“ENDOSCOPIC BRUSH CYTOLOGY AND BIOPSY CORRELATION IN UPPER GASTROINTESTINAL NEOPLASMS ”

Dissertation Submitted in partial fulfillment of the

requirements for the degree of

M.D. (PATHOLOGY) DEGREE EXAMINATION

BRANCH - III

GOSCHEN INSTITUTE OF PATHOLOGY AND ELECTRON MICROSCOPY

MADRAS MEDICAL COLLEGE

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CHENNAI

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APRIL 2011

CERTIFICATE

This is to certify that this Dissertation entitled **"Endoscopic brush cytology and biopsy correlation in upper gastrointestinal neoplasms "** is the bonafide original work of Dr. G. NANDINI, in partial fulfillment of the requirement for M.D.,(Branch III) in Pathology examination of the Tamilnadu Dr.M.G.R Medical University to be held in April 2011.

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ACKNOWLEDGEMENT

I express my sincere thanks to **Prof. Dr. J.MOHANA SUNDARAM, M.D., D.N.B., Ph.D.,** Dean, Madras Medical College and Government General Hospital, for permitting me to utilize the facilities of the Institution.

I take this opportunity to express my heartfelt sincere gratitude to my esteemed guide, **Prof. Dr. A. SUNDARAM, M.D.,** Professor and Director of Institute of Pathology and Electron Microscopy, Madras Medical College, Chennai for his keen interest, constant encouragement, wholehearted support, valuable suggestions and expert guidance throughout the study, without which this study would not have ever been possible.

I am thankful to **Prof.Dr.P.KARKUZHALI, M.D.,** Professor of Pathology, Institute of Pathology and Electron Microscopy, Madras Medical College for her advice, encouragement and suggestions during the study.

I am extremely thankful to **Prof. Dr. GEETHA DEVADAS, M.D., D.C.P.,** Professor of Pathology, Institute of Pathology and Electron Microscopy, Madras Medical College for her guidance, suggestions, constant cheer and support throughout the study.

I take the opportunity to express my thanks to **Prof. Dr. SUDHA VENKATESH, M.D.,** Professor of Pathology, Institute of Pathology and Electron Microscopy, Madras Medical College for her opinions and encouragement throughout the study.

I express my heartfelt thanks to **Prof.Dr.SHANTHA RAVISHANKAR, M.D.,** Professor of Neuropathology, Institute of Neurology, Madras Medical College for her valuable advice and encouragements during the study.

My thanks to **Prof. Dr. M. P. KANCHANA, M.D.,** Professor of Pathology, Institute of Obstretics & Gynaecology, Madras Medical College for all her encouragement and opinions about the study.

I convey my thanks to **Prof. Dr. K. RAMA, M.D.,** Professor of Pathology, Government Kasturba Gandhi Hospital, Madras Medical College for her suggestions and support during the period of study.

I thank **Prof. Dr. T. CHITRA, M.D.,** Professor of Pathology, Institute of Child Health, Madras Medical College for her help and encouragement during the course of the study.

I thank **Prof. Dr. S.PAPPATHI, M.D., D.C.H.,** Professor of Pathology, Institute of Pathology and Electron Microscopy, Madras Medical College for her support during the study.

I put across my thankfulness to **Prof. Dr. INDIRA, M.D.,** Professor of Pathology, Regional Institute of Ophthalmology, Madras Medical College, for her abets and aids during the study.

I thank **Dr. T.B. UMADEVI M.D.,** Professor and Head Department of Pathology Tanjore Medical College, for helping me choose the thesis topic and her support during the study.

I thank **Prof. Dr. Mohamed Ali, M.D., D.M.**, Head of Department of Medical Gastro Enterology, Madras Medical College for providing me the Endoscopic data, cytology samples and for his encouragement and support during the study.

I would also like to thank **Dr. S. Y. JAGANNATHAN** for helping me in the statistical analysis.

I express my heartfelt sincere thanks to all my Assistant Professors for their help and suggestions during the study.

I am thankful to all my colleagues, friends, technicians and staff of the Institute of Pathology and Electron Microscopy, Madras Medical College, Chennai for all their help and support they extended for the successful completion of this dissertation.

Words are not enough to thank my family for their understanding, moral support and encouragement.

CONTENTS

ABBREVIATIONS

GI	:	Gastro intestinal
HPV	:	Human papilloma virus
GIT	:	Gastrointestinal tract
WHO	:	World health organization
BC	:	Brush cytology
EB	:	Endoscopic biopsy
N:C	:	Nucleus : cytoplasm
SCC	:	Squamous cell carcinoma
MGG	:	May-Grunwald-Giemsa
H&E	:	Haematoxylin & Eosin
AC	:	Adenocarcinoma

KEY TO MASTER CHART

+	:	Present
+	:	Extension of growth from the primary site
R	:	Reactive atypia
D	:	Dysplasia
Pos	:	Positive
Neg	:	Negative
Unsat	:	Unsatisfactory
Sus	:	Suspicious
WD	:	Well differentiated
MD	:	Moderately differentiated
PD	:	Poorly differentiated
PD-S	:	Poorly differentiated diffuse type
+D	:	Inflammation with dysplasia
Hgic	:	Hemorrhagic
HPE NO:		Histopathology number
GE jn	:	Gastro oesophageal junction

INTRODUCTION

Upper gastrointestinal tract is a common site for neoplasms, especially malignant tumors. Worldwide, gastric adenocarcinoma is the second most common cancer and carcinoma oesophagus is the sixth leading cause of death.[1,2]

In India, according to the National Registry, oesophagus and stomach are the leading sites for the development of cancer. Esophageal and gastric cancers are the most frequent cancers found in Indian men, while esophageal cancer ranks third among women after carcinoma of breast and cervix.[3]

Early detection of malignancy greatly improves the survival rate of the patients. The 5-year survival rate of early esophageal cancer is 83.5% and early gastric cancer is more than 90%.[4] With the advent of fiberoptic endoscopy, application of cytologic methods has become more popular in detecting and diagnosing the lesions of the different segments of the gastrointestinal tract. The major advantage of the GI endoscopy is the direct visualization of the lesions, which is apparently useful in selective sampling of the tissue for diagnosis.[5]

Various techniques for collection of cytological samples have been described.[6] Endoscopic direct vision brush cytology is one among them. Brush cytology will retrieve epithelial cells from a larger surface area of mucosa than a tissue biopsy. As malignant cells posses a lower level of intercellular

cohesion than normal cells, brushing can selectively sample these dyshesive cells. This procedure is non-invasive, cost effective and has a rapid turn over time.

Despite being popular and clinically useful, brush cytology is not routinely being performed in the Government general hospital. Therefore, the present study was undertaken to evaluate its utility in diagnosing neoplasms of the upper gastrointestinal tract.

AIMS & OBJECTIVES

1) To study the cellular components & their morphological alterations in brush cytology smears obtained from the upper GI neoplasms.

2) To correlate endoscopic brush cytology with tissue biopsy of upper gastrointestinal neoplasms.

3) To correlate clinical and endoscopic features with histopathology.

4) To evaluate the utility of endoscopic brush cytology in the diagnosis of upper GI neoplasms and if possible as an alternative to biopsy which is an invasive technique.

REVIEW OF LITERATURE

History of endoscopy and its application:

Attempts for accessing the hidden cavities of the human body had been made long before the twentieth century, although instruments used for the purpose were inadequate and apparently dangerous. The history of visual exploration and examination of the body orifices dates back to the Egyptian and the Greco-Roman periods. Phillip Bozzini is credited with the earliest known attempt to visualize the interior of a body cavity with a primitive endoscope.

Rudolf Schindler, known as “the father of gastroscopy”, is credited for introducing the semiflexible endoscope in 1932.The modern era of gastrointestinal endoscopies began in 1957, when Basil Hirschowitz and Lawrence Curtis at the University of Michigan, developed the first fiberoptic endoscope.[7]

Before the advent of endoscopes, cellular samples were obtained by lavage methods. In these procedures, large amounts of fluid were given orally and the patients were maneuvered into various positions so that the liquid would make contact with the entire mucosal surface. This procedure was introduced by Beale in as early as 1858 and reemphasized by Marini in 1909.[8]Apparently these methods were cumbersome to the patients and hence were not very popular.

In 1950 Panico, Papanicoloau and Cooper[9] used a balloon covered with silk mesh to retrieve samples from the gastro intestinal tract. Alterations in the balloons were made by Shu and Zhon by reducing the size of the balloons, so that it could more easily be swallowed and readily accepted.[9]

Kameva et al, in 1964 introduced brushing cytology under direct vision using fiberoptic gastroscopy.[10] In this technique, samples of the gastrointestinal lesions are retrieved by passing cytologic brushes through a separate channel in the endoscope. Cytologic brushes are composed of nylon bristles with an outer protective sheath, which prevents loss of cellular material as it is removed from the endoscope.

Over the past 20 years there has been remarkable progress in the various techniques used in the diagnosis and management of carcinoma. In 1984, digital / video endoscopy was introduced by Welch Allyn Inc., with which we have been able to magnify and reproduce the endoscopic image on a television monitor.

Japanese pioneered fiberoptic gastroscopy and brushing cytology because of high rates of gastric carcinoma in Japan.[11,12]In China, cytology is being used for the diagnosis of esophageal lesions.[13]Accuracy of brushing cytology for combined gastric histologic and cytologic studies have been reported as early as 1974.[11] Thus diagnostic brushing cytology is a well-established technique for the diagnosis of precancerous and cancerous lesions

of upper gastro intestinal tract.In India, however very few institutions have adapted these techniques.[15,16,17]Further improvisation has lead to the development of chromo-endoscopy where dye is used for detection of early lesions**.**

NORMAL CYTOLOGY OF THE UPPER GI TRACT:

The upper gastrointestinal tract includes oesophagus, stomach and first part of the duodenum. The wall of the GIT consists of mucosa, submucosa, muscularispropria and serosa, except in oesophagus, which lacks the serosal layer.

CYTOLOGY OF OESOPHAGUS:

Cytological samples from oesophagus show superficial and intermediate squamous cells. Superficial cells are polygonal and have abundant eosinophilic cytoplasm, central pyknotic nucleus. Intermediate cells are predominant and show a vesicular nucleus. Parabasal cells are sparse and seen as single cells with round or ovoid contours with dense cyanophilic cytoplasm and relatively high nuclear: cytoplasmic ratio.[18]

Glandular cells may also be present occasionally. This could be a columnar cell normally present in the distal oesophagus or due to inadvertent sampling of the stomach. These cells are seen in small to large flat sheets with sharply defined edges, distinct cellular borders and small round nucleus.

Nucleoli are inconspicuous with finely granular, pale staining chromatin.[19]Contaminants like ciliated respiratory columnar cells, pigment containing alveolar macrophages and food debris may be present.[19]

CYTOLOGY OF STOMACH:

Smears from the stomach consist of large tightly cohesive aggregates of glandular epithelial cells. These aggregates are seen as flat sheets with smooth, sharply defined edges. Cell borders are well defined. Nuclei of the cells are small, round or slightly ovoid with granular chromatin and inconspicuous nucleoli. Cytoplasm is granular or slightly foamy in appearance. These features combine to create the classic honeycomb appearance, which reflects the maintenance of normal polarity. The background of the smears usually has small numbers of both mononuclear cells and segmented leukocytes. Squamous epithelial cells from the oral cavity and oesophagus are the most common contaminants.[19]

CYTOLOGY OF DUODENUM :

Normal duodenum show large, flat, sheets of uniform epithelial cells in a honeycomb pattern.[19]

ESOPHAGEAL NEOPLASMS

WHO HISTOLOGICAL CLASSIFICATION [20]

Epithelial tumors

Squamous cell papilloma

Intra epithelial neoplasia

Squamous

Glandular (adenoma)

Carcinoma

Squamous cell carcinoma

Verrucous (squamous) carcinoma

Basaloid squamous cell carcinoma

Spindle cell (squamous) carcinoma

Adenocarcinoma

Adenosquamous carcinoma

Mucoepidermoid carcinoma

Adenoid cystic carcinoma

Small cell carcinoma

Undifferentiated carcinoma

Others

Carcinoid tumor

Non-epithelial tumors

Leiomyoma

Lipoma

Granular cell tumor

Gastrointestinal stromal tumor

Benign

uncertain malignant potential

malignant

Leiomyosarcoma

Kaposi sarcoma

Malignant melanoma

Others

Secondary tumors

Squamous cell carcinoma and adenocarcinoma account for the most malignant tumors. Sarcoma and melanoma are rare.[21]

ETIOPATHOGENESIS

Dietary factors are thought to be the most important etiological factor in squamous cell carcinoma. N-nitrosamines present in the food in high risk regions in China and Iran are found to be carcinogenic to oesophagus.[22]Smoked meat, fish and dried vegetables may also contain carcinogens.[23]Pickled vegetables and moldy foods eaten in China often have fungi such as Fusarium moniliforme and Alternaria alternata.[24]Alcohol, smoking are also important risk factors.[25]

In India smoked fish, chillies, hot tea and coffee, especially salted tea consumed in Kashmir are associated with high risk.[22]Vegetables, pulses, buttermilk and vegetarian diet are considered to be protective.[22,26,27]

Radiation, thermal injury, and HPV infection also play an important role in carcinogenesis of oesophagus.[22,28,29]Genetic factors like amplification and over expression of oncogenes c-myc, c-fos, c-eas, c-sis, cyclin-D, c-erbB have also been found in carcinogenesis.[24]

Recently there has been an increase in incidence of esophageal adenocarcinoma in the western countries in patients with Barrett's oesophagus.[30]This occurs in a well-characterized sequence. In reaction to

chronic gastroesophageal reflux, metaplasia of the normal stratified squamous epithelium of distal oesophagus occurs, resulting in Barrett's epithelium. Further genetic alterations in this epithelium lead to dysplasia and ultimately to adenocarcinoma. Smoking and to some extent alcohol use has also been linked to the development of adenocarcinoma.[31]

PATHOLOGY

Squamous cell carcinomas occur predominantly in the middle third followed by the upper third and lower third of oesophagus.Depending on the depth of invasion squamous cell carcinoma is termed as early or advanced. The "early carcinoma" became known since 1960s, when increased survival was found in patients detected in the early stage and treated by surgical resection.[24]

Dysplasia and carcinoma in situ are being recently recognized with increasing frequency. Malignant squamous cells involving the entire thickness of the epithelium with an intact basement membrane characterize carcinoma in situ or intra epithelial carcinoma. If the malignant cells do not extend beyond lamina propria, it is termed as intramucosal carcinoma.Now early carcinoma is defined as only carcinoma in situ and mucosal carcinoma.

Superficial spreading carcinoma is used for the tumors having a lateral intramucosal spread of at least 2cm beyond the invasive lesion.[32]Grossly superficial carcinoma present as flat, verrucous, polypoidal, ulcerating and infiltrating growth.

Advanced squamous cell carcinoma is that which invades the muscularispropria and beyond. Microscopically they are seen as well differentiated, moderately differentiated and poorly differentiated squamous cell carcinoma.

Well-differentiated squamous cell carcinoma is made up of oval or polyhedral tumor cells with round to oval nuclei and prominent nucleoli. Keratin and epithelial pearls are present in the center of the tumor cell groups.[33] In moderately differentiated squamous cell carcinoma cells are slightly smaller, more pleomorphic. Focal keratin and mitoses may be present.[33]Poorly differentiated squamous cell carcinoma shows extremely pleomorphic cells with variable amount of cytoplasm, bizarre nuclei and prominent nucleoli. No keratin is present. The tumors extend in a longitudinal and circumferential fashion. Metastasis to cervical, mediastinal, gastric and celiac lymph nodes occur depending on the site of tumor.

Adenocarcinoma usually develops in the lower third close to the gastro esophageal junction. Grossly the tumors present as large ulcerated mass or nodules protruding into the lumen. Microscopically they are well differentiated or moderately differentiated glandular tumors similar to adenocarcinoma of stomach or intestine.[34]

Other variants are adenosquamous carcinoma, mucoepidermoid carcinoma and adenoid cystic carcinoma. Small cell carcinoma, primary melanoma are the other epithelial tumors. Sarcomas represent less than 2% of all malignant tumors of the oesophagus.[21]

CYTOPATHOLOGY

Early cancer shows few neoplastic cells, which are always single and scattered. Dysplastic cells are seen in large numbers. The background of the smear is clean.[35]Mildly dysplastic cells show hyperchromatic nuclei in the intermediate and superficial squamous cells. Nuclei are enlarged but not more than 3 times the size of that of normal cell. Nuclei are more than 3 times that of normal cell in the intermediate cells in case of severe dysplasia.[36]

Advanced carcinoma shows numerous neoplastic cells, which are often seen in sheets. Dysplastic cells are few in number and the smear background is dirty.

