DOI: 10.7860/NJLM/2022/55595.2624

Original Article

Pathology Section

A Clinicopathological Study of Premalignant and Malignant Lesions of Oesophagus- A Cross-sectional Study

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ABSTRACT

Introduction: Oesophageal cancer is the sixth leading cause of cancer related mortality and it ranks eighth among all malignancies in the world. There are multiple factors involved in the causation of oesophageal carcinoma.

Aim: To study the clinicopathological features of premalignant and malignant lesions of oesophagus including age, sex, risk factors, tumour location, histological type, grade and stage.

Materials and Methods: This is a prospective study of premalignant and malignant lesions of oesophagus conducted at Department of Pathology in a tertiary care centre from June 2013 to June 2014. Complete history of the cases including investigations and type of procedure done were obtained. Haematoxylin and Eosin (H&E) stained sections were prepared and cases reported as premalignant and malignant lesions were analysed for histopathological parameters.

Results: In the present study, 187 cases were studied, of which, malignant tumours accounted for 177 cases (83.49%) while premalignant lesions were 10 cases (5.34%). The mean age of oesophageal cancer is 56.4 years and that for premalignant lesions is 50.7 years. Overall male predominance was noted. Most of the malignant lesions were located in the middle third of the oesophagus. Most common histological type was squamous cell carcinoma (SCC) (89.27%) followed by Adenocarcinoma (9.6%) and Neuroendocrine Carcinoma (NEC) (1.13%). The most common macroscopic type was ulcerative type (50.8%). Most of the cases presented in stage II A (74%). Lymph node involvement was present in 25.92% of cases of SCC and 33.33% of cases of adenocarcinoma.

Conclusion: In the present study, SCC was the commonest histological type with peak incidence in 51-60 years. Dysphagia was the most common clinical complaint with tobacco being the major risk factor. Oesophageal carcinoma was quite common in this region. However, majority of the patients presented at advanced stage due to lack of awareness and delayed symptoms causing major challenge in management. Hence, thorough investigations including histopathological examination is mandatory, especially in older patients to rule out carcinoma oesophagus at the earliest, as the prognosis highly depends on histological type, grade and stage.

Keywords: Barrett's oesophagus, Oesophageal adenocarcinoma, Oesophageal cancer

INTRODUCTION

Oesophageal cancer is the sixth leading cause of cancer related mortality and it ranks 8th among all malignancies in the world [1]. The two main histological subtypes among the oesophageal cancers are squamous cell carcinoma (SCC) and adenocarcinoma (AC), together accounting for 90% [2] of oesophageal cancers globally. Other minor subtypes of oesophageal cancer include small cell carcinoma, sarcomatoid carcinoma, adeno squamous carcinoma, melanoma and adenoid cystic carcinoma.

Over the last five decades, the incidence of oesophageal adenocarcinoma has been increasing drastically [3]. It is believed that the relatively higher incidences of gastro-oesophageal reflux disease, obesity and Barrett's oesophagus [4-7] as well as the lower incidence of *Helicobacter pylori* [8] Infection are likely responsible causes for this in west. SCC still remains the prime histologic subtype in Asia. There is a significant geographical variation in the incidence of SCC.

The prognosis of patients with squamous cell carcinoma is poor with an overall tumour specific lethality rate of 95% [9]. The 5-year survival rate for patients who have operations with curative intent varies between 5-20% [10]. Main reasons responsible for the poor prognosis are late presentation and the propensity of early spread of disease [11].

There are multiple factors involved in the causation of SCC. Different causative agents may act synergistically in different geographical areas. Smokers and tobacco chewers are found to be more prone for oesophageal carcinomas [12]. Diets low in fresh fruits and vegetables but high in starch are associated with carcinogenesis of SCC [13]. Other nutritional risk factors for SCC are smoked foods and salt-pickled foods contaminated with fungal toxins or N- nitrosamine. There are many studies regarding human papilloma virus (HPV) prevalence in SCC. Other disorders related with higher risk of carcinoma oesophagus are diverticula, coeliac disease, achalasia and corrosive strictures.

Hence, in the present study, an attempt has been made to study the clinicopathological features of premalignant and malignant lesions of the oesophagus.

