Demographic and Histological Predictors of Survival in Patients With Gastric and Esophageal Carcinoma

Running title: Survival Rate in Patients with Gastric and Esophageal Carcinoma

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Implication for health policy/practice/research/medical education:

Gastric and esophageal cancers are heterogeneous diseases, but they share important features. They remain clinically asymptomatic until late in the disease process with consequent poor prognoses and high mortality rates. This study points to differences in disease characteristics and patient factors. Even so, the outcomes of these cancers are poor and improvements in diagnosis and management are urgently needed.

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Background:

Little is known about the possible influence of demographic and histological risk factors on the survival amongst patients with esophageal and gastric cancer. Based on available registry and follow-up information, this study compares 1-5 year survival rate of gastric and esophageal cancer.

Objectives:

This study compares 1-5 year survival rate of gastric and esophageal cancer.

Patients and Methods:

Through a concurrent (prospective) cohort study, all 366 patients with definite diagnosis of esophageal and gastric cancer who had been hospitalized at the Towhid Hospital, Sanandaj city, Kurdistan province western Iran during a five-year period from 2006 onwardS were recruited. The survival time of patients stratified by this grouping method were analyzed by Kaplan-Meier analysis and Cox regression.

Results:

Amongst 366 patients, 23 had esophageal adenocarcinoma, 94 esophageal squamous-cell carcinoma and 239 had gastric adenocarcinoma. Age at diagnosis ($P = < 0.001$) and tumor grad ($P = 0.008$), practice treatment ($P = < 0.001$) had significant association with the survival rates variation in patients with esophageal but not with gastric cancer patients. The five-year survival rates (by year) in esophageal cancer were 49%, 27%, 24%, 22% and 19%, respectively and in gastric cancer were 41%, 17%, 13%, 10% and 5.4%, respectively.

Conclusions:

Major differences between these cancers were seen in the survival rates of patients and the incidence classified by sex. Ages at diagnosis, histological types were prognostic factors for survival in patients with esophageal cancer and no in gastric cancer.

Key words:

Gastric Cancer; Esophageal Cancer; Histological Factor; Demographic Factor; Survival

1. Background

Gastric cancer remains a major cause of cancer mortality. Since last decades, gastric cancer mortality rate has decreased globally (1). However, still remains major public health concern with a poor prognosis and a high mortality (2). In contrast, the incidence of esophageal cancer is increasing (3). In the United States, the incidence of esophageal cancer has shown a six-fold rise caused by increasing the incidence of esophageal adenocarcinoma (4). In Europe there has also been an increase in the incidence of esophageal adenocarcinoma in men, but not in women (5). A similar pattern has already been found in Iran (6). The disease is highly lethal, with overall five-year survival rates less than 10%. The high mortality is due to the late onset of symptoms (7). In Ardabil province 2007, one- and five-years survival rates in patients with upper gastrointestinal cancer were 40.5% and 0.8% respectively (8). Geographic variation and temporal trends in the epidemiology of esophageal and gastric cancers vary according to tumor morphology and organ subsite. Geographic variations in IR Iran show that incidence and mortality of upper GI (Gastrointestinal) cancers is higher in West and North West regions and in the Kurdistan province in particular (9).

2. Ojbectives

Based on available registry and follow-up information, this study compares 1-5 year survival rate of gastric and esophageal cancer.

3. Patients and Methods

23.1. Source of Data

Data were sourced mainly from the patient reports of pathology laboratories and hospital database record. Through a concurrent (prospective) study using censes method; all eligible patients with upper GI cancers (134 esophagus, and 249 gastric cancer) who had been

hospitalized at the Towhid Hospital, Sanandaj city, Kurdistan province western IR Iran were recruited. Inclusion criteria were patients with definite diagnosis of upper GI cancer during a five-year period from 2006 onward. Samples were coded under the direct supervision of clinical pathologists according to the International Classification of Diseases for Oncology (10). Clinical data such as practice treatment were obtained through a structured questionnaire and the patients' clinical records. Vital status and date of death were determined through the by official death certificates, with a maximum follow-up of 90 months. Survival time (in months) was calculated from the date of diagnosis through the date of death or last follow-up. A failure was defined as death by any cause during the follow-up period and patients alive at the end of the follow-up period were censored. Overall, 17 patients were excluded from the analyses according to exclusion criteria (8 patients lost to follow-up, 9 illegible data, and 3 patients due to migration). Overall, 366 (127 esophagus, and 239 gastric cancer) patients were enrolled. Clinical and pathologic variables, which were sub-layered into age, gender, setting, histological type of tumor and practice treatment were entered into parametric regression models (by considering and not considering heterogeneity) for multivariate analysis in order to assess the relationships between the characteristics and prognostic factors for survivors. The present study was approved (Code No: 91002, Date: 22.08.2012) by the Ilam University of Medical Sciences, Ethics Committee on considering of publication data result in general.

