RESEARCH ARTICLE

Patho-epidemiological Features of Esophageal and Gastric Cancers in an Endemic Region: a 20-year Retrospective Study

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Abstract

Background: Gastric and esophageal cancers are among the most lethal human malignancies worldwide. Of all malignancies estimated in Iran (47,100), gastric and esophageal cancers were responsible for 7,800 and 3,500 deaths in 2008 respectively. The present study aimed to provide an image of patho-epidemiological characteristics with their trends during two past decades with emphasis on topographic, morphologic, and some demographic features. Materials and Methods: In a hospital-based retrospective study in 2009, all pathological reports from esophageal endoscopies and gastric biopsies through a 20 years period (1989-2008) were collected and analyzed in four interval periods (five years each). Also, all eligible samples in hospital archives were enrolled for further testing. Besides, demography, topography and morphology of all samples were determined and analyzed by statistical software. Results: No significant statistical difference was seen in frequency of esophageal and gastric tumors throughout the study. Esophageal cancer cases were older than gastric. Sex ratio was 2.33/1 and men had a higher rate of both esophageal and gastric tumors. Stomach cancer included 64.3% of all cases. Inferior third and end of esophagus were common locations for esophageal tumors whereas proximal stomach was common for gastric tumors. Squamous cell carcinoma and adenocarcinoma were common morphological types of tumors in esophagus and stomach respectively. Conclusions: Morphological trends showed an increase of esophageal adenocarcinoma and diffuse/intestinal ratio in stomach cancers. Trends in incidence from gastric cancer decreased based on topographic studies but we could not find a topographical trend toward cardia.

Keywords: Stomach - esophagus - neoplasm - adenocarcinoma - squamous cell carcinoma

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Introduction

Non-communicable diseases (NCDs) are the main cause for mortality and burden worldwide. Malignant neoplasms, an important and growing category of NCDs, are cause of 13.3% global death. From all malignancies in Iran (47,100), gastric and esophageal cancers were responsible for 7,800 and 3,500 death in 2008 respectively. At the same year in Eastern Mediterranean Region (EMRO), estimated burdens for these cancers were 260,000 and 238,000 (WHO Global Health Observatory Data Repository, 2011). A recent study from Golestan province (an endemic region of GI cancers), has reported stomach and esophagus cancers as first and second top incident malignancies (Roshandel et al., 2012). Incidence rate of esophageal and gastric cardia cancers has risen in recent decades in some regions of the world (Macfarlane et al., 1994; Devesa et al., 1998; Botterweck et al., 2000; Newnham et al., 2003; Zhou et al., 2008) but in some reports, incidence of esophageal cancer has not largely changed (Aragones et al., 2010). For better assessment of esophageal and gastric cancer, risk factors such as clinical manifestations, pathological characteristics, prognostic factors and survival need to be considered. Pathological characteristic controls the modality of treatment and has direct relationship with prognosis (Siewert et al., 2000; Moghimi-Dehkordi et al., 2008). Cancer registries have taking place for a longtime in developed countries, but they are fairly new. In Iran, cancer registry has a short history and information on esophageal and gastric cancers with pathological characteristics is limited to different local researches with relatively small sample size, different methods and diverse results (Abdi-Rad et al., 2006; Bafandeh et al., 2006; Moghimi-Dehkordi et al., 2008; Mousavi and Somi, 2009; Babaei et al., 2010). Failure to focus longitudinal studies on pathological characteristics is a potential weakness for having an image of these important cancers in Iran. This study aimed to draw an image of pathological characteristics and their trends during two past decades with emphasis on topographical,

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morphological, and some demographic characteristics.

Materials and Methods

Setting of study and sample

In a hospital-based retrospective study at Boo-Ali Sina (Avicenna) Hospital in 2009, all the pathological reports from endoscopic esophageal and gastric biopsies through a 20-year periods, five years interval (1989-2008) were collected to find out demographic, topographic, and morphological characteristics of the patients. Since the hospital did not have any surgery ward, all the samples had collected by endoscopy. Each sample belonged to one patient and we didn't check more than one sample for each case. All the eligible reported samples in the archive were enrolled and suspicious cases were excluded from this study.

