

Original Article

Esophageal cancer in northwestern Iran

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Abstract

BACKGROUND: Esophageal cancer (EC) is one of the most frequent and serious cancers worldwide, but its geographic distribution is disparate. Northern Iran is known as one of the hot spots for EC, but there is inadequate evidence available regarding its characteristics in northwestern region of Iran. Therefore, this study aimed to describe some demographic and histopathologic features of EC in this region of Iran. **MATERIALS AND METHODS:** 166 hospital referral patients from a hospital in the northwestern region of Iran who underwent endoscopic biopsy for the chief complaint of dysphagia or odynophagia, and were admitted with the pathologic diagnosis of esophageal cancer during 3 years were enrolled in this study. **RESULTS:** The mean age of the patient was 61.8 ± 12.0 years old. Male/female ratio was 0.84. With respect to the site of tumor, tumor was located in cervical esophagus in 7 cases (4.2%), upper thoracic in 5 patients (3%), middle thoracic in 64 patients (38.6%), lowers thoracic in 68 cases (41%), and cardia in 22 cases (13.2%). There was a significant difference among the site of tumor in different age groups ($P = 0.021$) and different sex groups ($P = 0.001$). In men, EC usually involves the lower parts, whereas in women it usually involves the upper parts of esophagus. Squamous cell carcinoma was the most common type of EC in all age groups, but the prevalence rate of adenocarcinoma seems to increase with age ($P = 0.045$). **CONCLUSIONS:** Demographic and histopathologic pattern of esophageal cancer in northwestern region of Iran is different from its histopathologic pattern in western countries in accordance with other reports from Golestan province in north-eastern region of Iran.

Key words: Adenocarcinoma, esophageal cancer, squamous cell carcinoma

Introduction

Esophageal cancer is the Sixth most frequent tumor disease worldwide,^[1] and the fifth most common disease in the developing countries.^[2] It is a lethal disease and its five-year survival is less than 5%.^[3-5]

A unique epidemiological feature of esophageal cancer is its disparate geographic distribution, with high incidence found within sharply demarcated geographic confines.^[2] Its incidence varies from 20 per 100,000 in the United States and Britain, to 160 per 100,000 in Honan province of China.^[4] Geographic high spots for esophageal cancer include areas in northern Iran,

Kazakhstan, Uzbekistan, Turkmenistan, and certain areas of China.^[2,6-8] Together these high-risk geographic areas appear to extend from northern Iran to China, along the path of Silk Road, and collectively called "Central Asian Esophageal Cancer Belt."^[6] Overall, 60% of esophageal cancers occur in "Esophageal Cancer Belt."^[4] The presence of disease in Iran is not of modern origin which is supported by the early Persian medical literature. Al-Jurjani (1040–1136 AD), the royal Islamic physician from Gorgan, Iran gave the first description of dysphagia and esophageal cancer.^[9]

As mentioned above, northern Iran including West Azarbaijan and Kordestan provinces in the northwest of Iran are high prevalent areas for this type of malignancy. This study is aimed to evaluate the demographic and histopathologic features of esophageal cancer in this region.

Materials and Methods

This hospital-based cross-sectional descriptive study was

Access this article online	
Quick Response Code: 	Website: www.indianjncancer.com
	DOI: 10.4103/0019-509X.82875
	PMID: 21768660

approved by the Scientific and Ethical Review Board of Urmia University of Medical Sciences. It was conducted at Imam-Khomeini Training Hospital because most esophageal cancer patients from West Azerbaijan and Kurdistan provinces are referred to this hospital. The location of West Azerbaijan and Kurdistan provinces in the northwest of Iran are depicted in Figure 1. Figure 1 also demonstrated the Golestan, Guilan, and East Azerbaijan provinces in which previous studies about esophageal cancer were reported from.