3.2. Statistical Analysis

The Kaplan Meier and Log rank statistic methods were used to compare survival rates in different subgroups. Using life table, survival rates and survival density function was assessed at year intervals. The Breslow (Generalized wilcoxon) statistics was used to compare median survival time in three age groups. The Cox hazards regression analysis was also used to

investigate the effect of the variables and adjusting the effect of demographical and pathological variables on survival. The Graphical (diagram Log (S) t vs. time) and analytical (Time-Varying covariate) methods was applied to test the appropriateness of Cox's proportional hazard (11). The Multiple Cox regression analysis was used to identify independent predictors for patient survival using a backward stepwise approach with an entry limit of $P < 0.1$ and a removal limit of $P < 0.05$. The survival time of patients stratified by this grouping method were analyzed by the Kaplan-Meier analysis and Cox regression as described earlier. T tests, chi-square tests and Fisher's exact test were used to compare patient characteristics and tumor factors between the populations. All statistical analyses were performed using SPSS16.0.

4. Results

Out of the 366 study patients, 23 (18.1%) were diagnosed with esophageal adenocarcinoma (AC), 94 patients (74.0%) with esophageal squamous- cell carcinoma (SCC) and 239 with gastric cancer. Adenocarcinoma intestinal type was the predominant histological type of gastric tumor129 (54%). Mean age ± standard deviation (SD) at diagnosis in patients with gastric cancer was 68.8 ± 11.97 years and 65.38 ± 11.62 in esophageal cancer (P = < 0.01) (Table 1).

Table 1. Characteristic of the Patients With Gastric and Esophageal Cancers

Factors	Gastric Cancer, No (%)	Esophageal Cancer, No (%)
Gender		
Male	178 (74.5)	70 (55.1)
Female	61 (25.5)	57 (44.9)
Age		
45 >	9 (3.8)	11 (8.7)
46-65	90 (37.7)	54 (42.5)
66 <	139 (58.8)	42 (48.8)
Setting		
City	120 (50.2)	82 (64.6)
Village	119 (49.8)	45 (35.4)
Histological type [a]		

AC/Intestinal	129 (54.0)	23 (18.1)
SCC/Diffuse	84 (35.1)	94 (74.0)
Other	26 (10.9)	10 (7.9)
Histology grade		
Poor	28 (11.8)	16 (12.6)
Moderate	25 (10.5)	35 (27.6)
Well	31 (13.0)	42 (48.8)
No difference	154 (64.4)	14 (11.0)
Practice treatment		
Surgery	19 (12.7)	15 (11.8)
Chemotropic	53 (35.3)	30 (23.6)
Radiotherapy	4 (1.7)	7 (5.5)

[a] Esophageal cancer (Adenocarcinoma type (AC), squamous- cell carcinoma type (SCC) and other (unknown type)); Gastric cancer (Intestinal type, Diffuse type and other (unknown type))

A majority of patients were male and older than 65 years in gastric cancer and 46-65 years age group in esophageal cancer. The median ± (SD) survival rate for patients with esophageal cancer was $10.0 ± 1.05$ months and for those with gastric cancer were $11 ± 0.46$ months. In those with esophageal cancer, patients with the histopathology of "SCC" had the lowest survival rate (median: 7 months); other cases lived more than 13 months after the diagnosis. Selected characteristics of the patients are shown in (Table 2 and 3).

