PATTERNS OF ESOPHAGEAL NEOPLASMS IN A REFERRAL DIAGNOSTIC CENTRE OF BANGALORE

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ABSTRACT: INTRODUCTION: Benign tumors of the esophagus are rare and are usually more bothersome than harmful. Carcinoma of esophagus is the sixth most common cancer in the world. The objective of this study was to understand the patterns of benign and malignant neoplasms encountered in oesophageal biopsies and to correlate with age, gender and clinical details. **METHODS:** A retrospective study was done in a referral diagnostic centre over a period of four years. The patient's age, gender, clinical details and endoscopy findings were noted. The biopsy was done on patients with weight loss and dysphagia. Special stains and Immunohistochemistry were done wherever necessary. **Statistical analysis used:** Chi square test and Fishers exact test were employed. **Ethics:** The study was approved by the Institutional Review Board. **RESULTS:** A total of 1110 consecutive oesophageal biopsies (13 resected specimens and 1097 endoscopic biopsies) were seen of which neoplasms accounted for 914 cases while 196 cases were non neoplastic. The malignant neoplasms (96.2%) far outnumbered the benign neoplasms in biopsy. Squamous cell carcinoma was the predominant histologic type (83.5%) of oesophageal neoplasm whereas adenocarcinoma constituted only 14.5% of all neoplasms in our study. Nine cases of small cell carcinoma, one case of adeno-squamous carcinoma and three cases of sarcomatoid carcinoma were noted. One case each of granular cell tumour, leiomyoma, gastrointestinal stromal tumour, non Hodgkin's lymphoma and malignant melanoma were observed. **CONCLUSIONS:** Malignant neoplasms far outnumbered benign neoplasms in biopsy. Male gender and age above 50 years were important risk factors. The mean age was similar for both the genders. Squamous cell carcinoma was the most common malignancy across all age groups in the referral diagnostic laboratory of Bangalore Barrett's esophagus is a consequence of chronic gastro esophageal reflex disorder which is the most important risk factor for adenocarcinoma of esophagus. Mesenchymal tumours of the esophagus are rare. Epidemiological factors governing the distribution of lesion need to be studied further.

MeSH term - esophagus
KEY-WORDS: esophageal neoplasms, esophageal malignancies
KEY MESSAGES: Malignant neoplasms far outnumbered benign neoplasms in biopsy. Squamous cell carcinoma was the most common malignancy followed by adenocarcinoma. Squamous cell carcinoma is the most common malignancy across all age groups. Other subtypes of carcinoma are rare. Mesenchymal tumours of esophagus are also rare.

INTRODUCTION: A diversity of benign and non-neoplastic lesions can be seen in the esophagus.[1] Esophageal cancer is the sixth most common tumour disease worldwide. [2] The prognosis of esophageal cancer is generally unfavourable even if the tumour is surgically removed at its early and operable stage.[3]

Squamous cell carcinoma is the most common malignancy in esophagus in Indian population.[4]Endoscopic screening may detect esophageal mucosal lesions at an early stage especially intestinal metaplasia and dysplasia so as to prevent progression of lesions to invasive cancer.[5]

Diagnosis is generally made by endoscopic biopsy or barium meal swallow or CT scan. The overall prognosis of malignant tumours is poor and survival rates of 4–14 years have been noted in different studies. [6,7,8.]

The aim of this study was to understand the patterns of neoplasms encountered in oesophageal biopsies and to correlate with age, gender and clinical details.

METHODS: This was a retrospective study over a period of 4 years .The patient's age, gender, clinical details and endoscopy findings were noted. Biopsy specimens were fixed in 10% formalin, followed by tissue processing and embedded in paraffin with the mucosal surface facing the cut end of the block. Serial sections, 3-5 µ thick were prepared and then stained with routine H & E stain. Additional sections were stained with Per-iodic Acid Schiff (PAS) stain wherever necessary. Immuno histochemistry was done wherever necessary.

Squamous cell carcinoma was diagnosed based on cytological atypia and invasion.

Small cell carcinoma: Histologically, Small cell carcinoma is characterized by neuroendocrine-like architectural patterns, including nested and trabecular growth with common features including peripheral palisading and rosette formation in the tumors.

Esophageal melanoma: Diagnostic criteria include a typical histologic pattern of melanoma and the presence of melanin pigment within the tumor cells; origin from squamous epithelium with junctional activity; junctional activity with melanotic cells in the adjacent epithelium. The diagnosis was confirmed by Immunohistochemistry. The tumour cells showed positivity for S100 and HMB-45.
Ethics: The study was approved by the Institutional Review Board.
Statistical analysis used: Fishers exact test and Chi square test were employed.

