

Original Article

Survival Rate of Gastric and Esophageal Cancers in Ardabil Province, North-West of Iran

Fatemeh Samadi MD*, Masoud Babaei MD**, Abbas Yazdanbod MD**, Mahdi Fallah MD***,
Mehdi Nourai MD PhD*, Dariush Nasrollahzadeh MD*, Alireza Sadjadi MD*,
Mohammad-Hossein Derakhshan MD*, Behrooz Shokuhi MD**,
Robab Fuladi BSc*, Reza Malekzadeh MD*

Background: Upper gastrointestinal cancer is the most common cancer in Ardabil Province, North-West of Iran, accounting for more than 50% of all cancer deaths in this area. We conducted this study to determine the present survival rate of patients with esophageal and gastric cancers before launching interventional studies.

Methods: A prospective follow-up study of 420 biopsy-proven patients (127 females, mean age: 64) with upper gastrointestinal cancer (141 esophageal and 279 stomach cancers) who were initially diagnosed in Aras Clinic, the main gastrointestinal referral center of Ardabil Province, from 2000 through 2004, was performed with collection of data on demographics, tumor characteristics, pathologic stage, treatment methods, complications, survival time, etc. Data were gathered through direct interview with patients or their families in 303 cases and evaluation of death certificates in 55 patients. Follow-up was from cancer diagnosis until death, or immigration. Survival according to stage of disease, Lauren tumor type, tumor location, surgery, and adjuvant chemotherapy was analyzed, and results were compared with those of western series.

Results: Sixty-two cases were lost to follow-up. The one- and five-year survival rates in the patients with upper gastrointestinal cancer in Ardabil Province were 40.5%, and 0.8%, respectively. In the univariate analysis, men had a slightly lower survival rate than women ($P = 0.21$) and patients with esophageal cancer had a longer survival rate compared to stomach cancer patients ($P = 0.15$). Patients who had undergone surgery ($P < 0.001$) and/or chemotherapy ($P < 0.001$) survived longer than those without such treatments. Tumor morphology, age at diagnosis, radiotherapy, alcohol, and opium consumption did not show any significant effects on the survival rate of patients. In multivariate analysis, only smoking was remained as an independent factor for stomach cancer ($P = 0.04$) while in esophageal cancer, surgery and grade of differentiation were significant predictors of survival.

Conclusion: Survival rate of stomach and esophagus cancer cases in Ardabil is relatively low. Intervention for early detection and therapy is necessary to increase survival.

Archives of Iranian Medicine, Volume 10, Number 1, 2007: 32 – 37.

Keywords: Ardabil • esophageal cancer • gastric cancer • Iran • survival

Introduction

Gastric cancer is the second leading cause of cancer death worldwide and is the most common type of cancer in Iran.^{1,2} Gastric and esophageal cancers are the most frequent causes of cancer-related deaths in Iran with the highest rates reported from northern part of the country.^{1,3,4} Survivals of gastric and esophageal cancers has been studied in multiple series with patients stratified by stage of disease, Lauren tumor type, tumor location, and

type of therapy. An association between survival and stage of cancer has been shown by all studies. Several authors also reported that 5-year survival have improved over the past several decades.²

Authors' affiliations: *Digestive Disease Research Center (DDRC), Tehran University of Medical Sciences, Tehran, **Ardabil University of Medical Sciences (AUMS), Ardabil, Iran, ***Tampere School of Public Health, University of Tampere, Finland.

Corresponding author and reprints: Reza Malekzadeh MD, Digestive Disease Research Center, Tehran University of Medical Sciences, Shariati Hospital, Kargar Shomali Ave., Tehran 14114, Iran. Fax: +98-21-8012992, E-mail: malek@ams.ac.ir.
Accepted for publication: 6 December 2006

Mortality rates of gastric cancer are particularly high in Asia, South America, and parts of Europe.

According to a study conducted by Digestive Disease Research Center (DDRC) during 1996 to 2000, upper gastrointestinal (GI) malignancies constituted nearly half of all malignancies in the province.⁵⁻⁷ The objective of this study was to estimate the survival rate of patients with gastric or esophageal cancer by histopathologic type, grade of tumor, treatment modalities, and location of tumor as well as some of the risk factors of upper GI malignancies such as consumption of alcohol or opium, cigarette smoking, and age at the diagnosis.

