The Epidemiological Trend of Esophageal Cancer in Mumbai, India, Over the Past Fifteen Years

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Abstract

Background:

There has been a definite change in the histopathological spectrum of esophageal cancer towards adenocarcinoma seen in developed countries. In India such studies were limited.

Materials and Methods:

We retrospectively evaluated patients with histologically proven esophageal cancer who were registered at the Tata Memorial Hospital (Mumbai, India) between 2003 and 2018. The primary aim was to analyze the time-trend of the histological pattern of esophageal cancer. Our secondary objectives included evaluating whether there was any correlation between age, sex, demographics, socioeconomic status, the presence of comorbidities and substance abuse and the histological type of esophageal cancer.

Results:

Among 7874 patients with esophageal cancer, 5092 (64.7%) were men, with M:F of 2.5:1. The median age was 57 years (IQR, 50-65); Of the 4912 patients in whom a history of tobacco or alcohol use had been elicited, 1360 (27.7%) patients denied substance abuse. Majority of tumor was in middle-third 2942 (41.5%). Squamous cell carcinoma was the histological type in 6413 (81.4%) patients. Multivariate analysis showed that female sex and substance abuse were positively associated with squamous cell carcinoma, while the presence of comorbidities and location of the primary in lower esophagus/GEJ were positively associated with adenocarcinoma.

Conclusions:

There is no evidence of an epidemiologic shift in the histopathologic spectrum of esophageal cancer in India over last two decades. Four out of five Indian patients with esophageal cancer have squamous cell histology. This is important to recognize, given the varying molecular spectrum and efficacy of therapeutic modalities based on histopathology.

Introduction

As per the World Health Organization, GLOBOCON 2020, esophageal cancer resulted in 6 million (3.1%) new cases and almost 5 million (5.5%) deaths worldwide.[1] In India, esophageal cancer is among the top 10 malignancies with an incidence of 52,396 (4.99%) which is slightly higher than the 2018 global average of 572,032 (3.2%).[2] According to the Indian National Cancer Registry Programme, there were 1,400,000 new cases of cancer diagnosed in India in 2020.[3] Approximately 2,73,982 (19%) cases were due to gastrointestinal malignancies and 52,000 (3.2%) cases were esophageal cancers. A higher incidence was seen in the northeast region where tobacco consumption is also higher. In India, esophageal cancer is the third most common gastrointestinal malignancy in both sexes, predominantly affecting males (M:F-1.5:1).[3]

Globally, the incidence of esophageal cancer is increasing [4]. There has been a distinct change in the histological trends of esophageal cancer across the globe. In developed nations like the USA, Europe and Australia, there has been a marked increase in the incidence of adenocarcinoma and particularly in the USA, there is now an epidemic of esophageal and gastroesophageal junction (GEJ) adenocarcinoma.[5] This rise in the number of cases of adenocarcinoma led to an evaluation of the risk factors associated with esophageal cancer, particularly starting from 1990. [6]Tobacco use, gastroesophageal reflux disease, Barrett's esophagus, and hiatus hernia were associated with an increased risk of esophageal adenocarcinoma.[6] The reason for the surge has been mainly attributed to a change in lifestyle and increasing obesity in the western world.[7] Asian countries with a high human developmental index like China and Malaysia have also recorded an increase in the incidence of adenocarcinoma.[8] But squamous cell carcinoma is still the commonest histological type in developing nations where tobacco use is more common.[5] Like other developing countries, India also has a higher incidence of squamous cell carcinoma.[9] But there are limited studies available from India after globalization and the era of the internet which introduced an increasingly Western lifestyle.

Regarding the primary site in the esophagus, some studies have identified the lower third while others have suggested that the middle third esophagus was the most common site of squamous cell carcinoma. There are very few timetrend studies regarding the histologic subtypes and the location of the primary tumor of esophageal cancer from the developing world. These studies have failed to show a significant increase in the incidence of adenocarcinoma over time.[10] [9]

We present the epidemiology of esophageal carcinoma and the time-trends in the histology and the location over a period of 15 years from a single, tertiary care cancer hospital in western India.

