

Epidemiology of upper gastrointestinal cancers in Iran: A sub site analysis of 761 cases

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Abstract

AIM: To define the sub site distribution of upper gastrointestinal cancers in three provinces of Iran.

METHODS: The study was carried out in three provinces in Iran: Ardabil, Golestan, and Tehran. In Ardabil and Golestan, the data was collected from the sole referral center for gastrointestinal cancers and the local cancer registry. For Tehran province, data from two major private hospitals were used. All gastric and esophageal cancer patients diagnosed during the period from September 2000 and April 2002 were included in the study.

RESULTS: A total of 761 patients with upper gastrointestinal cancers were identified, 314 from Ardabil, 261 from Golestan, and 186 from Tehran. In Tehran, the relative rate of cancer increased from the upper esophagus to the distal stomach. In Golestan, the reverse pattern was observed. In Ardabil, the mid portion (distal esophagus and proximal stomach) was involved most frequently.

CONCLUSION: There were considerable variations in the sub site of upper gastrointestinal cancers in the three provinces studied. We cannot provide any explanation for this variation. Further research aimed at explaining the discrepancies in sub site distribution of upper gastrointestinal cancers may help identify important risk factors.

INTRODUCTION

Gastric cancer is the third most common malignancy worldwide^[1]. According to a recent report by Iran's ministry of health, cancer is the third most common cause of mortality, constituting 14% of all deaths in Iran. Upper gastrointestinal (GI) cancers cause 55% of all cancer-related deaths in Iran, with gastric cancer being the most common. Gastric cancer accounts for nearly 50% of all GI cancers^[2]. The incidence of squamous cell carcinoma of the esophagus and cancer of the stomach are very high as compared to their incidence in western countries^[3,4].

A major problem in classifying upper GI cancers is the lack of a universally accepted and clearly reproducible anatomic landmark separating the gastric cardia from the distal esophagus. Even when the landmarks are defined, cancer frequently destroys the anatomy to the extent that the landmarks become unrecognizable. Therefore, misclassification of gastric cancer occurs frequently^[5,6].

Recently, several studies have indicated an increase in the incidence of adenocarcinoma of the distal esophagus compared to cancer of the gastric cardia in western countries. These studies postulate that a significant proportion of adenocarcinomas of the distal esophagus may have been misclassified as cancer of gastric cardia, leading to the apparent increase in cardia cancer^[6,7].

In view of recent recognition of the importance of the sub site involvement in upper GI cancers, we aimed to examine the sub sites of upper GI cancers in Tehran and two provinces in north Iran.

MATERIALS AND METHODS

Subjects

The study was carried out in three provinces: Golestan, Ardabil, and Tehran. Golestan, located in the south-east of the Caspian Sea, is distinguished from other Caspian littoral provinces by an ethnic composition that has 40% Turkmen ethnicity. This province is located on longitude 51°-56' E, and latitude 36°-38' N, with an altitude of 50-500 meters above sea level.

Ardabil is situated near the south-western border of the Caspian Sea on 48°-49' E, 38°-39' N, and altitude of 3010 m. In this mountainous land, 98% of the population is of Azeri ethnicity.

Tehran is the most densely populated province of Iran and is located between the other two provinces (51°-52' E, 35°-36' N, altitude 1100-1700 m). Tehran has a diverse ethnicity which is representative of the entire Iranian population. Western lifestyle is prevalent in Tehran. By contrast; traditional lifestyle is still dominant in Golestan and Ardabil.

Methods

The data was collected from three different sources. The first source was Atrak clinic located in Gonbad, the main Turkmen-resident city of Golestan. Atrak clinic is the sole referral center for gastroesophageal cancers in the region and it also hosts an active cancer surveillance program. We estimate that over 95% of cancers in the region are registered in this center.

The second source was Aras clinic established in Ardabil for the management of gastroesophageal cancers. This clinic is also the sole referral center for such cancers in the Ardabil province and is a host to another active cancer surveillance program registering over 95% of cancers in the region.

The third source was two private general hospitals in Tehran. These two hospitals together are the primary referral centers for nearly 2 million upper socioeconomic class residents of Tehran.

All patients with gastric and esophageal cancer diagnosed during the period from September 2000 to April 2002, were included in the study. An essential inclusion criterion was that the subjects were born in the specified provinces and had been residing there for at least the last 10 years.

Endoscopic and pathologic tests were performed by the same team, according to the study protocol in the regions^[8]. Uniform endoscopic, surgical, and histologic criteria were used to define the tumor sub site.