Cytologic brushings in adenocarcinoma show malignant cells with lack of intercellular cohesion. Cell aggregates have a frayed irregular margin. Within the aggregates also, there is a haphazard array of crowded and overlapped abnormal nuclei indicating loss of polarity. Nuclei are hyperchromatic, pleomorphic, with irregular nuclear membrane and prominent nucleoli . Smear background is dirty indicating tumor diathesis and necrosis.[19]

GASTRIC NEOPLASMS

WHO HISTOLOGIC CLASSIFICATION[20]

Epithelial Tumors	**Nonepithelial Tumors**
Intraepithelial neoplasia – Adenoma	Leiomyoma
Carcinoma	Schwannoma
Adenocarcinoma	Granular cell tumor
Intestinal type	Leiomyosarcoma
Diffuse type	Gastrointestinal stromal tumor
Papillary adenocarcinoma	Kaposi sarcoma
Tubular adenocarcinoma	Others
Mucinous adenocarcinoma	**Malignant lymphomas**
Signet-ring cell carcinoma	Marginal zone B-cell lymphoma of MALT-type
Adenosquamous carcinoma	Mantle cell lymphoma
Squamous cell carcinoma	Diffuse large B-cell lymphoma
Undifferentiated carcinoma	**Carcinoid tumor**
Others	**Secondary tumors**

Adenomas are benign tumors, which are composed of dysplastic glandular cells and are associated with an increased risk of progression to adenocarcinoma.

ETIOPATHOGENISIS

The most important etiological factor in gastric carcinogenesis appears to be environmental.Recently H. pylori has been implicated, as an important etiological factor in gastric carcinoma[37].H. pylori infection is a long-standing disease that may lead to atrophic gastritis and intestinal metaplasia. Both these are precancerous conditions for intestinal type of gastric carcinoma through the stage of dysplasia.

The incidence of gastric carcinoma is known to be higher in individuals of blood group A, a family history of gastric cancer or pernicious anemia[38,39].The two most important pre-cancerous conditions leading to gastric carcinoma are hyperplastic polyps and atrophic gastritis[24].All gastric carcinoma are preceded by various stages of dysplasia, carcinoma in situ and superficial carcinoma. In most instances these are seen in a background with chronic atrophic gastritis and intestinal metaplasia.

PATHOLOGY

GASTRIC CARCINOMAS

In stomach 90% of malignant tumors are adenocarcinomas. The anterior wall, posterior wall, lesser and greater curvature are involved in the order of frequency. Grossly they are divided into 5 types according to modified **Borrman classification**[24]. They are

1. Superficial carcinoma (Type 0 or early carcinoma)
2. Polypoid carcinoma (Borrman type 1 carcinoma)
3. Fungating carcinoma (Borrman type 2 carcinoma)
4. Ulcerated carcinoma (Borrman type 3 carcinoma)
5. Diffusely infiltrative carcinoma (Borrman type 4 carcinoma, Linitisplastica)

Type 0 was not included in Borrman's original classification. It is applied by the Japanese Research society for gastric cancer, to early gastric carcinomas[24].Early gastric carcinoma refer to neoplasms confined to the mucosa and submucosa independent of the status of regional lymph nodes[40].Gastric carcinoma have different modes of growth. Some grow in a cohesive fashion and form large masses, where as others invade by individual cells. This varied growth pattern has lead to a number of histologic classifications.

Lauren's classification 1965

Intestinal

Diffuse

Ming's classification 1977

Expanding

Infiltrative

Japanese Society for Gastric Cancer classification 1981

Papillary

Tubular

Poorly differentiated

Mucinous

Signet ring

Microscopically the epithelial composition of gastric carcinoma shows a majority of mucous cells that are goblet cells containing intestinal acidic mucins. Other mucous cells secrete only neutral glycoprotein. These resemble foveolar or pyloric gland cells. Gastric type mucous cells are rare[24].The non-mucous tumor cells are mostly immature absorptive cells with a distinct striated border, paneth cells and parietal cells. Stroma of gastric carcinoma may also show distinctive features. Desmoplasia is prominent in the infiltrative carcinoma and lymphocytic infiltration is prominent in some solid undifferentiated carcinoma[24].

Lauren's classification divided gastric carcinomas into two types namely Intestinal (53%) and Diffuse (33%). Intestinal type is thought to arise from metaplastic epithelium[33].Microscopically well-differentiated tumors consist of mucin secreting columnar cells where the production of mucin varies. Poorly differentiated carcinoma has a predominantly solid pattern. Diffuse type is best represented by the classical linitis plastica and is currently designated as signet ring cell adenocarcinoma. It has a high incidence among the young population[41].

Grossly the carcinoma begins in the prepyloric area. The wall is thickened due to submucosal fibrosis, subserosal thickening, which can lead to pyloric obstruction[24].Microscopically diffuse growth of malignant cells are seen associated with extensive fibrosis and inflammation. Glandular formations are rare. Most of the mucin produced is intracytoplasmic, thus resulting in a typical signet ring appearance[35].

The disadvantage of Lauren's classification was that intestinal type was named because of its histomorphology where as diffuse carcinoma was named depending on its biological behavior. Hence the two were not entirely compatible[24].So Ming in 1977, classified gastric carcinoma based on the pattern of tumor growth and invasiveness as- expanding and infiltrative[42].The difference in growth pattern is related to cell adhesion molecules such as E-cadherin, which is largely preserved in the expanding carcinoma and is lost in the infiltrating carcinoma. The microscopic patterns of tumor growth are

reflected in the gross appearance of the tumor. The expanding carcinoma shows sharply demarcated tumor mass, where as the infiltrative carcinoma has indistinct tumor boundaries and do not form gross masses.

The Ming and Lauren classification has some similarities. Intestinal type carcinomas are expanding carcinomas and the diffuse carcinomas are infiltrative carcinoma. The solid carcinoma unclassified in the Lauren's classification is an expanding carcinoma[24].WHO classification of gastric tumors in the year 2000 divides the tumors according to their histological type and is now followed universally.

CYTOPATHOLOGY

Cytological brushings from intestinal type of adenocarcinoma show malignant cells, which are arranged individually, as well as in aggregates. The cell aggregates have frayed margins indicating loss of cohesion. Nuclei are crowded, compressed and are overlapped indicating loss of polarity. Nucleus is hyperchromatic with irregular nuclear membrane, granular chromatin and 1-2 nucleoli. Background shows granular, necrotic debris and neutrophils[40].

Diffuse adenocarcinoma shows malignant cells, which are signet ring cell type, seen as single large cytoplasmic vacuoles filled with mucin, which pushes nucleus to the periphery. Nucleus may be hyperchromatic or bland looking. Nuclear contours are sharply angulated or pointed. Nucleoli are variable. The cytomorphologic presentation of early gastric carcinomas does not differ from that of more advanced tumors except that it has a relatively clean smear background[40].

Benign peptic ulcers may also show a similar cytomorphologic picture but intercellular cohesion and polarity are well maintained. Although huge nucleoli may be seen in repair, chromatin remains finely granular and evenly distributed and truly hyperchromatic[43].

DUODENAL NEOPLASMS

In duodenum, adenocarcinoma is the most frequent malignancy seen in the portion generally accessible to endoscopy. They occur most commonly at the papillae of Vater and are seen as exophytic mass on endoscopy[34].

Histologically, adenocarcinoma shows varying degree of differentiation and often has a papillary configuration[34].

Cytologically these neoplasms resemble adenocarcinoma of the intestinal type in stomach and Barrett associated adenocarcinoma in the oesophagus. So these smears are generally cellular with individually dispersed malignant cells and cohesive aggregates. Each cell has a single large hyperchromatic nucleus with prominent nucleoli . Cytoplasm may contain distinct mucin vacuoles[19].

Brush cytology in cancerous upper gastrointestinal neoplasms:

Young et al[44] compared cytologic techniques inclusive of brushings and touch imprints with that of endoscopic biopsy in 329 cases (of which 61 were malignant) wherein the final diagnosis was based on either the clinical follow

up for a minimum period of 2 years or, established by laparotomy and histology of the resected tissue. They adopted a 5-tiered grading system for gastric / duodenal BC. Accordingly, grade 1comprised of normal cells; Grade 2 comprised benign but atypical cells which were further categorized as mild, moderate and severe atypia. Grades 4 and 5 comprised smaller and larger number of malignant cells respectively; while the grade U was an unsatisfactory group. With brushings, both the direct smears and indirect smears (made from saline suspension containing the material adherent to the bristles of brush after making the direct smears) were evaluated. The sensitivity and specificity of combined brush / imprint cytologic techniques were 91.8% and 100% respectively, while it was 68.9% and 97.6% respectively for endoscopic biopsies. As for the individual cytologic techniques, direct smears made from brushings gave a sensitivity rate of 81.6%, while indirect smears yielded a sensitivity rate of 73.3% in detecting malignancy. The best results were obtained with biopsy touch imprints with a sensitivity rate of 86.4%.

The same authors[45] in their 4 years' prospective study on endoscopic cytology (brush and imprint cytology) and histology for diagnosing the carcinoma of the oesophagus and the cardia, found biopsy touch preparation to be more accurate with a sensitivity of 100% as compared to 82 % for BC and 89% for EB. As imprint cytology reflected the EB, it could sample tumors which were primarily submucosal; also, when there was extensive necrosis, imprints could display well preserved malignant cells from the deeper layers, in

contrast to the brushings which contained only the degenerate cellular debris. They reported a false positivity rate of 1.5% with EB. Between imprint cytology and EB, cytology was proved to be superior; because material said to be unsatisfactory or inadequate for histologic interpretation could still yield a positive result at a 'cellular level', as even a few viable malignant cells in an imprint were sufficient for diagnosis. Although they considered imprint cytology to be superior to brush cytology, they also emphasized on the need for multiple imprints and hence biopsies, in order to avoid the possibility of false negative reports. Nonetheless, they stated that BC should be reserved for cases with severe stenosis interfering with manipulation of biopsy forceps. The disadvantage of imprint cytology was that despite being highly accurate in identifying malignancy; similar to BC, it is unlikely to provide information about the depth of invasion, and also the method is generally less specific in typing of tumors in comparison to histology.

The same authors[46] in 1982, retrospectively analysed 296 cases of gastric lesions; based on the cellular characteristics of benign atypical and malignant gastric epithelial cells, they emphasized that features such as anisocytosis, anisonucleosis, variation in N:C ratio, abnormal nucleoli, variation in nuclear chromasia, granularity and clumping can be seen even in benign atypical cells. However, they stated that such features as fine 'foamy' cytoplasmic vacuolation, abnormal mitotic figures, irregular multinucleation and 'opaque glass' nuclei always favour malignancy. Further, they observed

that reduced intercellular adhesiveness can be present even in severe atypia. They noticed that morphologic details were better with imprint cytology than that with BC, which was attributed to the smaller quantity of contaminating cellular debris. Significantly, these authors explored the possibility of distinguishing between severe benign atypia and malignancy. With respect to this, they concluded that no single cellular characteristic can be considered to be of significance for separating the severe benign atypia from actual malignancy.

Wang et al[47] studied 683 brushings from the lesions of oesophagus and stomach during a period of one year from January 1989 to December 1989. They found that cytologic brushings covered a relatively wider contiguous area and had a tendency to collect loosely cohesive cells, which they felt was the reason for the superiority of brush cytology in detecting early malignancies in some of the instances. They also found it to be superior to histology in detecting fungal infections. The other advantages of brush cytology (BC) listed by these authors included rapid turnaround time, minimal invasiveness and a good recognition of lymphoid cells. In their scientific article, along with their study, they reviewed 9 other studies from the literature that compared brush cytology (BC) with endoscopic biopsy (EB); they found that in 7 of these studies, the diagnostic sensitivity of cytology was superior to histology. The number of cases in these studies ranged from 98-250. A diagnostic sensitivity range of 77-94% was noted with BC alone, while it was 74-93% with

endoscopic biopsy (EB) alone. When BC and EB were combined, the sensitivity range increased to 88-100%. These results emphasized the significance of BC in the diagnosis of GI malignancy. The disadvantages of BC noted by these authors were slightly higher false positive rate than the EB; inability to distinguish between dysplasia / carcinoma in situ / invasive carcinoma; inability to detect lesions located in deeper regions such as lamina propria, submucosa and muscularispropria; and inability to determine whether inflammatory cells seen in the samples from non-infectious inflammatory lesions such as reflux esophagitis or gastritis represent an existing inflammation, or are due to the procedure itself.

Kobayashi et al[48] in their study involving 173 patients noted diagnostic accuracy of 77.6% for biopsies (132 of 170 cases) and 83.8% for BC (78 of 93 cases). A combined use of biopsy and brushings yielded a higher diagnostic accuracy of 88.0%. Diagnostic accuracy with biopsy was poor in lesions manifesting with mucosal elevation (58.8%), thick fold (58.1%) and tight cardiac stenosis (45.5%); while BC yielded better results with a diagnostic accuracy of 81.8%, 90% and 71.4% respectively. Thus, in these 3 types of gross lesions, supplementary application of brushing increased the diagnostic accuracy by 20%, compared with that of biopsy alone.

Keighley et al[49] compared the accuracy of BC before and after biopsy for diagnosis of gastric carcinoma in 347 patients. The total number of errors was significantly less ($P<0.01$), when brushing was performed first. Owing to

bleeding following biopsy, there was difficulty in localizing the site of malignancy, as well as in interpretation of the post biopsy brushings; hence, the authors found post biopsy BC to be less reliable. In their study, a false positive rate of 0.58% was noted with biopsies whereas there were no false positive or negative reports on BC.

In another study from India, Vidyavathi et al[50] evaluated brushings from 75 patients who presented with upper GI symptoms and correlated them with the biopsy findings. In this study, for the purpose of statistical analysis, brushing smears from the cases with frank growth on endoscopy that were reported as 'suspicious for malignancy' were included in the positive group. Of the 75 cases, 65 (86.66%) were positive by cytology and 58 (77.33%) were positive by histology. They obtained an overall sensitivity rate of 98.03% and a specificity rate of 81.11%. BC in their study had a false positive rate of 2.7%. The authors concluded that BC is a useful adjunct to biopsy for diagnosing upper GI malignancy. They also stated that tumor diathesis on highly cellular cytologic smears may be an indication of invasive carcinoma.

Cook et al[51] studied endoscopic gastric brushings and biopsies from 234 patients during a period of 5 years from 1973-1978 and noted sensitivity rates of 85% and 86% for BC and EB respectively. Despite the sensitivity rate went up to 91% with combined brushings and biopsies, they concluded that cytology should be reserved for situations wherein difficulty is encountered in obtaining adequate tissue for histologic examination, and for cases with a high suspicion

of malignancy but yielded negative biopsies; and for lesions at the cardia. In their study, they reported a false positive rate of 2.1% with brush cytology (BC) and a false negative rate of 4.3% with endoscopic biopsies (EB).

Kasugai et al[11] selectively employed BC for the diagnosis of cancers of the cardia with marked strictures, which yielded 87% diagnostic accuracy in 45 of 52 cases studied during a period of 4 years. The same authors[48] compared the results of BC of carcinoma of the lower oesophagus (116 cases), carcinoma of the gastric cardia (119cases) and carcinoma of the stomach (63 cases involving the sites other than cardia) with those of biopsies. For carcinomas of the oesophagus and cardia diagnostic accuracy with brushings was higher than that of biopsies (97 % vs. 90% for carcinoma of oesophagus; 78% vs.73 % for carcinoma of cardia). In the remaining 63 cases of the carcinoma of stomach, biopsy gave more diagnostic accuracy (biopsy vs. brushings = 83% vs.78%). In all the 3 locations, results were better with combined brushing and biopsy examination with 99% diagnostic accuracy for esophageal carcinoma; 89% for carcinoma of the cardia; and 94% for carcinoma of the stomach in sites other than cardia. They noted an overall false negative rate of 0.8% with EB.

Zargar et al[52] in a study involving 300 patients with gastroesophageal malignancy reported 83% and 87.9% positivity for malignancy with BC and EB respectively. The diagnostic accuracy increased to 98.8%, when results of BC and biopsy were combined. The final diagnosis of malignancy was based on the histologic findings of subsequent surgical specimens, lymph node

biopsies and metastases; or on concurrent forceps biopsy results, along with the clinical follow-up data compatible with malignancy. In their study, the final diagnosis of benign lesions was made when both brushing and biopsy specimens were negative for malignancy; or when repeat endoscopy confirmed the healing of the lesion; or when the patient remained disease free for at least one year from the initial diagnosis of the lesion. They also compared brushings before and after biopsy in 256 of their 300 cases of gastroesophageal malignancies. Similar to the Keighley et al study[49], the accuracy of BC was significantly higher when the brushing was performed before biopsy than after biopsy ($P<0.01$). But the diagnostic yield of the biopsy was not significantly different with the brushings before (92.7%) or after the biopsy (93.2%)

Qizilbash et al[53] studied brushings and biopsies from 250 patients. Of the 44 proven cancers of the upper GI tract, brushing and biopsy techniques yielded 88.6% and 93.2% positive results; with the combined technique it increased to 95. 4%. False negative reports occurred in cases of large tumors with necrotic surfaces, or in infiltrative tumors at the cardio-esophageal junction. None of the biopsies had false positive results, while one brushing sample was false positive. In general, these authors emphasized on the superiority of the material (biopsy or brushing samples) obtained under direct vision, in comparison with the routine lavage samples. Exemplifying their only false positive cytologic diagnosis, they also stressed on the difficulty often faced by the cytopathologists in distinguishing the spectrum of benign, atypical

changes from that of carcinoma. Like Kobayashi et al and Kasugai et al, they were also of the view that brush cytology should be reserved for cases where biopsy results are negative or, a stricture prevents adequate tissue sampling. They also stressed on the difficulty often encountered in distinguishing metaplastic goblet cells from signet ring cancer cells. Interestingly, their study had a single case of leiomyosarcoma, which on BC was interpreted as leiomyoma, owing to the lack of obvious malignant features.