Materials And Methods

General study details

This was a retrospective analysis of consecutive patients who had a diagnosis of carcinoma esophagus. The study was conducted in the Department of Medical Oncology at the Tata Memorial Hospital, a tertiary cancer center in Mumbai, India between January 1, 2003, and December 31, 2018. Deidentified

clinicodemographic details were analyzed, hence ethical clearance was not sought. The study was conducted according to the ethical guidelines established by the Declaration of Helsinki, Good Clinical Practice Guidelines and the Indian Council of Medical Research.

Patients

We included all patients with histopathologically proven malignancy of the esophagus who were registered at the hospital during the study period. We included only patients who had a baseline endoscopy with a biopsy along with a radiological investigation, either computerized tomography scan, positron emission tomography scan, or a barium swallow. We included adult patients, i.e., age over 18 years, and excluded patients with histopathology other than adenocarcinoma or squamous cell carcinoma, and mixed histologies. We also excluded patients with missing data, and those without radiological and endoscopic details, as the location of the tumor could not be definitively determined in these patients. Patients in whom the tumor originated in the hypopharynx or the upper airway extending into esophagus were excluded. Patients with metastatic disease to the esophagus from another primary site were also excluded.

Variables

Our primary objective was to analyze the time-trend of the histological pattern of esophageal cancer over the past 15 years. Our secondary objectives included determination of the commonest histologic type and the location of the primary tumor of esophageal cancer in Indian patients and evaluating whether there was any correlation between age, sex, demographics, socioeconomic status, the presence of comorbidities, substance abuse and the histological type of esophageal cancer.

Study methodology

We identified the patient numbers from the Information Technology Department of the hospital. We excluded duplicate entries. The data regarding the epidemiology, and clinical features of all the patients were recorded from the electronic medical records. We recorded the variables such as age, sex, socioeconomic status, substance abuse, comorbidities, site of cancer, histopathology and endoscopic details. Tumors were divided into 4 groups for the purpose of location based on the distance from the incisors: upper-third (16–24 cm), middle-third (25–32 cm), lower-third (below 32 cm) and GEJ (the point where the distal esophagus met the proximal stomach). Tumors that spanned more than one part of the esophagus were classified based on the part in which the maximum extent of the tumor was present. For tumors that obstructed the esophageal lumen such that the endoscope could not pass beyond the obstruction, the location of the tumor was determined based on the contrast enhanced CT scan (CECT) appearance. In case of involvement of two segments, the segment which showed the maximal disease on the CECT was taken into consideration. In case there was a discrepancy in the location noted on the endoscopy and the CECT scan, the segment involved on the CECT was considered due to the better anatomic details noted on the CT scan where nodal disease and disease extent could be better appreciated.

Statistical Analysis

Data were analyzed using StataCorp. 2015 (Stata Statistical Software: Release 14. College Station, TX: StataCorp LLC.) and the Statistical Package for the Social Sciences (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). We did not calculate a sample size for the study; we included all eligible patients within the timeframe of the study. Data were summarized using mean and standard deviation for continuous variables which were distributed normally, or median and interquartile range for continuous data which were distributed non-normally. Categorical variables were represented as frequencies and percentages. Chi-square test for linear-by-linear association was used to assess the trend of the histological type of the tumor overall and by subgroups of demographics, substance abuse, location, and the histological type of the tumor. The trend of the histologic tumor type was compared between subgroups using the difference between the two slopes of the subgroups and concluding if the trend between the two subgroups was significantly different from each other depending on the corresponding p-value. The chi-square test was used to find any association among the demographics, substance abuse and the tumor histology. Significant risk factors in the univariate analysis were then modelled in a multivariable logistic regression model using backward likelihood ratio method for variable selection. A p-value of < 0.05 was considered statistically significance.

Results

We included 7874 patients in the study (Figure 1).