RESULTS: A total of 1110 consecutive oesophageal biopsies (13 resected specimens and 1097 endoscopic biopsies) were seen of which neoplasms were seen in 914 cases while 196 cases were non neoplastic. Twenty seven cases of non-diagnostic biopsies were excluded. M: F ratio was 1.6:1.

The mean age was 56 years while age range was 2-85 years for all biopsies. The biopsies were done on patients with complaints of weight loss and other ominous symptoms.The age range for neoplastic biopsies ranged from 25-85 years (Figure 1). Endoscopy findings showed ulcerative lesion in 61.7% , ulceroproliferative lesion in 30 % cases exophytic lesion in 5% cases, endophytic lesion in 3% cases) & Smooth sub mucosal lesion(0.3%)

Barrett's esophagus: Barrett's esophagus was reported in 59 cases (5.4%) including five cases where there was glandular dysplasia. (Figure 1). The M:F ratio was 2:1.
Neoplastic lesions: Nine hundred fourteen biopsies showed neoplastic pathology. The malignant neoplasms (99.7%) far outnumbered the benign neoplasms in biopsy. (Figure 2).
Dysplasia: Dysplasia of the squamous lining was reported in 24 cases in the present study.
Glandular dysplasia was reported in five cases of Barrett's esophagus.

Esophageal carcinomas Eight hundred eighty cases of esophageal carcinoma were seen in the present study out of which squamous cell carcinoma was the most common subtype.

Squamous cell carcinoma accounted for majority of neoplasms affecting the upper and the middle thirds of esophagus. Of the 344 neoplasms in lower oesophagus, 128 were adenocarcinomas and 182 were squamous cell carcinomas.

Squamous cell carcinoma was the predominant histologic type (83.5%) of oesophageal neoplasm whereas adenocarcinoma constituted only 14.5% of all neoplasms in our study . The result was statistically significant ($p<0.001$).

Squamous cell carcinoma: Squamous cell carcinoma was the most common malignancy accounting for 739 cases (84%) of all carcinomas with a Male : Female ratio of 1.1:1. Mean age was 58 years. The occurrence of squamous cell carcinoma in individuals below 40 years was 6.2%(Figure 3 and Table 1). Chi square test was applied and the results were significant statistically ($x2=306.425$, $p=.000<0.01$, HS) Moderately differentiated squamous cell carcinoma was the most common grade (74%).Sixty five cases (9%) were well differentiated squamous cell carcinoma while 124 cases (17 %) were poorly differentiated squamous cell carcinoma. Twelve resected specimens of esophagus showed squamous cell carcinoma. Seven out of twelve cases showed nodal metastasis. The extent of lesion could be determined in the esophagectomy specimens. According to TNM staging the tumour was T3 in ten cases while one case each was reported as T2 and T4. (Figure 4)

Adenocarcinoma: Adenocarcinoma was the second most common malignancy of esophagus (14.5%). Male: Female ratio was 3.7:1.Mean age was 54 years (Table 2). Fishers exact test was done and age-gender distribution was not statistically significant (Fishers exact test p=.429, NS). The tumour was located in distal esophagus in 103 cases while in 25 cases the tumour was seen at gastro- esophageal junction. None involved the middle or upper esophagus. Moderately differentiated adenocarcinoma was reported in 52 cases (40.6%) while well differentiated adenocarcinoma and poorly differentiated adenocarcinoma accounted for 35(27.3%) and 26 cases(20.5%) respectively. Thirteen cases had signet ring cells (10%) while two cases showed mucinous adenocarcinoma (1.6%).The adjacent mucosa showed features of Barrett's esophagus in 22 cases. One esophagectomy specimen showed features of moderately differentiated adenocarcinoma with a TNM staging of T2N0.

Small cell carcinoma: Nine cases (1%) of small cell carcinoma were seen in the present study accounting for one percent of all carcinomas. M: F ratio was 2:1. The mean age was 68.5 years. (Figure 5)

Adenosquamous carcinoma: One case of adenosquamous carcinoma was reported in a 56 year old male in the lower third of esophagus accounting for 0.1% of all carcinomas.

Sarcomatoid carcinoma: Three cases were reported as sarcomatoid carcinoma accounting for 0.3% of all carcinomas. The mean age was 60 years with an M: F ratio of 2:1. Two cases had lesions in the lower esophagus while one case showed involvement of middle esophagus. The tumours were polypoid on endoscopy. Microscopically the tumours were comprised of epithelial and spindle cell

elements. The sarcomatous component was a high grade spindle cell sarcoma blending imperceptibly with malignant squamous cell component. Immunohistochemistry was performed for the three cases. The epithelial component was positive for cytokeratin while the sarcomatoid component showed diffuse staining for Vimentin.