Wang et al[54] retrospectively reviewed 13 brushing samples from 10 patients with biopsy proven premalignant glandular lesions of the upper GIT; 3 of these patients manifested with dysplasia in Barrett's oesophagus; 4 with gastric adenomas and 3 with duodenal adenomas. One case of dyplasia in Barrett's and 4 adenomas had coexisting adenocarcinomas. Although, they took EB findings as the gold standard for a final diagnosis; in cases of discrepancy between EB and BC, the malignancy was confirmed by the histology of surgically resected specimens, or by the clinical course of the disease. In all these cases they evaluated (i) the nature of cell groupings (tight 3-D clusters, flat sheets and / or loose clusters); (ii) presence of any abnormal epithelial cells; (iii) dyshesion at the edge of cell groups; (iv) single atypical epithelial cells; (v) mitoses / atypical mitoses; (vi) nuclear overlap within the cell groups; (vi) irregular nuclear spacing; (vii) distinct cell borders; and (viii) more than one cell population.

The cytologic features observed in pure premalignant glandular lesions were: (i) cohesive 3-D clusters; (ii) more or less uniformly enlarged nuclei; (iii) increased N:C ratio; (iv) presence of crowding and molding; (v) cells arranged in an orderly / palisading fashion; (vi) mild to moderate nuclear pleomorphism and atypia; and (vii) the presence of nucleoli in some cells and absence of macronucleoli.

In cases with coexisting premalignant glandular lesion and adenocarcinoma the authors observed following features:

(i) The adenomatous and carcinomatous elements could be distinguished from each other by the degree of atypia, pleomorphism and dyshesion

(ii) Atypical cells tended to be more pleomorphic

(iii) There was a prominent dyshesion with significant presence of single atypical epithelial cells.

In these cases, dyshesion was the only feature which showed a statistically significant difference between a pure premalignant glandular lesion and premalignant glandular lesion with coexisting adenocarcinoma. Notably, a mere presence of mitosis was found not of much importance in discriminating between the two lesions. Nonetheless, atypical mitoses, though rare, were helpful in predicting a frank malignancy. Despite the differences were subtle

between the two lesions, these authors were of the opinion that as with the cervical smears, a definitive diagnosis of a premalignant glandular lesion of the upper GI tract should be based solely on the cytologic examination. For these cases, the authors recommended a detailed histologic examination of the resected lesion with an extensive sampling.[54]

Oesophagus is the most common site of cancer in the GI tract. The commonest region of oesophagus involved is 20 to 40 cm from the incisor teeth[55]. Most esophageal carcinomas become symptomatic only at an advanced stage and therefore, early detection of esophageal cancer is of a high prognostic significance. Berry et al[56] emphasized on the poor prognosis of the advanced esophageal cancer in their article which dealt with the cytologic screening of 500 asymptomatic individuals for early diagnosis of esophageal cancer. Fifty patients with an established diagnosis of esophageal cancer served as control in this study. Of the 500 cases studied, 15 (3%) were positive for malignant cells of which 10 were early esophageal cancers and the others included cases of carcinoma-in-situ, microinvasive and advanced stage esophageal cancers. Overall, dysplastic cells were detected in 26 cases and all the diagnoses were confirmed on histologic examination. There were no false positive results. Thus, their study concluded that cytologic screening is potentially valuable in the detection of early esophageal cancer and preinvasive lesions. In their study, noteworthy was the fact that the brushing procedure was well tolerated by all the individuals who underwent cytologic screening; this included 3 patients with esophagealvarices.

In the subsequent years, authors like Shu[9] also conducted the cytologic mass survey with 555 cytologic and 155 biopsy specimens and documented a 1:2 ratio of early esophageal carcinoma to that of severe dysplasia. Based on such features as the cell type; degree of cellular differentiation; cell border and nuclear-cytoplasmic (N:C) ratio, they proposed a cytologic grading system for squamous cell carcinoma (SCC) of the oesophagus. Accordingly, the SCC cells were divided into well differentiated, moderately differentiated and poorly differentiated cells. Moderately differentiated SCC cells were the most commonly observed in the smears made from an early esophageal carcinoma.

The author[9] compared the rates of detection of early and advanced carcinoma of the oesophagus with cytologic, endoscopic and radiologic techniques. They found that cytology provided optimal results in early esophageal carcinoma with a 93.8 to 94% detection rate in comparison to 75-91.7% and 66.7-82% with those of endoscopy and radiography respectively. However, the radiographic studies proved optimal in detecting advanced esophageal carcinoma with 98-100% diagnostic accuracy, as compared with that of cytology (87.8-99%). Endoscopy was not performed in their advanced cases. Based on their (155 biopsy specimens studied) finding that fungal infection was 10 times more common with dysplastic epithelium than the normal epithelium, they suggested that the presence of fungi in non-cancerous lesions over a long period of time may be a possible risk factor for the development of malignancy. Their observations revealed that esophagitis and

the dysplasia of oesophagus occurred at least 10 years earlier than the esophageal carcinoma; and a more severe dysplasia showed an association with a higher rate of severe inflammation. The amount of fungi in the specimen coincided with the number of inflammatory cells.

Takeda et al[40] studied 119 cases of early gastric carcinoma and noted that the intestinal type occurred in both sexes mostly in the older age group, while the gastric type was more common in the younger age group. They described in detail, the cytomorphologic aspects as well as the histomorphologic features of the two types of gastric carcinoma. In their study, none of the early intestinal type of carcinomas had metastasized, while one case of the early gastric type of carcinomas had metastasized at diagnosis. In view of the intestinal type of early gastric carcinoma carrying better prognosis than the gastric type, the authors emphasized on the importance of differentiating the 2 types of early gastric cancers. They also studied the surface epithelial changes such as intestinal metaplasia, proliferative epithelium or, a combination of both, which often occur in the gastric mucosa adjacent to cancers.

MATERIALS AND METHODS

Patients having upper gastrointestinal symptoms like dysphagia, vomiting retrosternal pain, anorexia, increased loss of weight, mass abdomen etc. were subjected to endoscopy. Endoscopy was done by using fiber-optic video endoscope . Patients with lesions in the oral cavity and pharynx, as well as those with esophagealvarices were excluded from the study.

All the relevant clinical details including the age, sex, clinical presentation, endoscopic findings and the clinical diagnosis of the patients were noted. A prior written consent for endoscopy and the tissue retrieval was obtained from each patient. Using fiber-optic forward viewing “PENTAX Video Endoscope 2901”, with processor “PENTAX EPK 100 P” (PENTAX Medical Company, HOYA Corporation, Tokyo, Japan) the endoscopy was carried out. This instrument has an electronic video camera, and a working channel through which samples can be collected by means of cytology brush and biopsy forceps. After having noted down the endoscopic findings and made a provisional impression; the brush was passed through the channel and advanced to the lesion.

In all of the cases, a pre-biopsy brushing was done. The brushing was done at least once, with a small non-disposable, “Endoscopic Cytology Brush” (OLYMPUS CYTOLOGY BRUSH BC-24 Q) made of nylon and designed in such a way that it remains ensheathed before and after the brushing is

performed, in order to avoid contamination and loss of material in the endoscope channel, while being introduced or withdrawn. In each case, the brush was moved onto the lesion back and forth for collecting the material. After withdrawing the brush, the material was smeared onto clean, dry, labelled glass slides with utmost care to obtain adequate and well preserved material. A minimum of 2 to a maximum of 5 smears were made with each brushing. Some of the smears were air-dried for May-Grünwald-Giemsa (MGG) staining, while some were wet fixed in 95% ethanol for Papanicolaou and H & E staining.. A minimum of four biopsies were obtained immediately after collecting the brushings, using OLYMPUS ENDOJAW biopsy forceps FB-222U. The biopsies were fixed in 10% buffered formalin; routinely processed and paraffin embedded. The histologic sections were stained with Hematoxylin& Eosin (H&E); whenever necessary, special stains for mucin were performed.

Cytologic evaluation was done before the histologic sections were made ready for evaluation. The cytologic details evaluated were the cellularity (sparse / cellular); the type and nature of cells (epithelial – squamous / glandular or inflammatory); the pattern of arrangement (loose / tight cohesiveness, monolayers, papillary, irregular, singly dispersed); evidence of intestinal metaplasia; the presence of reactive atypia; the material in the smear background (clean / non-specific debris / inflammatory / fibrinous / mucoid / bloody / necrotic); The cytologic features were interpreted with appropriate clinical background.

Malignant lesions were diagnosed as per the usual criteria such as nuclear / cellular pleomorphism, high N:C ratio, hyperchromasia, irregular nuclear margins, abnormal mitotic activity (when present) and prominent / irregular nucleoli. In cases of SCC, an attempt to assess the degree of differentiation was made based on the criteria laid down by Shu[9]. Accordingly, well differentiated SCC was diagnosed when malignant cells on brush smears exhibited

(i) Polygonal / bizarre / spindle / tadpole / fiber shapes

(ii) Abundant red / orangeophilic cytoplasm

(iii) Slightly increased N:C ratio

(iv) Abundant deeply stained chromatin and

(v) Opaque (India ink) or clear nuclear structures.

Moderately differentiated SCC was diagnosed when malignant cells displayed

(i) Round to oval shaped cells resembling parabasal cells

(ii) Relatively rich cytoplasm with bluish staining

(iii) Moderately increased N:C ratio

(iv) Clear nuclear structures with single or multiple nucleoli.

Poorly differentiated SCC was diagnosed with

(i) Small cells or more unevenly sized large cells

(ii) Cells with scanty cytoplasm

(iii) Cells having an obvious high N:C ratio

(iv) Nuclei exhibiting very deeply stained and clumped chromatin

Absence of nucleoli was considered as a common finding in poorly differentiated SCC by Shu. In our experience, as it was not so, this particular feature was not strictly applied for our cases of poorly differentiated SCC.

An attempt to differentiate between the intestinal and diffuse types of gastric adenocarcinoma was made based on the criteria given by Takeda et al[40]. Accordingly intestinal type of gastric carcinoma was diagnosed when the cancer cells were

(i) Seen in sheets or groups (well differentiated type) with a predominant single cell population (less well differentiated type)

(ii) Columnar (well differentiated type) or cuboidal to ovoid nature (less well differentiated type) with granular cytoplasm and ovoid nuclei with occasional cerebriform convolutions, or nuclei with large prominent nucleoli. (apart from these features, presence of well differentiated glandular structures was also taken as evidence of intestinal type of gastric carcinoma)

Features considered for the diagnosis of diffuse type of gastric carcinoma were

(i) Cells seen singly or in loose clusters with

(ii) A remarkable variation in cell size and shape (cellular pleomorphism)

(iii) Large cells with foamy cytoplasm, or large cytoplasmic vacuoles (signet ring cells), mixed with smaller cells having granular cytoplasm

(iv) Nuclei of the larger cells exhibiting prominent nucleoli and smaller cells displaying pronounced, coarse chromatin clumping and

(v) More striking nuclear pleomorphism.

Apart from these features, discrete, smaller atypical cells with macrophage like appearance and discrete malignant signet ring cells entangled in the mucoid back ground were also taken as evidence of diffuse type of gastric adenocarcinoma.For the purpose of statistical analysis, those smear reported as suspicious for malignancy, with endoscopy showing frank growth were included in the malignant group. False positive cytology reports were defined as malignant smears, in the presence of a negative biopsy and clinical findings.

Endoscopic biopsies and surgically resected specimens were examined by histopathologists who were blind to the cytologic findings and the diagnoses. The cytologic diagnoses were correlated with those of clinical and histopathologic diagnoses. The results were statistically analysed. Sensitivity, specificity, positive and negative predictive values of brush cytology (BC) were calculated in comparison with histopathology using the following formulae.

BC diagnosis	***Histopathology diagnosis***	
	Malignant	***Non-malignant***
Malignant	TP	FP
Non-malignant	FN	TN

TP => True positive, FP => False positive, TN => True negative, FN => False negative

Sensitivity (in %) = $\frac{TP}{TP + FN} \times 10_0$

Specificity (in %) = $\frac{TN}{TN + FP} \times 10_0$

Positive predictive value (in %) = $\frac{TP}{TP + FP} \times 10_0$

Negative predictive value (in %) = $\frac{TN}{TN + FN} \times 10_0$

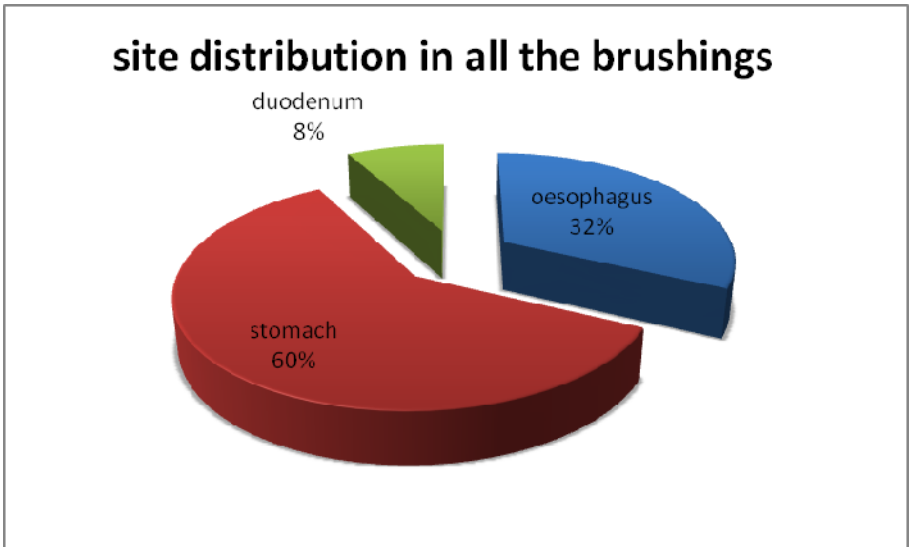
Diagnostic accuracy (in %) = $\frac{TP + TN}{TP + TN + FP + FN} \times 10_0$

RESULTS AND OBSERVATIONS

A total of 50 patients who presented with upper gastrointestinal tract symptoms and showed lesions suspicious of malignancy on endoscopy were subjected to brush cytology and concurrent biopsy during the study.

Out of this 16 cases (32%) showed esophageal lesions, 30 cases (60%) showed gastric lesions and 4 cases (8%) were from duodenum as shown in chart 1.

CHART 1:-

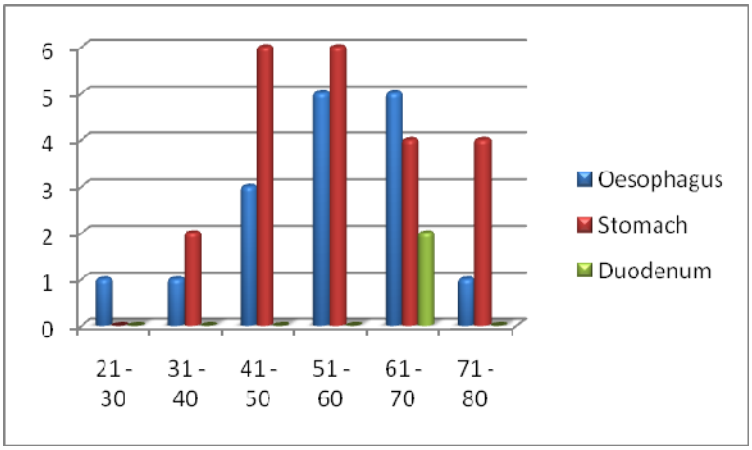


Age:- The age of these patients ranged between 21 and 80 years.The youngest patient with malignancy was 30 yrs old.The commonest age group for malignancy was 51 to 70 yrs.The mean age for malignancy among females was 55 and for males 60 years.The age distribution with respect to the sites among malignant cases is shown in table 1and chart 2.

TABLE 1 :- AGE DISTRIBUTION OF CASES

Age Range	Oesophagus	Stomach	Duodenum	Total
21 - 30	1	0	0	1
31 - 40	1	2	0	3
41 - 50	3	6	0	9
51 - 60	5	6	0	11
61 - 70	5	4	2	11
71 - 80	1	4	0	5
Total	16	22	2	40

CHART 2:-

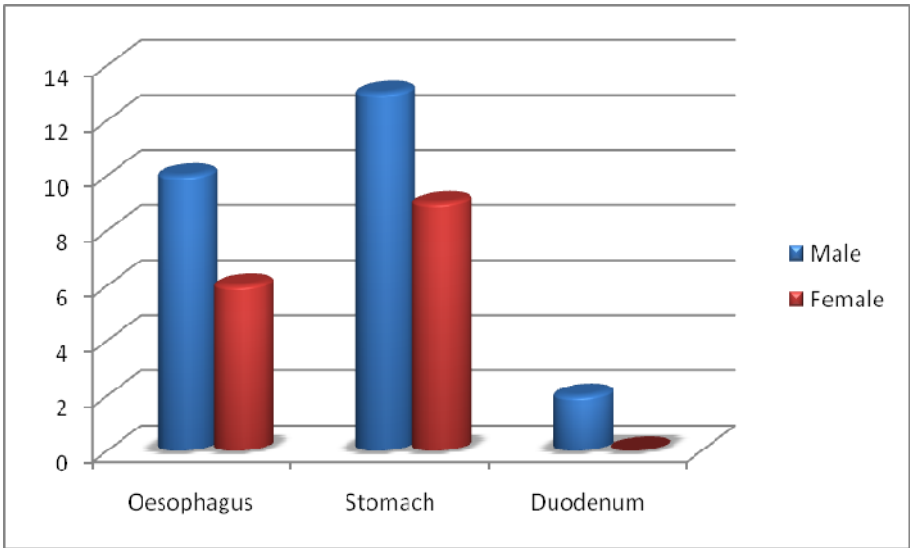


Sex:-Of the 50 patients taken for the study 34 (68%) were male and 16(32%) were females. The male: female ratio was 2.13:1. The sex distribution among histopathologically proven malignancies is shown in Table 2 and chart 3.