Age and Histology

In the overall cohort, there were 6413 (81.4%) cases of squamous cell histology. There was no time-trend noted in the incidence of squamous carcinoma in the whole cohort from 2003 to 2018 ($p=0.143$) (Table 1). In the cohort of patients who were older (≥ 60 years), 2791 (81%) patients had squamous cell carcinoma and 618 (18.1%) had adenocarcinoma (online resource). By analyzing the time-trend for older patients for each year, a significant decline was noted in the incidence of squamous cell carcinoma ($p=0.0015$) from 88.1% in 2008 to 78.8% in 2017 and 83.7% in 2018. However, there was no change in the incidence of squamous cell carcinoma during this time for patients below the age of 60 years. Additionally, there was no significant difference in the slopes of the time-trend between the two age groups; both groups had a predominance of squamous cell carcinoma ($p=0.1497$). (Online Resource 1 and 2).

Table 1
Demographics

Clinicodemographic features		Frequency in number (%) N=7874
Age in years	≤60	4005 (50.9)
	>60	3869 (49.1)
Sex	Male	5092 (64.7)
	Female	2782 (35.3)
Hospital category of the patient, based on the financial status	Private category (Full payment)	1469 (18.7)
	General category (Subsidized payment)	5317 (67.5)
	No charge (Free treatment provided)	1088 (13.8)
Substance abuse	Smoking	938 (11.9)
	Smokeless Tobacco	1597 (20.3)
	Alcohol	61 (0.8)
	None	4322 (54.9)
	Smoking/Smokeless tobacco + alcohol	593 (7.5)
	Smoking + Smokeless tobacco	363 (4.6)
Comorbidities	No	6738 (85.6)
	Yes	1136 (14.4)
Types of comorbidities	Diabetes	395(34.7)
	Hypertension	589 (51.84)
	Ischemic heart disease	152 (13.3)
Upper endoscopy	Yes	6644 (97.2)
	No	189 (2.8)
Site of esophagus	Upper	906 (12.8)
	Middle	2942 (41.5)
	Lower	2331 (32.8)
	Gastroesophageal junction	917 (12.9)
Histopathology	Squamous	6413 (81.4)
	Adenocarcinoma	1461 (18.6)

Based on histology, in male patients, 3890 (76.4%) had squamous cell carcinoma, and 1202 (23.6%) had adenocarcinoma. Among the female patients, 2523 (90.7%) had squamous cell carcinoma and 259 (9.3%) had adenocarcinoma (Online Resource). Among the male patients, the incidence of squamous cell carcinoma declined from 78.5% in 2008 to 73.9% in 2017 and then increased to 77% in 2018 ($p=0.0051$). However, there was no change in the incidence of squamous cell carcinoma during this time for the female patients ($p=0.5481$). There was no significant difference in the time-trend slopes for the two sexes ($p=0.104$).

(Online Resource 3)

Site in the esophagus

The commonest primary site was the middle-third of the esophagus, which was noted in 2942 (41.5%) patients, followed by the lower-third in 2331 (32.8%). On evaluating the time-trends from 2003 to 2018, we found that there was no significant change in the location of the primary site over time (Figure 2). However, we found that there was a significant predilection for the primary tumor site based on the histology. Among the four sites, squamous cell carcinoma was noted most commonly in tumors originating in the upper-, middle- and lower-third esophagus ($p < 0.001$), while adenocarcinoma occurred most commonly in tumors of the GEJ ($p < 0.001$).

Substance abuse

We evaluated various risk factors like smoking, alcohol intake, and the use of smokeless tobacco. However, we were unable to evaluate obesity as a risk factor as the weights of the patients had not been consistently recorded. Smokeless tobacco was the predominant form of substance abuse noted. The time-trend for squamous cell carcinoma was significant only in the presence of at least one risk factor ($p < 0.0001$). There was no significant difference in the slope of time-trend between the groups in the presence or absence of substance abuse ($p= 0.3365$).

Comorbidities

There was no change in trend associated with comorbidities.

