	2	2	2	1	1	1	2	2	1	1	1
3	7534/13	38	1	2	1	2	2	2	1	2	2	3	2	2	2
4	6993/13	61	1	1	1	2	2	1	2	1	1	2	1	5	1
5	4229/13	40	2	1	1	1	2	1	2	2	1	2	2	5	5
6	6350/13	23	2	2	1	2	2	2	2	2	2	3	2	4	4
7	4371/13	58	1	2	1	2	2	2	1	2	2	1	2	4	4
8	5150/13	62	1	1	1	2	2	2	1	1	2	3	2	4	4
9	4850/13	54	1	1	1	2	2	1	1	2	2	2	2	2	2
10	2150/12	57	1	1	1	2	2	1	1	2	1	1	1	2	2
11	5580/13	68	2	2	2	1	2	2	2	2	1	1	2	5	13
12	5823/13	62	2	1	1	2	2	2	2	2	2	1	2	2	2
13	708/05	48	1	1	1	2	2	2	1	2	2	3	2	4	4
14	5783/13	25	2	2	1	2	2	2	2	2	2	3	2	4	4
15	6042/13	42	2	1	2	2	1	2	2	2	2	2	2	4	5
16	4796/13	36	1	1	2	2	2	1	2	2	2	1	1	2	2
17	5817/13	58	1	1	1	2	1	2	1	1	1	1	1	1	1
18	5549/13	47	2	1	2	2	2	2	2	2	2	2	2	5	5
19	6264/13	50	2	1	1	2	2	2	2	2	2	3	2	4	4
20	3410/13	43	1	1	2	2	2	1	2	2	1	1	1	2	2
21	6375/13	28	2	1	2	2	2	2	2	2	2	3	2	4	4
22	4722/13	44	1	1	1	2	2	1	1	1	2	1	1	5	13
23	2778/11	53	1	1	1	2	2	2	1	2	2	1	2	5	2
24	1272/12	63	1	1	2	2	2	2	2	2	2	2	2	5	5
25	3767/10	46	1	1	2	2	2	2	1	2	2	3	2	4	4
26	4254/13	56	1	1	1	2	2	2	1	2	2	3	2	4	4
27	1243/10	54	1	1	2	2	2	2	1	2	2	2	2	5	2

28	6121/11	49	1	2	1	2	1	2	2	2	2	1	1	2	2
29	4879/13	58	1	1	2	2	2	2	2	2	2	2	2	5	5
30	3343/11	51	1	1	2	2	2	2	1	2	2	3	2	2	2
31	1657/12	59	1	1	1	2	2	2	2	2	1	1	1	2	2
32	2335/13	57	1	1	1	2	2	2	1	1	2	3	2	4	4
33	3698/12	60	1	1	2	2	2	2	1	2	2	1	1	5	5
34	4465/13	47	1	1	1	2	2	2	1	2	2	1	2	5	5
35	5767/13	65	1	1	2	2	2	2	2	2	2	1	2	2	2
36	6757/10	45	1	1	2	1	2	2	1	1	2	3	3	5	5
37	2712/12	55	1	2	1	1	2	2	1	2	2	2	2	5	5
38	199/14	58	1	1	1	2	2	2	1	2	2	3	2	4	4
39	307/14	54	1	1	1	2	1	1	1	1	2	1	1	2	2
40	611/14	66	1	2	1	1	2	2	2	2	2	1	2	4	4
41	457/10	46	1	1	2	2	2	2	1	1	2	3	3	5	5
42	1511/11	48	1	1	1	2	2	2	2	1	2	3	2	4	4
43	5344/13	58	2	1	1	1	1	1	2	2	2	1	2	4	4
44	731/14	59	1	1	1	2	2	2	1	2	2	2	2	5	5
45	852/12	61	1	2	2	1	2	2	2	2	2	1	2	2	2
46	6542/12	67	1	1	1	2	2	2	1	2	1	3	3	5	5
47	4856/13	42	1	1	1	2	2	2	1	1	2	2	2	4	4
48	5988/13	62	1	2	2	1	2	2	2	2	2	1	2	2	2
49	2654/12	53	1	1	2	2	2	2	1	2	2	3	3	5	5
50	934/10	64	1	1	1	2	2	2	1	2	2	2	2	2	2

Biopsy : 1- Barrett’s metaplasia, 2 – gastric metaplasia, 3 – dysplasia, 4 – oesophagitis, 5 – non-specific changes

Staining pattern : 1 – uniform staining, 2 – patchy staining, 3 – absent staining; Other parameters : 1-present, 2 - absent

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.3393/ME-1/Ethics/2013 Dt:02.05.2013
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study of mehtylene blue chromoendoscopy for the early diagnosis of barrett's metaplasia, dysplasia and early esophageal adenocarcinoma" - For dissertation purpose submitted by Dr.S.Mukundan, DM (Med. Gastro), PG Student, GRH, Chennai.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE
09 OCT 2013
Kilpauk, Chennai-10.

9/10/13.

CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,
Chennai