MATERIALS AND METHODS

This is a prospective study of premalignant and malignant lesions of oesophagus held at Pathology Institute of RGGH and Madras Medical College, Chennai, India, between June 2013 to June 2014. In the present study, 187 cases were studied. This study was approved by the Institutional Ethics Committee of Madras Medical College (EC Reg No. ECR/270/Inst./TN/2013). Written informed consent was obtained from all the patients whose biopsy/surgical specimens were included in the study.

Sample size calculation: Sample size was estimated using Danial's formula.

(copy the formula from Archives of Orofacial Sciences 2006; 1: 9-14) [14].

The sample size obtained using this formula was 113.

Inclusion criteria: All endoscopic biopsies and resected specimens of oesophagus for malignant and premalignant lesions were included in the study.

Exclusion criteria: Patients with history of chemoradiation and biopsies with inadequate tissue material were excluded from the study.

Study Procedure

Complete history of the cases including investigations along with type of procedure done were obtained. Haematoxylin and Eosin (H&E) stained 4 µm thick sections of the paraffin tissue blocks of the cases were prepared and cases reported as premalignant and malignant lesions were selected.

The variables studied amongst the total study population and samples were- age, gender, occupation, habits (smoking, alcohol and tobacco chewing), residency (urban and rural), symptoms, type of resection, site of growth, (upper, middle and lower oesophagus), size of growth, gross appearance (ulceroproliferative, ulcerative, nodular, infiltrative), histological types according to World Health Organisation (WHO) classification [15] and Tumour Node Metastasis (TNM) staging according to American Joint Committee on Cancer (AJCC), grade (well differentiated [16], moderately differentiated and poorly differentiated), presence of lymph node involvement were studied.

STATISTICAL ANALYSIS

The statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 15.5 which consisted computing the frequency counts and percentages for qualitative variables and mean for the quantitative variables.

RESULTS

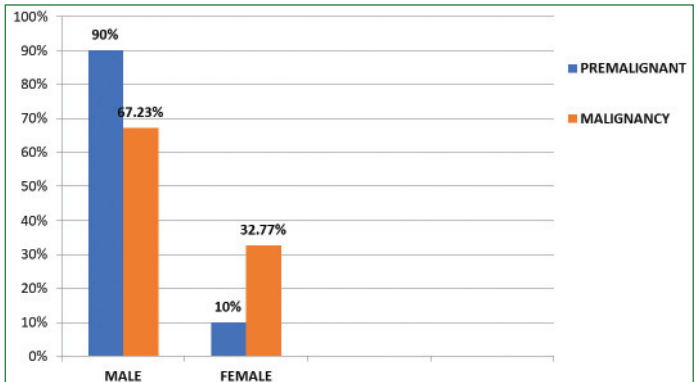
In the study period, total number of oesophageal lesions received were 212. Among the 212 oesophageal specimens, 26 cases were resected specimens and 186 were small biopsies. Of these, malignant tumours accounted for 177 cases (83.49%). Of the remaining 35 cases, premalignant cases (Barrett's oesophagus and dysplasia) were 10, non neoplastic cases were 25. Thus the distribution of premalignant cases were 4.72% among the oesophageal specimens.

Premalignant cases showed the peak incidence at 51-60 years with a mean age of 50.7 years . Malignant lesions had a peak incidence in the age group of 51-60 years. The youngest age of presentation observed was 22 years in the present study. The mean age is 56.4 years [Table/Fig-1].

Age (in years)	Premalignant	Malignant lesions
<40	2 (20%)	28 (15.82%)
41-50	2 (20%)	47 (26.55%)
51-60	4 (40%)	54 (30.51%)
>61	2 (20%)	48 (27.12%)
Total	10 (100%)	177 (100%)

[Table/Fig-1]: Age-wise distribution of premalignant and malignant lesions.

Among the 177 cases of malignancies, 119 (67.23%) cases were reported in males and 58 (32.77%) cases were reported in females. The male to female ratio was 2.05:1. Among the premalignant lesions, males constituted 90% and female constituted 10% [Table/Fig-2].



[Table/Fig-2]: Gender-wise distributions in premalignant and malignant lesions.