Trend for type of histopathology

Squamous cell carcinoma was the commonest histologic subtype among all esophageal and GEJ carcinomas, regardless of age, sex, substance abuse, and comorbidities. There was no time-trend variation; squamous cell carcinoma remained the commonest histologic type consistently through the entire period of the study. (Figure 3)

Univariate and multivariate analysis

Epidemiological factors like age, sex, comorbidities, substance abuse, financial status, and the site of the esophageal lesion were evaluated in the univariate analysis by Chi-square test for independence. On the univariate analysis (Online Resource 4), the absence of comorbidities, female sex, presence of substance abuse and the primary site of the esophageal lesion were found to be significant predictors of squamous histology.

The four factors that were positive on the univariate analysis were taken to perform a multivariate analysis by logistic regression analysis (Table 3). Women had 3.43 times higher chance of having squamous cell carcinoma compared to males (OR, 3.43; 95% CI, 2.85- 4.11; p = 0.001). The presence of any form of substance abuse increased the odds for squamous cell carcinoma by 1.49 times (95% CI, 1.28-1.75; p = 0.001). The absence of comorbidities like diabetes, hypertension or ischemic heart disease was associated a 30% higher chance of having squamous cell carcinoma (OR, 1.3; 95% CI, 1.07 – 1.57). Location in the mid-third esophagus was not a statistically significant predictor of squamous cell carcinoma but lesions in the lower esophagus (OR, 0.033; 95% CI, 0.019 – 0.059) and GEJ (OR, 0.006; 95% CI 0.003 – 0.011) had a significant association with squamous cell carcinoma. i.e., lesions in both the lower-third and GEJ had less chances of being squamous cell carcinoma as compared to upper-third and middle-third esophageal lesions.

Table 3
Multivariate analysis

Factor	Variables	Odds Ratio	95% lower confidence interval	95% upper confidence interval	p-value
Gender	Male (ref)				
	Female	3.432	2.859	4.119	<0.001*
Substance abuse	None (ref)				
	One or more	1.498	1.281	1.752	<0.001*
Comorbidities	Yes (ref)				
	No	1.300	1.070	1.570	0.007*
Site in esophagus	Upper (ref)				
	Middle	0.711	0.378	1.334	0.288
	Lower	0.033	0.019	0.059	<0.001*
	GEJ	0.006	0.003	0.011	<0.001*
Ref = Reference; * = statistically significant					

Discussion

Esophageal cancer is a dreaded cancer with a dismal prognosis, having a case fatality rate of 90%[11]. Most esophageal cancers could be avoided by changing lifestyle, avoiding substance abuse and consuming nutritious diet. Esophageal squamous cell carcinoma and adenocarcinoma have different risk factors, pathogenesis and possibly, treatment approaches and outcomes. In our retrospective study on the epidemiology and time-trends of esophageal cancer over the past 15 years at our tertiary care oncology referral center, we found that squamous cell carcinoma continued to be the commonest histological subtype, far outnumbering adenocarcinoma. The trend of squamous histologic predominance was noted throughout the duration of the study. There was no trend noted of an increase in the incidence of adenocarcinoma. The results of our study will be useful for planning cancer prevention approaches and for optimizing the management strategies for esophageal cancer in India.

The median age of diagnosis in our study was 57 years. This was similar to another retrospective study conducted in Mumbai in which the median age was reported to be 54.8 years. [10]A similar study in southern India had reported a median age of 55.8 years,[12] but a study conducted in northern India had reported a higher median age of 62 years.[13] Reports from other Asian and African countries also have noted similar findings [5][14]whereas Western countries like the USA have reported a median age at diagnosis of approximately one decade later.[2] According to our study, 43% of the affected population were in the geriatric age-group (age ≥ 60 years) compared to 51% in a study conducted in northern India. In the older patients in our study, we noted a decline in the incidence (88% in 2008 to 78% in 2017) without any change in histological trend of squamous subtype; no such change was noted in the younger population. However, studies conducted in the USA showed an increase in the incidence of squamous subtype in the geriatric population and a decrease in the younger population. [15]This decline in the younger population was not noted in our study in India possibly due to the prevalence of smoking and other risk factors but the reason behind the decreasing trend in the geriatric population is unclear.[16]