One hundred and sixty six patients who underwent endoscopic biopsy for the chief complaint of dysphagia or odynophagia, and were admitted with the pathologic diagnosis of esophageal cancer within 3 years were enrolled in this study. The following data were obtained: gender, place of birth, location of Residency, age at diagnosis, literacy level, past medical history (including anemia, achalasia, gastroesophageal reflux, caustic

esophageal injury), alcohol consumption, smoking, clinical manifestation, inspection findings, anatomical site, and pathological type of tumor. Statistical analysis was performed using SPSS software ver16 package. Frequencies were provided using descriptive statistics. Chi-square analysis and Fisher's exact test were used to investigate the significant relationship among different demographic, endoscopic and pathologic features. *P*-values lower than 0.05 were considered statistically significant.

Results

During the 3-year period of study, 166 patients underwent esophagectomy for the pathologic diagnosis of esophageal cancer. The mean age of the patient was 61.8 ± 12.0 years old, which ranged from 23 to 87 years old. Male/female ratio was 0.84.

Some demographic, endoscopic, and histopathologic features of the patients and the distribution of different pathologic diagnoses of esophageal cancer among different age, sex, residential, and educational groups were demonstrated in Table 1.

Also the distribution of patients based on their tumor site in different age, sex, residential, and smoking groups were demonstrated in Table 2.

Only one patient (0.6%) had history of alcohol consumption, but 65 patients (39.2%) had history of tobacco smoking.



Figure 1: The location of West Azerbaijan province (this study) in the northwest of Iran, compared with the place of previous reports from Iran (the East-Azerbaijan, Guilan, and Golestan provinces).

Table 1: The distribution of patients and their different pathologic diagnosis according to age, sex, residential, educational status and the site of tumor (endoscopy)

	Total	Adenocarcinoma	SCC
Age (mean \pm S.D.)	61.8 \pm 12.0	68.6 \pm 9.4	60.4 \pm 12.1
Age	20-49	-	21/135
	50-69	14/27	82/135
	\geq 70	13/27	32/135
Sex	Male	15/27	58/135
	Female	12/27	77/135
Residence	Urban	7/27	28/135
	Rural	20/27	107/135
	Missing	32	-
Educational Status	Illiterate	19/27	69/135
	Elementary and guidance school	8/27	63/135
	High school	3 (1.8)	3/135
Site of tumor	Cervical	-	7/135
	Upper thoracic	-	5/135
	Mid thoracic	1/27	62/135
	Lower thoracic	7/27	60/135
	Cardiac	19/27	1/135

Figures in parenthesis are in percentage

Table 2: The distribution of tumor site in different Age, sex, residential, smoking groups

		Upper parts (cervical to mid-thoracic)	Lower parts (lower thoracic and cardiac)	P-value
Age	20-49	13	9	0.006
	50-69	51	47	
	≥70	12	34	
Sex	Male	23	53	0.000
	Female	53	37	
Residency	Urban	16	19	0.573
	Rural	60	71	
Smoking	Smoker	26	39	0.230
	Non-smoker	50	51	

Ninety eight (58%) had a history of anemia, which was hypochromic microcytic anemia according to complete blood count in all esophageal cancer (EC) cases. Eight patients reported to have a history of gastroesophageal reflux disease. Three patients (1.8%) had a past medical history of achalasia (based on the clinical manifestations and endoscopic findings which were provided in the patient's medical file). There was no history of caustic esophageal injury.

The clinical manifestation of esophageal cancer was dysphagia in 155 subjects (93.4%), loss of appetite in 5 (3%), and weight loss in 6 (3.6%) of cases. During physical examination, cachexia and cervical lymphadenopathy were noted in 155 (93.4%) and 11 (6.6%) patients, respectively. No case with palpable abdominal mass was reported.

In general, there were 135 patients (81.3%) with squamous cell carcinoma (SCC) and 27 patients (16.3%) had adenocarcinoma and 4 persons (2.4%) had other pathologic types of cancer. With respect to the location of tumor, our findings were as follows: cervical esophagus in 7 cases (4.2%), upper thoracic in 5 patients (3%), middle thoracic in 64 patients (38.6%), lower thoracic in 68 cases (41%), and cardia in 22 cases (13.2%).

