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Histopathological study of endoscopic biopsies of Oesophagus

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Abstract
Introduction
Upper Gastrointestinal tract disorders are the most commonly encountered problems in clinical practice with a high degree of morbidity and mortality. Carcinoma esophagus is a fatal tumour with poor prognosis. Good prognosis depends largely on early detection of thetumour. Endoscopic biopsy plays an important role in their early diagnosis and management.
Objectives
1. To study the spectrum of histopathological lesions of oesophagus
2. To study the correlation between malignant lesions of oesophagus with age, sex and clinical presentation.

Methodology: A prospective study on endoscopic biopsies of Esophagus was conducted from August 2013 to July 2015.
Results: Our study included 55 endoscopic biopsies of esophagus. Commonest age group of presentation was 61-70 years with male to female ratio of 1.5:1. Dysphagia was the most common clinical complaint (70.9%), middle1/3rd was the commonest site of presentation (67.3%). Of the 55 cases non neoplastic lesions were (5.4%), neoplastic lesions were (87.3%) with squamous cell carcinoma being the commonest lesion (74.5%) followed by adenocarcinoma (7.3%). Among squamous cell carcinomas well differentiated were (19.5%), moderately differentiated were (65.9%) and poorly differentiated were (14.6%). Among adenocarcinomas moderately differentiated were (75%) and poorly differentiated were (25%).
Conclusion: Squamous cell carcinoma was the commonest condition in our study. Lesions were common in 6th and 7th decade with dysphagia being the most common complaint. Hence dysphagia in older patients should be investigated and confirmed with endoscopic biopsy to rule out carcinoma esophagus in highly suspicious cases.

Keywords: esophagus, endoscopic biopsy, squamous cell carcinoma

Introduction
The epidemiology of upper gastrointestinal disease is a fascinating topic of research that is evolving rapidly. Medications for gastroesophageal reflux disease is now the largest single item on the health care budget of many countries. Following long term medication by proton pump inhibitors there is a change in the incidence of gastroesophageal reflux disease; possibly that has lead to increased incidence of cancer of lower oesophagus and cardia.
Lesions of the esophageal mucosa are ideally suited for examination by fiberoptic endoscopy because they are readily accessible and can easily be sampled for specific histologic, microbiologic investigation with available biopsy forceps [1].
Abnormal radiographic studies such as those suggestive of mass lesion, ulcers, or strictures, require further endoscopic evaluation and biopsy [2].
Endoscopic biopsy is a simple and accurate non invasive outpatient procedure. It is not only used for diagnosis of upper gastrointestinal lesions, but also for monitoring the disease and detection of its complications [3].
Acquired diseases of the oesophagus run the gamut from highly lethal cancers to the persistent heartburn that may be chronic and incapacitating or merely an occasional annoyance [4].
The definitive diagnosis of disorders of oesophagus rests on confirmation by histopathology and is one of the basis for planning the treatment [3].

The most common diagnostic problems encountered with esophageal biopsy specimens involve the evaluation of oesophagitis and its consequences. Esophagitis can be caused by diverse agents such as physical, chemical, and biologic agents, butthe most common culprit is gastroesophageal reflux, with infectious organisms holding a distant second place [5].

Patients who are suffering from symptomatic heartburn and regurgitation are clinically classified as gastroesophageal reflux disease, in the absence of oesophageal mucosal abnormalities as nonerosive reflux disease [6].

Dysphagia is one of the commonest clinical complaint that may be caused by a variety of upper gastrointestinal disorders, ranging from benign to malignant. These conditions include neuromuscular or structural disorders causing dysmotility either in the oropharynx or oesophagus (oesophageal body, lower oesophageal sphincter or cardia). The true prevalence of dysphagia is not known, but it is reported to be 16% to 22% after 50 years of age. Often it leads to the finding of an anatomical or motility disorder of the oesophagus. As a part of the alarm symptoms, dysphagia needs to be investigated thoroughly on an urgent basis to establish early diagnosis in the course of patient's management so as to rule out any ongoing serious pathology such as a neoplastic process [7].