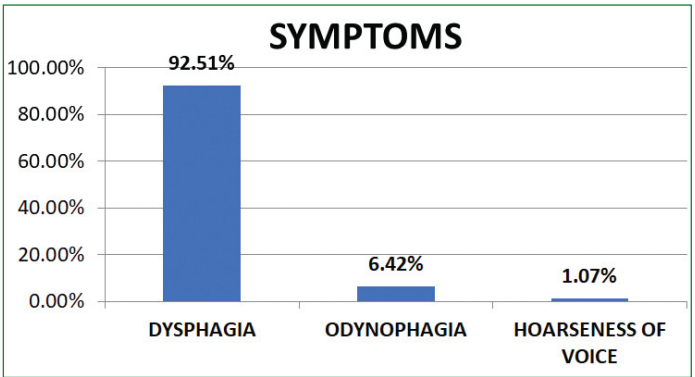
Among the various occupations involved, labours constituted 37.29% of malignancies followed by farmers with 28.24%. Among the premalignant lesions, labours constituted 50% and next shared by farmers and housewives with 20%.

In the present study, 48.46% were the users of tobacco who are prone to an increase in the risk of oesophageal carcinoma, followed by the habits of alcohol and smoking which accounts to 25.99% and 25.55% respectively [Table/Fig-3].

Habits	Premalignant	Malignant	Total
Smoking	8 (80%)	58 (25.55%)	66
Alcohol	1 (10%)	59 (25.99%)	60
Tobacco	1 (10%)	60 (48.46%)	61

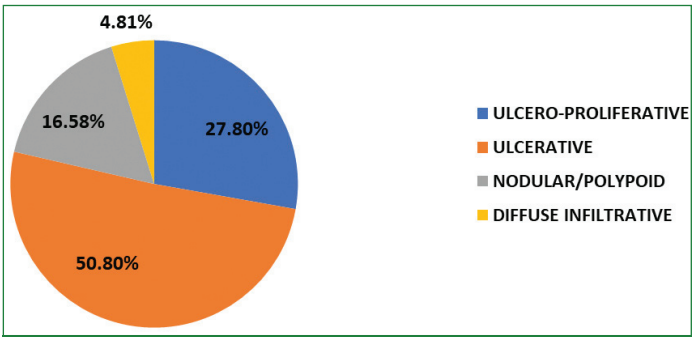
[Table/Fig-3]: Personal habit-wise distributions in premalignant and malignant lesions.

In the present study, the most common symptom was dysphagia constituting 92.51% followed by odynophagia (6.42%) and hoarseness of voice (1.07%) [Table/Fig-4].



[Table/Fig-4]: Symptoms wise-distributions in premalignant and malignant lesions.

In the present study, the commonest macroscopic type was ulcerative (50.8%) followed by ulcero proliferative (27.8) and polypoid/nodular (16.58%) [Table/Fig-5].



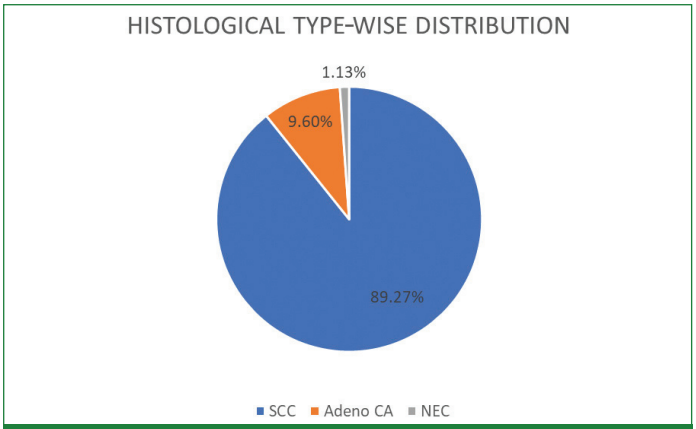
[Table/Fig-5]: Distributions of various gross types of Oesophageal cancer.

Out of 187 cases, majority of cases (168) measured <=5 cm, remaining cases (19) showed >5 cm in size.

