

## Clinico-epidemiological Profile of Esophageal Cancer in North Indian Population

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### Abstract

**Objective:** Esophageal cancer is a highly aggressive malignancy with poor outcomes in majority. Its incidence is dramatically on the rise with squamous cell carcinoma being commonest histotype worldwide followed by adenocarcinoma. The aim of the present study was to evaluate the time trends in esophageal cancer in north India.

**Methods:** Clinico-histological profile of all patients with esophageal cancer was evaluated over a time period which was 15 years and divided into 3 groups of 5 consecutive years each. Based on endoscopy findings the site specific tumor location was ascertained. Biopsy material/sections from resection specimens were examined for tumor histotype and grade.

**Results:** A total of 896 cases of esophageal cancer were diagnosed. There were 466 (52%) male and 422 (48%) female with mean age of  $57.73 \pm 12.39$  years (range 15-95 years). The upper, middle and lower thirds of the esophagus was involved in 200 (22.32%), 366 (40.85%) and 330 (36.83%) cases respectively. Squamous cell carcinoma was the predominant histological type (793 cases, 88.50%) followed by adenocarcinoma (103 cases, 11.50%). All the tumors (566, 63.17%) involving the upper and the middle thirds of esophagus were squamous cell carcinomas. Of 330 cases involving the lower esophagus, 103 (31.21%) were adenocarcinomas and 227 (68.79%) were squamous cell carcinomas.

**Conclusions:** The study shows squamous cell carcinoma as a major histological type of cancer even in the lower and middle parts of the esophagus. No significant change in trend was observed in the three time periods as regards the mean age and gender distribution.

**Keywords:** Esophageal; Cancer; Histotype; Squamous; Adenocarcinoma.

### Introduction

Esophageal cancer is the seventh most common incident cancer worldwide.<sup>1</sup> The number of new cases added to the global burden in 2020 were 604,100 according to the GLOBOCAN estimates of cancer incidence and mortality.<sup>2</sup> The malignancy is highly aggressive and is associated with poor outcome in majority of the cases.<sup>3</sup> Globally, the 5 years survival is about 15%-25%.<sup>4</sup> Squamous cell

carcinoma (SCC) is the predominant histological type worldwide which accounts for approximately 90% of the esophageal malignancies.<sup>5</sup> It is followed by adenocarcinoma (AC). Rare malignancies include sarcoma and small cell carcinoma which comprise less than 1% - 2% of esophageal cancers.

The "Asian Esophageal Cancer Belt" comprising of Turkey, Iran, Kazakhstan and northern and central China, has a high preponderance of esophageal



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squamous cell carcinoma. The estimate is more than 100 cases/100000 person years.<sup>6</sup> Over the past few decades it has been seen that in countries like United States, Australia, United Kingdom and Western Europe, the incidence of esophageal adenocarcinoma has shown a sharp increase. Endoscopic biopsies are performed for the tissue diagnosis of esophageal cancer. Histopathology not only provides the diagnosis but also helps in sub-typing of the cancer which has a prognostic connotation.

Many studies on time trends in esophageal cancer have been done in the western population.<sup>7-12</sup> However, from the Asian region only a few studies have been done on the subject.<sup>13,14</sup> A study from South India observed SCC to be the most common type of esophageal cancer with frequent involvement of the distal third.<sup>15</sup> However, in another study spanning over two decades, no change in trend for pattern and frequency of SCC involving different parts of esophagus was observed.<sup>16</sup> Various studies have shown variability in the observations with striking differences.

Due to scarcity of studies on the subject in the Indian subcontinent, the present study was planned to decipher the trends in demographics, histomorphological subtypes and site specific location in esophageal cancer in north India.

## Materials and Methods

The present study was an observational study (from January 2003 to December 2017) conducted in the department of Pathology, Government Medical College and Hospital, Chandigarh, India in collaboration with the departments of General Medicine & General Surgery. The study was done after obtaining requisite clearance from the Institute Ethics committee. All patients irrespective of age and gender with histopathologic confirmation as on biopsy/resection specimens were included. Case files were tracked from the Medical Records Department. Clinical and demographic profile of all patients with esophageal cancer was recorded.