Patients and Methods

A prospective review of all the 420 biopsy-proven patients with upper GI cancers (141 esophagus, and 279 stomach) who were initially diagnosed at the referral unique clinic for upper GI malignancies located in the main city of Ardabil for 5 years, from 2000 through 2004, was planned. There were 293 males and 127 females with a mean age of 64 (range: 20 – 90) years.

International classification of disease for oncology (ICD-O-3) was used for coding morphology and topography of tumors. In this study, we looked at the parameters such as overall survival, demographic data, symptoms and signs, risk factors, histopathology, and socioeconomic status.

We contacted patients or their families through visiting their residential place and performed a direct interview with them. All of the interviews were done by a physician or a trained nurse. With this method, we collected data from 303 cases. We found date of death of other 55 patients by evaluation of official death certificates. Information on 62 patients was missing due to inaccessible home address, address change, or immigration. Data on risk factors and demographic variables were obtained from questionnaires which completed at the time of diagnosis at Aras Clinic. Survival analysis was performed using STATA software, release 8. Kaplan-Meier method was used to estimate the survival probability and Cox proportional hazards model was used for multivariate analysis of risk variables.^{8,9,17}

Results

Among 358 observed patients at the end of the

study, 331 patients were dead and only 27 were still alive. Fifty-five percent of patients were rural inhabitants. Demographic and socioeconomic characteristics of patients are shown in Table 1. Dysphagia was the most common presenting complaint observed in 44% of patients; weight loss was another common presenting feature reported by 15% of patients.

According to univariate analysis (log-rank test), the factors influencing the overall survival rate for both cancers together were undergoing surgery (either alone or in combination with chemo/radiotherapy for both stomach and esophagus: $P < 0.009$), receiving chemotherapy (in combination with surgery: $P = 0.001$; chemo-therapy alone: $P = 0.087$), and tumor grades ($P < 0.001$); undifferentiated type had the lowest survival (median: 5 months) while those with well-differentiated tumor had the longest survival (median: 9 months). After further stratification by site of tumor, differentiation of tumor and chemotherapy did not reach the statistical significance anymore for esophagus. Age at the diagnosis, tumor site (stomach or esophagus), tumor morphology, alcohol drinking, and opium

Table 1. Baseline characteristics of patients.

	Stomach cancer	Esophagus cancer
	n (%)	n (%)
Sex		
Female	62 (22.2)	65 (46.1)
Male	217 (77.8)	76 (53.9)
Age group		
< 40	10 (3.6)	3 (2.1)
40 – 49	14 (5.0)	13 (9.2)
50 – 59	45 (16.1)	28 (20.1)
60 – 69	109 (39.1)	40 (28.4)
≥ 70	101 (36.2)	57 (40.4)
Residence		
Rural	141 (51.5)	86 (62.3)
Urban	133 (48.5)	52 (37.7)
Education		
0	191 (89.3)	111 (95.7)
1 – 5 years	16 (7.5)	4 (3.5)
6 – 8 years	1 (0.5)	1 (0.9)
9 – 12 years	4 (1.9)	0 (0)
>12 years	2 (0.9)	0 (0)
Smoker		
No	147 (64.5)	70 (56.5)
Yes	81 (35.5)	54 (43.6)
Alcohol		
No	218 (98.2)	120 ()
Yes	4 (1.8)	2 (1.6)
Opium		
No	208 (93.7)	112 (91.1)
Yes	14 (6.3)	11 (8.9)