Method of diagnosis

All samples were collected based on their numbers in archive. New cuts from preserved blocks were prepared. Pathologist was blind to the previous diagnoses in the reports. Repeated blind check was performed by another pathologist only if there was a large difference between two previous diagnoses. Final decision was made by all the previous diagnoses. To evaluate prognostic significance, Lauren classification was used.

Classifications

Topography: For esophageal cancer, location of the lesion classified as superior or esophageal upper (EUT: first 15-21 centimeters from dental arch), esophageal middle (EMT: 22-31 centimeters), inferior or esophageal lower (ELT: 32-41 centimeters), esophageal lower end (ELE: only for adenocarcinoma of lower end of esophagus), and unknown or esophageal not otherwise specified (ENOS).

For gastric cancer, location of the tumor was defined as GC (cardia), GF and B (fundus or body or both), GDIS (pylorus or antrum or both), overlap locations (GM1: cardia-fundus and body, GM2: fundus and body-distal (without cardia), GM3: total gastric (cardia, fundus and body, distal)), and Gastric Not Otherwise Specified or unknown (GNOS). GR is standing for relapse.

Morphology: There are two main categories of malignancies in the upper gastrointestinal tract: common and certain carcinoma and uncertain carcinoma.

Common carcinomas are dividing to adenocarcinoma (AC) and squamous cell carcinoma (SCC). There are four types of AC: intestinal, diffuse, mixed and non specified AC (ANOS) (Nagini, 2012).

SCC is dividing to four categories based on the grade of differentiation: squamous well differentiated (SWD), squamous moderately differentiated (SMD), squamous poorly differentiated (SPD), and squamous not otherwise specified (SNOS).

Uncertain carcinoma are poorly differentiated carcinoma (CPD) that could be either poorly differentiated AC, poorly differentiated SCC, carcinoma not otherwise specified (CNOS), or epithelial differentiation but with doubt on glandular differentiation.

Statistical analysis

PASW Statistics 18.0 software (IBM Corporation, release 2009) were used for statistical analyses. Descriptive statistical methods (frequency, mean±standard deviation, crosstabulation, and median) were used for describing data and somer's d statistic was used to find out any specific directional measure and trend during the time. Chi square test, independent samples t-test and analysis of variance (ANOVA) were performed to explore relationship between different categorical and numerical variables.

Results

Throughout the study, 1134 biopsy samples were reported as malignant tumors and studied in two different groups: group 1: esophageal (405, 35.7%), and group 2: gastric cancers (729, 64.3%). The results showed the highest cumulative incidence rate in the first period of study (1989-94, 29.6%) for both groups, but no significant statistical difference was seen in frequency of esophageal and gastric tumors throughout the study. Figure 1 shows trend of registered patients of esophageal and gastric tumors.

Demography

The mean age for all patients was 65.4±12.1 with a median of 67 years. The mean age were changed throughout the study, started from 62.1±12.6 in the first five years and had reached to 67.8±11.8 in the last. The difference between periods was statistically significant ($p<0.001$) and in a post-hoc analysis, the mean age in the first five years was different from all next three periods ($p=0.002$, <0.001, and <0.001).

Male patients (794 cases, 70%) had a large predominance (Sex ratio=2.33/1). Men had a higher age than women (66.3±11.5 vs. 63.2±13.3) and there was a significant difference between two sexes ($p<0.001$).

Esophagus- The mean age in group 1 was 66.3±11.8 and median was 68 years. The youngest and oldest patients were 27 and 100 years old. In group 1, there were 245 (60.5%) male cases with higher rate of esophageal tumors (60.5%). Sex ratio was 1.53.

Stomach- The mean age in group 2 was 64.8±12.3 and showed a statistically significant difference from group 1 ($p=0.049$) and the median was 66 years. The youngest and oldest patients of gastric cancer were 9 (a case of malignant lymphoma) and 93. In group 2, a greater

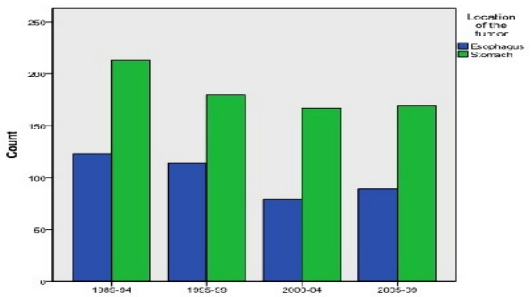

Figure 1. Trend of Registered Patients of Esophageal and Gastric Tumors

male predominance was seen (549, 75.3%) with higher rate of gastric tumors (75.3%). Sex ratio was 3.04 and in both sexes gastric tumors were more common although frequency of esophageal and gastric tumors were close in females (52.9% and 47.1% in women vs. 69.1% and 30.9% in men). Overall, we found a significant difference between two sexes at the location of the tumor (p<0.001).