Mesenchymal tumours: One case of Granular cell tumour was seen in a 34 year old female. Upper GI endoscopy showed a single sessile polyp in the lower esophagus measuring 4mm in diameter. The endoscopic diagnosis was granular cell tumour which was confirmed by histopathological examination and S 100 positivity.

One case of gastrointestinal stromal tumour (GIST) was seen in the lower esophagus of a 65 year old male in the present study. GIST was confirmed by CD 117 positivity. The lesion was 1.5 cm in diameter on endoscopy. Mitotic count was 2 mitoses per 50 high power fields.

One case of leiomyoma was seen in the middle esophagus of a 56 year old male presenting as a polyp. CD117 staining was negative in this case thus ruling out the possibility of GIST. (Figure 6).

Other lesions

One case each of esophageal melanoma and lymphoma were also reported in the present study.

DISCUSSION: In the present study 22 lesions (2%) showed showed mature normal squamous epithelium free of significant pathologic changes, suggesting that normal mucosa is present in endoscopic lesions, or endoscopy does not always take the lesions

Oesophageal carcinoma is the leading cause of death from cancer. [9] Squamous cell carcinoma has been the most common esophageal malignancy in India. In the Western world, esophageal adenocarcinoma has surpassed in incidence squamous cell carcinoma. [4] Squamous cell carcinoma is more common in China and other oriental countries. [9]

Most of the oesophageal carcinomas are either squamous cell carcinomas or adenocarcinomas. Approximately three quarters of all adenocarcinomas are found in the distal oesophagus, whereas squamous cell carcinomas are more evenly distributed between the middle and lower third. Oesophageal carcinoma is the most common tumour in African Bantus .Squamous cell carcinoma is more common in China and other oriental countries. The cervical oesophagus is an uncommon site of the disease.[6,10,11,12]

The mean age in the present study was 59 years for females and 60 years for males much higher than seen in the study by Anwar et al.[12] In contrast the mean age of occurrence of lesion was earlier for women in the study by Cherian et al. [4] The age range for neoplastic biopsies ranged from 25-85 years with M: F ratio of 1.6:1.Majority of the neoplasms were seen in the middle third (51.6%)followed by lower third(36.4%). However in the study by Anwar et al[12]majority of the neoplasms were seen in the lower third including gastro-oesophageal junction. The cervical esophagus is an uncommon site of disease. [13]

Most common presentation of esophageal carcinoma is that it begins as nonspecific retrosternal discomfort or indigestion. As the tumor enlarges the initially intermittent dysphagia becomes progressive and predominant symptoms such as weight loss, odynophagia, anaemia, chest pain and occasionally hematemesis following. Anorexia, weight loss ensues with decreased

nutritional intake.[9] Most of our cases had undergone biopsy for ominous symptoms such as weight loss and dysphagia.

Squamous cell carcinoma was the most common carcinoma of esophagus exhibiting male preponderance similar to the studies by Cherian et al and Anwar et al .[4,12] Moderately differentiated squamous cell carcinoma was the most common grade in the present study comparable to the study by Anwar et al. [12] Squamous cell carcinoma was most commonly seen in the middle third unlike the study by Cherian et al where lower third was the most common site. [4]

Adenocarcinoma showed a strong male preponderance akin to the study by Cherian et al [4]. However in the study by Anwar et al[12] there was a female predominance. Signet ring cells were seen in 10% of cases of adenocarcinoma . Mucinous adenocarcinoma was seen in 1.5% . Moderately differentiated adenocarcinoma accounted for 40.6% of the cases. Similar findings have been reported in the study by Paraf et al . [14]

Low incidence of small cell carcinoma was reported by Jing-Ping Yun et al comparable to the present study. Male predominance was also noted in the study by Gouri et al. The lesions were seen predominantly in the middle esophagus(67%) in the study by Jing-Ping Yun and Gouri et al similar to the present study .[15,16.]

The prevalence of adenosquamous carcinoma was found to be 1% in a study by Yachida et al. Adenosquamous carcinoma have been reported to have better prognosis as compared to conventional adenocarcinoma and squamous cell carcinoma .Noguchi et al have reported a case of Adenosquamous carcinoma in a 72 year old male with Barrett's esophagus[17,18].