The esophagus was divided into three parts; upper esophagus 16 to 24 cm from the incisors, middle esophagus 24 to 32 cm, lower esophagus 32 cm until the gastro-esophageal junction based on endoscopy findings and the tumor location was ascertained according to site involved. Biopsy material/sections from resection specimens were fixed in 10% formal saline and processed by paraffin embedding technique. Sections of 3-5 microns in thickness were cut and stained with hematoxylin

and eosin (H & E).

Sections were examined to determine the definitive histotype of esophageal cancer. Grading into 3 grades; well differentiated, moderately differentiated and poorly differentiated was done taking into account the tumor differentiation. The status of resection margins and lymph node involvement was recorded in case of resection specimens. Descriptive statistics were used to describe various epidemiological and histopathological parameters in esophageal cancer.

## Results

Over a span of 15 years, 896 cases of esophageal cancers (squamous cell carcinoma and adenocarcinoma) were diagnosed.

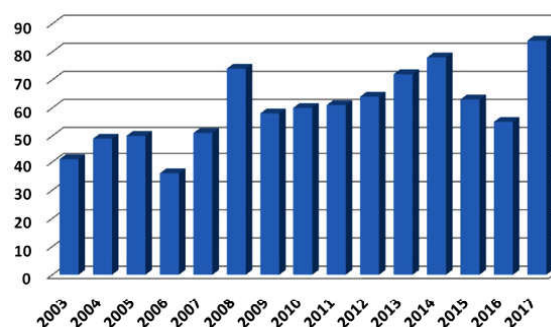


Fig. 1: Bar graph showing number of cases with esophageal cancer from 2003-2017.

Cases with diagnosis of malignancy other than squamous cell carcinoma and adenocarcinoma were excluded from this analysis. Inadequate/superficial biopsies and inconclusive biopsy reports were also excluded. The time period of 15 years was divided into 3 groups.

Table 1: Demographic data of patients with esophageal cancer (n=896)

Time period	Number of cases (%)	Male	Female	Mean age with standard deviation
2003-2007	227	134	93	58.61 ± 14.01 years
2008-2012	317	162	155	56.43 ± 11.49 years
2013-2017	352	178	174	58.31 ± 14.14 years
Total	896	466	422	57.73 ± 12.39 years

of 5 consecutive years (2003-2007, 2008-2012 and 2013-2017) each to analyze the trends.

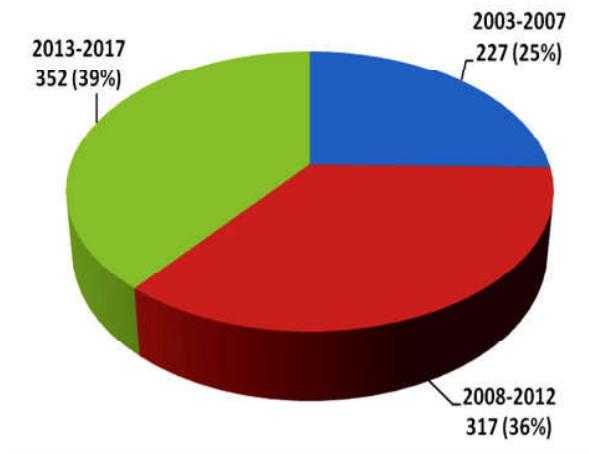


Fig. 2: Pie chart showing cases with esophageal cancer over the three time period slots.

Out of 896 total cases, there were 466 (52%) male and 422 (48%) female patients.

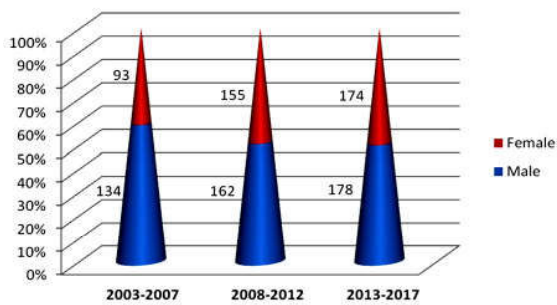


Fig. 3: Gender-wise distribution of cases over the total time period shown as a cone chart.