TABLE 2 :- SEX DISTRIBUTION OF MALIGNANT CASES

Site of malignancy	Male	Female	Total
Oesophagus	10	6	16
Stomach	13	9	22
Duodenum	2	0	2
Total	25	15	40

CHART – 3:-

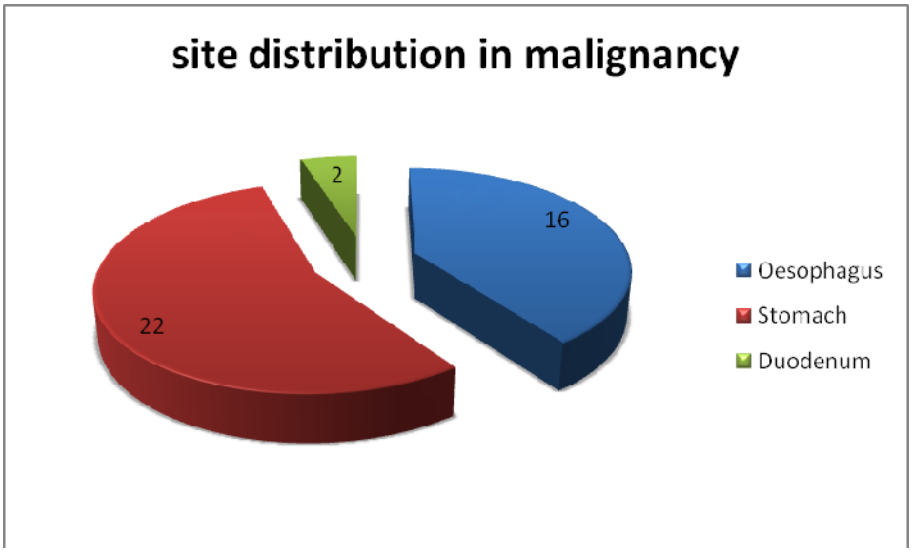


Site of malignancy:- Of the 40 histopathologically proven cases of malignancies 16 were from oesophagus,22 from stomach and 2 from duodenum as shown in table 3 and chart 4.

TABLE 3 :-SITE DISTRIBUTION OF MALIGNANT CASES

Site of Malignancy	Total
Oesophagus	16
Stomach	22
Duodenum	2
Total	40

CHART 4:-

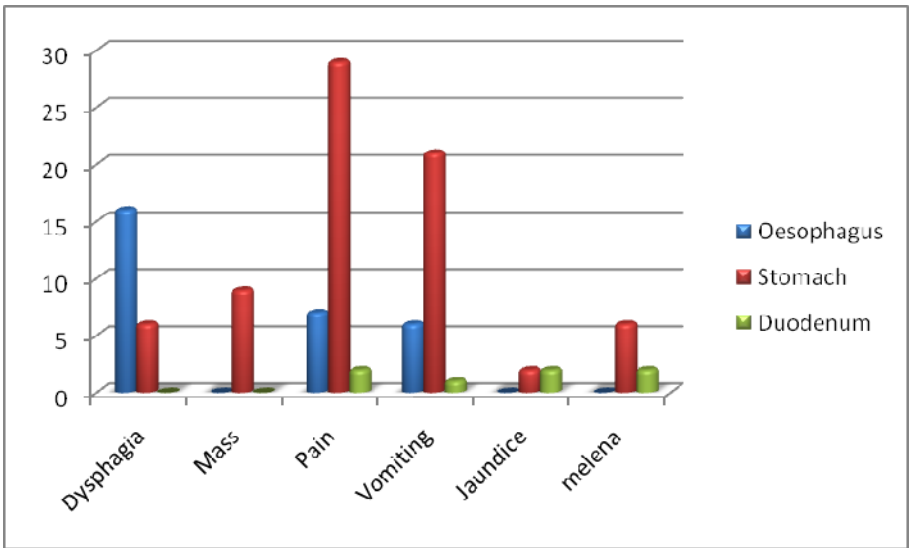


Clinical symptoms :- Pain abdomen was the commonest symptom seen in 38 patients, followed by vomiting and dysphagia in 28 and 22 patients respectively during the study. Other clinical symptoms with which the patients presented are shown in Table 4 and chart 5.

TABLE 4:- CLINICAL SYMPTOMS DISTRIBUTION

Site of the lesion	Dysphagia	Mass	Pain	Vomiting	Jaundice	Melena
Oesophagus	16	0	7	6	0	0
Stomach	6	9	29	21	2	6
Duodenum	0	0	2	1	2	2
Total	22	9	38	28	4	8

CHART 5:-

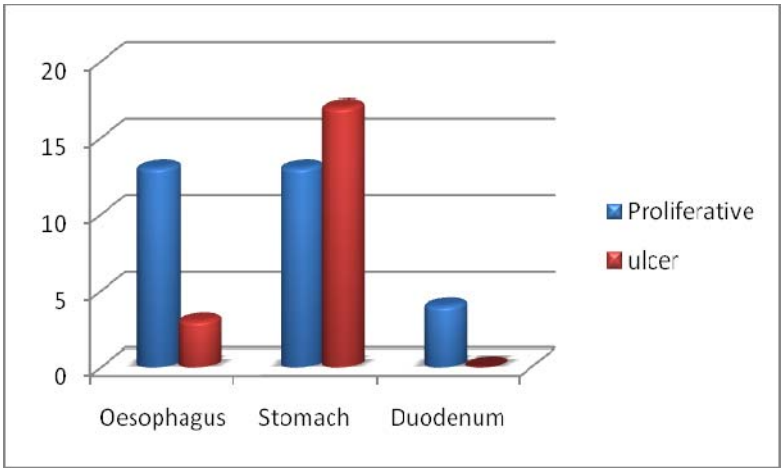


Endoscopic findings: On endoscopy 13 cases (81%) had a proliferative growth in the oesophagus and only 3 (19%) had an ulcer during the study. In the stomach endoscopy revealed 17 (57%) cases with ulcer and 13 (43%) cases with a proliferative growth. Of the 4 cases with duodenal lesions, endoscopy revealed a proliferative growth in all the 4 cases. The distribution of endoscopic findings is shown in Table 5.

TABLE 5:- ENDOSCOPIC FINDINGS

Site of the Lesion	Proliferative	Ulcer
Oesophagus	13	3
Stomach	13	17
Duodenum	4	0
Total	30	20

CHART 6 :-

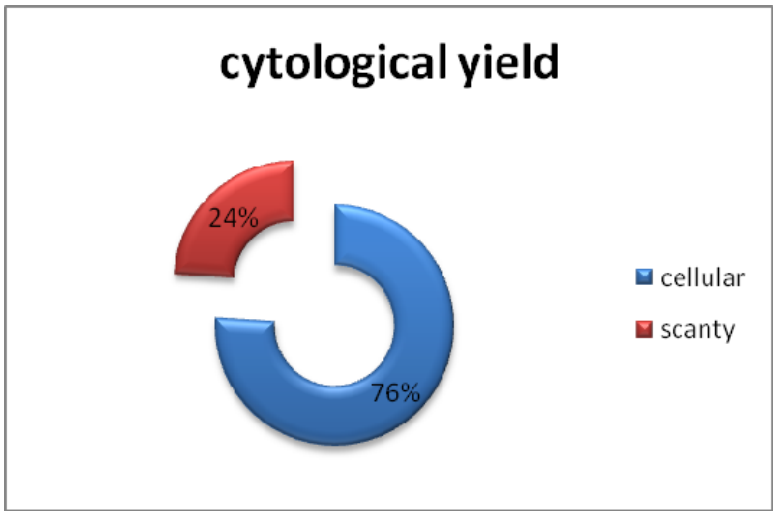


Cytological Findings: Of the 50 smears during the study, smears were cellular in 38 (76%) and scanty in 12 (24%) as shown in table 6 and chart 7. Smears were positive for malignancy in 35 cases, suspicious for malignancy in 5 cases , negative in 8 cases and unsatisfactory for evaluation in 2 cases.

TABLE 6 :-CYTOLOGICAL YIELD

Cellular	38
Scanty	12

CHART 7 :-



OESOPHAGUS:

Among 16 patients who had esophageal lesions, the majority of patients (10 patients ,62.5%) were seen in the age group of 51 -70 years. The youngest patient was 30 years old and oldest patient was 71 years as shown in Table 1.

There were 10 males and 6 female patients. Male: female ratio was 1.67:1.

On cytology, brushing smears obtained showed, 15(93.75%) positive cases and 1(6.25%) case was suspicious for malignancy.

Biopsy of the lesions showed 16 (100%) positive cases.. The correlation of these cases is shown in Table 7.

TABLE 7 COMPARISON OF BIOPSY AND CYTOLOGY IN LESIONS OF OESOPHAGUS

Cytology		**Histopathology**		
		Positive	**Negative**	**Total**
Positive	15	15	0	15
Suspicious	1	1	0	1
Total	16	16	0	16

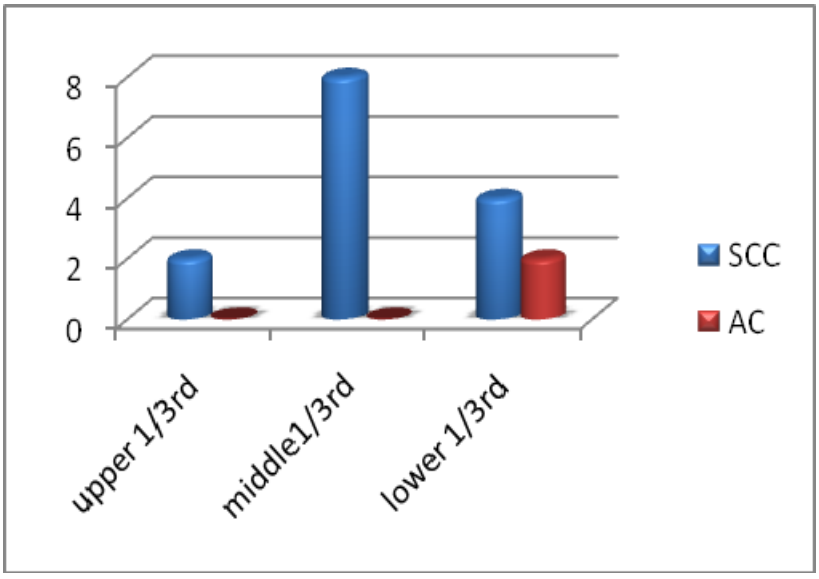
Cytology and biopsy were positive in 15 cases . There was 1 suspicious smear, which proved positive in biopsy.

The most common site of malignancy in oesophagus was the middle 1/3 region (8 cases) and the most common malignancy reported was SCC; this was so, even in the lower 1/3 of the oesophagus. AC was observed only in the lower 1/3 of the oesophagus as shown in table 8 and chart 8.

TABLE 8 :- SITE DISTRIBUTION IN OESOPHAGUS

Site of Malignancy	SCC	AC
Upper 1/3rd	2	0
Middle1/3rd	8	0
Lower 1/3rd	4	2

CHART 8:-



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Out of the 16 positive cases on biopsy, 14 (87.5%) were squamous cell carcinoma, 2 were adenocarcinoma (12.5%) . Squamous cell carcinoma was well differentiated in 2 cases (14.29%), moderately differentiated in 9 cases (64.29%) and poorly differentiated in 3 cases (21.43%).

STOMACH:

Among the 30 cases who had gastric lesions, maximum number 9 (30%) were seen in the age group of 51-60 years and minimum number 3(10%) were seen in 31-40 years. The youngest age of malignant tumor was 35 years as shown in Table 2.

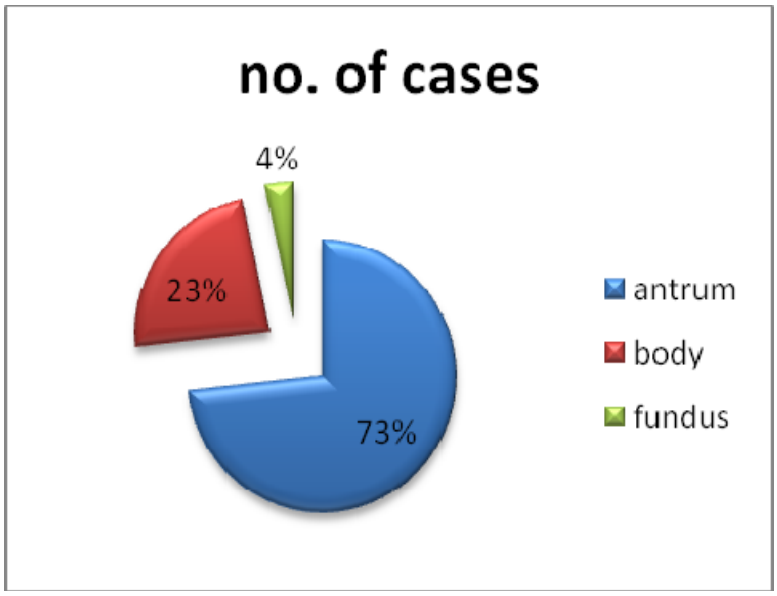
There were 20 males and 10 females. The male: female ratio was 2 **:** 1.

Endoscopy revealed 17 (56.67%) cases with ulcer and 13(43.33%) cases with a growth. Majority of the lesions were seen in the antrum 22 (73.33%), 7 (23.33%) in the body, and 1 case (3.33%) in the fundus as shown in table and chart 9. Of these one case showed growth extending from stomach to duodenum.

TABLE 9:- SITE DISTRIBUTION IN STOMACH

Site of Malignancy	No. of Cases
Antrum	22
Body	7
Fundus	1

CHART 9:-



Brushing smears were positive in 18 cases (60%), suspicious in 4 cases (13.33%), negative in 6(20%) cases and unsatisfactory in 2(6.67%) cases. Smears showed an inflammatory background in 25 , mucinous in 15 cases and 8 cases showed hemorrhage.

Signet ring cells were seen in 2 cases. Out of 18 positive smears, 16 were confirmed positive by biopsy.One case had an inadequate biopsy but had a subsequent node biopsy showing adenocarcinomatous deposit and cytology smears showed unequivocal positivity .Hence it was taken as positive for statistical analysis. One case had a negative biopsy.Out of 6 negative smears all came out as negative in biopsy. Of the 4 suspicious smears 3 showed malignancy in biopsy.2 cases showed unsatisfactory brush smears due to dense inflammatory background. Both proved positive for malignancy in biopsy. The correlation is shown in the Table 10.

TABLE 10 COMPARISON OF BIOPSY AND CYTOLOGY IN LESIONS OF STOMACH

Cytology		**Histopathology**		
		Positive	**Negative**	**Total**
Positive	18	17	1	18
Suspicious	4	3	1	4
Negative	6	0	6	6
Unsatisfactory	2	2	0	2
Total	**30**	**22**	**8**	**30**

Biopsy was positive in 21 cases (66.67%), of which 5 were well-differentiated adenocarcinoma, 5 were moderately differentiated adenocarcinoma and 9 were poorly differentiated adenocarcinoma . 2 cases were signet ring carcinoma (32.43%).One case which showed inadequate initial biopsy showed subsequent adenocarcinomatous deposit in node and unequivocal malignancy in cytology smears. Hence it was taken as positive for statistical analysis.

DUODENUM:

Of the 4 duodenal lesions, 2 were in the age group of 61- 70years, one was 46 years old, and one was 21 years.

All the 4 patients were males.

Endoscopy revealed a growth in all the 4 cases. Smears were positive in 2 (50%) cases and negative in 2 cases (50%).

Biopsy was positive in 2 cases and negative in 2 cases. The correlation is shown in Table 11.

Table 11 **COMPARISON OF BIOPSY AND CYTOLOGY IN LESIONS OF DUODENUM**

Cytology		**Histopathology**		
		Positive	**Negative**	**Total**
Positive	2	2	0	2
Negative	2	2	0	2
Total	**4**	**4**	**0**	**4**

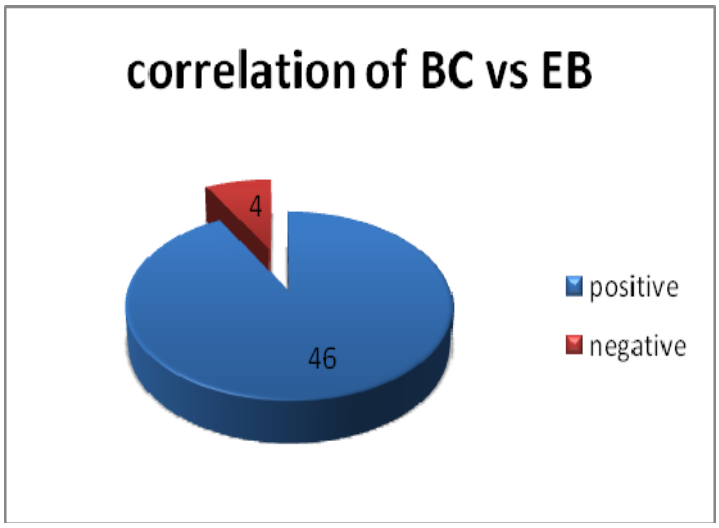
BRUSH CYTOLOGY VS. ENDOSCOPIC BIOPSY DIAGNOSIS*:*

Out of 50 cases which had brushings and concurrent representative biopsies, 46(92%) cases had concordant cytologic & histopathologic diagnosis as shown in table 12 and chart 10.

