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Original Article

Geodemographic Variations in Subtypes of Esophageal Carcinoma among Afghanis and Pakistanis Patients in Northwest Pakistan

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Abstract

Objective:
To determine the variation in occurrence of two major histological types of esophageal cancer stratified by various factors.

Patients & Methods: 122 cases were selected between June 2011 and June 2013, at Northwest General Hospital and Research Center (NWGH & RC) Khyber Pakhtunkhwa. The selected patients were either from Khyber Pakhtunkhwa (26) or Afghanistan (96). The H&E stained slides were re-assessed microscopically. Types of carcinoma and demography of disease were evaluated. The variation in occurrence of the two subtypes of cancer was determined through multivariate analyses using morphology as dependent factor and gender, geographic area and anatomical location of the esophagus as independent factors.

Results: Majority of the lesions were of squamous cell type (87%). Adenocarcinoma was marginally more prevalent among Pakistanis as compared to Afghanis (23% vs. 10%). The number of younger patients was high in Afghanis as compared to Pakistanis (87.5% vs 12.5%). 76 (62%) patients were male with no significant difference of the proportions of gender between the two nationalities. Majority of the malignancies (n = 76, 62%, 95% CI = 53 – 71%) were located in the lower esophagus. For the outcome of squamous cell carcinoma, the Odds Ratio of being an Afghani was 2.7 while for that of adenocarcinoma it was 0.3. Both measures fail to achieve statistical significance (z = 1.3, P = 0.083).

Conclusions: Squamous cell carcinoma was the most common malignancy in both populations. Adenocarcinoma was marginally more prevalent in Pakistanis while esophageal carcinoma was common in younger patients in Afghanis that may point towards different etiology and pathogenesis of the disease. Further large-scale studies are therefore required to evaluate these factors.

Keywords: Esophageal carcinoma, Geographic area of residence, squamous cell carcinoma

Introduction

Esophageal cancer is reported to be the 6th to 8th most common malignancy world-wide.[1,2] About 80% of esophageal neoplasms are malignant, the majority histologic subtypes being either squamous cell or adenocarcinomas. Squamous cell carcinoma is found mostly in developing countries and is associated with tobacco, hot fluids ingestion, malnutrition, low fiber intake, and alcohol use.[3,4]

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Adenocarcinoma, on the other hand, is seen predominantly in the developed countries and is reported to be related to obesity and chronic gastro-esophageal reflux disorder, which leads to a pre-malignant clinical state, Barrett's esophagus, a precursor to adenocarcinoma.[5,6]

These malignancies of esophagus are known to be very aggressive, with an increasing incidence and a five-year survival rate of less than 10%.[2,7 & 8-10] About 482,300 new esophageal cancer cases were estimated to have been diagnosed the world over in 2008, while 406,800 deaths from esophageal cancer were documented during the same year.[11] Incidence rates

for esophageal cancer vary widely among the various geographical regions of the world, with the difference between the highest and the lowest rates reaching up to 100-fold.[12] World-wide, the highest rates are found in southern and eastern Africa and eastern region of Asia, and the lowest rates in western and middle Africa and Central America.[11]

There is also a racial predilection in the type of esophageal carcinoma. The incidence of squamous cell esophageal carcinoma is fivefold higher among persons of African descent in America, while that of adenocarcinoma is fourfold more common among those of Caucasian descent. These profound differences in biological and epidemiological profiles of the two subtypes of esophageal carcinoma have led to suggestions that the two should be viewed as separate disease entities altogether.[1]

The highest risk area for esophageal cancer, stretching from Northern Iran through Central Asia to north-central China, is often referred to as "the esophageal cancer belt", of which Pakistan has been described to be an extension.[13,14] Ninety percent of cases reported in this belt are squamous cell carcinomas.[15,16] According to 2008 reports, Pakistan ranked 36th on the incidence rates of esophageal cancer in the world, along with Ireland and Djibouti, with an annual incidence of 5.9 cases per 100,000 of population.[17] Small scale studies conducted at local treatment facilities in Pakistan have reported esophageal cancer to be from 3rd to 10th most common malignancy.[18,19] Esophageal malignancy has been reported to be more prevalent in the Northwestern area of the country, the majority being squamous cell carcinoma and mostly in the upper third of esophagus.[20,21] Comparing the incidence between the ethnic groups, esophageal carcinoma has been found to be the commonest malignancy among male Afghan patients while being the 2nd commonest among Afghan females. By contrast, it was the 6th commonest cancer among males and the 5th commonest among females from Northwest Pakistan.[22]

Patients and Methods

122 cases were selected after reviewing the histopathology reports in pathology department of Northwest General Hospital and Research Centre (NWGH & RC). All were endoscopic biopsies done over a period of two years. The H&E slides were re-assessed microscopically. Among these 106 were squamous cell carcinoma and 16 were adenocarcinoma. As stage of disease was not included in the study no information was collected about that parameter. Northwest general hospital and research Centre is located in the heart of Peshawar city catering patients living in the province of Khyber Pakhtunkhwa (KP) and Afghanistan, therefore patients whose geographic area of residence was either KP or Afghanistan were selected and these were 26 and 96 respectively.