Table 2. Median of Survival of the Patients With Esophageal Cancer

Factors	Median of Survival, (CI 95%)	P value
Gender		
Male	10 (7.97 - 12.03)	0.480
Female	12 (6.46 - 17.54)	
Age		
45 >	25 (10.94 - 31.33)	< 0.001
46 - 65	18 (10.94 - 25.06)	
66 <	6 (4.6 - 7.4)	
Setting		
City	10 (8.05 - 11.95)	0.148
Village	14 (10.05 - 17.95)	

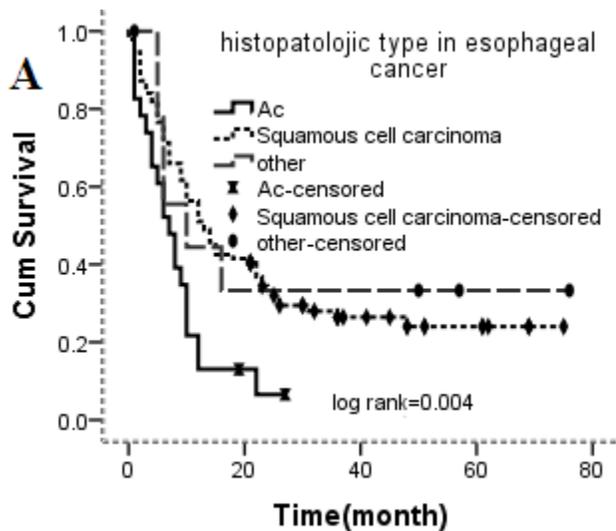| Histological type [a]		
AC	7 (4.18 - 9.82)	
SCC	13 (9.34 - 16.66)	< 0.001
Other	10 (7.93 - 12.07)	
Histology grade		
Poor	7 (1.12 - 12.88)	
Moderate	22 (6.06 - 37.94)	
Well	9 (6.80 - 11.20)	0.008
No difference	12 (7.41 - 16.59)	
Practice treatment		
Surgery	12 (4.42 - 19.57)	
Chemotropic	5 (3.92 - 6.07)	< 0.001
Radiotherapy	5 (2.91 - 7.09)	

[a] Adenocarcinoma type (AC), squamous- cell carcinoma type (SCC) and other (unknown type)

**Table 3.** Median of Survival of the Patients With Gastric Cancer

Factors	Median of Survival, (CI 95%)	P value
Gender		
Male	11 (9.54 - 12.06)	0.361
Female	13 (11.46 - 14.86)	
Age		
45 >	12 (7.98 - 16.02)	
46 - 65	12 (8.54 - 16.46)	0.220
66 <	10 (8.71 - 11.29)	
Setting		
City	11 (9.47 - 12.53)	0.198
Village	10 (10.08 - 11.92)	
Histological type		
Intestinal	11 (9.82 - 12.18)	
diffuse	13 (11.21 - 14.79)	0.611
Other	10 (9.19 - 10.81)	
Histology grade		
Poor	10 (7.06 - 12.94)	
Moderate	16 (13.94 - 8.06)	
Well	13 (9.17 - 16.83)	0.309
No difference	11 (10.09 - 11.91)	
Practice treatment		
Surgery	12 (8.90 - 15.10)	
Chemotropic	9 (6.48 - 15.52)	0.367
Radiotherapy	7 (4.45 - 9.55)	

Gender and setting of patients had no significant effects on survival rate variation in univariate analysis in both cancers. Age at diagnosis (P = < 0.001), practice treatment (P = < 0.001), histology grad (P = 0.008) and tumor histology (P = 0.004) were significant association on the survival rates variation in patients with esophageal and no significant association in gastric cancer patients (Figure 1).
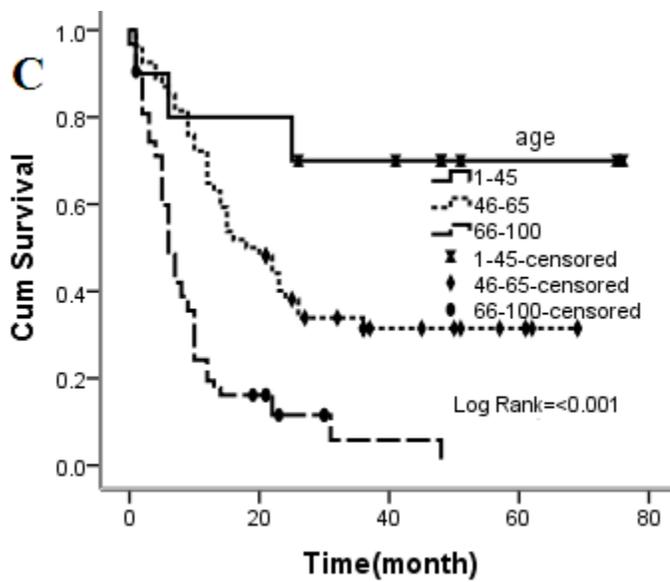
Figure 1 The Associations Between Demographic and Histological Factors and Survival in Esophageal and Gastric Cancer Patients
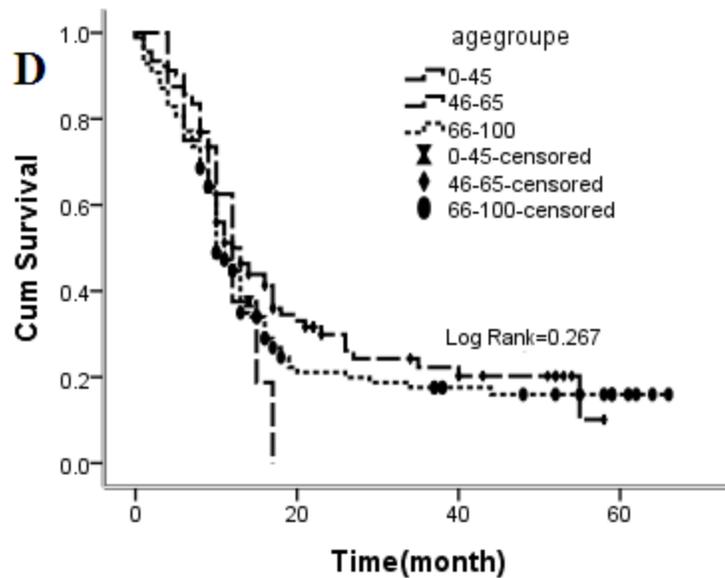