The Fisher's exact test demonstrated a significant difference for the site of esophageal tumor between different age groups ($P = 0.021$). The cancers of the lower parts of the esophagus are demonstrated to be more common in older people in our region.

Multinomial logistic regression revealed that the site of tumor has correlation with age, even when controlled for morphology (histopathology) and sex (OR: 3; 95% CI: 0.94-9.73).

According to chi-square analysis, there was no significant difference among the frequency of anemia in different locations of tumor ($P = 0.967$).

SCC was the most common type of EC in all age groups, but the prevalence rate of adenocarcinoma (AC) seems to increase with age ($P = 0.045$). Mean age of patients with AC was significantly higher than that of patients with SCC (68.6 ± 9.41 versus 60.4 ± 12.1 years, $P = 0.001$).

There was a significant difference among the site of tumor in different sex groups ($P = 0.001$). By recoding the data, among men, 23 (30.3%) had tumor in upper parts (from cervical esophagus to mid-thoracic parts) and 53 (69.7%) were in lower parts (lower thoracic and cardiac esophagus). Among women, in 53 (58.9%) cases tumor was located in upper parts of esophagus, while in 37 cases tumor was in lower parts ($P = 0.000$). So in men, EC usually involves the lower parts, whereas in women it usually involves the upper parts of esophagus. Regarding the type of tumor, SCC was the most common type of EC in both sex groups (76.3% in men and 85.6% in women), and there was no significant difference among the type of tumor in two sex groups. Most of esophagus SCC (ESCC) patients were women and most of AC patients were men.

Discussion

In Europe and America ESCC is mainly caused by tobacco and alcohol use and is more common in men than in women.^[10] In Golestan province of Iran, which has one of the highest incidence rates of EC in the world, women are as likely to have a diagnosis of EC as men.^[11] In the study of Gholipour *et al.*, in East-Azerbaijan province of Iran, prevalence of AC was higher among men and prevalence of SCC was higher among women.^[12] In this study, in contrast with the findings of western countries, most of the ESCC patients were women and most of AC patients were men.

In this study, male to female ratio was 0.84 which was in contrast with the sex ratio in western countries

(3–5),^[1,7] but it is the same as result of a study in Turkmen Sahra of Iran or other high prevalent regions of the world.^[3] This may be due to the fact that men and women are exposed differently to the same risk factors in these regions.

Mean age of patients was 61 years, which is in accordance with other high risk populations.^[2] Second age group constituted 59.6% of patients that is in accordance with finding of other studies.^[1] The literature proposed that esophageal adenocarcinoma now occurs more frequently in younger patients,^[4] but no one of our adenocarcinoma patients was under 40 years old.

Almost all of our study subjects were born in the village and spend the first decade of their life in rural areas. In the study of Islami *et al.* from Golestan province of Iran, most of the patients are from rural areas too. Since our hospital is a governmental and referral hospital, it is normal that most of our patients are people of low socioeconomic status and poor health condition which can only use insurance services in such public settings. Throughout the world, the risk of esophageal carcinoma increases markedly with decline of socioeconomic class. People of high socioeconomic class often have more access to fresh fruits and vegetables or clear water.^[6] Further studies are needed for better identification of the influence of socioeconomic factors. In our study, there was no significant difference among the site or the type of tumor in two different residential groups.

Although educational status is a reflection of socioeconomic status, we studied this item separately. Over 50% of our patients were unable to read and write. Only 43.5 % of patients graduated from elementary school. We believe that illiteracy and low socioeconomic class are major etiologic factors in the pathogenesis of this severe disease. In the authors' point of view, illiteracy may play a synergic role with the socioeconomic status in people's bad nutritional diet in our province, because due to favorable agricultural conditions of West Azerbaijan and availability of various fruits and vegetables, they are achievable for almost everyone in the province, but due to bad nutritional habits and lack of cultural programs in order to reform fore mentioned habits, the people do not have suitable nutritional diet. For example, in rural areas of west Azerbaijan, instead of eating fresh vegetables, people preserve them for at least 3–4 months and then they consume it as pickled vegetables.