Presenting symptom was taken from the physician request slip. Complete information on risk factors was not available as it was a retrospective review of chart therefore; factors playing a role in the etiology of the disease were not included. Gastroenterologist examined the esophageal lesions by endoscope and divided the lesion according to their locations into upper, middle and lower third of esophagus. Lower border of cricoid cartilage at the level of 16 cm from incisors to the level of bifurcation of trachea 24 cm from incisor was taken as upper third. From 25 cm to 32 cm as the middle-third and from 33 cm to the gastroesophageal junction at 40 cm was considered lower third. Out of 122 cases 18 were located in the upper third, 23 in the middle third and 81 were located in the lower third.

Data analyses were performed with Statistical Package for Social Sciences (SPSS) version 16.0. Preliminary (bivariate) analyses were conducted to determine associations between the predictors under study and esophageal cancer subtype. Multivariate analysis was done using Logistic Regression to assess the magnitude of association between selected variables and point of interest. Analysis of variance was used to compare continuous variables across categorical variables with more than two categories. Chi square test was used for comparing categorical variables with more than two categories. Two group comparisons regarding continuous variables were done using t tests for independent samples while z-approximations of binomial distribution were used to compare two groups on categorical variable. P value <0.05 was considered as significant.

Results

Geodemographic details of the patients are given in Table 1. Overall, the majority of lesions were of the squamous cell type (n = 106, 87%). Only 16 cases (13%) were adenocarcinoma. Moderately differentiated squamous cell carcinoma was the most common. Out of 122 patients 26 (21%) were of Pakistani origin, while 96 (79%) were Afghans. 76 (62%) of the patients were male while 46 (38%) were female. Between the two

nationalities, there was no statistically significant difference of the proportions of genders (p = 0.585). Age was normally distributed and ranged between 19 to 90 years, with mean age of 56.6 years. Eight patients (6.5%) were less than 35 years of age. A majority of these younger patients (7 out of 8; 87.5%) were Afghanis while only one was Pakistani (12.5%). Among these younger patients, the single 25-year-old Pakistani was a female, while for Afghanis, there were almost equal younger male (4; 57%) and female (3; 43%). This difference in the proportion of nationalities among the younger patients was statistically significant (z = -3.0, p = 0.002).

Table 1. Geodemographic details of the patients

Geographic area	SCC (Count %)	AC (Count %)	Total Count (%)
Afghani	86 (89.6)	10(10.4)	96 (100)
Pakistani	20 (76.9)	6 (23.1)	26 (100)
Gender			
Male	67 (88.2)	9 (11.8)	76(100)
Female	39 (84.8)	7 (15.2)	46(100)
Location			
Upper third	23 (100)	0 (0)	23 (100)
Middle third	23 (100)	0 (0)	23 (100)
Lower third	61 (80.3)	15 (19.7)	76(100)
Total	106 (86.9)	16 (13.1)	122 (100)

SCC: Squamous cell carcinoma, AC: Adenocarcinoma

There was no significant difference of ages between Pakistani and Afghan patients (p = 0.53). Females were significantly younger than males for the whole group (p = 0.003) as well as for Afghanis (p = 0.01). For Pakistani patients, although the mean age of females was less than that of males (51 years vs. 58 years), the difference did not reach statistical significance (p = 0.08). Although the two-tailed test was not significant for the difference of the type of lesion between the nationalities, adenocarcinoma was marginally more prevalent among Pakistanis than Afghanis (23% versus 10%), (p=0.04).

Majority of the malignancies (n = 76, 62%, 95% CI = 53-71%) were located in the lower Esophagus. The proportion of lesions in the middle and upper Esophagus was exactly equal (n = 23, 19%, 95% CI = 12-27%).

For the outcome of squamous cell carcinoma the Odds Ratio of being an Afghani was 2.7 while for that of adenocarcinoma it was 0.3. Both measures fail to achieve statistical significance (p = 0.08).

All the lesions in the upper esophagus were of squamous cell type. While the majority (n = 22, 4%, 95% CI = 78 – 100%) of lesions in the middle Esophagus were also of squamous cell type.