Topography

Topographic studies displayed that tumors of 729 cases (64.3%) were belonged to stomach and 405 (35.7%) to esophagus. Based on pathological assessment, we could not certify the topographic site of tumor in more than a half of samples.

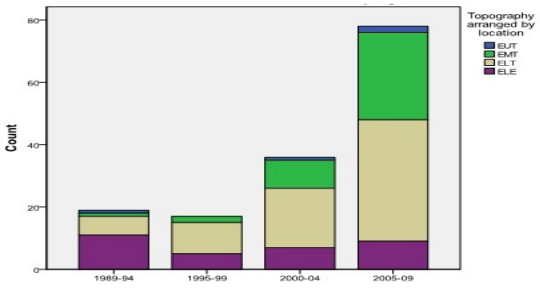

Figure 2. Trend of Changes in Topographic Sites for Esophageal Tumors

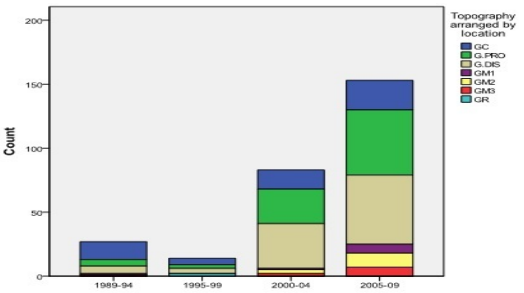

Figure 3. Trend of Changes in Topographic Sites for Gastric Tumors

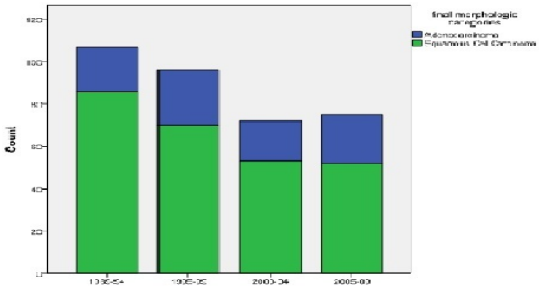

Figure 4. Trend of Main Types of Esophageal Carcinomas

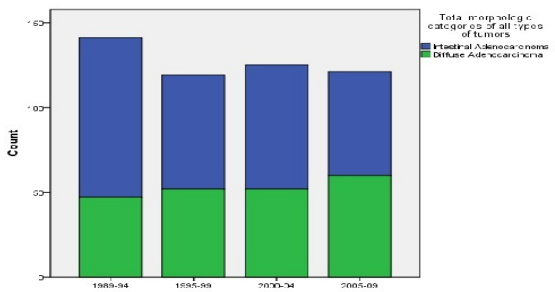

Figure 5. Trend of Changes in Main Types of Gastric AC

ELT was common topographic site for esophageal tumors in men (54.5%) whereas EMT was common (40.8%) in females and difference was significant between two sexes (p=0.037). In gastric tumors, common topographic site was GDIS in both sexes (32.1% and 47.7%).

Our results showed that ELE was common topographic site of tumors in the first five years of the study (57.9%) and ELT was common in three next intervals and the 20 years trend was significantly different between topographic sites (p<0.001). Figure 2 shows the trends of changes in different topographical sites of esophageal tumors.

Among gastric cancers, GC was common in first and second periods of study (51.9, and 35.7%) and GDIS was common in third and forth (42.2, and 35.3%). The trends were significantly different (p=0.008). Figure 3 shows the trends of changes in topographical sites of gastric tumors.

Morphology

Morphology results displayed that AC was common upper GI tract tumor (60.9%). Alternatively, SCC (23.1%), uncertain carcinomas (10.5%), and other tumors (4.8%) were associated to upper GI. Two main types of AC (intestinal and diffuse) were responsible for more than a half of all tumors (51.7%) and intestinal type was common carcinoma (30.6%).