Oesophageal cancer is the eighth most common cancer world wide. Adenocarcinoma is predominantly disease of Western Europe, Australia, and North America; Squamous cell carcinoma predominates in Southeastern Africa, Southern Russia, Asia.

The prognosis is poor for patients with esophageal cancer, prompting the search for new treatment strategies. Risk factors for squamous cell carcinoma are alcohol and tobacco use, poverty, caustic oesophageal injury, achalasia, tylosis, Plummer-Vinson syndrome, and frequent consumption of very hot beverages [4].

Barrett esophagus is one of the strongest risk factor and known precursor for adenocarcinoma oesophagus, a lethal malignancy with a rapidly rising incidence. Other risk factors include obesity, smoking, and diet low in fruits and vegetables. Currently endoscopic biopsy for histopathology is one of the gold standard method for diagnosing Barrett esophagus as well as development of dysplasia and carcinoma [10].

Endoscopic mucosal resection is currently the only method which reliably determines the depth of invasion of superficial cancers and is an important aspect of staging cancer [11].

Objectives

1. To study the spectrum of histopathological lesions of oesophagus
2. To study the correlation between malignant lesions of oesophagus with age, sex and clinical presentation.

Materials and Methods

The present study included 55 endoscopic biopsies of oesophagus. They were taken from the patients clinically suspected of oesophageal lesions in gastroenterology section, JJM Medical college, Davangere in Karnataka, India from 1st August 2013 to 31st July 2015. Brief clinical history was taken from the patients which included age, sex, chief complaints, endoscopic findings and endoscopic diagnosis.

After obtaining the informed consent from the patient, endoscopic biopsies were taken by an experienced gastroenterologist. Entire tissue was routinely processed and embedded in paraffin with mucosal surface uppermost. Five micron thick sections were cut perpendicular to this surface and four to five sections were prepared on each slide. Each section was stained with H and E, studied microscopically. The findings were then correlated with the age, sex, and clinical presentation. Special stains like Periodic acid Schiff (PAS), Alcian blue, and mucicarmine were performed whenever necessary.

Ethical clearance for the study was obtained.

Inclusion Criteria

All the endoscopic biopsies of oesophagus

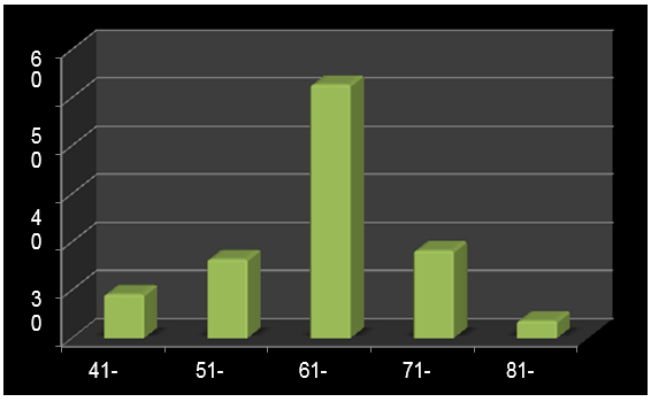
Exclusion Criteria

1. Resected oesophageal lesions
2. Patients with contraindications to undergo endoscopy and biopsy like medically unstable patients such as hemodynamic instability, hypoxia, cardiac arrhythmia, esophageal perforation.
3. Unwilling patients

Statistical analysis: Chi square test was used to study the correlation between malignant lesions of Esophagus with clinical presentation.

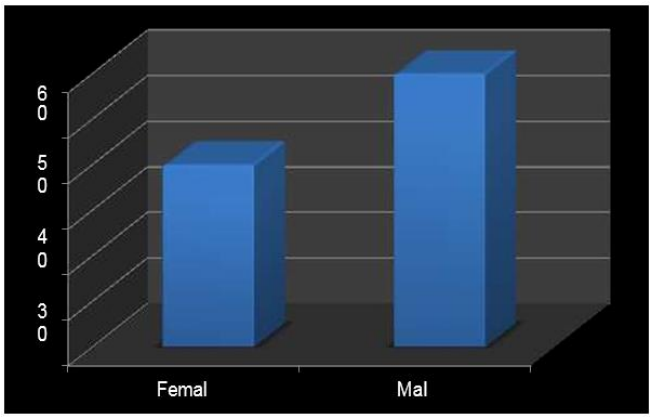
Results

The present study included 55 endoscopic biopsies between the period of August 2013 to July 2015. The following results were observed.