A) By Histological of Tumor in Esophageal Cancer
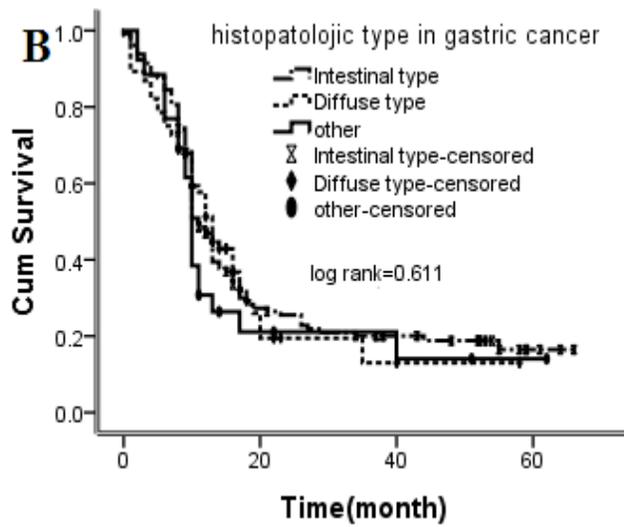
B) By Histological of Tumor in Gastric Cancer

C) By Age at Diagnosis in Esophageal Cancer

D) By Age at Diagnosis Gastric Cancer

Potential prognostic factors in patients with gastric cancer showed that tumor histology, histology grad, practice treatment gender, age, and place of residence on the prognosis was not significant in a multivariate model adjusted for follow-up time. For esophageal cancer Cox-regression analysis using demographic and histological factors 45 > year as reference revealed that patients whose 46-65 year at diagnosis (HR = 3.43, 95%, CI = 1.03-11.41, P = 0.044), 66 < year (HR = 9.78, 95% CI = 2.93-32.64, P = < 0.001) had an increased risk for disease progression and death. Cox-regression analysis for poorly grade as reference revealed that patients whose tumors with moderately differentiate (HR = 0.52, 95%, CI = 0.25 - 1.07, P = 0.078), well differentiate (HR = 0.98, 95%, CI = 0.51-1.85, P = 0.951) had a decreased risk for death from esophagus cancer. Cox regression coefficient (β) analysis shows patient with tumor locate in middle of esophageal (β = -0.91) and upper of esophageal (β = -0.13) have lower death rates compression to tumors that located in lower of esophagus. Similar results were obtained for tumor grade (Table 4).