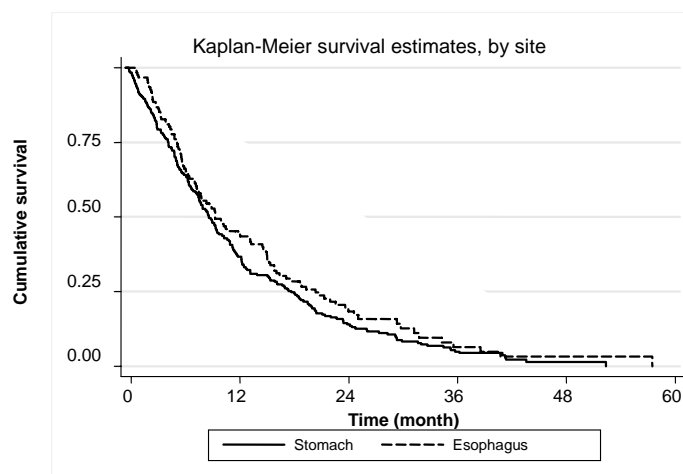


Figure 1. Comparing survival probability of patients with gastric and esophageal cancers using Kaplan-Meier survival analysis.

consumption had no effects on survival rate of patients with upper GI cancer.

The 1 and 5-year survival rate for all upper GI cancer patients was 40.5%, and 0.83%, respectively. In terms of overall cumulative survival observed for five years, patients with esophagus cancer had a slightly higher survival rate than patients with stomach cancer ($P = 0.15$). Figure 1 shows that patients with esophageal cancer had a better survival than those with gastric cancer ($P = 0.15$). Survival of patients with stomach cancer in cardia was slightly better than those with tumor involving other gastric regions ($P = 0.19$).

Only 28% of patients had undergone a curative resectional surgery. About 25% of patients did not receive any treatment at all (Table 2).

Figure 2 shows the difference between cumulative survival of patients with operated esophageal cancer and those with no surgery, regardless of other additional treatments ($P < 0.001$).

The mean (median) survival rate for patients with esophageal cancer was 12.1 (9) months and for those with gastric cancer was 11.8 (9) months. In those with stomach cancer, patients with the histopathology of “signet ring cell carcinoma” had

the lowest survival rate (median: 8 months); other cases lived more than 23 months after the diagnosis.

Figure 3 shows that in the entire follow-up, the overall mortality was higher for those with stomach cancer than esophagus. The mortality rate increased steeply from the time of diagnosis for one year, when the rate became steadier for stomach than esophagus cancer, which had a decline after the third year.

The effect of tumor site, gender, age, and place of residence on the prognosis was not significant in a multivariate model adjusted for follow-up time. The mortality ratio of esophageal vs. gastric malignancies was 0.86 (CI_{95%}: 0.6 – 1.1). This ratio for residential place (urban vs. rural) was 1.03 (CI_{95%}: 0.8 – 1.3).

The multivariate analysis of potential prognostic factors in patients with stomach cancer showed that smoking status had a significant prognostic value associated with 81% increase in mortality rate ($P = 0.04$). Nevertheless, place of residence, age, and sex had no prognostic values for stomach cancer, after adjustment for other variables included in the model. Based on this database, surgery and chemotherapy seem to be effective treatments for stomach cancer while

Table 2. Treatment modality among patients with upper GI cancer.

Cancer	Surgery alone (%)	Chemotherapy alone (%)	Radiotherapy alone (%)	Surgery and chemo/radiotherapy (%)	Supportive care (%)	Total
Stomach	14.0	4.3	0.4	12.5	25.8	279
Esophagus	19.1	6.4	0.0	12.1	24.1	141
Both	15.7	5.0	0.2	12.4	25.2	420

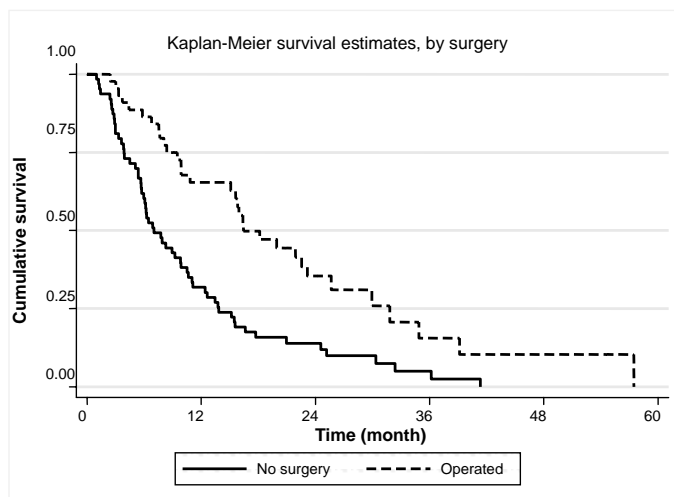


Figure 2. Survival of patients with esophageal cancer, effect of surgery using Kaplan-Meier method.

radiotherapy associated with higher mortality, although none of these findings reached statistical significance. Mortality in educated patients was half of that in illiterates ($P = 0.10$). Those with diffuse type of adenocarcinoma of stomach had 37% higher mortality than those with the intestinal type of adenocarcinoma ($CI_{95\%}$ for mortality ratio: 0.30 – 6.33).