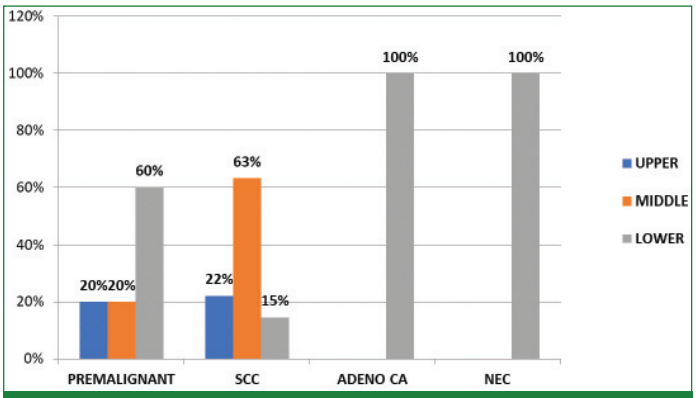
Of the total 177 oesophageal carcinomas, squamous cell carcinomas were the most common accounting for 158 cases which accounts for 89.27% of carcinomas. Adenocarcinoma constituted 17 cases accounting for 9.60% of the cases, Neuroendocrine Carcinoma (NEC) constituted 2 cases accounting for 1.13% of carcinomas arising from oesophagus [Table/Fig-6].

Out of 158 SCC cases 63.29% were located in middle oesophagus, 22.15% in upper oesophagus and 14.56% in lower oesophagus. Among the AC and NEC, all were located in lower oesophagus. Most of the premalignant lesions were located in lower 1/3rd of oesophagus [Table/Fig-7].

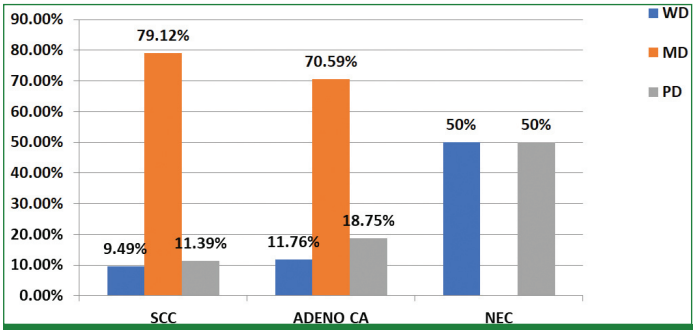
Among the SCC 79.12% were moderately differentiated. About 11.39% were poorly differentiated and 9.49% were well-differentiated. Among the AC, 70.59 % were moderately differentiated. 18.75% were poorly differentiated and 11.76% were well-differentiated. Among the NEC, 50% well-differentiated and 50% poorly differentiated [Table/Fig-8].



[Table/Fig-6]: Histological type-wise distributions in malignant lesions.
SCC: Squamous cell carcinoma; CA: Carcinoma; NEC: Neuroendocrine carcinoma

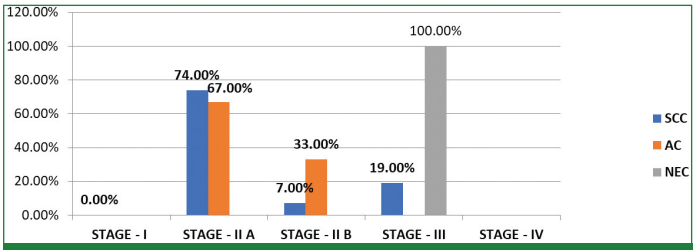


[Table/Fig-7]: Site wise-distributions in premalignant and malignant lesions.
SCC: Squamous cell carcinoma; Ca: Carcinoma; NEC: Neuroendocrine carcinoma



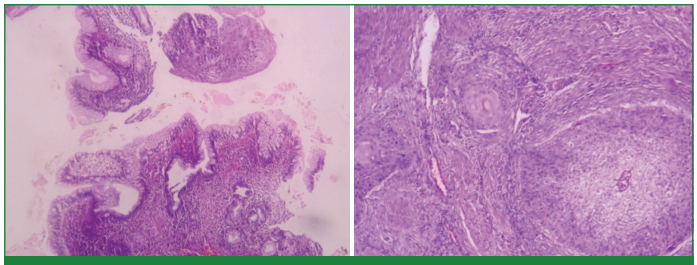
[Table/Fig-8]: Histological grade-wise distributions in malignant lesions.
WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated

Among the SCC, most of the cases were in stage IIA (74%) followed by stage III. Among the AC, most of the cases were in stage IIA (67%] followed by stage IIB (33%]. Among the NEC, all cases were in stage III [Table/Fig-9].