TABLE 12:- CORRELATION OF CYTOLOGY WITH BIOPSY

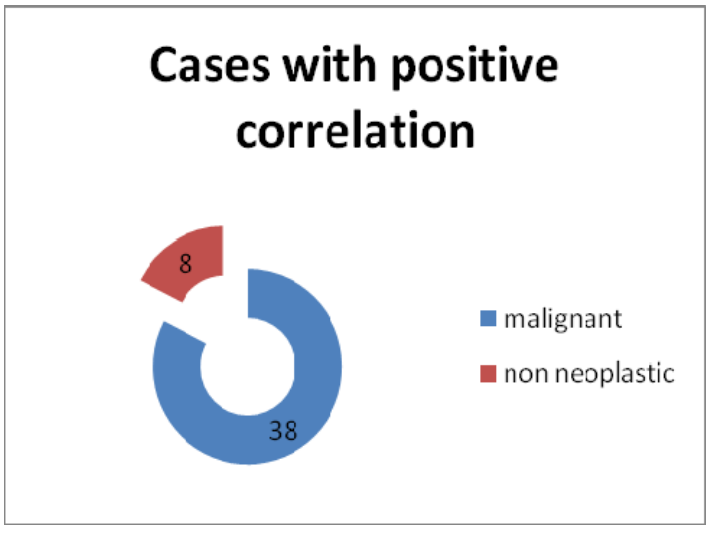
Correlation	**No. of Cases**
Positive	46
Negative	4

CHART 10:-



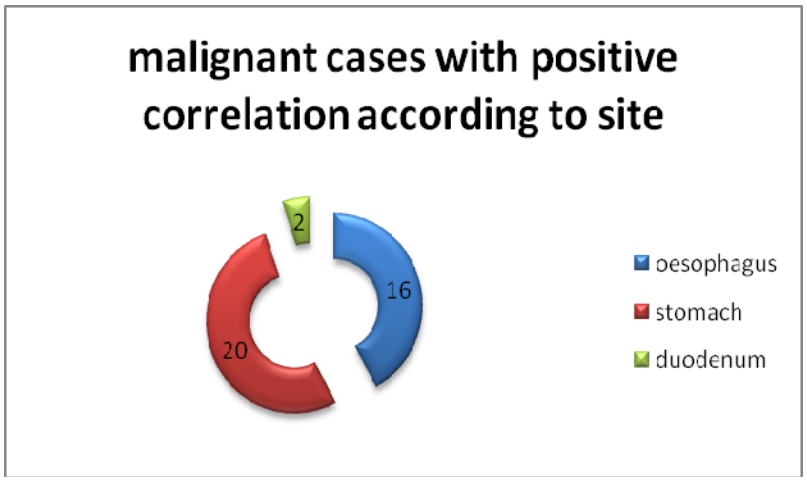
In those 46 cases, 38 (82.61%) were malignant and 8 (17.39%) were non-neoplastic as shown in chart 11.

CHART 11:-



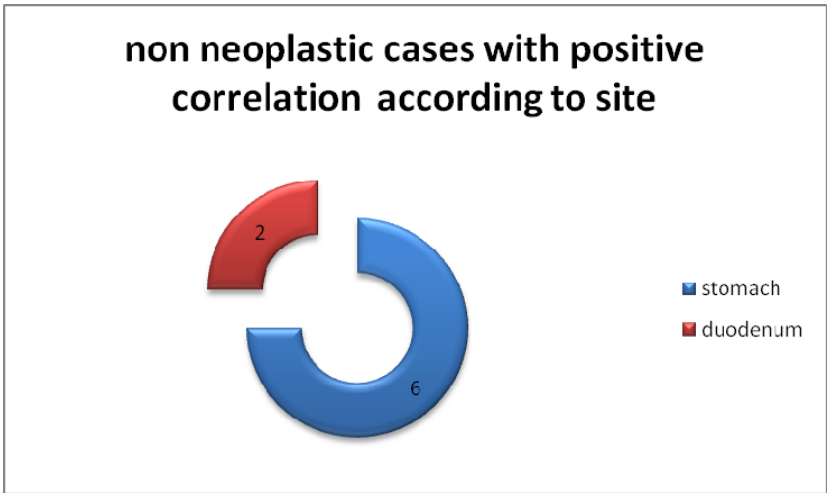
Of the 38 malignancies, 16 (42.11%) were from the oesophagus, 20 (52.63%) from the stomach and 2(5.26%) from the duodenum as shown in chart 12.

CHART 12:-



Of the 8 non-neoplastic cases, 6 (75%) were gastric and 2 (25%) were duodenal lesions as shown in chart 13.

CHART 13:-



Diagnostic accuracy of brush cytology in relation to histopathology*:*

The present study reported 95% sensitivity and 80% specificity. Positive and negative predictive values were 95% and 80% respectively. Overall diagnostic accuracy was 92%.

Sensitivity	95%
Specificity	80%
Positive predictive value	95%
Negative predictive value	80%
Diagnostic accuracy	92%

There were 4 cases whose cytologic diagnoses did not correlate with the histopathologic diagnosis. Of these, all the four were gastric lesions. Their cytological and histopathological diagnosis have been summarised in the table 13.

TABLE 13 :- CASES WITH DISCORDANT CYTOLOGY AND BIOPSY

S. No	Cytologic Diagnosis	Histopathological Diagnosis
1.	Unsatisfactory smear	Moderately differentiated adeno carcinoma
2.	Unsatisfactory smear	Poorly differentiated adeno carcinoma
3.	Positive for malignancy	Negative for malignancy(unrepresentative biopsy)
4.	Suspicious of malignancy	inflammatory changes

DISCUSSION

The primary role of gastrointestinal tract cytology is cancer detection. Its potential, using gastric washings, has been described even before the advent of endoscopes. Endoscopy allows visualization of mucosal lesions and at the same time permits sampling of cytology and biopsy for a definitive diagnosis.

According to the National Cancer Registry, oesophagus and stomach are the leading sites for the development of cancer in India. Esophageal and gastric cancers are the most frequent cancers found in Indian men, while esophageal cancer ranks third among women after carcinoma of breast and cervix[3].

In the present study, 50 brushing samples from 50 patients were evaluated to assess the role of BC in the diagnosis of various neoplastic lesions of the upper GIT in comparison with EB specimens. With all the relevant clinical details, an elaborate cytologic examination was performed in all the cases to arrive at a fairly accurate diagnosis. An attempt to differentiate the grades of SCC and to distinguish between the intestinal and diffuse types of gastric adenocarcinoma was also made.

Clinical presentation:

All the patients subjected to endoscopic examination and BC presented with upper GI symptoms. The age of these patients ranged from 21 to 80 years; patients with malignancies were in the age range of 30 to 80 years with a male

to female ratio of 1.67: 1. There was no significant difference in the mean age at presentation between the two sexes (Men - 60 years, Women - 55 years); most malignancies occurred in the 6th and 7th decade.

Samples for cytologic and histopathologic examination were collected, only when the lesion was visible on endoscopy. The findings on endoscopy are elaborated in Table 5.

Out of the 50 cases,16 were from oesophagus ,30 from stomach and 4 from duodenum. Of the 6 cases from lower 1/3rd of oesophagus,5 showed extension to OG junction. One case of antral growth showed extension to pyloro duodenal junction and into the duodenum.

Quality of BC smears: Good quality smears are of particular importance for interpretation of BC. According to Koss and Melamed[57], brush material generally provides 2 to 4 satisfactory smears in a satisfactory single brushing. In our study, the number of smears in each case ranged from 2 to 6 with an average of 4 smears (which we felt ideal), which could be made with a grossly particulate brushing specimen obtained, when the brushing procedure was technically well performed.

Most of the smears had good cell-yield, with cellular and sparse material being observed in 38 (76%) and 12(24%%) cases respectively. Of the 12cases with a sparse cell-yield on BC,9 cases had diagnostic concordance between BC and EB. One of the sparsely cellular smear was non-representative.Also one of

the cellular smears had dense inflammatory background which obscured the lesional cells. Hence they were reported as unsatisfactory for evaluation.

Cytobrush tends to cover a wider area of the lesion and hence recovers a better representative sample.[47] In the present study, even when the BC smears were sparse, at least 1 or 2 smears made from the same brushing procedure were adequate for giving a diagnosis / opinion on BC.

MALIGNANT OESOPHAGEAL LESIONS:

The commonest malignant lesion of oesophagus encountered on BC was SCC (14 cases), of which 2, 9 and 3 cases were well differentiated , moderately differentiated and poorly differentiated SCC respectively. There were 2 cases of adeno carcinoma which arose in the lower 1/3rd of the oesophagus.

The malignant lesions (inclusive of SCC & AC) reported on BC from the oesophagus accounted for 41% (16 cases). As noted by various other authors[57,58] SCC was the commonest malignancy of the oesophagus in the present study with 14 (87.5%) cases; this was so even in the lower 1/3 region, although middle 1/3 rd was the commonest location recorded for SCC. Adenocarcinoma of the oesophagus (2 cases) (12.5%) was exclusively seen in the lower 1/3 region and one out of the 2 cases showed involvement of cardia as well.

In the study done by Bhargava et al,[16] middle and lower third showed equal incidence where as in the study by Shroff et al, [15] lower third was the predominant site involved, as shown in Table 14.

TABLE 14:- DISTRIBUTION OF OESOPHAGEAL MALIGNANCY

Name of the Study	Upper1/3	Middle1/3	Lower1/3
Bhargava et al[16]	1(1.78%)	27(48.21%)	28(50.01%)
Shroff et al[15]	5(15.62%)	11(34.37%)	16(50%)
Present study	2(12.5%)	8(50%)	6(37.5%)

The assessment of the degree of differentiation of the SCC was concordant between BC and EB in 12 of the cases in the present study. Shu, in his article[9] mentions 'lack of nucleoli' as a usual finding in poorly differentiated SCC cells; on the contrary, 2 of our cases of poorly differentiated SCC displayed prominent nucleoli in almost all the cells on both BC and EB.

MALIGNANT GASTRIC LESIONS:

In the stomach, majority of the lesions were in the antrum, followed by the body and fundus respectively. This was comparable to the study by Suvarna et al, [59] as shown in Table 15.

TABLE 15 :-DISTRIBUTION OF GASTRIC LESIONS

Site in stomach	Suvarna et al.[59]	Present study
Antrum	37(52.85%)	22(73.33%)
Fundus	8(11.42%)	7(23.33%)
Body	9(12.85%)	1(3.33%)
Gastroesophageal Junction	5(7.14%)	nil

Poorly differentiated adenocarcinoma was the most frequent histological type of gastric carcinoma in the present study.

Malignant lesions on gastric BC were reported based on the general cytomorphologic features of adenocarcinoma. Interpretation needed more cautious approach with respect to the distinction between the intestinal and diffuse types of gastric adenocarcinoma on BC; as always there was some degree of cytomorphologic overlapping.

Owing to their prognostic significance, the importance of differentiating between the two types of gastric adenocarcinoma has been rightly emphasized by Takeda et al.[40] However, this differentiation is subject to variation between cytology and histopathology. On brush cytology, 21were of intestinal and 1 of diffuse type. Although signet ring cells were more frequent in the diffuse type, they were encountered in the intestinal type as well, although less frequently .

One of our cases which was reported as ‘intestinal type’ on BC were subsequently reported as ‘diffuse type’ on EB. Though it is said that the adenocarcinoma cells of the intestinal type usually have columnar or cuboidal shape, [40,57] in the present study it was relatively difficult to appreciate it on BC . Apart from exhibiting pleomorphism, these cells tended to exhibit cytoplasm bloated with mucin vacuoles, which rendered them a round / ovoid shape. In cases of adenocarcinoma of the diffuse type, the cells were more often discrete. Signet ring cells as well as discretely scattered usual type of adenocarcinoma cells were also present . Nuclei were eccentrically placed, but not in all the cells.

DUODENAL LESIONS:

Out of the 4 cases from duodenum,all of them were proliferative lesions. Only one yielded a cellular smear. Though the other three had sparsely cellular smears they were representative and a diagnosis could be reached in all the 4 cases. All the four cases of cytology correlated well with biopsy,two of them positive for malignancy and two non neoplastic lesions.

Accuracy of diagnoses on Brush cytology:

Brush cytology was positive for malignancy in 35 cases (70%), suspicious in 5 (10%) cases, negative in 8(16%) cases and unsatisfactory in 2(4%) cases. Biopsy was positive in 40 cases (80%), inflammatory or

dysplastic in 10 cases(20%) . The suspicious cases were taken as positive for statistical analysis.

The overall sensitivity of the study is 95% and specificity is 80%. The diagnostic accuracy of BC in our study was 92% . Different studies have reported sensitivity ranging between 68.9% and 91.8% and specificity ranging between 96.8% and 100%. There are also studies which have compared the sensitivity, specificity and diagnostic accuracy of BC and EB taking into account the final diagnoses on the resected specimens or, with the clinical follow up data.

Some studies have evaluated the utility of combined BC and EB in detecting malignancies and claimed that it increased the diagnostic accuracy. In the present study, such an exercise was not possible as 90% of our cases did not have surgical resection specimens. The following table 16 compares the rates of sensitivity and specificity and diagnostic accuracy between our study and various other studies in the literature.

TABLE 16 :- DIAGNOSTIC ACCURACY (%) OF BC & EB IN VARIOUS STUDIES

Study	***Diagnostic accuracy (%)***		***Sensitivity (%)***		***Specificity (%)***	
	BC	***EB***	***BC***	***EB***	***BC***	***EB***
Kochhar et al[60]	NA	NA	88.6	90.5	NA	NA
Young et al[45]	82	89	NA	NA	NA	NA
Qizilbash et al[53]	88.6	93.2	NA	NA	NA	NA
Cook et al[51]	NA	NA	85.1	86.5	96.8	100
Keighley et al[49]	87	83	NA	NA	NA	NA
Zargar et al[52]	87.9	93.9	NA	NA	NA	NA
Kobayashi et al[48]	83.8	77.6	NA	NA	NA	NA
Witzel et al[61]	85	83	NA	NA	NA	NA
Kasugai et al[48]	In Ca oesophagus					
	97	90	NA	NA	NA	NA
	In Ca cardia					
	78	73	NA	NA	NA	NA
	In Ca stomach					
	78	83	NA	NA	NA	NA
Vidyavathi et al[50]	NA	NA	98.03	-	81.11	-
Young et al[44]	NA	NA	91.8	68.9	100	97.6
Malhotra et al[62]	86.6	90	NA	NA	NA	NA
Winawer et al[63]	68	50	NA	NA	NA	NA
Shroff et al[15]	97.1	75.36	NA	NA	NA	NA
Present study	92	-	95	-	80	-

Ca – Carcinoma; NA – data not available

There were two false negative cases and this was due to scanty cell yield in one case and dense inflammatory infiltrate obscuring the lesional cells in one case. There were 2 false positive cases. These cases had an ulcer in stomach on endoscopy. The marked hyperchromasia of regenerating epithelium from the ulcer edge could be the reason for the positive cytology. The table 17 shows comparison of rate of false positivity and negativity of BC between our study and the other studies in the literature.

Table 17	**Comparison of false positivity & negativity rate among various studies**			
Study	***False positivity rate (%)***		***False negativity rate (%)***	
	Brush cytology	***Biopsy***	***Brush cytology***	***Biopsy***
Young et al[45]	0	1.56	NA	NA
Behmard et al[64]	3	0	0	0
Cook et al[51]	2.1	0	0	4.3
Keighley et al[49]	0	0.58	0	0
Kasugai et al[11]	0	0	0	0.8
Vidyavathi et al[50]	2.67	0	0	0
Malhotra et al[62]	NA	NA	0	10
Jan et al[55]	0	NA	13.97	NA
Present study	4	-	4	-

NA → data not available

In a study of 160 patients by Cook et al[51], 5 false positive cases (3.1%) were seen. Ricardo et al[65] also had 5 false positive cases (1.3%) in their study. This has been attributed to regenerating cells from benign gastric ulcers, because morphologically the distinction between severe benign atypia and malignancy is difficult..Wang et al[47] in their study, indicate that combining cytology with biopsy increases the false positive rates, but will also increase the sensitivity of the procedure.

The sensitivity of this study is 95%, and this emphasizes the usefulness of brush cytology as a screening procedure. Although definitive surgical treatment is rarely based on a positive or suspicious smear, the inclusion of the "suspicious" category alerts the clinician about the possibility of malignancy. Patient management is altered in these situations so that a repeat endoscopy and biopsy becomes mandatory.

Though multiple biopsies also increase the areas sampled, cytologic brushing seems to have the advantage of covering a relatively large area and tendency to selectively collect loose dyshesive cells. This may explain the superiority of cytology in detecting malignancy in the initial procedure itself.