Esophagus- Among esophageal tumors, SCC was common tumors (64.4%) and SMD was common subtype of SCC (35.8%). AC were responsible for near one

Table 1. Frequency of Different Topographic Sites for Esophageal Tumors

	Frequency	%	Percent within certain topographical sites	Percentage based on anatomic region
EUT	4	1.0	2.7	2.7
EMT	40	9.9	26.7	26.7
ELT	74	18.3	49.3	70.6
ELE	32	7.9	21.3	
ENOS	255	63.0		
Total	405	100.0	100.0	100.0

*EUT: esophagus, upper third; EMT: esophagus, middle third; ELT: esophagus, lower third; ELE: esophagus, lower end; ENOS: Esophagus, not otherwise specified

Table 2. Frequency of Different Topographic Sites for Gastric Tumors

		Frequency	%	Percent within certain topographical sites	Percentage based on anatomic region	
Total proximal	GCardia	57	7.8	20.7	55.3	
	GF and B	86	11.8	31.3		
	GM1	9	1.2	3.3		
Distal	GDIStal	99	13.6	36.0	36.0	
Distal+proximal	GM2	14	1.9	5.1	8.7	
	GM3	10	1.4	3.6		
GR		2	0.3			
GNOS		452	62.0			
Total		729	100.0	100.0	100.0	

*Gcardia: gastric, cardia region; GF and B: gastric, fundus and body; GM1: gastric, cardia-fundus and body; GM2: gastric, fundus and body-distal (without cardia); GM3: total gastric (cardia, fundus and body, distal); GNOS: gastric not Otherwise specified; GR: gastric, relapsed

Table 3. Morphology of All Tumors (total, gastric and esophageal) Based on Biopsies

Type	Sub-type	Count	Percent of total	Esophageal	% of esophageal tumors	Gastric	% of gastric tumors
Intestinal AC	AI	347	30.6%	52	12.8%	295	40.4%
Diffuse AC	AD	238	21.1%	27	6.7%	211	29.0%
mixed diffuse and intestinal AC	ADI	33	2.9%	4	1.0%	29	4.0%
Not specified AC	ANOS	72	6.3%	6	1.5%	66	9.1%
Total adenocarcinoma		690	60.9%	89	22%	601	82.5%
Squamous cell carcinoma (SCC)	SNOS	20	1.8%	20	4.9%		
	SWD	43	3.8%	43	10.6%		
	SMD	145	12.8%	145	35.8%		
	SPD	53	4.7%	53	13.1%		
Total SCC		261	23.1%	261	64.4%		
Uncertain carcinoma		120	10.5%	41	10.2%	79	10.9%
Other tumors		55	4.8%	14	3.4%	41	5.5%
Missing		8	0.7%	-	-	8	1.1%
Total		1134	100%	405	100%	729	100%

*AC: Adenocarcinoma; AI: adenocarcinoma, intestinal type; AD: adenocarcinoma, diffuse type; ADI: adenocarcinoma, mixed intestinal and diffuse types; ANOS: adenocarcinoma, not otherwise specified; SNOS: squamous cell carcinoma, not otherwise specified; SWD: squamous cell carcinoma, well differentiated; SMD: squamous cell carcinoma, moderately differentiated; SPD: squamous cell carcinoma, poorly differentiated

fourth (22%) of esophageal tumors. Most of esophageal carcinomas were belonged to male patients (77.5% for AC and 55.2% for SCC) but results from SCC suggested that male and female patients consist of 67.6% and 85.4% cases respectively. Statistical analysis showed a significant difference between sexes ($p<0.001$). The mean age of AC and SCC was 65.7±11.9 and 66.2±11.7 and the difference was not statistically significant. The mean age of well differentiated SCC was the highest among specified SCC tumors 68.1±12.0.

Common morphology for esophageal tumors was SMD (74, 30.2% for men and 71, 44.4% for women).

Trend of AC was increased throughout the study from 57.2% in the first five-year period to 66.9% in the last whereas SCC was decreased from 25.2% to 20.2% and changes was significant throughout the study ($p=0.007$, Figure 4). However, the incidence rate of SWD tumors showed an increase from 9.3% in first five years to 25% in the last. SMD was decreased from 62.8% to 51.9%, but the trend of changes was not significant.