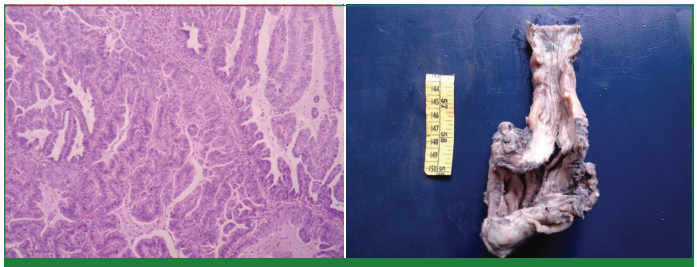


[Table/Fig-9]: Stage wise-distributions in malignant lesion.

Out of 31 resected specimens, among the SCC most of the cases showed invasion upto serosa (66,67%), followed by muscularis propria (33.33%) [Table/Fig-10,11]. Among the adenocarcinomas, most of the cases showed invasion upto muscularis propria (66, 67%), followed by serosa (33.33%) [Table/Fig-12]. Grossly, the resected specimens of SCC showed diffusely infiltrative growth in some cases [Table/Fig-13] while, ulceroproliferative growth in others [Table/Fig-14].



[Table/Fig-10]: Microscopy of Barrett's oesophagus characterised by columnar epithelium with intestinal metaplasia (10X H&E). **[Table/Fig-11]:** Microscopy of moderately differentiated squamous cell carcinoma shows neoplastic squamous cells arranged in sheets and nest with less ordered growth with hyperchromatic nuclei (10X H&E). (images from left to right)



[Table/Fig-12]: Microscopy of well differentiated adenocarcinoma shows neoplastic cells arranged in glandular pattern exhibiting nuclear pleomorphism and hyperchromasia (10X H&E). **[Table/Fig-13]:** Gross: Squamous cell carcinoma- diffusely infiltrative growth. (images from left to right)

[Table/Fig-14]: Gross: Squamous cell carcinoma -ulceroproliferative growth.

In the present analysis, the involvement of lymph node was present in nine cases and absent in 22 cases.

DISCUSSION

In western countries, there is a progressive decline in incidence of squamous cell carcinoma but cases of adenocarcinoma is increasing. [17]. However, incidence of squamous cell carcinoma shows a wide variation in Asia, Africa and Iran [18]. The current study showed squamous cell carcinoma as major histological subtype constituting 89.27%, followed by adenocarcinoma and neuroendocrine carcinoma accounting for 9.6% and 1.13% respectively.

Oesophageal malignancy is extremely rare in people with less than 40 years of age and its incidence increases every decade [19].

In the present study, the age range was 22 to 71 years of age. The highest incidence of oesophageal malignancy occurred in 50 to 60 years age group. This is in concurrence with the study done by Shalija Kotwal [20] in which 45.2% cases were in 50 to 60 years. In this study, premalignant cases showed the peak incidence at fifth decade, while in the study done by Ajani MA et al., premalignant lesions peaked in sixth decade [21].

Oesophageal malignancies showed a male predominance with male to female ratio being 2:1. This is in concurrence with the study done by Neetha Y et al., [22]. Premalignant lesions also showed a male predominance in concurrence with the study done by Ajani MA et al., [21]. The increased incidence in male population could be due to association with habits and dietary factors. The current study is concurrent with Giri PA et al., where the percentage of tobacco consumption associated with oesophageal malignancy was high compared to alcohol and smoking [23]. The current study showed, dysphagia as the most common presenting symptom followed by odynophagia and hoarseness of voice. This is concurrent with Aledavood A et al., where dysphagia was seen in more than 90% of cases [24].