Table 4. Multivariate Cox Regression Analyses for Patients With Esophageal Cancer

Characteristics	β	HR (95% CI)	P value
Age	-	overall	< 0.001
45 >	reference	1	reference
46 - 65	1.23	3.43 (1.03-11.41)	0.044
< 65	2.28	9.78 (2.93-32.64)	< 0.001
Histology grade	-	overall	0.085
Poor	reference	1	reference
Moderate	-0.64	0.52 (0.25-1.07)	0.078
Well	-0.02	0.98 (0.51-1.85)	0.951
Location of tumor	-	overall	0.009
Lower	reference	1	reference
Middle	-0.91	0.40 (0.22-0.73)	0.003
Upper	-0.13	0.53 (0.33-0.85)	0.009

The five-year survival rates (by year) in esophageal cancer were 49%, 27%, 24%, 22% and 19% respectively and in gastric cancer were 41%, 17%, 13%, 10% and 5.4% respectively (Figure 2).
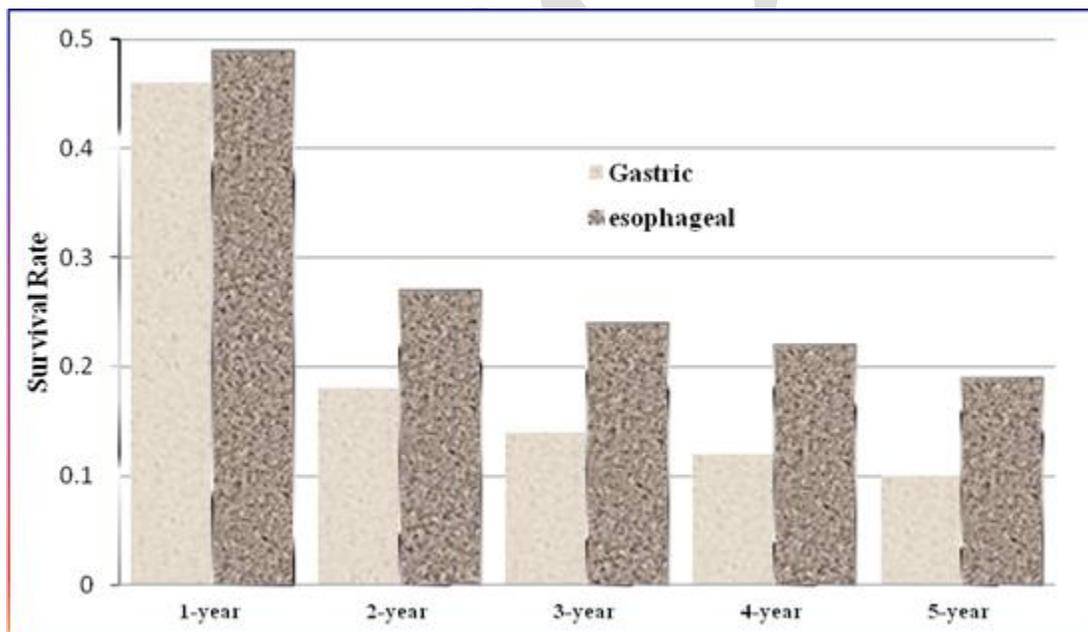
Figure 2. 1 - 5 Year Survival Rates of Gastric and Esophageal Cancer

Figure 2 shows that patients with esophageal cancer had a better survival than those with gastric cancer (P = 0.305). Overall one-year survival in the cases of esophageal cancer included in the present study was 49.0%, with survival rates being higher in the group of women compared to the men (19.7% versus 13.8%) (P = 0.48). Similar results were obtained for patient with gastric cancer (Table 5).

Table 5. 1 - 5 Year Survival Rates of Gastric and Esophageal Cancer Related to Demographic and Histological Factors

Survival Variables Cancer		Survival rates, (%)					Med Tim Survival By Month
		1-year	2-year	3 -year	4-year	5-year	
Gastric	Gender						
	Male	45.1	18.2	13.5	12.6	7.3	11.56
	Female	48.2	21.3	19.7	15.6	15.6	11.90
	Age						
	45 >	62.3	46.7	24.2	18.1	13.3	15.00
	46-65	49.3	24.3	17.2	15.3	12.1	12.62
	66 <	43.4	17.1	14.2	11.3	8.5	11.08
	Histological type						
	Intestinal	47.3	23.3	18.1	16.3	12.5	11.59
	Diffuse	50.5	7.1	4.0	4.0	4.0	13.78
Esophageal	**Gender**				19.5		
	Male	46.2	23.3	19.5		13.7	11.27
	Female	52.3	29.7	24.1	19.0	19.0	13.45
	Age						
	45 >	80.2	80.2	68.3	68.3	68.3	60.0
	46 - 65	72.1	38.5	31.1	27.2	27.2	20.25
	66 <	24.5	8.3	4.2	4.2	0.0	7.98
	Histological type						
	AC	21.2	19.2	5.1	1.2	0.0	7.67
	SCC	56.2	32.1	25.5	22.0	19.0	15.43