Graph 1: Age distribution of oesophageal lesions most common affected age group in our study was 61-70years.

In our study out of 55 patients 29 (52.7%) cases were in the age group of 61 to 70 years, next frequent age group affected was 71-80 years 10 (18.2%) cases, lesions were less frequent below 50 years of age. (Graph 1)



Graph 2: Sex distribution of oesophageal lesions

There were 33 male and 22 female patients with a male to female ratio of 1.5:1. Males were predominantly affected (Graph 2)

Chief complaints in the studied patients

Most common clinical complaint in our study was dysphagia (70.9%), next common was weight loss (12.7%), followed by epigastric pain (9.1%) cases, and vomiting in (7.2%) cases.

Dysphagia in our cases was progressive, initially for solids later progressed to liquids.

Site wise distribution of oesophageal lesions

Lesions were most common in the middle 1/3rd of oesophagus in the present study which accounted for 37 (67.3%) cases. Next common site was lower 1/3rd 16 (29.1%) cases, followed by upper 1/3rd 2 (3.6%) cases.

Distribution of oesophageal lesions

Neoplastic lesions constituted majority of the cases in our study 48 (87.3%) cases, non-neoplastic lesions were 3 (12.7%) cases. In our study inconclusive cases constituted 4 (7.3%) cases. No opinion was possible in these cases as the biopsy material was inadequate, it showed few necrotic bits of tissue with few inflammatory cells on microscopy. Hence repeat biopsy was advised in these cases.

Distribution of non neoplastic lesions of oesophagus

Non neoplastic lesions in our study were Inflammatory lesion of oesophagus, Hyperplastic mucosa, Granulation tissue all of which constituted 1case each (33.3%) of total non-neoplastic lesions.

Table 1: Distribution of neoplastic lesions of oesophagus

Diagnosis	No of cases	Percentage
Barrett's esophagus	1	2.1%
High grade intraepithelial neoplasia	2	4.2%
Squamous cell carcinoma	41	85.4%
Adenocarcinoma	4	8.3%
Total	48	100%

In our study squamous cell carcinomas were the predominant lesion accounting for 41 (85.4%) of cases of all the neoplastic lesions, next common was adenocarcinoma 4 (8.3%) cases, followed by high grade intraepithelial neoplasia 2 (4.2%) cases (Fig 1), and Barrett's esophagus 1 (2.1%) case. (Table 1) (Fig 2).

Distribution of malignant lesions of oesophagus

Squamous cell carcinoma was the predominant malignant lesion accounting for 41 (91.1%) cases of malignant lesions, followed by adenocarcinoma 4 (8.9%) cases.

Table 2: Distribution of age in relation to malignant lesions of oesophagus

Diagnosis	41-50	51-60	61-70	71-80	81-90	Total No. of cases	Percentage
Squamous cell Carcinoma	4	7	19	10	1	41	91.1%
Adeno Carcinoma	0	1	2	0	1	4	8.9%
Total	4 (8.8%)	8 (17.8%)	21 (46.7%)	10 (22.3%)	2 (4.4%)	45	100%

Most common age group affected by Squamous cell carcinoma and adenocarcinoma was between 61- 70 years. (Table 2)

Table 3: Distribution of sex in relation to malignant lesions of oesophagus

Sex	Squamous cell carcinoma	Adenocarcinoma	Total
Male	29	3	32 (71.1%)
Female	12	1	13 (28.9%)
Total	41	4	45 (100%)

Malignant lesions of oesophagus were more in male patients compared to females.