The current study showed that maximum percentages of oesophageal malignancies were located in the middle third followed by upper and lower third of oesophagus. This is concurrent with Neetha Y et al., [22] and Kuylensterina R et al., [25] where the most common anatomical site involved was middle third of oesophagus. In the present study, middle third of oesophagus was the commonest site for squamous cell carcinoma. Adenocarcinoma was commonly seen in lower third of oesophagus. This was in concurrence with the study done by Shalija Kotwal [20]. The increasing incidence of adenocarcinoma in the lower oesophagus is related to malignant transformation of Barrett's oesophagus.

Grossly oesophageal lesions start as a small grey white plaque like thickenings. Over a period of time, they grow as a tumourous masses and encircle the lumen producing a stricture. In the study done by Pun CB et al., exophytic or ulcerative growth was the common growth pattern for SCC and polypoidal growth for adenocarcinoma. In the present study, the commonest growth pattern observed was ulcerative growth, found in 50.8% of cases [26].

In the present study, most of the cases were <5 cm in size. This is almost similar with the study done by Aledavood A et al., [24] where 52.5% cases were <5 cm in size and 47.5% cases were >5 cm in size. In the current study, 80% of premalignant lesions were Barrett's oesophagus which is concurrent with the study done by Asma Shabbier et al., 74.5% of premalignant lesions were Barrett's oesophagus [27].

In the study, done by Neetha Y et al., all the adenocarcinoma oesophagus were of moderately differentiated grade. In the present study, 70.59% of adenocarcinoma were of moderately differentiated grade [Table/Fig-15] [22,26,28].

Study done by	No.of patients	Well differentiated	Moderately differentiated	Poorly differentiated
Wang J et al., [28]	51	9 (17.65%)	31 (60.78%)	11 (21.54%)
Pun CB et al., [26]	68	25 (36.76%)	37 (54.42%)	6 (8.82%)
Neetha Y et al., [22]	290	66 (22.73%)	213 (73.45%)	11 (3.8%)
Current study	158	15 (9.49%)	125 (79.12%)	18 (11.39%)

[Table/Fig-15]: Degree of differentiation of oesophageal squamous cell carcinoma in various studies [22,26,28].

The current study showed squamous cell carcinoma as major histological subtype constituting 89.27% followed by adenocarcinoma and Neuroendocrine carcinoma accounting for 9.6% and 1.13% respectively. This study is almost similar with study of Yeole BB [29] where SCC constituted about 90% and adenocarcinoma of about 10%. In most of the studies, moderately differentiated grade is the most frequent grade of SCC oesophagus. In the present study, the also majority SCC were in moderately differentiated grade followed by poorly differentiated and well differentiated.

In the present study, for both SCC and adenocarcinoma oesophagus, the common clinical staging was stage 2. In the study done by Hasan MM et al., [30] the commonest clinical staging of oesophageal cancer was stage 2 followed by stage 3. In the study done by Mchembe MD et al., [31], staging was documented in only 104 patients and of these,102 (98.1%) patients were diagnosed with advanced stage (stage 3 and 4).

Limitation(s)

Oesophageal cancer is a fatal disease and so, it is highly important to know the risk factors and incidence of premalignant lesions of the oesophagus. The major limitation of the present study is the number of premalignant lesions studied. So, multicentric studies should be conducted on premalignant lesions and its progression to malignancy. Similarly, awareness, screening and early diagnosis could assist in achieving a better prognosis.

CONCLUSION(S)

In the present study, SCC was the commonest histological type with peak incidence in 51-60 years. Dysphagia was the commonest clinical complaint with tobacco being the major risk factor. Oesophageal carcinoma was quite common in this region. However, majority of the patients presented at advanced stage due to lack of awareness and delayed symptoms causing major challenge in management. Hence, thorough investigations including histopathological examination, is mandatory especially in older patients to rule out carcinoma oesophagus at the earliest, as the prognosis highly depends on histological type, grade and stage.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 14, 2022
- Manual Googling: Feb 17, 2022
- iThenticate Software: Mar 21, 2022 (14%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 11, 2022**
Date of Peer Review: **Mar 05, 2022**
Date of Acceptance: **Mar 17, 2022**
Date of Publishing: **Jul 01, 2022**