The limitation of cytology is its inability to distinguish between dysplasia/ carcinoma in situ and invasive carcinoma. A tumor diathesis and a high cellularity in a smear may indicate invasion but not with certainty. Another controversy is whether the brushing should be performed before or

after biopsies. Some of the authors prefer to perform the brushing after biopsy believing that it might decrease the yield of biopsy. Some believe that the accuracy of brushing is higher when performed before biopsy.[14] In the present study brushing was done before biopsy.

To conclude, though biopsy is used as a routine procedure in diagnosis of gastrointestinal tract lesions, cytology is useful because it is inexpensive, gives a rapid diagnosis and offers minimal discomfort to the patient. Cytology can be used as an adjunct to biopsy in the diagnosis of upper GIT neoplasms. With increased experience and adherence to strict criteria for malignancy, and use of a “suspicious” category, malignancy can be effectively detected and treated.

SUMMARY AND CONCLUSION

- 50 adult patients who had clinically or radiologically suspected or diagnosed lesions in the oesophagus, stomach and the duodenum underwent elective diagnostic upper GI endoscopy with concurrent cytology and biopsy sampling over a period of 2 years.

- Patients included 34 males and 16 females and the ratio was 2.13**:**1. Age of the patients ranged from 21-80years. Majority were in the age group of 51-70 years.

- Pain abdomen was the most common symptom seen in 38 patients, followed by vomiting in 28 patients.

- On endoscopy 16 cases (32%) showed lesions in the oesophagus, 30 in the stomach (60%) and 4 in the duodenum (8%).

- In the oesophagus, 50% of the lesions were in the middle third .

- In the stomach,73% of the lesions were in the antrum .

- In brush cytology 40 cases (80%) were positive for malignancy of which biopsy was positive in 38 cases and 2 were false positive. Of the 10 cytology negative cases 8 were negative in biopsy and 2 were false negative in cytology .

- Squamous cell carcinoma was predominant in oesophagus and adenocarcinoma in stomach and duodenum.

- As compared to Endoscopic biopsy, which is considered as the gold standard, Brush cytology reported 95% sensitivity and 80% specificity. Positive and negative predictive values were 95% and 80% respectively. Overall diagnostic accuracy was 92%.

Brush cytology is a highly sensitive and fairly specific test with a good diagnostic accuracy. Although difficult; with meticulous efforts, it is possible on brush cytology to assess the degree of differentiation of SCC and to distinguish between the diffuse and intestinal types of gastric adenocarcinoma. Even if the cell-yield is sparse; with a cautious approach, a reasonable, if not precise diagnosis can be offered on brush cytology. Overall, it is a highly useful adjunct to endoscopic biopsy.

ABBREVIATIONS

GI	:	Gastro intestinal
HPV	:	Human papilloma virus
GIT	:	Gastrointestinal tract
WHO	:	World health organization
BC	:	Brush cytology
EB	:	Endoscopic biopsy
N:C	:	Nucleus : cytoplasm
SCC	:	Squamous cell carcinoma
MGG	:	May-Grunwald-Giemsa
H&E	:	Haematoxylin & Eosin
AC	:	Adenocarcinoma

CYTOLOGY REPORT:

SAMPLE : CELLULAR SCANTY

ARRANGEMENT :

CELLS :

NUCLEUS :

BACKGROUND :

OTHER CELLS :

IMPRESSION:

HISTOPATHOLOGY REPORT

NORMALMUCOSA:

INFLAMMATORY CELLS:

NEOPLASM:

:

IMPRESSION:

CORRELATION:

CELLULAR SMEARS

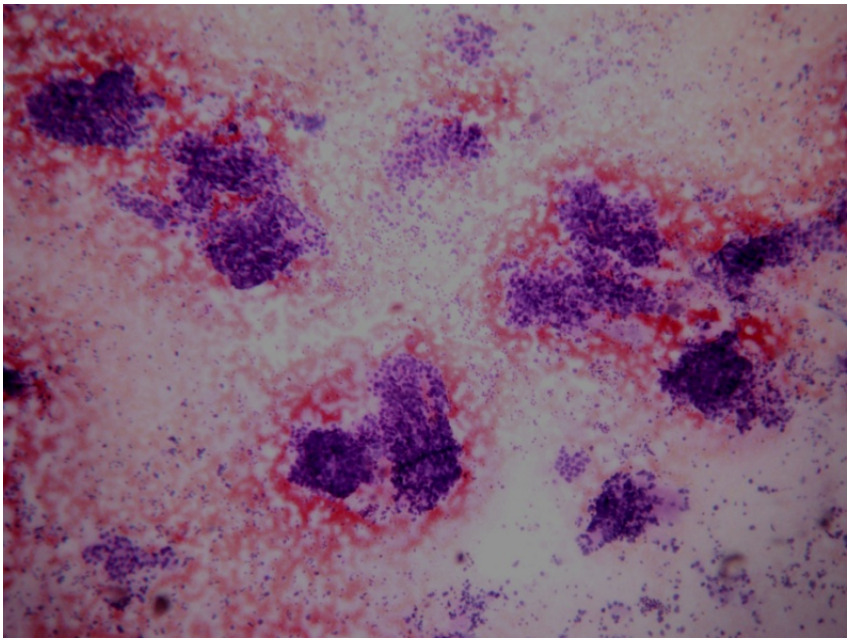


Figure 6: H&E X 40

NORMAL OESOPHAGUS

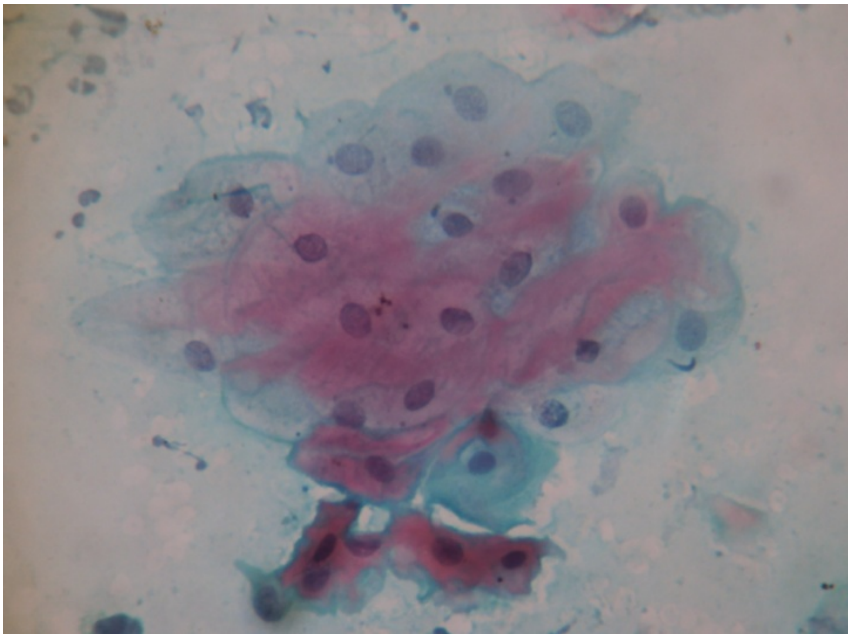


Figure 7 :NORMAL SQUAMES.PAP STAIN X 400

WELL DIFFERENTIATED SCC

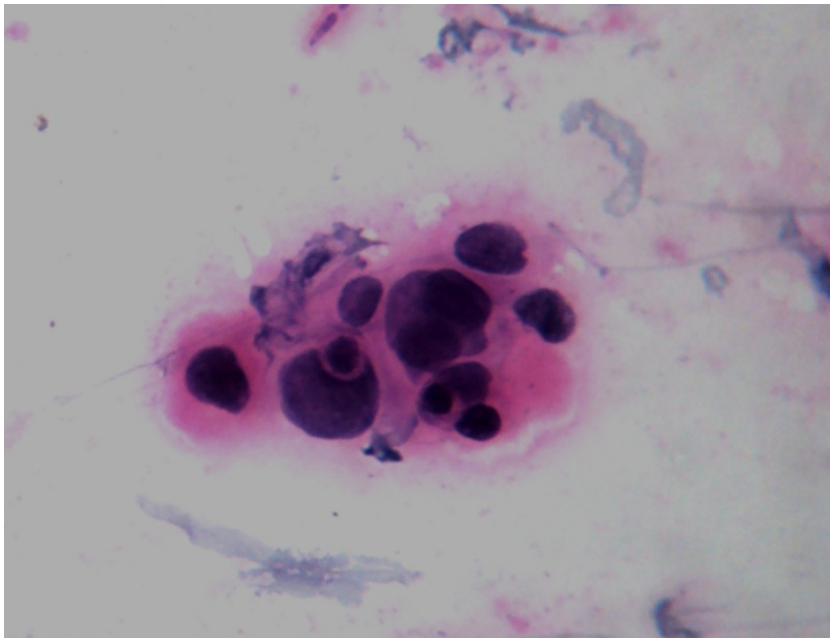


Figure 8 : MALIGNANT SQUAMES.H&E X 400

WELL DIFFERENTIATED SCC

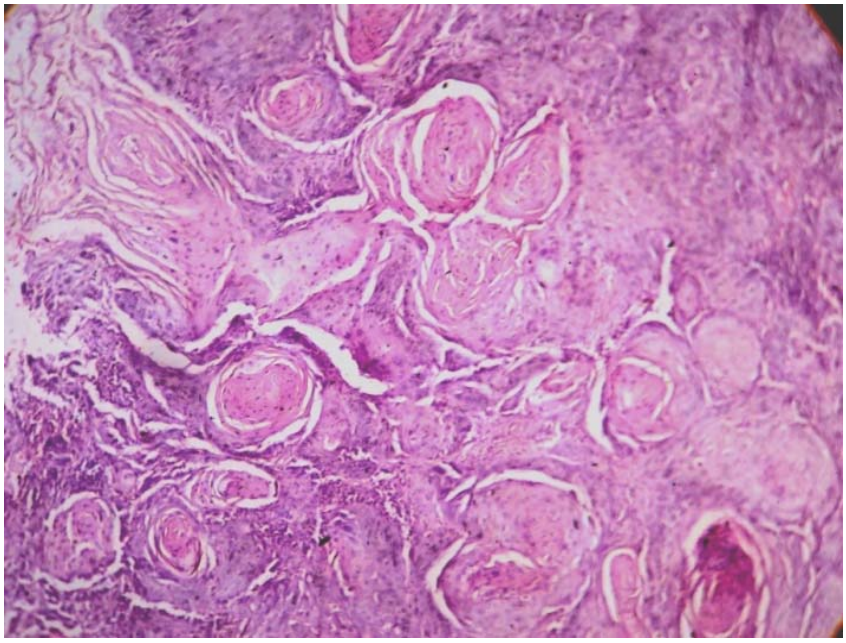


Figure 9 : H & E X 100

MODERATELY DIFFERENTIATED SCC

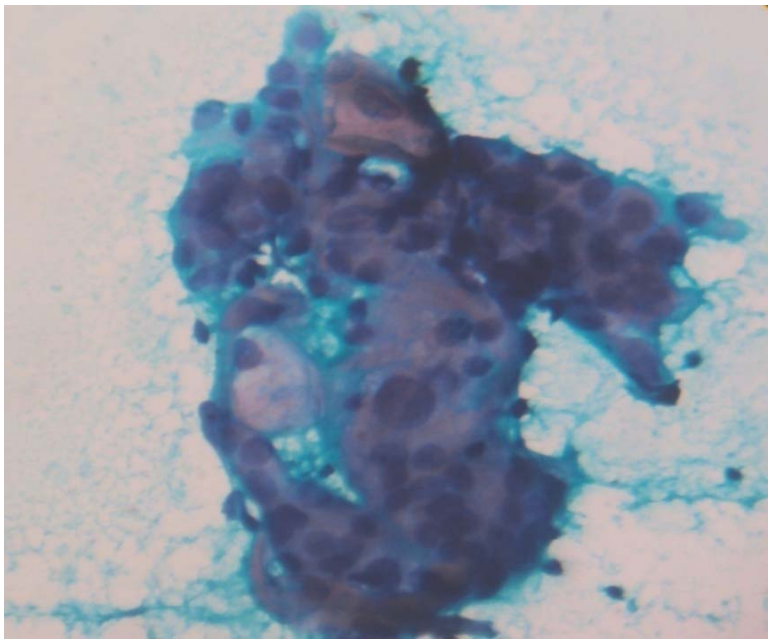


Figure 10 : PAP STAIN X 400

MODERATELY DIFFERENTIATED SCC

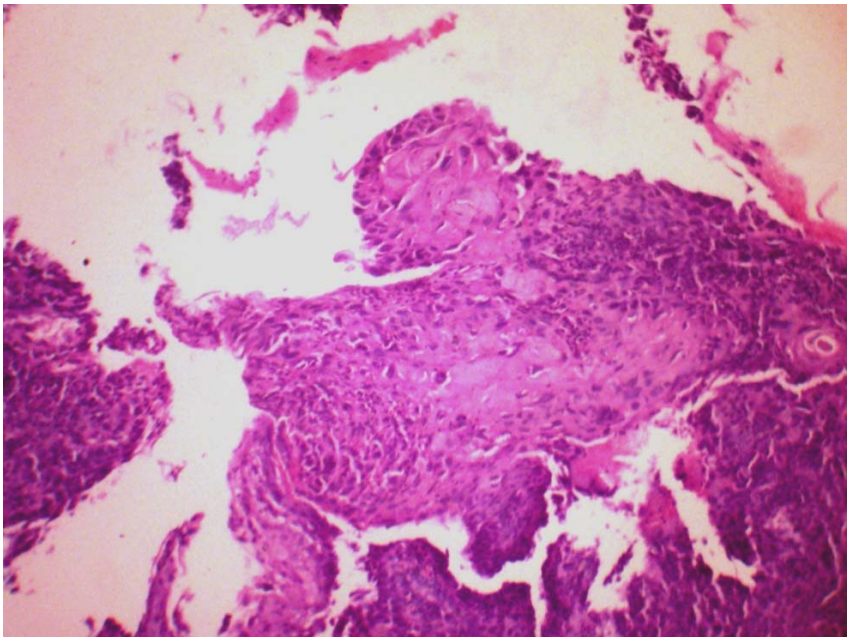


Figure 11 : H&E X 100

POORLY DIFFERENTIATED SCC

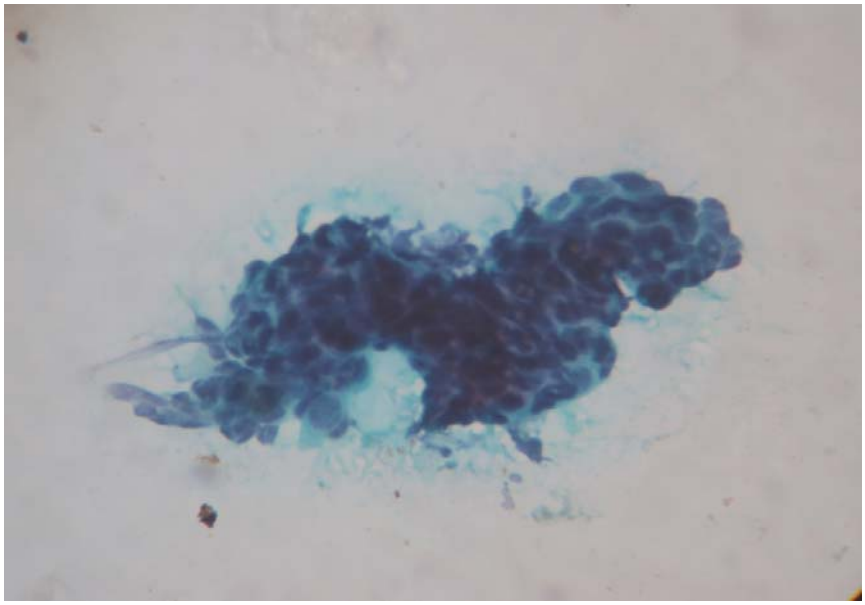


Figure 12 : PAP STAIN X 400

POORLY DIFFERENTIATED SCC

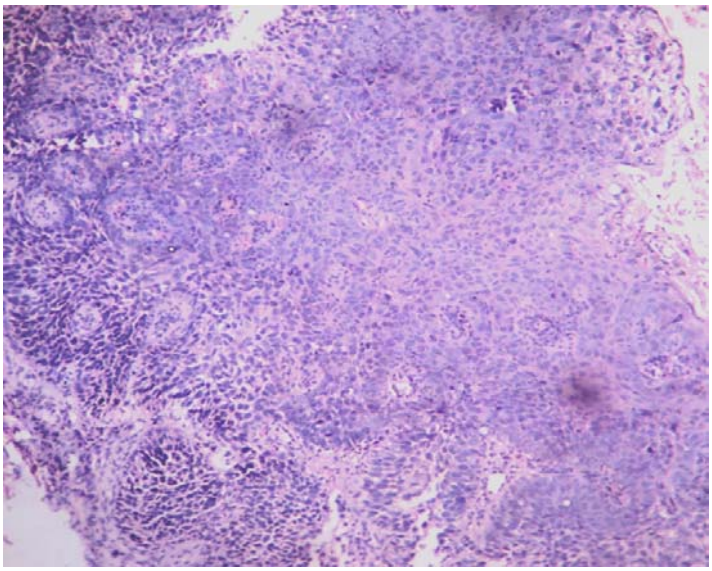


Figure 13 : H & E X 100

ADENOCARCINOMA OF OESOPHAGUS

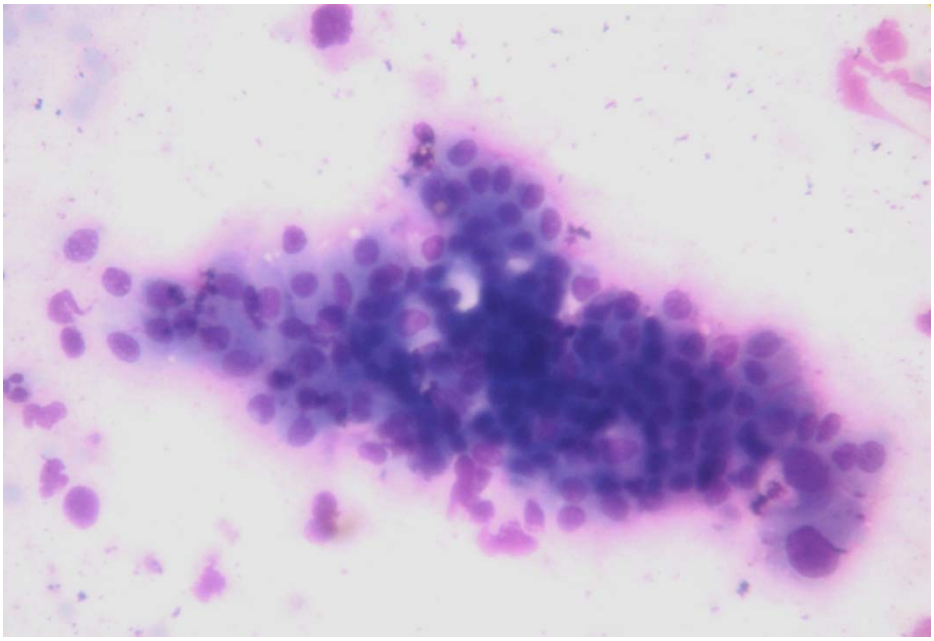


Figure 14 : MGG X 400

ADENOCARCINOMA OF OESOPHAGUS

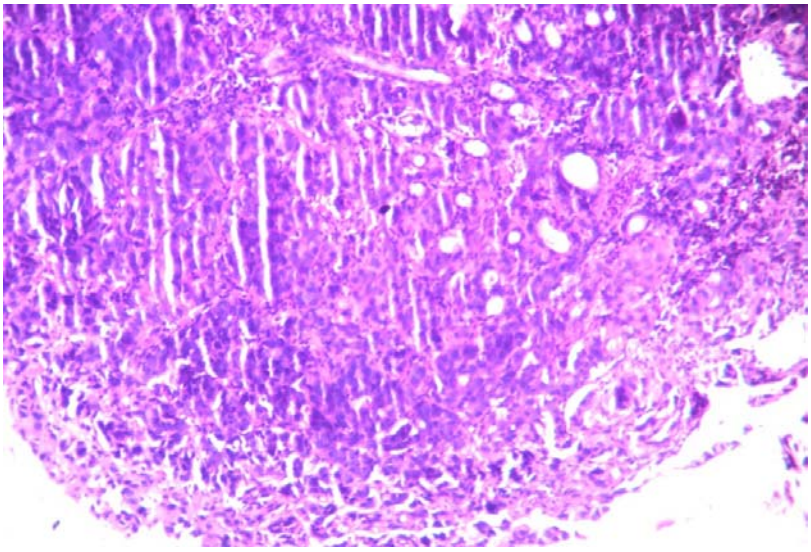


Figure 15 : H & E X 400

UNSATISFACTORY SMEAR

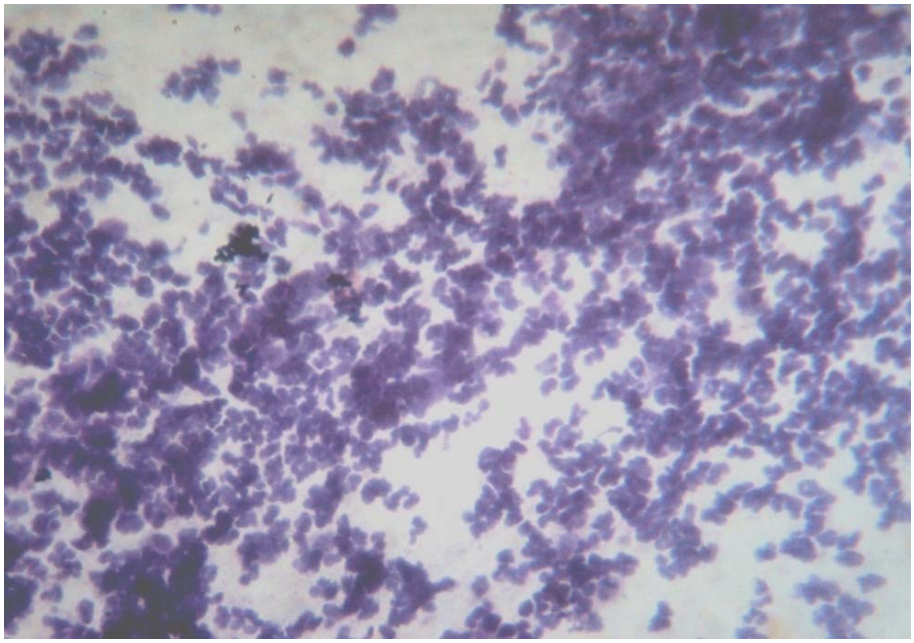


Figure 16 : DENSE INFLAMMATORY BACKGROUND OBSCURING THE LESIONAL CELLS H&E X 400

NORMAL CYTOLOGY OF STOMACH

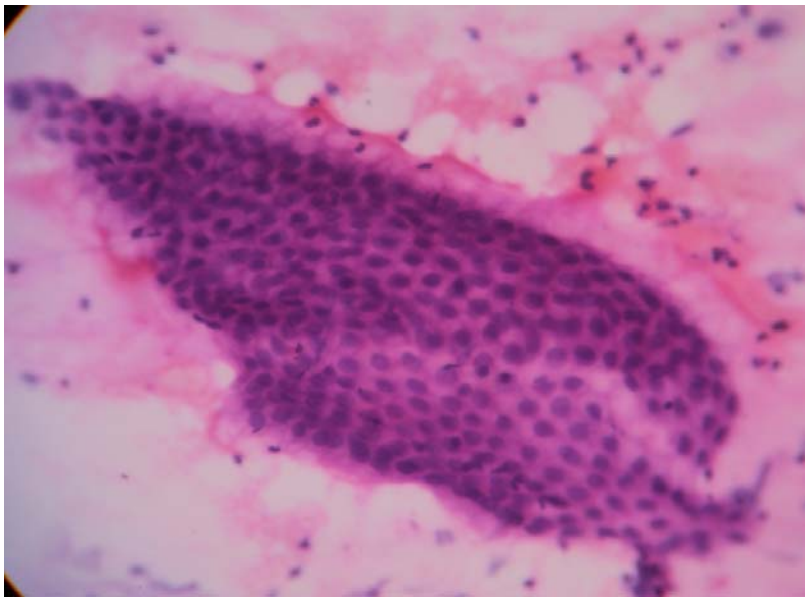


Figure 17 : MONOLAYERS OF NORMAL MUCOSA FORMING HONEY COMB LKE STRUCTURES H & E X 400

REACTIVE ATYPIA

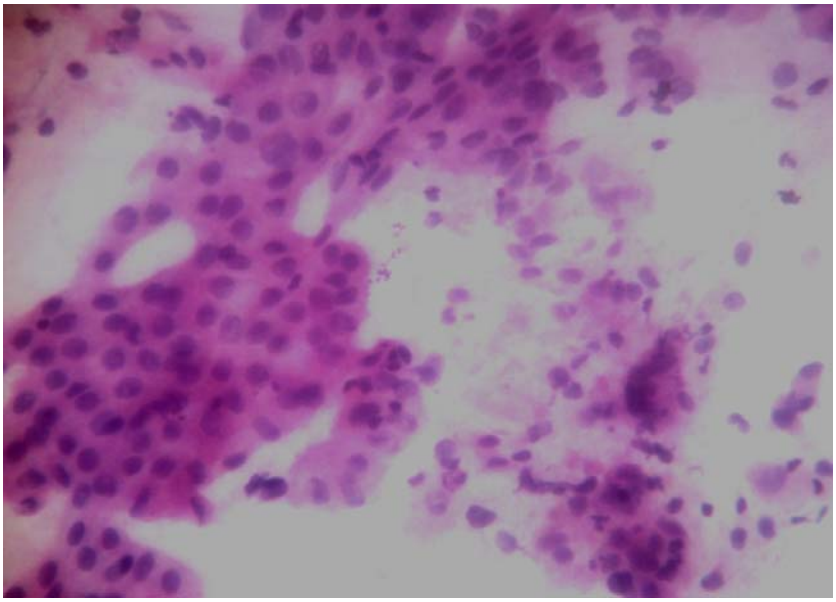


Figure 18 : INCREASED ACIDOPHILIA OF CYTOPLASM, H&E X 400

GASTRIC ULCER

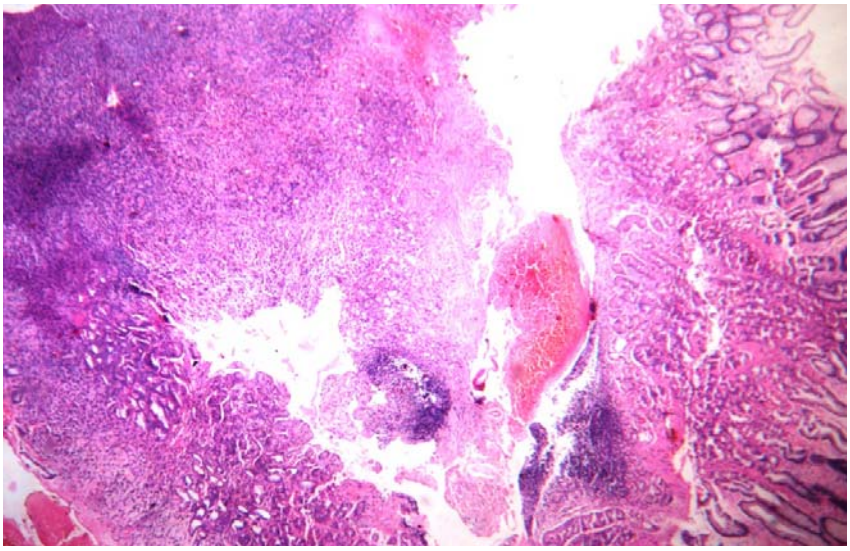


Figure 19 :GRANULATION TISSUE H&E X 400

WELL DIFFERENTATED ADENOCARCINOMA OF STOMACH

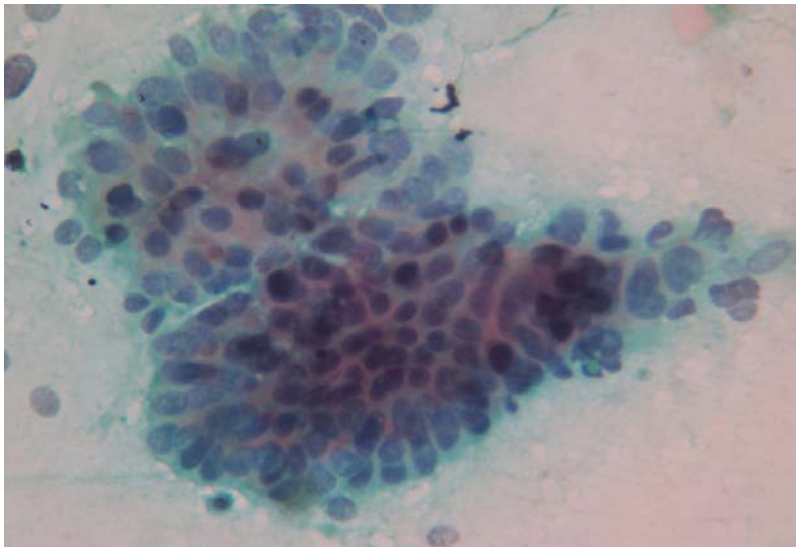


Figure 20 : GLANDULAR CLUSTERS,PAP STAIN X 400

WELL DIFFERENTIATED ADENOCARCINOMA

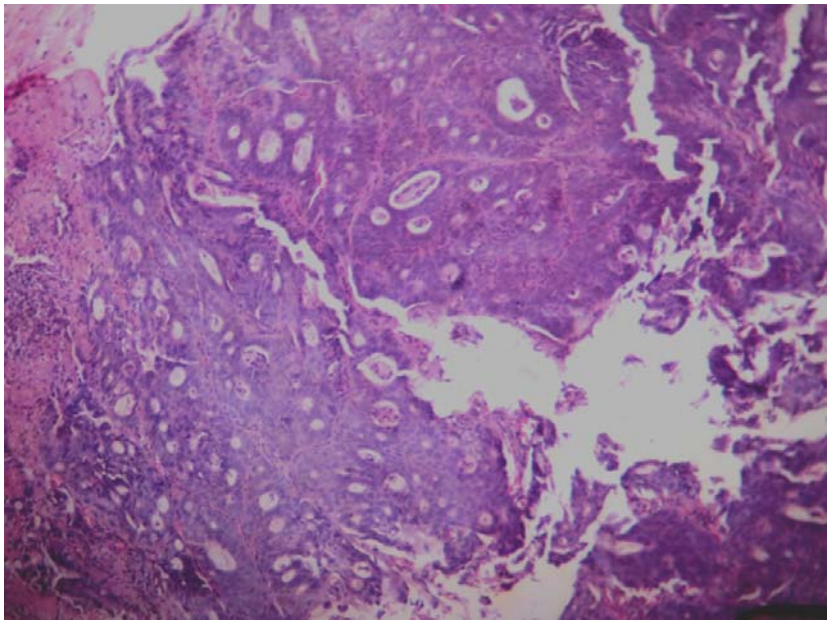


Figure 21 : H & E X 100

MODERATELY DIFFERENTIATED ADENOCARCINOMA

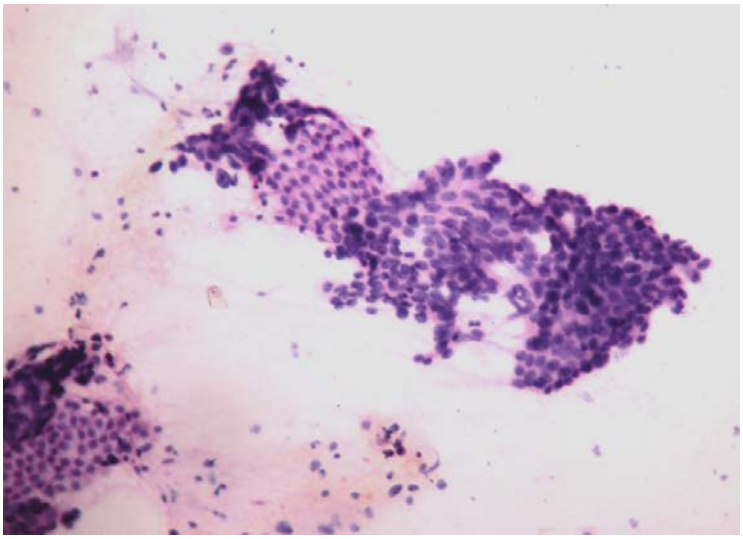


Figure 22 : NORMAL CELLS ADMIXED WITH MALIGNANT CELLS,H&E X 100

MODERATELY DIFFERENTIATED ADENOCARCINOMA