Stomach- Within all gastric tumors, AC was responsible for 82.5%. The common AC was intestinal (40.4%) and diffused type (29.0%). Well differentiated intestinal AC was common subtype of intestinal (14.5%). Among gastric AC, intestinal type had a higher age (67.2±10.1 vs. 63.5±13.4) and the difference between two types (intestinal and diffuse) was significant ($p=0.001$). Intestinal AC was common morphologic type (347, 30.8%) and in male patients AI was common (269, 34.1%). In females squamous cell carcinoma had the highest frequency (117, 44.8%). Among gastric tumors, the highest incidence rate was AIW (106, 14.7%) while in esophageal tumors, moderately differentiated squamous cell carcinoma was common (145, 35.8%). In both sexes, AC was common gastric tumors (85.8% in male vs. 85.9% in female) and among subtypes of gastric AC, intestinal type was the highest in both sexes (43.1% in male vs. 35.9% in female) and AIW was common type. Within subtypes of diffuse AC, signet ring cell carcinoma was common type after not otherwise specified in both sexes (28.2% in men vs. 27.3% in women).

When trends of the two main types of gastric AC (AI and AD) were assessed, intestinal type was changed from 66.7% to 50.4% (versus change from 33.3% to 49.6% for diffuse AC) and these changes were significant ($p=0.013$, Figure 5). The trend of changes in frequency of signet ring cell subtype was not significant (Even after combining all categories with signet ring cell in tumor).

Discussion

Esophagus, a recent report from an adjacent province in Iran has shown similar age status and sex ratio that confirms our results (Mansour-Ghanaei et al., 2012). In agreement with previous studies (Kumar, 2007; Bennett and Goldblum, 2009), our result explained that SCC was common esophageal cancer in both sexes and mostly had moderate degree of differentiation but AC was observed mostly in male sex in compatible with other studies (Botterweck et al., 2000). The highest incidence rate of SCC in esophagus, were observed in the middle third (Kumar, 2007; Bennett and Goldblum, 2009; Yahyapour et al., 2012) and in our study, most of esophageal cancers in female were seen in the middle while lower third was the most common site in male. This difference might be related to higher incidence rate of AC in male and its location that made it predominant. This finding is compatible with previous study (Newnham et al., 2003) and a recent one from Iran (Mansour-Ghanaei et al., 2012). Our observation showed that AC of lower end of esophagus was considered as a lower third tumor, thus it is the most common location for cancer. This finding is also similar to other study (Bafandeh et al., 2006) but our study was performed based on a retrospective revision of files so it is possible to have some difficulties about distinguishing between lower esophageal end and cardiac tumors.

Proportion of SCC and AC among all esophageal cancers widely varies in different studies from different countries. While we found a ratio of 2/1 for SCC/AC and SCC has majority of tumors in some other reports too (from Japan (26/1) (Shibata et al., 2008) and Iran (4/1) (Mansour-Ghanaei et al., 2012)), in the US, SCC

and AC are equal and even a higher rate of AC in recent decades has been recorded (Kumar, 2007; Bennett and Goldblum, 2009).

Several line of studies have shown a decrease in proportion of SCC in recent decades (Devesa et al., 1998; Botterweck et al., 2000; Makhdoomi et al., 2005; Aragones et al., 2010; Gopala Krishnappa et al., 2013) but the severity varied between different countries (Triboulet and Mariette, 2008). In Japan there wasn't any change (Shibata et al., 2008). Some parts of north of Iran (Golestan province) located in the worldwide belt of esophageal cancer. According to cancer registry report on 2006, we have had 90% SCC among all esophageal cancers in Golestan province. Similar study was performed from Tabriz province (in northwest of Iran) (Bafandeh et al., 2006). In our study in Qazvin province (one of central provinces of Iran), this rate was 64% which was closed to the results obtained from Tabriz province (Bafandeh et al., 2006). This finding suggested that the proportion of SCC among all esophageal cancers is related to its prevalence. Therefore in case of a lower rate of esophageal cancer, the proportion of SCC was decreased. To find out these changes in pathological pattern, risk factors frequency like decrease in smoking (result in lower rate of SCC or rising AC due to more gastroesophageal reflux) and Barrett's esophagus rates (result of obesity or anti-H.pylori treatments, deletion of an inhibiting factor on AC of lower end of esophagus) need to be considered. Interestingly, there are some evidences to suggest that H.pylori infection may protect to develop gastroesophageal reflux disease (GERD) and its complications but this idea is still controversial (Kumar, 2007; Bennett and Goldblum, 2009). Mean age of patients in our study was similar to previous studies (Bafandeh et al., 2006, Kumar, 2007). In addition, our results suggested that sex ratio was 1.53 which is more than study performed in Tabriz province (Bafandeh et al., 2006).