The sub-site of esophageal tumors was recorded as upper, middle, or lower based on the endoscopy or surgery report. If the location of the main tumor bulk was not obvious, the cancer was recorded as "esophageal".

Non-cardia gastric cancers were defined as those where the center of the tumor was located over 2 cm distal to the gastro-esophageal junction. The gastro-esophageal junction was defined as the most proximal site of the gastric folds. Non-cardia gastric cancers were further divided into antrum, body, and fundus, according to the location of the main bulk of tumor. If the main bulk was

Table 1 The demographic characteristics of patients in the study

	Ardabil	Golestan	Tehran	Total
Patients No.	314	261	186	761
Age, yr (SD)	63 (10.8)	64.4 (11.8)	60.1 (12.7)	62.8 (11.7)
Male/Female	224/90	161/100	123/63	508/253
Urban/Rural residents	97/217	85/176	186/0	368/393

not obvious, the cancer was recorded as "gastric".

Adenocarcinomas of the gastro-esophageal junction area were classified according to the WHO/IARC guidelines as a tumor which crosses the gastro-esophageal junction regardless of the main site of the tumor bulk. Adenocarcinoma of esophagus was located entirely above the gastro-esophageal junction, and adenocarcinoma of gastric cardia was located below the gastro-esophageal junction and was centered within 2 cm from the junction.

Statistical analysis

Statistical analysis was performed using SPSS for windows, version 11.5. Analysis of variance was applied for comparison between normal numeric variables and chi-square for categorical variables.

RESULTS

A total of 761 patients with a confirmed diagnosis of gastric and esophageal cancer were identified. Of the patients included, 41.3% were from Ardabil, 34.3% from Golestan, and 24.4% from Tehran. The demographic characteristics are shown in Table 1.

The mean age of the subjects was 63 years (SD 12, range 18-96). There was no difference with respect to the age of the subjects in the three provinces (ANOVA, $F = 2.7$, $P = 0.64$). The male to female ratio was 2.0; there was no difference in the sex ratios between the three provinces ($\chi^2 = 9.16$, $P = 0.10$).

None of the subjects from Tehran resided in rural regions. This observation is in agreement with the fact that 87% of Tehran's population resides in urban areas. In Ardabil and Golestan provinces this ratio was 43.1%, and 54.5% respectively.

In 54 (7%) cases, the location of the tumor sub site was determined by review of the surgical report. Endoscopic data was used in the remaining subjects. Localization to a specific sub site was not possible in 5.2% of gastric cancers and 2% of esophageal cancers. The details of the anatomic distribution of cancers are shown in Table 2.

DISCUSSION

We observed distinct patterns of sub site involvement of upper GI cancers in the three geographic regions of Ardabil, Gonbad and Tehran. Tehran province had a higher rate of antral cancer compared to esophageal or junctional cancers. By contrast, in Ardabil and Golestan provinces, junctional and esophageal cancers were more common respectively, compared to antral cancers.

Table 2 The distribution of upper gastrointestinal cancers in three provinces of Iran *n* (%)

	Ardabil	Golestan	Tehran	Total
Stomach	178 (56.7)	93 (35.6)	137 (73.7)	408 (53.6)
Antrum	49 (15.6)	18 (6.9)	64 (34.4)	131 (17.2)
Body	47 (15.0)	32 (12.3)	29 (15.6)	108 (14.2)
Fundus	0 (0)	1 (0.4)	3 (1.6)	4 (0.5)
Cardia	82 (26.1)	41 (15.7)	21 (11.3)	144 (18.9)
Unspecified	0 (0)	1 (0.4)	20 (10.8)	21 (2.8)
Junction	24 (7.6)	13 (5.0)	13 (7.0)	50 (6.6)
Esophagus	112 (35.7)	155 (59.4)	36 (19.4)	303 (39.8)
Lower	41 (13.1)	42 (16.1)	21 (11.3)	104 (13.7)
SCC	26	41	18	85
ADC	15	1	3	19
Mid	57 (18.2)	91 (34.9)	9 (4.8)	157 (20.6)
Upper	14 (4.5)	19 (7.3)	3 (1.6)	36 (4.7)
Unspecified	0 (0)	3 (1.1)	3 (1.6)	6 (0.8)
Total	314	261	186	761

SCC: Squamous cell carcinoma; ADC: Adenocarcinoma.

The disparity in the relative frequencies of upper GI cancers in different regions could be explained by variations in the environmental and genetic factors. There are several reports that dietary, behavioral, life style and environmental factors may play a causative role in high-risk populations^[9].