Male: female ratio for malignant lesions of oesophagus in our study was 2.5:1. cases each. (Table 3)

Table 4: Histological grading of esophageal carcinoma

	Well differentiated	Moderately Differentiated	Poorly Differentiated	Total
Squamous cell Carcinoma	8 (19.5%)	27 (65.9%)	5 (12.2%)	40 (97.6%)
Basaloid squamous cell Carcinoma	0	0	1 (2.4%)	1 (2.43%)
Adenocarcinoma	0	3 (75%)	1 (25%)	4 (100%)

In our study 41 cases were squamous cell carcinoma with various degrees of differentiation, 8 (19.5%) were well differentiated (Fig 3), 27 cases (65.9%) were moderately differentiated (Fig 4) and 6 (14.6)% were poorly differentiated (Fig 5) squamous cell carcinomas. 4 cases were adenocarcinoma, out of these, moderately differentiated accounted for 3 (75%) cases of the total adenocarcinomas (Fig 6), poorly differentiated carcinoma constituted 1 (25%) case of total adenocarcinomas (Fig 7) (Table 4).

Histological subtypes of adenocarcinoma oesphagus

Among four cases of adenocarcinoma, tubular carcinoma (50%) was the commonest subtype followed by both papillary and mucinous variants constituting (25%) each.

In our study there was 1case (25%) of Papillary adenocarcinoma oesophagus, histologically composed of an infiltrating tumour composed of papillary structures and glands lined by pleomorphic columnar cells with vacuolated to eosinophilic cytoplasm. Core of the papillae showed fibrovascular connective tissue.

In our study Tubular adenocarcinoma esophagus were 2cases accounted for (50%) of the total adenocarcinomas. Histologically displayed infiltrating tumour arranged in the form of tubules lined by pleomorphic columnar epithelium showing moderate atypia. Adjacent area shows detached bit of squamous epithelium and Barrett mucosa lined by goblet cells.

There was 1 case (25%) of Mucinous adenocarcinoma, histologically displayed infiltrating tumour composed of tumour cells arranged in cords and small nests. Tumour cells are large pleomophic cells having scant cytoplasm with hyperchromatic nuclei which are embedded in a mucinous matrix. Mucin component constituted >50% of tumourcomponent. Periodic Acid Schiff (PAS) stain was used to demonstrate mucin.

Table 5: Correlation between clinical complaints and Esophageal Carcinoma

	Squamous cell Carcinoma	Adenocarcinoma
Dysphagia	34 (75.6%)	1 (2.2%)
Weight loss	6 (13.3%)	0
Epigastric pain	0	4 (8.9%)
Vomitting	1 (2.2%)	0
Total	41 (91.1%)	5 (8.9%)
Chi square=35.973 p-value = <0.00001		

The chi square statistic is 35.973. The p-value is <0.00001. The result is significant at<0.05.

Dysphagia was the most common clinical complaint for squamous cell carcinomas in our study (75.6%) cases of malignant lesions, followed weight loss in (13.3%) cases.

Epigastric pain was the most common complaint in adenocarcinoma accounting for (8.9%) cases of all malignant lesions. (Table 5)

Correlation between biopsy site and Esophageal Carcinoma

The most common site of biopsy for squamous cell carcinoma was middle 1/3rdseen in (68.9%) of cases of total malignant lesions, followed by lower 1/3rd (17.8%) of cases, and upper 1/3rd in (4.4%) cases.

The most common site of biopsy for adenocarcinoma was lower1/3rd (8.9%) of malignant lesions.