Only one patient (0.6%) of our cases had alcohol consumption in spite of the fact that most of the patients had SCC. Our finding is similar to results of the study of Kamangar *et al.* in 2007 in Golestan

province of Iran.^[6] Then alcohol is unlikely to be a major cause of esophageal cancer in our region in contrast with western countries, where heavy alcohol consumption increases the risk of EC 5–15 times,^[13] low alcohol intake in this population maybe due to Islamic beliefs of our people in which the alcohol consumption is prohibited.

Tobacco smoking is a major risk factor for ESCC in Western countries, where it increases the risk by approximately 3–5-folds.^[14] However, in Golestan province of Iran, the prevalence of ever smoking ranged from 1% among rural women to 39% in urban men, and there is a weak to moderate association between the frequency of smoking and esophageal carcinoma.^[15]

In west Azerbaijan province, the frequency of ever tobacco smoking among EC patients was 39.2% overall, which is significantly higher than the rate of smoking in EC patients in Golestan province (13.8%).^[15] It is remarkable that out of 67 patients with history of smoking only one patient had history of alcohol consumption. Regarding the fact that tobacco smoking is a risk factor for SCC, and the predominant pathology in our study was ESCC, it seems that in West Azerbaijan, smoking plays an important role in the pathogenesis of esophageal cancer.

Most common pathologic finding in our study was SCC (81.3%), which was almost similar to other high prevalence regions such as Golestan province of Iran but it is different from Western countries, where adenocarcinoma tumors constitute over 50% of esophageal carcinomas.^[11] The rate of SCC was to some extent lower in our province compared to reports from other provinces of Iran (86.9% in East-Azerbaijan,^[12] 82.5% in Guilan,^[16] and 82.5% in Kurdistan^[17]). There were no previous report from West Azerbaijan to study the trend of tumor morphology in our region, but regarding the developed countries, the epidemiology of esophageal cancer shifted dramatically from predominantly squamous carcinoma (seen in association with smoking and alcohol), to adenocarcinoma (in the setting gastroesophageal reflux and Barrett's esophagus).^[4] In our study, SCC was the most common type of EC in all age groups, but the prevalence rate of adenocarcinoma seems to be increasing with age. AC patients in our study were significantly older than ESCC patients, in accordance with the findings of a similar report from East Azerbaijan.^[12] There was no significant difference among the type of tumor in the two sex groups.

With respect to the site of tumor, the most frequent site was lower thoracic part with 68 (41%) versus

64 (38.6%) for middle thoracic part of esophagus. Some other studies categorized the site of tumor into upper, middle, and lower thirds. In Caspian littoral of Iran, the most prevalent part of esophagus reported in 1973 to be lower third,^[18] but in recent reports, EC is more frequent in middle third of esophagus,^[11] similar to the findings of western countries.^[4] However, in our region (West Azerbaijan in our study, and East Azerbaijan which reported by Gholipour *et al.*^[12]) the most prevalent site for EC is confined to be lower third of esophagus. It is hard to interpret these different findings, but it could be attributed to difference in nutritional habits in our region compared to other parts in northeastern Iran. Another interesting finding in our study is that a low involvement of cardia was seen in our patients (13.2%), whereas in western studies this rate was 32%.^[4]

Conclusion

Demographic and histopathologic pattern of esophageal cancer in northwestern region of Iran is different from its histopathologic pattern in western countries, in which the adenocarcinoma is the most common morphology of EC, but in our region SCC is more prevalent in all age groups. Sexual pattern of SCC and AC patients are different in our region from its pattern in western countries or even the Golestan province of Iran. Our findings in association with the report from Eastern Azerbaijan indicated that esophageal cancer had a different demographic, endoscopic, and histopathological pattern in Azerbaijan provinces compared with western countries or even compared with recent reports from Caspian Littoral in some cases.

Acknowledgment

The authors would like to thank Urmia University of Medical sciences for the grants provided for this study.

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Source of Support: Urmia University of Medical Sciences,
Conflict of Interest: None declared.