HP infection is a well recognized factor involved in the pathogenesis of gastric cancer^[10,11]. All the three provinces studied have *HP* prevalence rates of nearly 90%^[12,13]. Therefore, in the present study, *HP* infection is unlikely to have accounted for the observed disparity in the sub-site prevalence of cancer.

Gastro-esophageal reflux (GER) is another risk factor associated with lower esophageal and cardia cancers^[14]. The prevalence of GER, defined as having reflux symptoms at least once a week, has been found to be 21.2% in Tehran^[15] and 30% in Golestan^[16,17]. The endoscopic prevalence of erosive GER in Ardabil was 34.7%^[12]. The progressive increase in the prevalence rate of GER from Tehran to Golestan to Ardabil correlates with the increase in the rate of cancer of gastric cardia in these provinces, from 11.3% in Tehran to 15.7% in Golestan and 26.1% in Ardabil (Table 2). It is possible that the prevalence of GER may explain the differences in cancer rate, especially that of cardia cancer. However, other explanations are required to determine the basis of the other cancer variations in the present study.

In the west, adenocarcinoma of the distal stomach (non-cardia cancer) has shown a decreasing incidence over the last 50 years^[9]. By contrast, adenocarcinoma of the cardia of the stomach and the adjacent gastro-esophageal junction has increased over the past 25 years. This increase is occurring at rate that exceeds that of any other cancer^[18-21]. The opposite trends in the incidence may indicate distinct etiologies for the cancer at these two sub sites of the stomach. Moreover, cancers at these sub sites differ with respect to the underlying gastric phenotype. Non-cardia gastric cancers occur in patients with *HP*-induced atrophic gastritis and accompanying hypochlorhydria. These patients usually have elevated

serum gastrin and low serum pepsinogen levels^[10,22]. On the other hand, cancer of the cardia and gastro-esophageal junction occur in subjects with normal acid secretion and is generally not associated with *HP* infection^[10,23].

Although the distinctive patterns observed in gastric cardia and non-cardia cancers have received much attention in explaining the underlying etiology of cancer, junctional cancers have not excited much interest.

One type of cancer pattern is observed in western countries where the incidence of junctional cancer is increasing while that of non-junctional esophageal cancer (SCC) is decreasing. The other pattern is observed in high incidence regions such as Linxian in China and North Iran. In these areas, an increase in junctional cancer is accompanied by high rates of esophageal SCC (not only of the lower esophagus), which is in sharp contrast to the pattern in the west where esophageal SCC is uncommon^[8,12]. As with the case of cardia *vs* non-cardia gastric cancers, it is possible that distinct etiologies are involved in the pathogenesis of junctional cancers such that junctional cancers associated with high rates of esophageal SCC may have different etiologies than those not associated with high rates of high esophageal SCC.

In summary, the present study represents the largest report from Iran identifying sub site involvement of upper GI cancers. We observed distinct pattern of cancers in the three provinces of Tehran, Ardabil, and Golestan. There is no clear explanation for this disparity, although we postulate that different etiologic factors are likely to be involved.

COMMENTS

Background

Gastric cancer is the world's third most common malignancy. Defining the exact origin of gastric cancers is sometimes difficult especially when the gastro-esophageal junction is involved. This difficulty often leads to misclassification of cancers, especially those arising from the gastric cardia and the lower esophagus.

Research frontiers

The incidence of cancer of the gastric cardia and the lower esophagus has shown a rapid change in several areas of the world. This rapid change offers a unique opportunity to study the etiology of these cancers. Many scientists are working on the epidemiologic characteristics of these changes in order to identify the etiologic factors. Thus, the exact determination of the sub site of origin of cancers and their epidemiology is very important.

Innovations and breakthroughs

The decreased prevalence of *H pylori* infection in some areas is believed to have resulted in a decrease in the incidence of gastric cancers. On the other hand, the increase in prevalence of gastro-esophageal reflux disease is believed to have lead to an increase in lower esophageal cancer.

Applications

We observed different patterns of sub site involvement in different parts of Iran. This difference could indicate different etiologies. Further epidemiologic studies aimed at identifying the probable etiologic factors are required.

Terminology

Gastric cardia is the most proximal 2 cm of stomach located distal to the gastro-esophageal junction.

Peer review

In this prospective study, the authors studied the sub site distribution of upper

gastrointestinal cancers in three provinces of Iran and they found that there are considerable variations in the sub site of upper gastrointestinal cancers in the three provinces studied.

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