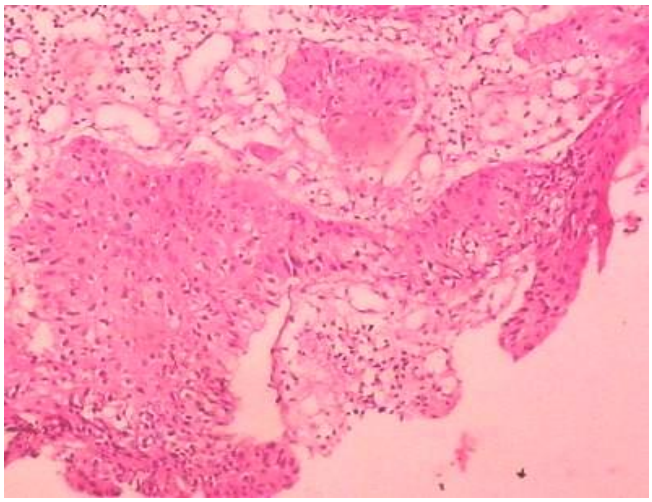


Fig 1: High grade Intraepithelial Neoplasia of Esophagus (X 100, H&E Stain) Inset: Architectural disarray, loss of polarity and cellular atypia involving upper half of the epithelium (X 400, H&E Stain)

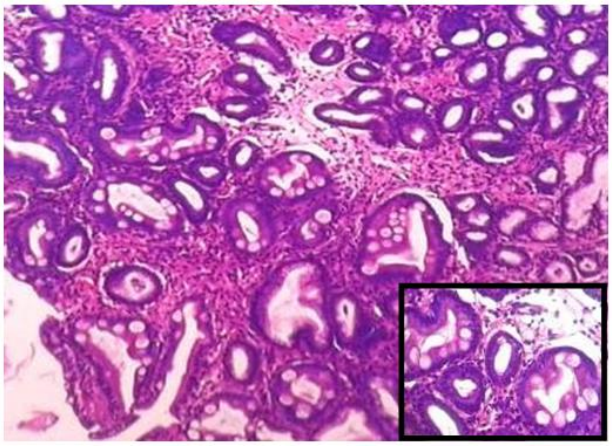


Fig 2: Barrett Esophagus (X 100, H&E Stain) Inset: Typical metaplastic glands lined by goblet cells (X 400, H&E Stain)

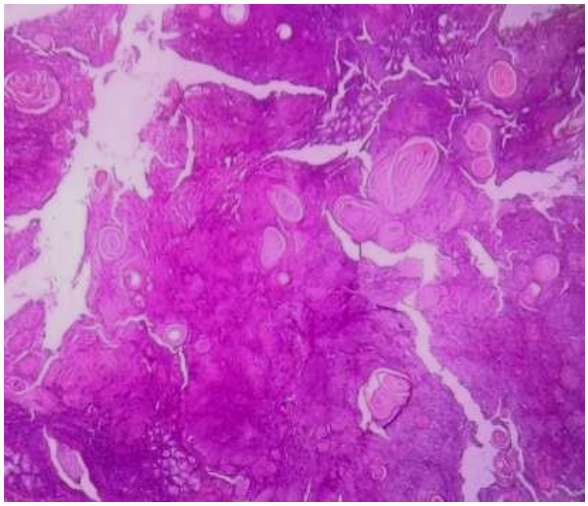


Fig 3: Well differentiated Squamous cell carcinoma of Esophagus (X 100, H&E Stain)

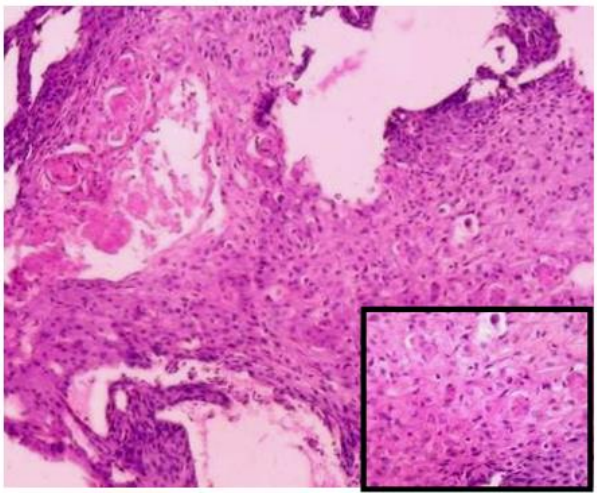


Fig 4: Moderately differentiated Squamous cell carcinoma Esophagus (X 100, H&E Stain) Inset: Individual cell keratinization (X 400, H&E Stain)