5. Discussion

Geographic variability in prognosis of gastric cancer patients has been well documented (12, 13). The minimum and maximum survival rates have been reported in European countries and East Asia respectively (14). Similarly, the five-year survival rates for gastric cancer vary from 10% to 55% worldwide (15). In IR Iran the prognosis of patients with gastric cancers remains poor (9, 14) As a result, both diseases are among the deadliest forms of cancer (16). In our study, the five-year overall survival rate for patients with esophageal cancer in this population (19%) is very poor and women had a better survival rate than men (0.345). This result agrees with a report from Europe (17). According to our data, there was significant difference in survival rates between patients with SCC and those with AC of the esophagus. These results are in contrast with studies in the United Kingdom (1987 to 2000) (18) and Germany (1982 to 2000) (19), which showed that AC has a more favorable prognosis than SCC in esophageal cancer patients. In general, esophageal cancer five-year survival (19%) was poor, but it was slightly better than that for gastric cancer (5.4%) (P = 0.361). These figures are different from those found in the countries such as England and South Korea (20, 21). Major differences between these cancers were seen in the survival rates of patients and the incidence classified by sex (Table 1). The present results showed that patients' gender had no significant impact on survival rate in both cancers. Median survival time for man and women for esophageal cancer was (10.0 ± 1.03) and (12.0 ± 2.83), respectively and for gastric cancer were (11.0 ± 0.53) and (13.0 ± 0.94), respectively. Sex was not an independent prognostic factor in either Chinese patients (p = 0.23) (22) or white patients living in the United States (P = 0.28) (23). Overall survival was significantly worse only in male white compared with Chinese patients (median survival time, 12.4 versus 14.5 months, respectively; P < .01) (22), But, some studies have found better survival rate for women (24).

For esophageal cancer; patients under age 45 had significantly better survival in unvarited analysis. The reasons for this are likely to include a combination of better general health, more effective response to treatment and earlier diagnosis in younger people overall. Differences in underlying tumor biology may also play a part. Previous report indicated better survival in young patients (22). On the other hand, some other studies have not same report (16). Cell histology is another tumor related factor that might affect patient survival. Our finding is in conformity with previous reports showed that better survival for AC of esophagus (25). In this study, the Lauren classification (based on tumor histology) did not have prognostic significance for five-year survival of gastric cancer patients in either population (log rank = 0.611). Treatment is likely to be the greatest determinant of cancer patients' survival. Surgical results in treatment of esophageal cancer have improved significantly over recent years, however. Medical centers now report that patients undergoing surgery alone have median survival rates between 13 and 19 months, 2-year survival rates between 35% and 42%, and 5-year survival rates of 15% to 24% (26), in present study in patients that surgery was only option to treatment median of survival and 4-year survival rate in esophageal cancer was (12 ± 3.86 month) and (% 21.3), respectively (P = < 0.001). In patient that radiation therapy was only option to treatment for esophageal and gastric cancer the mean survival rate was (5 ± 1.06 month) and (7 ± 1.29 month), respectively. Radiation therapy has been used in the past as a single-modality approach with curative intent. However, except for those with very early-stage disease, radiation has had little impact on long-term survival (27). Chemotherapy has been given preoperatively, postoperatively, or both median survival rates were (5 ± 0.548 month) for esophageal and (9 ± 1.28 month) for gastric cancer. Multimodality treatment approaches have evolved over recent years in response to the frequent loco regional and distant recurrences identified after surgery or radiation therapy alone.

The strength of the study was assured by the availability of homogeneous samples data with details of tumor histology and pathology, using Cox multiple to adjustment result variables on survival and calculation of five survival rates separately for sub-groups analysis. There are limitations with the present study in which the survival rate unable to predict future events for a particular person. Meanwhile, it was not possible to consider changes in characteristics after diagnosis, which may have affected survival. Hospital series often provide more optimistic data; there are challenges in interpreting registry information regarding the health care system in IR Iran. They are of limited value because of unavoidable selection bias, in particular in case selection and patient's characteristics. In conclusions, Gastric and esophageal cancers are heterogeneous diseases, but they share important features. They remain clinically asymptomatic until late in the disease process with consequent poor prognoses and high mortality rates. This study points to differences in disease characteristics and patient factors. Even so, the outcomes of these cancers are poor and improvements in diagnosis and management are urgently needed.

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