The male: female ratio was 1.1:1. The mean age of the study population was  $57.73 \pm 12.39$  years (range 15–95 years)

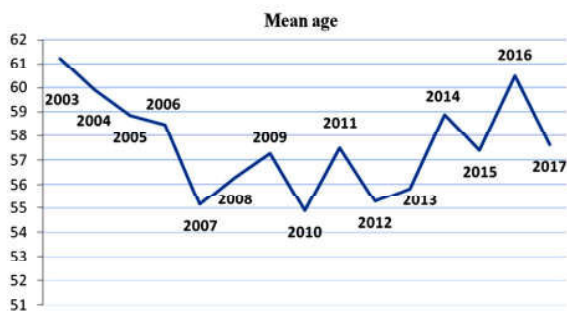


Fig. 4: Graphic representation of mean age of patients over 15 years.

Esophageal cancers in the upper, middle and lower thirds of the esophagus were seen in 200 (22.32%), 366 (40.85%) and 330 (36.83%) cases respectively.

Squamous cell carcinoma was the predominant histological type with 793 (88.50%) cases while adenocarcinoma comprised 103 (11.50%) cases in the current study. The ratio of SCC to AC observed during 2003-2007, 2008-2012 and 2013-2017 were 7.4:1, 9.2:1 and 6.8:1 respectively. The distribution of cases over different sites in esophagus; upper, middle and lower is shown in Figure 5.

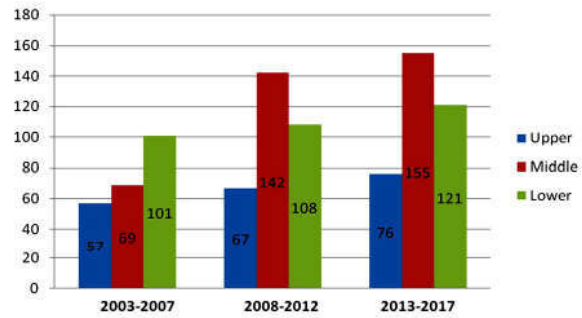


Fig. 5: Location wise distribution of cases in esophageal cancer.

All the tumors (566, 63.17%) involving the upper and the middle thirds of esophagus were squamous cell carcinomas.

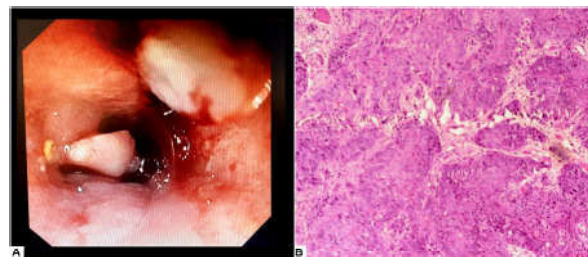


Fig. 6: A Upper gastrointestinal endoscopy shows a circumferential, nodular infiltrative growth in middle esophagus B Histopathology of endoscopic biopsy shows squamous cell carcinoma (H & E, x100).

of 330 cases involving the lower esophagus, 103 (31.21%) were adenocarcinomas and 227 (68.79%) were squamous cell carcinomas.

### Discussion

The age standardized incidence rates for esophageal cancer in 2020 among men and women were 18.2 and 6.8 per 100,000 respectively in Eastern Asia, which is the highest in the world.<sup>2</sup> The risk factors for esophageal squamous cell carcinoma include tobacco smoking, heavy alcohol consumption, and certain dietary factors.<sup>6,17</sup> Areca nut chewing often mixed with tobacco seen in regions like Southeast Asia and India is associated with risk of developing squamous carcinoma. Genome-

wide association studies have shown genetic and epigenetic susceptibility factors in the development of squamous carcinoma. The esophageal adenocarcinoma has gastroesophageal reflux disease, obesity, and an inverse association with *Helicobacter pylori* infection as risk factors. About 10% of patients diagnosed with gastroesophageal reflux disease (GERD) will develop Barrett's esophagus which is a well known precursor lesion for esophageal adenocarcinoma.