Stomach, in the present study, the mean age of patients was about 65 years old which was less than Chinese study (Zhou et al., 2008) and another report from Iran (Aghaei et al., 2013) but similar to some other studies and references (Kumar, 2007; Lauwers, 2009; Babaei et al., 2010; Rampazzo et al., 2012; Rodríguez-Vargas, 2013). In Iran, a study from Khuzestan province (in south of the country) showed a mean age of 60 years (Hajiani et al., 2006) subsequently a study from a referral center in Tehran showed mean age of 56 years (Abdi-Rad et al., 2006). The result obtained from later study showed a large difference from our study. We suggested that one reason for these differences could be the variation in the method of sampling. In our study, samples were provided through endoscopic biopsy but the method of sampling in center of Tehran (Abdi-Rad et al., 2006) was surgery. Considering an average of 10 months survival for patients of gastric cancer in Iran (Sadighi et al., 2005), we assumed that many cases of higher age didn't enter to the study.

Sex ratio in our study was higher than some other studies (Newnham et al., 2003; Hajiani et al., 2006; Mousavi and Somi, 2009; Rampazzo et al., 2012; Aghaei et al., 2013; Rodríguez-Vargas, 2013) and what has been reported in Global Cancer Statistics (Jemal et al., 2011). In addition, increasing in mean age of patients during the term of the study was similar to other studies (Popielaet al., 2002; Zhou et al., 2008).

Morphology, result obtained from morphological study showed that common morphologic gastric cancer was AC and predominance of intestinal type. Our study was similar to the other studies, (Zhou et al., 2008; Mousavi and Somi, 2009; Babaei et al., 2010; Rampazzo et al., 2012; Rodríguez-Vargas, 2013).

We found a gradual decrease in the ratio of intestinal/diffuse types of AC result from widespread treatment following decrease in gastritis due to H.pylori (as a risk factor for intestinal type of gastric adenocarcinoma) in recent decades. Also, we found an increase in proportion of diffuse type during the term of study which wasn't applicable to signet ring type. In other words, rising in proportion of diffuse type was not due to an increase in proportion of signet ring type. These findings were in contrast to some studies but similar to some reports (Kaneko and Yoshimura, 2001; Henson et al., 2004).

Topography, although the topographic distribution of gastric cancer throughout the study was compatible with reference books (Kumar, 2007; Lauwers, 2009) there were some differences at frequency and topography of gastric cancer with domestic and abroad studies.

For example, gastric cancer in north of Iran is 5 folds more frequent than south (Mousavi and Somi, 2009) and in Ardebil province (that has the highest rate of gastric cancer in Iran (Babaei et al., 2010)) the rate of cardiac cancer is 3 folds more than other regions of the country.

In our study, topographic distribution of gastric cancer showed a large difference with result obtained from Ardebil province (with a higher rate of cardiac tumor, Babaei et al., 2010) and was more compatible with Khuzestan province (with a higher rate of distal tumors, Mousavi and Somi, 2009).

On the other hand, the rate of cardiac cancer in present study was lower than some studies from the US, UK, European countries (Babaei et al., 2010), and China (Zhou et al., 2008) with topographical location more than 30% of all gastric cancers. In contrast, the rate of cardiac cancer in other reports was less than ours including studies from Japan, Korea, and South America with a rate of 10% (Babaei et al., 2010) and from Brazil with 14.3% (Rampazzo et al. 2012). Because there are a few western pattern of topography of gastric cancer, thus the trend overall might be reverse. In some other studies, mostly from Asia, the trend is similar to our study and there is no trend of migration to cardia, maybe due to traditional eastern nutritional habits (Lee et al., 2003; Makhdoomi et al., 2005).