Even in the lower esophagus, the majority of the lesions (N = 66, 80%, 95% CI = 70 -79%) were of squamous cell type. Only 30% (n = 15) of the lesions in the lower esophagus were adenocarcinoma.

Discussion

Esophageal cancer showing marked variations in epidemiology is the most virulent cancer regardless of recent advances in diagnosis and treatment options. Esophageal cancer despite its existence in every country and race shows striking uneven geographic distribution with high incidence rates in China, India, Iceland, Japan, United Kingdom and regions around Caspian Sea.[23] Asian cancer belt for esophageal cancer extends from Iran to Turkmenistan, Northern Afghanistan, Uzbekistan, Kazakhstan, Northern China, Siberia and Mongolia.[24] Baluchistan not only shares long border with Afghanistan but also cultural and dietary similarities in addition to addictive habits of oral and nasal use of naswar are contributory factors for high rates of Esophageal cancer.[18] Khyber Pakhtunkhwa also sharing similar etiological factors have high incidence of esophageal cancer as compared to other regions of Pakistan and may represents along with Baluchistan the extension of Asian cancer belt.[17] In our study 26 patients were from KP and 96 from Afghanistan. Less than 1/3rd of cases were from KP reflecting the fact that the esophageal carcinoma is the leading malignancy in Afghans.

Esophageal cancer is the malignancy arising from the surface epithelial lining of esophagus. Two main types of esophageal cancer are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EADC). Both are different in their etiology, epidemiology, pathogenesis and patterns of behavior. ESCC is the most common malignancy of esophagus.[3] In our study 87% of the cases were ESCC and 13% were EADC which is comparable to studies in developing countries where squamous cell carcinoma is the dominant histology.[11] However incidence of EADC increased over the last three decades.[4] EADC develops as a sequence of genetic and phenotypic variations termed as Barrett's metaplasia dysplasia neoplasia sequence but causes for increase in the incidence of EADC remains largely unclear. Adenocarcinoma was marginally more prevalent among Pakistani patients.[5]

Mean age at diagnosis was 56 years in our patients (range 19-90 years). Data obtained from Scotland showed 72 years to be median age at presentation.[25] Mean age in various studies is 63.1 and 67 years.[26,27] [27]. Although difference in ages of Pakistani and Afghani patients was not significant, there is statistically significant difference in the proportion of nationalities among the younger patients.

Male to female ratio was 1.6:1, which is comparable to the results obtained from this region.[28] Between the two nationalities, there was no statistically significant difference in the proportions of genders. This may be due to addictive habit of oral and nasal naswar use, dietary habits and poor social status. Around the rest of the world the incidence of esophageal cancer is four to six times higher in men than in women for all age groups, except is China, northern Iran and the former USSR where the ratio is 1:1.[29]

Dysphagia was the presenting complaint in 100% of the cases and as 65% of the lumen must be occluded before patient presents with dysphagia, this means that our patients were at advanced stage at the time of presentation. Majority of the malignancies (62%) were located in the lower esophagus. The proportion of lesions in the middle and upper esophagus was exactly equal (19%). While in China Zhang et al reported squamous cell carcinoma located in the middle and adenocarcinoma located mainly in the lower esophagus.[30]

Many factors are held responsible for squamous cell carcinoma of esophagus, although no definitive precursor or etiological factor has been identified. These include tobacco use, low socioeconomic status, decreased intake of fruits and vegetables, hot beverages, traditional and eating habits. Most of these acts systemically rather directly explains more common involvement of lower third of esophagus in our study.

An association has been found between infection with human papillomavirus (HPV) and esophageal cancer. The incidence of HPV according to pooled data from Asian countries like Japan, China, Hong Kong, India, Pakistan and Korea ranged from 13-63% and overall incidence was 22%.[31]

Studies conducted in northern areas of Pakistan have identified meat cooked in animal fat, dried salt pickled meat, or meat cooked over charcoal to be blamed along with oral/ nasal use of naswar/tobacco and consumption of lot of hot beverages (kahwa) as contributory factors for esophageal cancer.[21]

Conclusion

Although variations in subtypes of esophageal cancer in Afghans and Pakistani patients were not statistically significant in terms of geodemography except for difference in proportion of nationalities among younger patients and also adenocarcinoma was marginally more prevalent in Pakistanis. This study may act as a baseline data for further large-scale studies to understand the epidemiology, etiology and pathogenesis of esophageal cancer and therefore improve its management. These not only include surgery, chemo radiotherapy but also developing preventive strategies especially life style modification programs and use of HPV vaccines so as to prevent KP, the northwest Pakistan to be extension of 'Asian Cancer belt'.

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