Sarcomatoid carcinoma is described to have a predilection for middle esophagus.[19]The tumour is also known as polypoid carcinoma. In the present study too all three cases presented as polypoidal lesions. The tumour is described to be common in men as noted in our study. Virchow first described sarcomatoid carcinoma of the esophagus in 1865, and today it represents approximately 2% of esophageal carcinomas[20].

Granular cell tumour was seen in a 34 year old female. Similar age distribution has been noted by Percinel et al. The lesion in our case was solitary in the distal esophagus while in the study by Fried et al, the lesion was multifocal. [21,22,] Distal esophagus was the most common site in the study by Zhong et al.[23]

In the study by Miettinen et al, the majority of the leiomyomas were found in the distal esophagus while our case had lesion in the middle esophagus[24].Esophageal GISTs are malignant tumors that are diagnosed at an advanced stage and have a poor prognosis. Some smaller (3cm) tumors are found incidentally and may have a good prognosis after complete excision. [24] In contrast to the other digestive tract tumors, most esophageal mesenchymal tumors are true leiomyomas rather than GISTs.[25] In a study by Shingare et al majority of the lesions were seen in the lower third. [26]

In the study by Y Naomoto et al, melanoma was located at the middle thoracic esophagus. [27] Primary malignant melanoma affecting the esophagus is a rare and fatal disease with a poor prognosis. Sabanathan et al. documented that approximately 50% of patients have metastatic disease at presentation and long-term survival is extremely rare.[28]

One case Non Hodgkin's Lymphoma (diffuse large cell type) was seen in a 42 year old female who presented with dysphagia. The tumour cells were positive for CD 45, CD20 and negative for CD3 on Immunohistochemistry. The gastrointestinal tract is the most common extra nodal site of non-

Hodgkin's lymphoma accounting for 5%-20% of all cases[29,30,31] Gaskin et al reported a case of esophageal large cell non Hodgkin's lymphoma in mid esophagus in a 76 year old male. [32]

Our study is in agreement with study by Cherian et al and shows that squamous cell carcinoma is the most common malignancy of esophagus followed by adenocarcinoma. Cases of Barrett's esophagus with glandular dysplasia were also noted. Mesenchymal neoplasms of esophagus were rare in our study. The high occurrence of malignant tumours in our study was due to the fact that the biopsies were done for patient with weight loss and ominous symptoms. Neoplasms of the upper third of esophagus are less common.

This study points to the importance of investigating larger numbers of oesophageal neoplasm cases by sub sites and histological types .The epidemiological factors governing the distribution of neoplasms need to be studied further with special reference to risk factors and prognosis.

CONCLUSIONS:

Malignant neoplasms far outnumbered benign neoplasms in biopsy.

Male gender and age above 50 years were important risk factors.

The mean age was similar for both the genders.

Squamous cell carcinoma was the most common malignancy across all age groups in the referral diagnostic laboratory of Bangalore

Barrett's esophagus is a consequence of chronic gastro esophageal reflex disorder which is the most important risk factor for adenocarcinoma of esophagus.

Mesenchymal tumours of the esophagus are rare.

Epidemiological factors governing the distribution of lesion need to be studied further.

Age group	MALE	FEMALE	Total
less than 21	0	0	0
21-30	3	2	5
31-40	22	19	41
41-50	77	65	142
51-60	84	70	154
61-70	91	88	179
71-80	90	86	176
above 80	22	20	42

Table 1: Distribution of squamous cell carcinoma by age and gender

x2=.887, p= .990>0.05, NS-

AGE Group	Male	Female
less than 21	0	0
21-30	8	1
31-40	17	2
41-50	20	3
51-60	22	6

61-70	20	9
71-80	9	5
Above 80	5	1

Table 2: Distribution of adenocarcinoma by age and gender.

Fishers exact test p=.429, NS

Diagnosis	Number of cases
Squamous cell carcinoma	46
Adenocarcinoma	28
Granular cell tumour	1

Table 3: Distribution of cases in the age group of 21- 40 years.

Diagnosis	Number of cases
Squamous cell carcinoma	296
Adenocarcinoma	51
Leiomyoma	1
Small cell carcinoma	2
Sarcomatoid Carcinoma	2
Adenosquamous	1

Table 4: Distribution of cases in the age group of 41-60 years.

Diagnosis	Number of cases
Squamous cell carcinoma	397
Adenocarcinoma	49
Small cell carcinoma	7
Sarcomatoid carcinoma	1
GIST	1
Melanoma	1
Lymphoma	1

Table 5: Distribution of cases in the age group above 61years.