In the Asian region studies have shown a seeming trend towards rise in the incidence of esophageal adenocarcinoma in Singapore.<sup>18,19</sup> This possibly may be due to increasing prevalence of reflux and obesity and the decreasing prevalence of *H. pylori* infection. In Hong Kong a decline in incidence of esophageal adenocarcinoma was observed while Japan and Taiwan noted stability in the incidence over the past few years. In our study squamous cell carcinoma was the predominant histological type with 793 (88.50%) cases while adenocarcinoma comprised 103 (11.50%) cases. This reiterates that esophageal adenocarcinoma remains uncommon in the Asian population.

The incidence rate of esophageal cancer in males is higher than females, with the male to female ratio range being 5-10:1.<sup>15</sup> In the current study, out of 896 total cases, there were 466 (52%) male and 422 (48%) female patients with the male: female ratio of 1.1:1. The overall mean age of the study population was  $57.73 \pm 12.39$  years (range 15-95 years) and during the three time periods no significant variation in age was seen. The higher mean age observed in the present study could be attributed the increased longevity in our population. No significant change in trends was observed in the three time periods of 5 years each distributed over a span of 15 years as regards the mean age and gender distribution.

Very few studies have assessed distribution of tumor location at various esophageal sites.<sup>15,16</sup> The studies addressing this have shown variability in their observations. About two thirds of the SCCs showed an even distribution in the lower two thirds of the esophagus in New Zealand. No change in site distribution was seen over a considerable time period in an Italian study.<sup>20</sup> A study from south India showed an increase in the number of cases involving the lower esophagus. Mehrotra et al,<sup>21</sup> reported the middle third of esophagus being the most common site of esophageal cancer. In our study, over the three time period slots, the initial period, 2003-2007 observed a predilection in tumor location site for lower esophagus. Of the 227 tumors observed in this time frame, 101 (44.49%)

were in the lower part of the esophagus. Over the next decade out of 669 tumors, only 229 (34.23%) were at this site. During this time, the middle part of the esophagus had majority of tumors (297/669, 44.39%). Hence a shift in trend from lower to middle part of esophagus as the commonest site of tumor involvement was noted. Overall, esophageal cancers in the upper, middle and lower thirds of the esophagus were seen in 200 (22.32%), 366 (40.85%) and 330 (36.83%) cases respectively. During the entire period of 15 years, the commonest site of involvement observed was middle part of the esophagus.

Squamous cell carcinoma and adenocarcinoma are the predominant cancer histotypes involving the esophagus.<sup>22,23</sup> In a study by Ansari et al,<sup>24</sup> 80% of esophageal cancers were squamous cell carcinomas in the north Indian population. In the current study also squamous cell carcinoma was the commonest histological type with 793 (88.50%) cases while adenocarcinoma comprised 103 (11.50%) cases. This could be because majority of our patients were bidi/cigarette smokers and belonged to lower socioeconomic strata. The upper and middle esophagus has a predilection for squamous cell carcinoma whereas the lower esophagus commonly shows involvement by adenocarcinoma. In our study, all the tumors (566, 63.17%) involving the upper and the middle thirds of esophagus were squamous cell carcinomas. Of 330 cases involving the lower esophagus, 103 (31.21%) were adenocarcinomas and 227 (68.79%) were squamous cell carcinomas. Hence it is drawn that even in the lower part of the esophagus, we observed squamous cell carcinoma to be preponderant and not adenocarcinoma.

Early detection of esophageal tumors is of utmost importance as surgical resection is possible for loco-regional tumors.<sup>25-27</sup> However, majority of the tumors are inoperable or metastatic by the time they are diagnosed. Chemotherapy and radiation are the options available for those with inoperable tumors and recurrent or metastatic disease.<sup>28-31</sup> The prognosis yet remains poor. Comprehensive genomic profiling has shown a promise in identifying clinically relevant genomic alterations in esophageal cancers for the potential use of targeted molecular therapies.<sup>32,33</sup> As of now there are no molecularly directed agents approved for ESCC.

The present study has the limitations of a retrospective analysis. This is not a population based study giving true incidence rates but based on data from a tertiary care hospital. Nevertheless,

the study shows squamous cell carcinoma as a major histological type of cancer even in the lower esophagus and middle part of the esophagus to be the preferred site of cancer involvement. No significant change in trend was observed in the three time periods of 5 years each distributed over a span of 15 years as regards the mean age and gender distribution.

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