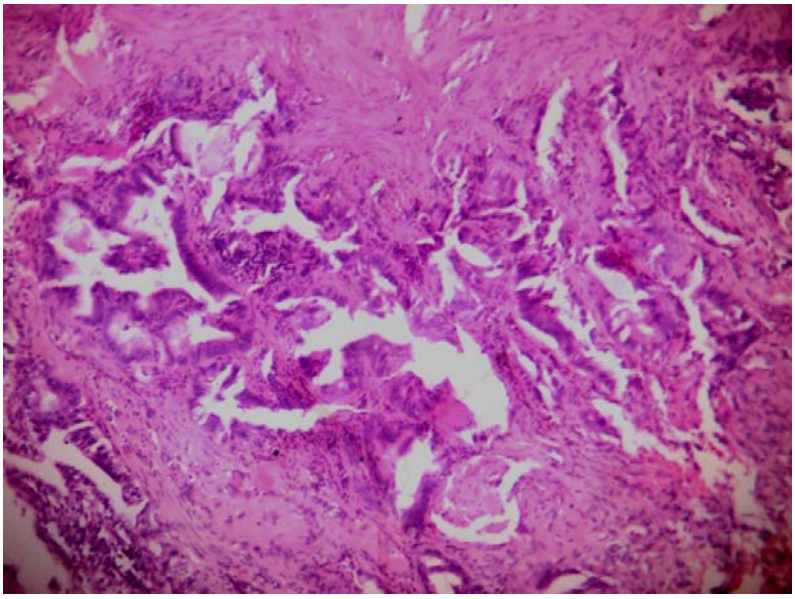


Figure 23 : H & E X 100

POORLY DIFFERENTIATED ADENOCARCINOMA

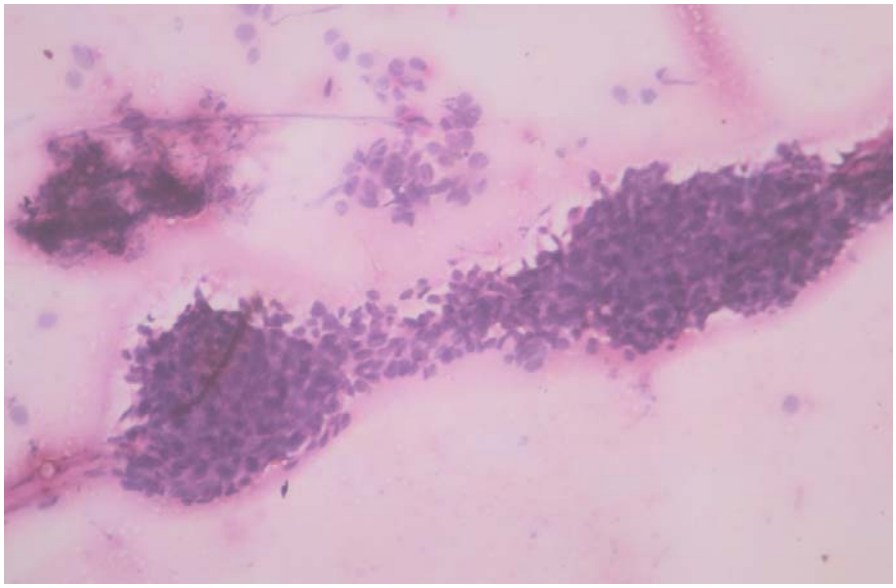


Figure 24 : ILL FORMED ACINI, H & E X 100

POORLY DIFFERENTIATED ADENOCARCINOMA

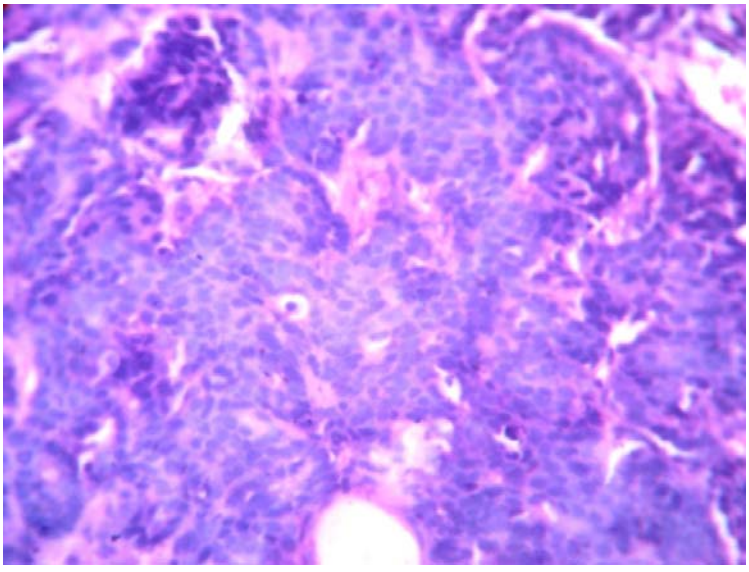


Figure 25 : H & E X 100

SIGNET RING CELLS IN DIFFUSE TYPE

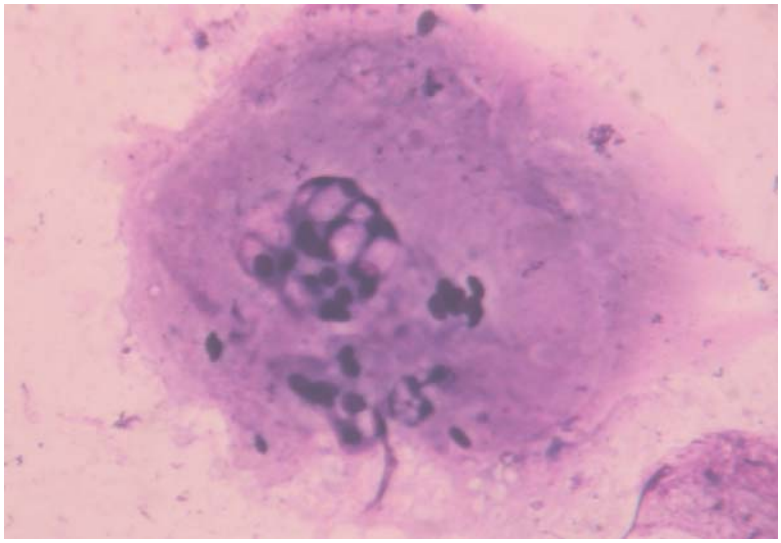


Figure 26 : MGG X 400

DIFFUSE TYPE OF ADENOCARCINOMA

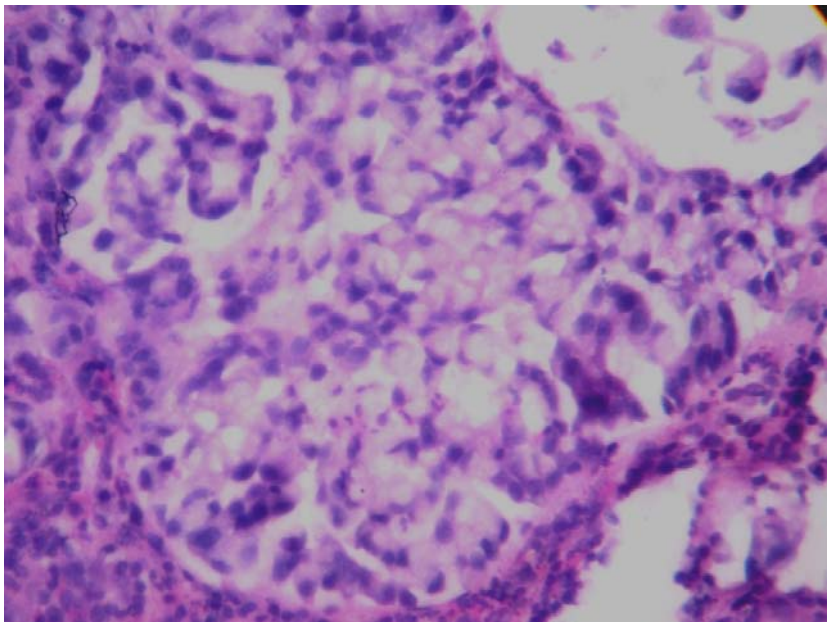


Figure 26 : H & E X 400

NORMAL CYTOLOGY OF DUODENUM

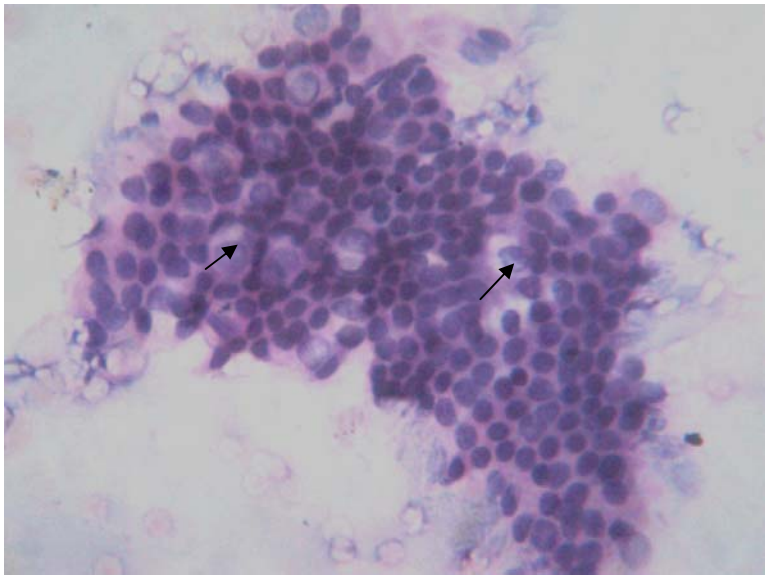


Figure 27 : → SHOWS GOBLET CELLS AMIDST COLUMNAR CELLS H & E X 400

ADENOCARCINOMA OF DUODENUM

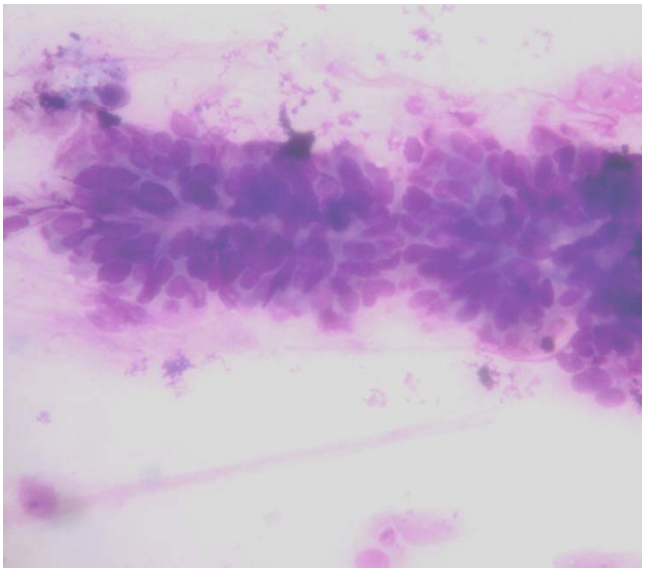


Figure 28 : PAPILLAROID CLUSTERS,MGG X 400

MUCINOUS ADENOCARCINOMA OF STOMACH

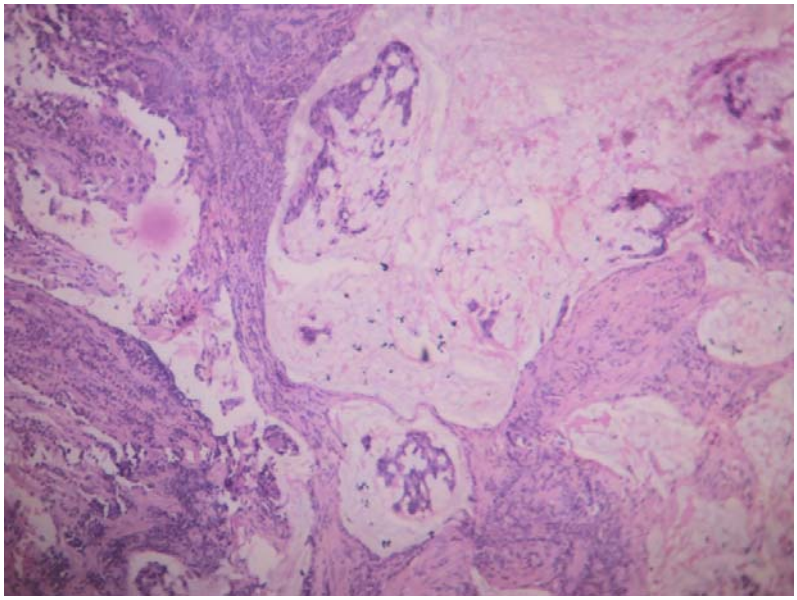


Figure 29 : H & E X 100

ADENOCARCINOMA OF STOMACH

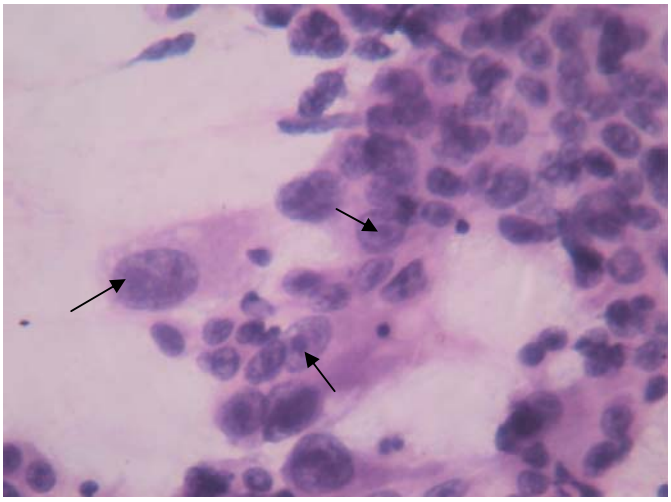


Figure 30 : CELLS SHOW PROMINENT NUCLEOLI H & E X 400

VIDEO ENDOSCOPE WITH THE PROCESSOR

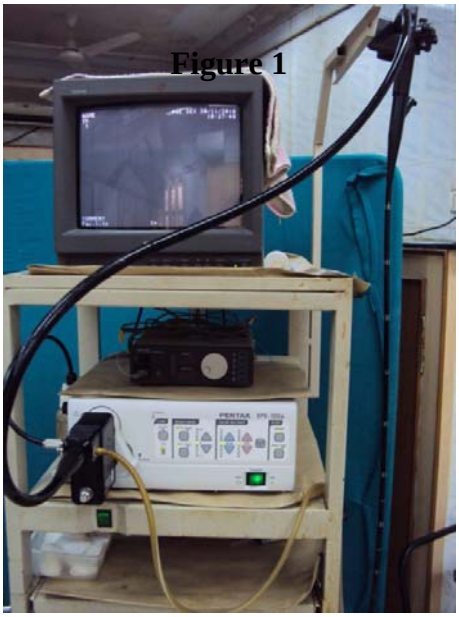


Figure 1

CYTOLOGY BRUSH

Figure 2

BIOPSY FORCEPS

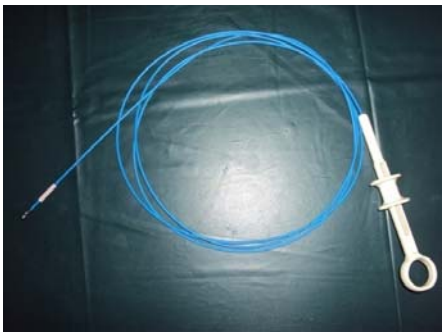


Figure 3

PROLIFERATIVE GROWTH 2ND PART OF DUODENUM

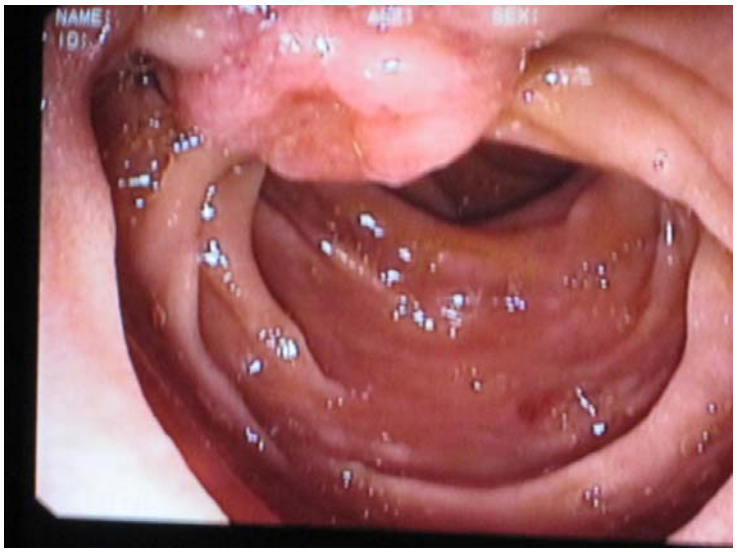


Figure 4

ULCERATIVE GROWTH FUNDUS OF STOMACH

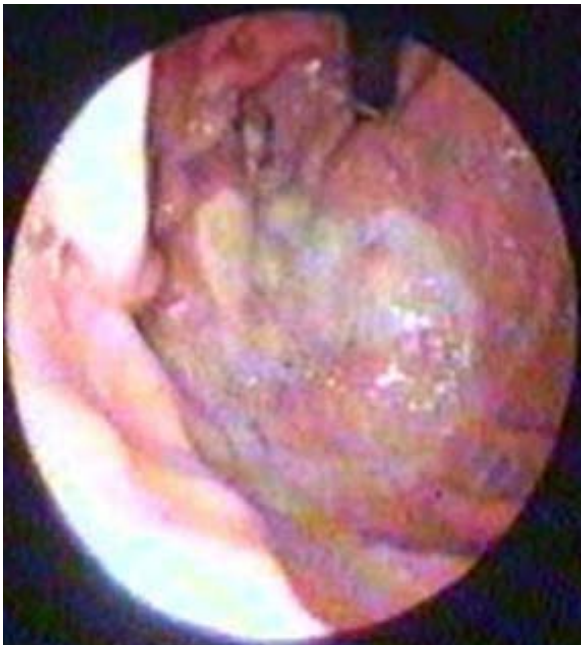


Figure 5

CORRELATION OF BRUSH CYTOLOGY AND ENDOSCOPIC BIOPSY OF UPPER GIT NEOPLASMS

CASE NO:
CYTO NO: DATE : HPE NO:
NAME : AGE : SEX :
IP / OP : WARD :
HOSPITAL :

CLINICAL HISTORY:
DIFFICULTY IN SWALLOWING:

DYSPHAGIA : SOLIDS: LIQUIDS:

PAIN ABDOMEN : MASS ABDOMEN**:**

LOSS OF WT: LOSS OF APPETITE:

HEMATEMESIS: MELENA:

FAMILY HISTORY :

DIET : VEG/ NONVEG

INVESTIGATIONS:

Hb TC DC

ENDOSCOPY: ULCER GROWTH

ESOPHAGUS

STOMACH: CARDIA

FUNDUS

BODY

ANTRUM

PYLORUS AND DUODENUM

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