One possible interpretation for this migration is a change in topographic classification and its defects in the studies. Decrease in defects of the reports of topographical classification is associated with more report of cardiac tumors.

In a study from UK in 1998, more than ¾ of gastric cancers had specific morphology with unknown subtypes in more than 50% of cases (Newnham et al., 2003). In addition, a large percentage of gastric cancers in registries in past decades didn't have histological confirmation and

increasing diagnosis of cardiac tumor has showed an association with rising in histological confirmation (Islami et al., 2004; Aragones et al., 2010). Another possible explanation might be a more tendency in reporting cardiac tumors. In past decades, pathologists didn't mention to separate cardiac tumors from other parts of the stomach. Indeed, an independent code for cardiac tumors was used since 1970 in Europe although there wasn't a consensus in determination of anatomical location of cardia until 1999 (Aragones et al., 2010).

One important suggestion that need to be considered in morphological and topographic changes would be error due to investigation criteria. For example, study from Golestan province on 1969-71 (Islami et al., 2004) showed the ratio of esophageal /gastric cancer was estimated about 8/1 but in another study on 2001 (Islami et al., 2004) it was estimated about 2/1.

This notable change might be result of changing in the technique of diagnosis because endoscopy had not been used in the older study and it's possible to diagnose many of cardiac tumors as esophageal cancer (due to dysphagia) (Islami et al., 2004).

In another study from Iran (Abdi-Rad et al., 2006) researchers showed a trend of increasing of proximal tumors and the trend was more obvious in lower ages. In our study, the mean age was about 10 years more than above study. This could be a possible explanation for our results that showed no significant trend toward proximal tumors. Pivotal role of endoscopy in diagnosis of tumors is a key to interpret age and topography changes in our study.

Samples in our study were enrolled from archive of pathology ward of Bou-Ali Sina (Avicenna) hospital that has found out as the first endoscopy and pathology centre in the city.

Throughout the study, ratio of diffuse/intestinal type and mean age of gastric cancer has been increased but mean age of cases with diffuse type was lower than intestinal.

One possible explanation for this diversity might be involving younger and more symptomatic patients for endoscopy and when gradually the technique became more popular, older and less symptomatic patient underwent endoscopy. With above statement, we can explain a predominance of cardiac cancer compared to all types of gastric cancers because it is more symptomatic (Islami et al., 2004; Kumar, 2007).

Although there was no trend of proximal migration of the gastric cancer, with focusing on the last two five years period of the study, we might find a reduction in the percentage of distal areas from 42.5 to 35.3 due to fewer defects in topographic determination.

Limitations, we had a few cases of exclusion due to either failure to find blocks or conflict in definitive diagnosis of malignancy (8 cases). Morphological determination based on WHO classification was difficult in some cases (or sometimes impossible) because of endoscopic origination of samples. Although that was not a serious problem to validity of data because Lauren's classification is more common todays.

In some samples, differentiations between intestinal and diffuse types, diffuse type and malignant lymphoma were not possible due to inadequate amount of sample or necrosis and lack of IHC staining. Altogether, these discrepancies were not notable to affect results of the study.

In conclusion, morphological changes and types of the tumors in the present study were mostly similar to others reports. A single morphological classification for all samples was one of the strengths of this study in contrast with registry-based studies such a classification neither unchangingly exists nor does not exist.

Morphological study of esophageal and gastric cancers showed similar changes to other studies. Morphological trends (increasing esophageal adenocarcinoma and diffuse/intestinal ratio in stomach cancer) could be a result of changing in nutritional habits or H.pylori treatment. Male/female ratio in gastric cancer and AC of esophagus in this study was more than other studies (may be due to difference in risk factors).

Topography of gastric cancer in our study was compatible to the studies from low incidence regions (domestic or abroad) like southern areas of the country but cardiac involvement was not so high. We couldn't find a topographical trend toward cardia that could be a real or fake result. It's important to consider the roles of diagnostic criteria, type of sample for pathological diagnosis (endoscopic or surgical) and the popularity of using endoscopic procedures in the society as some determinants in epidemiological and topographical changes of cancers. In addition, it seems that there's a relationship between topographical changes of esophageal and gastric cancers with the frequency of disease in a geographical area.

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