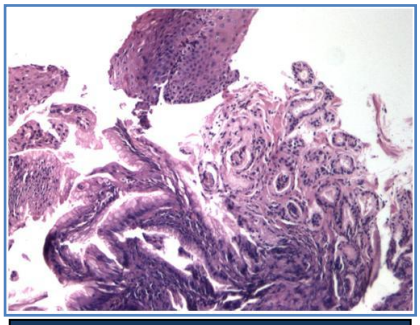

Figure1:Barrett's esophagus

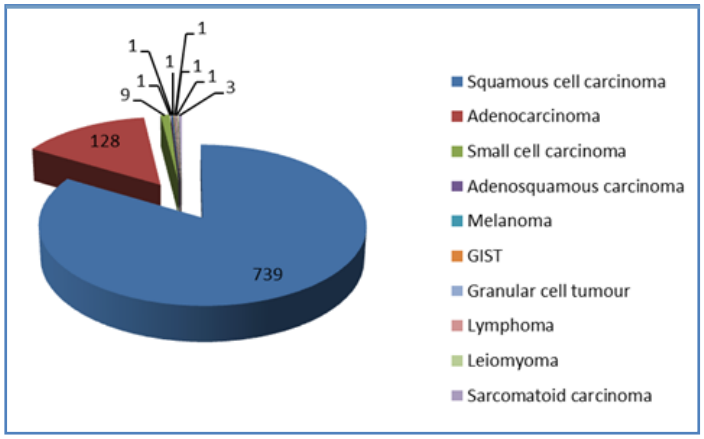

Figure 2: Distribution of neoplastic lesions of esophagus

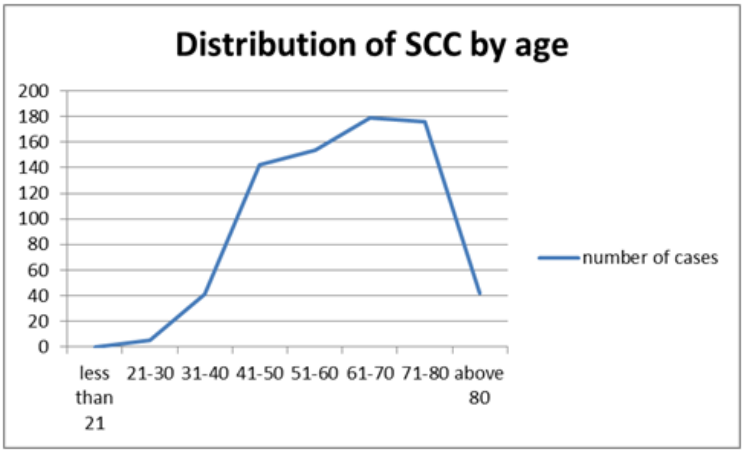

Figure 3: Distribution of squamous cell carcinoma by age

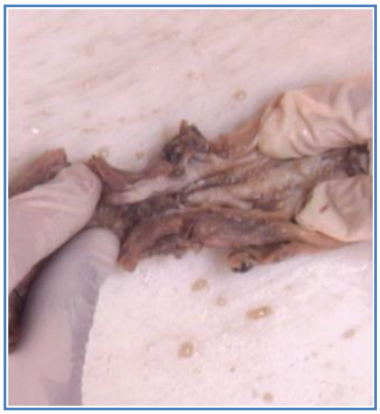

Figure 4: Esophagectomy done for a case of Squamous cell carcinoma (ulcerative cut surface)

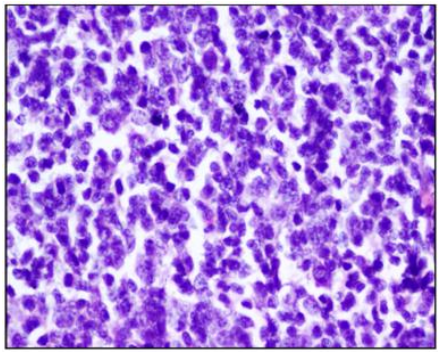

Figure 5: Small cell carcinoma esophagus

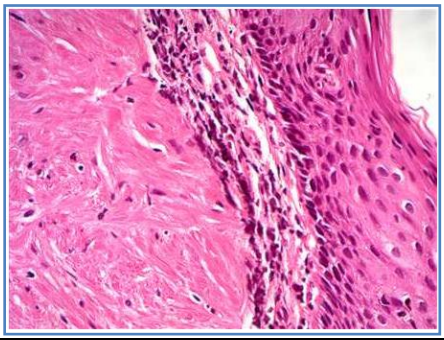

Figure 6: Leiomyoma esophagus

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