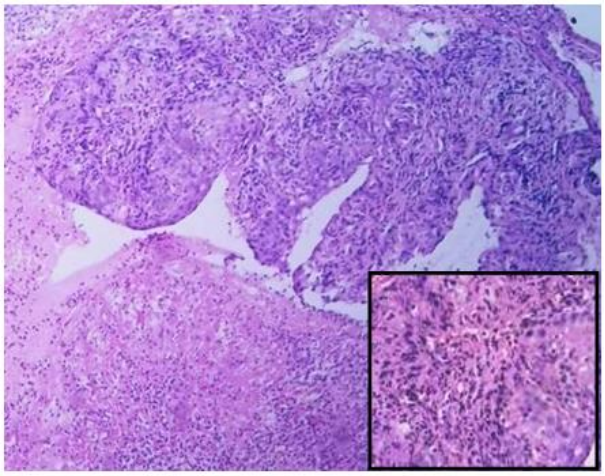


Fig 5: Poorly Differentiated Squamous cell carcinoma Esophagus (X 100, H & EStain) Inset: Atypical squamous epithelium showing marked nuclearpleomorphism (X 400, H&EStain)

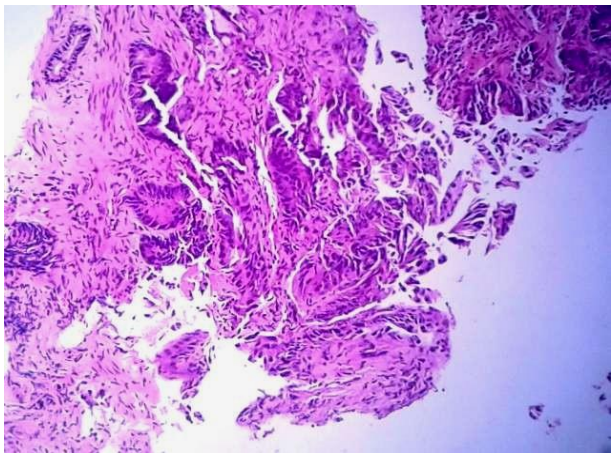


Fig 6: Moderately differentiated Adenocarcinoma Esophagus (Tubular variant) (X 100, H&E Stain)

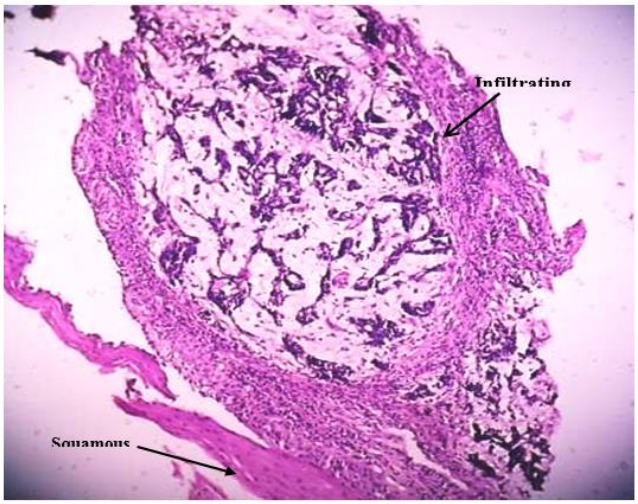


Fig 7: Poorly differentiated adenocarcinoma esophagus (M*ucinous variant*) (X 100, H&EStain)

Discussion

In the present study, a total of 55 endoscopic biopsies of oesophagus were studied from August 2013 to July 2015.

Comparison of endoscopic biopsy lesions of oesophagus

In our study malignant lesions were predominant constituting (87.2%) oesophageal lesions which is similar to study conducted by Bukhari *et al* (2009) [12] neoplastic lesions-73%, Islam *et al*. (2014) [13] neoplastic lesions-81.8% and Shah *et al*. (2015) [14]. neoplastic lesions-84.4%. In our study non neoplastic lesions constituted 5.5% of cases and in remaining 7.3% of cases repeat biopsy was advised as the biopsy material was inadequate.