In patients with esophageal cancer, taking all other factors (e.g., age, gender, other treatments, etc.) into account, surgery was significantly associated with lower mortality while radiotherapy seemed to be associated with higher mortality ($P = 0.46$). Drinking alcohol was highly associated

with the increased mortality of esophageal cancers (hazard ratio = 7.5; $CI_{95\%}$: 0.82 – 69.1).

Discussion

According to studies in Ardabil Province, upper GI cancers have high incidence and mortality. These cancers include around half of total cancers and more than half of causes of cancer-related deaths.^{3, 6, 7} The average age at diagnosis in our patients was 64 years while the mean age at presentation in our neighboring country, Pakistan, is 56 years.⁸ These cancers are, therefore, disease of the elderly in this province.^{5, 8}

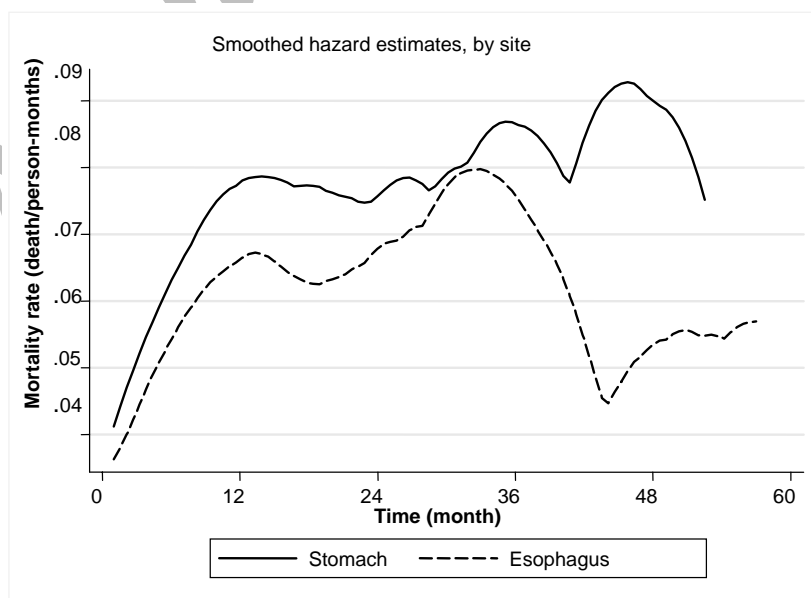


Figure 3. Mortality rate by site of cancer (smoothed hazard estimates).

Squamous cell carcinoma of the esophagus (85%) was the predominant histology seen in our study, with adenocarcinoma (14%) being less common. These data are consistent with data from most of other Asian countries.^{11, 13} These figures are different from those found in the developed countries where adenocarcinoma is becoming a more common type of histology in esophageal cancers.^{13, 16, 18} In our study, the survival of patients with esophagus cancer was slightly more than patients with stomach cancer ($P = 0.26$); these figures are different from those found in the countries such as England and South Korea.^{11, 19} Women with esophagus cancer had a slightly longer survival than men in Ardabil Province; these data are consistent with data from European countries.^{16, 20} Signet ring cell histopathologic type of tumors in this study had significantly lower survival than other types of histopathology in patients with stomach cancer. Nonetheless, in another study, there was no difference between types of histopathology.¹⁴

The average survival time in our patients is similar to other developing countries such as Pakistan. The median time of survival in our study was 9 months while in Pakistan it was 7 months.⁸ These data, however, are different from those reported from England, Korea, and China.^{11, 12, 19}