We found that men were most commonly affected; both squamous and adenocarcinoma were common in men and the male : female ratio was 2.2:1 which was similar to the national average of 2.6:1 reported by the National Cancer Programme Registry conducted by the Indian Council of Medical Research [3] with no change in trend observed. Studies conducted in Jammu and Kashmir had reported a male : female ratio of 1.4-1[13]; studies from southern India during different time periods also showed a male : female ratio around 2.16-2.15:1.[12] This was attributed to the higher percentage of tobacco use in various forms seen across the country in men. As per the Global Adults Tobacco Survey (GATS) 2016-2017 in India, 42% of adult males had a history of tobacco usage compared to only 10.6% of adult females [16]. The relatively high incidence of esophageal cancer in women in Kashmir was similar to that noted in central Asian countries, commonly called the esophageal cancer belt. Regional factors might have influenced the higher occurrence in women[17]. Developed countries like the USA, Europe and Australia have reported a higher incidence in men whereas China, Iran and Africa have reported an equal incidence in both the sexes.[15] [18][17] [19]

Tobacco usage was directly correlated with an increased number of squamous cell carcinoma cases in Taiwan [20] where the incidence was found to be more than 70% in those who consumed tobacco. Similarly, sub-Saharan Africa also had a higher number of cases of squamous cell carcinoma where tobacco consumption in males was around 90%.[21] Comorbidities like diabetes and hypertension have been reported to be associated with a higher incidence of adenocarcinoma in developed countries.[22] Similarly in our study, a history of substance abuse was associated with a higher incidence of esophageal adenocarcinoma there was no change in time-trend in the population.

In our study, 6413 (81.4%) patients had squamous cell carcinoma compared to 1461 (18.6%) patients with adenocarcinoma. The ratio of squamous to adenocarcinoma was 5:1, which was similar to other studies conducted across southern and central India.[9][10]. However, in a cross-sectional study conducted in Kashmir, 340 (98%) patients had squamous cell carcinoma. This could be due to the greater prevalence of tobacco usage and alcohol in both the men (82%) and women (61%) in Kashmir.[13] Few other Asian countries like Singapore, China and Iran reported a decline in the incidence of squamous cell cancer however no such decline was noted in our study. The higher ratio of squamous cell carcinoma (81.3%) compared to adenocarcinoma (18.7%) indicates that we are not likely to soon see a change in the histological trend in esophageal cancer in our country. Risk factors like smoking, alcohol consumption, lower socioeconomic status and poor nutritional status are the possible reasons for such a high incidence in the developing nations, suggesting the long-term policy goal of primary prevention of esophageal cancer.

The most common site of origin of the esophageal lesion was the mid-esophagus in 3942 (41.5%) closely followed by lower esophageal malignancy in 3331 (32.8%). This observation has been reported by most of the other studies conducted in India[12][9][10], however some studies have also shown a higher occurrence in the lower esophagus.[19] In contrast, western countries have noted a rise in the trend of lower esophageal malignancy, particularly adenocarcinoma. Based on our study, there was no significant rise in the occurrence of adenocarcinoma, which was 17.6% in 2003 and 20.4% in 2018. This change in trend of esophageal cancer document in USA as early as 1980.[22] In countries like Taiwan [23], Africa[21], China[8] and central and south America[24], the incidence of squamous cell carcinoma is over 70%. Similarly, developed nations like Australia, America, and Sweden have a higher incidence of adenocarcinoma in excess of 60% [18](Table 2).