Comparision of most common age group of presentation for oesophageal carcinoma

Most common age group of presentation in our study was 61-70 years which is slightly higher compared to study conducted by Leenadevi *et al*. (1980) [15], Prabhakar *et al*. (1988) [16] and Chitra *et al*. (2004) [17] in which the most common age group affected was between 51-60 years.

Comparison of sex ratio distribution of Esophgeal Carcinoma

The ratio of male: female in esophageal carcinoma in our study was 2.5:1. Esophageal carcinomas were more in males compared to females which is in accordance with the studies conducted by Khodaskar *et al*. (1982) [18], Sankaranarayanan *et al*. (1991) [19], Khuroo *et al*. (1992) [20], Chitra *et al*. (2004) [17] and Bathija *et al*. (2014) [21].

Comparison of site of biopsy in Esophageal Carcinoma:

In our study most common site of carcinoma esophagus was middle 1/3rd accounted for (68.9%) of cases. Next common site was lower 1/3rd (26.5%) cases followed by upper 1/3rd (4.4%) cases.

Our observation is similar to study conducted by Makdhoomi *et al*. (2005) [22], Balazs *et al*. (2013) [23], Rashmi *et al*. (2013) [3], Jayanthi *et al*. (2006) [24], Wu *et al*. (2003) [25] and Semnani *et al*. (2005) [26].

Comparison of type of growth in esophgeal carcinoma

In the present study polypoidal type of growth was most common endoscopic finding next common was ulcerative growth followed by infiltrative growth which is similar to study conducted by Shah *et al*. (2015) [14] with slight higher number cases presenting as polypoidal growth in our study.

Comparision of most common chief complaint in esophgeal carcinoma

In the present study dysphagia was the most common complaint accounting for 77.8% of cases which is similar to study conducted by Durrani *et al*. [27] (Dysphagia-86%), Bukhari *et al*. [12] (Dysphagia-90%), and Hussain *et al*. [28] (Dysphagia-89.2%).

Comparison of frequency of esophageal squamous cell carcinoma and adenocarcinoma among malignant lesions

In our study squamous cell carcinoma was the predominant histological pattern encountered accounting for 91.1% of neoplasms, followed by adenocarcinoma 8.9% cases which is similar to study conducted by Shah *et al*. (2015) [14], Durrani *et al*. (2009) [27] , Bukhari *et al*. (2009) [12], Jayanthi *et al*. (2006) [24] and Bhurgi *et al*. (2004) [29].

Esophageal cancer is histologically classified as squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma results from non- keratinized stratified epithelium and more common in developing countries.

Among the esophageal carcinoma, 41(91.1%) were squamous cell carcinomas. Histologically well differentiated squamous cell carcinoma was composed of good number of epithelial pearls, with intercellular bridges and minimal nuclear pleomorphism.

Moderately differentiated squamous cell carcinoma displayed only few horn pearls and moderate degree of pleomorphism.

Poorly differentiated squamous cell carcinoma displayed marked cellular and nuclear pleomorphism with absence of epithelial pearls and intercellular bridges.

Li TJ *et al*. [30] in their study of basaloid squamous cell carcinoma noted that basaloid squamous cell carcinoma occurred more often in males with a mean age of around 55-60years, more often in the middle 1/3rd with predominance of solid or basaloid areas. In our study there was a case of basaloid squamous cell carcinoma in a male patient aged 63 years; it was polypoidal growth in middle 1/3rd with predominance of solid areas which is similar with the above study.

Conclusion

In our study, squamous cell carcinoma was the commonest condition followed by adenocarcinoma.

Most common affected age group was 6th to 7th decade with a mean age group of 63.5

Middle1/3rd was the common site of presentation for squamous cell carcinoma, lower 1/3rd for adenocarcinoma.

Dysphagia was the common presenting complaint (70.9%). Hence dysphagia should be thoroughly investigated in the older age group to rule out carcinoma esophagus particularly in this region as the prognosis highly correlates with staging. Currently endoscopic biopsy followed by histopathology is the gold standard method for diagnosing mucosal lesions of upper gastrointestinal tract.

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