The overall survival rate for our series (both men and women) was 40.5% after one year, 16.9% after two, 6.5% after three, 2.5% after four, and less than 1% after five years. These data are different from those reported from developed countries or China.^{13, 14, 16} For example, in China the 1 to 5-year survival rates in the patients with stomach cancer were reported to be 54.2%, 41.8%, 37.9%, 34.0%, and 30.5%, respectively.¹⁰ In the multivariate Cox proportional hazards model for

stomach cancer, the only statistically significant explanatory variable was smoking status, which shows ever-smoking is associated with lower survival (adjusted for other factors in the model, Table 3). In our multivariate Cox proportional hazards model for esophageal cancer, the only statistically significant explanatory variable was surgery, which showed that patients who had undergone surgery had 51% lower mortality than those who had received other treatment modalities (i.e., chemotherapy and radiotherapy).

Although there are reports that surgery improves the survival, even in stage IV upper GI cancers,¹⁵ judgment on the effect of any treatment on survival, based on these data, is not correct, because those patients who take a treatment like surgery are different from others in respect to their health condition like cardiovascular status; it is more likely that only those patients with healthier condition can undergo surgery. Therefore, a better survival of operated patients might be attributed to their health status that made them being selected for surgery. The same argument may be applicable to those who underwent radiotherapy, which had a higher mortality; the patients might have been chosen for this treatment for they had nonoperable metastasized tumors. This issue should be further studied by randomized controlled trials.

Although staging of tumor had not been recorded in our database, these results may reflect that higher proportion of patients with advanced tumor stage were visiting this referral tertiary clinic. Another reason for obtaining such a short survival rate might be due to the fact that we have a 15% loss in the follow-up; if we suppose all of them were alive, the survival rates could be substantially higher. Therefore, results of this study may not be representative of all upper GI cancer

Table 3. Effects of explanatory variables on stomach and esophagus cancer mortality using Cox proportional hazards model.

Variable	Gastric cancer		Esophageal cancer	
	Mortality ratio	(95% CI)	Mortality ratio	(95% CI)
Sex (female/male)	0.97	0.47 – 2.00	1.29	0.72 – 2.33
Age	1.00	0.97 – 1.04	0.99	0.97 – 1.02
Residence (urban/rural)	0.75	0.45 – 1.27	1.30	0.76 – 2.24
Surgery	0.67	0.33 – 1.34	0.49	0.27 – 0.89
Chemotherapy	0.59	0.27 – 1.30	0.62	0.30 – 1.26
Radiotherapy	1.59	0.39 – 6.52	1.52	0.50 – 4.67
Smoking	1.81	1.02 – 3.23	0.87	0.49 – 1.56
Alcohol drinking	—	—	7.51	0.82 – 69.10
Opium use	—	—	0.92	0.35 – 2.41
Adenocarcinoma / SCC	—	—	0.67	0.28 – 1.61
Differentiation (well or moderate / poor or non-)	0.93	0.55 – 1.57	0.32	0.13 – 0.82
Education (yes/no)	0.50	0.10 – 2.47	1.32	0.44 – 3.93

cases in Ardabil or Iran, but could demonstrate the fact that the majority of patients with upper GI cancers at a referral clinic, have a short survival after diagnosis.

In conclusion, the overall survival rates for upper GI malignancies in this gastroenterology clinic in Ardabil Province are relatively low. Since stage of cancer is a very important factor influencing survival of patients with upper GI cancer, these short survival rates can be due to the fact that patients with upper GI cancer in Ardabil are, in general, referring to physicians at late stages of the disease. Surgery might be an effective treatment for all patients with upper GI cancer in Ardabil, especially for those with cancer of esophagus.¹ Smoking is associated with decreased survival of patients with stomach cancer.

Acknowledgments

We thank Dr. Shahnam Arshi (Dean of Ardabil University of Medical Sciences), Dr. Hamid Jafarzadeh (Health Deputy of Ardabil University of Medical Sciences), Dr. Jaffar Bashiri (Chief of Ardabil Health Center), Dr. Zolfaghari, Dr. Seraj Mohajeri (Chief of Sabalan Hospital in Ardabil), Mr. Firuz Amani, and all of the Ardabil health personnel for helping us in conducting this study.

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