Table 2
Data from epidemiological studies done in other countries and in India

Study name/location	Male: Female ratio	Squamous cell carcinoma (%)	Adenocarcinoma (%)	Most common site of tumor	Time frame of the study
Central and South America (26)	2-5:1	70	30	Middle esophagus	1997-2008
Australia, Sweden and USA (27)	4.6:1 5.7:1	48; 37; 50	52; 63; 50	Lower esophagus	1970-2015
Sub-Saharan Africa (24)	4:1	78.1	21.3	Middle esophagus	1992-2010
Taiwan (23)	11:1	85; 90	6-7	Middle esophagus	1979-2003
USA (25)	3.1:1	51	49	Lower esophagus	1973-2009
Chokshi <i>et al.</i> [10]	1.7:1	80	16	Mid esophagus	1996-2015
Gupta <i>et al.</i> [4]	1.8:1	61	37	Mid esophagus	2014-2016
Samarasam <i>et al.</i> [9]	2.5:1	76	24	Lower esophagus	2010-2016
Cherian <i>et al.</i> [12]	2.16:1	92	8	Lower esophagus	1989-2004
Sekar <i>et al.</i> [31]	2.6:1	81.4	18.6	Mid esophagus	2003-2018

Until approximately a decade ago, the histology of esophageal carcinoma did not have much therapeutic implication. [25]Recently, the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial long term data showed that the addition of neoadjuvant chemoradiotherapy to surgery improved overall survival in both histologies of esophageal cancer. However, of note, the patients with squamous cell carcinomas, who were treated with neoadjuvant chemoradiotherapy and surgery had an unprecedented median overall survival of 81.6 months (95% CI, 47.2–116.0), while patients with adenocarcinoma had a median overall survival of 43.2 months (95% CI, 24.9–61).[26] This study suggested that the histology of the tumor may affect disease outcomes. [27]Similarly, in the Checkmate 577 trial in which nivolumab was used as adjuvant therapy following neoadjuvant chemoradiotherapy and surgery, a prespecified subset analysis showed that patients with squamous histology had a better disease free survival of 22.9 months compared to patients

with adenocarcinoma, in whom the disease free survival was 19.7 months; however, the primary site of disease did not result in much change in the disease free survival (esophagus 24.0 months vs GEJ 22.4 months).[28] The molecular profile of esophageal carcinoma differs based on histology; *ERBB2* and *FGFR2b* are potentially targetable mutations in esophageal adenocarcinoma while the *EGFR* pathway has been targeted in esophageal squamous cell carcinoma.[29] Given the significant difference between the epidemiology of esophageal cancer in our patients compared to Western studies, the results of studies that have been predominantly conducted in Western populations may not be directly applicable to our patient population.

Since ours was a single center study, caution needs to be exercised when extrapolating the results to the Indian population at large. Ideally, in order to study the epidemiological trends, it would have been better to use data from population-based cancer registries. However, it is important to note that our hospital is the largest tertiary care cancer hospital in India and has a large volume of patients from all over the country. Thus, the data of the patients registered at our center, may be fairly representative of the data of general Indian patients with cancer. In our study, there was a lack of data regarding the patients' body mass index and other nutritional factors. There was also a lack of details regarding premalignant conditions like Barret esophagus, and dysplastic changes in the esophagus. Genetic alterations and molecular changes should be assessed in the current era of immunotherapy and targeted agents; we did not have these details.

Conclusions

In India, esophageal cancer is common in the fifth decade and men are most commonly affected. There is no evidence of an epidemiologic shift in the histology of esophageal cancer over the past 15 years. Squamous cell carcinoma is still the commonest histology with the mid-third esophagus being the commonest location of esophageal cancer.

Declarations

Ethics approval and consent to participate:

Deidentified clinicodemographic details were analyzed, hence ethical clearance was not sought.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest:

The authors declare that they have no competing interests

Funding : None

Authors contribution:

AS and VN made substantial contributions to the conception and design of the work and the acquisition, analysis and interpretation of data, statistical analysis and have drafted the work and writing the manuscript

AR VP NM SC AS substantial contributions to the design of the work and the acquisition, analysis and interpretation of data, have drafted the work

SM substantial contributions to the statistical analysis of the work

RK AM AJ NP RD SB RB substantial contribution to the interpretation of data analysis of data.

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Figures

Figure 1

Flowchart of the methodology for inclusion of patients in the study

Figure 2

The time-trend of the location of the primary tumor site in the esophagus. Tumor sites were divided into upper, middle, lower third of esophagus and gastroesophageal junction.

Figure 3

The annual time-trend of the histopathological type of the esophageal tumor