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Postoperative Survival in Gastric Cancer Patients and its Associated Factors: A Time Dependent Covariates Model

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Abstract

The gastric cancer in Iran is the fourth in the general population. This study was designed to determine the five-year survival rate of gastric cancer patients, and to assess its associated factors. We analyzed the data using a time-dependent covariates model, and recommend it for analyses of similar data. 281 gastric cancer patients with adenocarcinomatous pathology who had been operated on at the Iran Cancer Institute between 1995 and 1999 were enrolled in this study. The patients' survival after surgery was determined, and its relationship with other variables were assessed. Kaplan-Meier, Cox and Breslow method were used, and an alpha level of 0.05 was considered significant. The five-year survival rate and the median life expectancy were 22.6% and 19.00 months, respectively. The Cox model showed that age, lymph node metastasis, recurrence, and disease stage influenced the chances of survival. It was also shown that lymph node metastasis and disease stage correlated with time of relapse, while age, distant metastasis and disease stage affected survival after relapse, and age correlated with survival of patients without recurrence. Gastric cancer patients in Iran have a low five-year survival rate. One of the most important reasons seems to be delayed consultation and diagnosis.

Keywords: *Gastric cancer, Cox proportional hazards model, Breslow estimator*, *Time dependent model*

Introduction

During the recent years, improved hygiene in Iran has reduced deaths from infectious diseases, but cancers have become a major contributing factor to the Iranian population death rate. Lack of precise and efficient cancer registries makes the number of cancer patients and the annual occurrence of new cases unknown. However, estimates show that the standardized occurrence in 1998 in the capital, Tehran, was 130.9 and 109.8 in 100,000 for men and women, respectively (1). Considering the probable underestimations, the exact number of cancer deaths is not known either, but it has been estimated that in 1998 more than 27 thousand cancer deaths occurred in the 70 million Iranian populations (1).

Several reports have stated that gastric cancer is prevalent in Iran, being the second most common cancer in men and the fourth in the general population. Unfortunately, gastric cancer patients in Iran seek medical attention when the disease has reached an advanced stage and is therefore very lethal (1-3).

Determining patients' survival rate is a very important aspect of cancer research. In this regard, several studies have been carried out in different countries. In case of gastric cancer patients, the postoperative five-year survival rate has been reported as 29.6% in China, 4.4% in Thailand, 37.0% in the United States, 22.0% in Switzerland, and 30.0% in France (4-8). Various factors affecting survival in these pa-

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tients such as age, disease stage, and occurrence of metastasis have also been investigated (4-26). This study was designed and carried out to determine the five-year survival rate of Iranian gastric cancer patients who received surgical treatment at the most important cancer treatment center in Iran, the Iran Cancer Institute, and to evaluate some affecting factors.

Today, many medical and epidemiologic investigations are dedicated to the study of patient survival probability. In these studies, focus lies on patient death due to a definite cause, while some events that can alter final results often happen to patients. Should these intermediate events and their time of occurrence be overlooked, they may bias the results of the study (21-24). It has been suggested that such variables be entered into the model as time-dependent. In this study we analyzed the data using a time-dependent covariates model, and recommend it for analyses of similar data.

Materials and Methods

In this study, 281 gastric cancer patients with adenocarcinomatous pathology who were admitted and operated on at the Iran Cancer Institute from March 1995 to March 1999 were enrolled. The postoperative survival of these patients was determined. Right censor was applied since the final day to those who survived the study period, and other certain dates for those who were lost to follow-up. Two hundred and seven patients deceased during the study period, in 11 of which death had other causes and so were right censored from their death dates.

Individual variables such as age (at the time of surgery), gender (male- female), and those related to the disease such as its site (cardia- antrum- other), stage (I- II- III- IV), presence of metastases (positive- negative), site of metastasis (lymph nodes- liver- distant), type and extent of surgery [Total Gastrectomy (TG)- Subtotal Gastrectomy (SG)- Distal Gastrectomy (DG)- Partial Gastrectomy (PTG)- Proximal Gastrectomy (PX.G)], number of affected lymph nodes and complementary or secondary treatments received (chemotherapy- radiotherapy- surgery-combination), relapse, and the interval between surgery and relapse were assessed for their effect on patients' survival.

Staging was based on the 6th edition of the TNM system. In the analyses, methods of Kaplan Meier, Cox proportional hazards model, Breslow estimator were used in S- PLUS 2000 and R software, and an alpha level of 0.05 was considered significant.

Results

The studied patients were male in 71.2% of cases and their median age was 68 yr (range, 32 to 96 yr). The cancer site was the cardia in 39.9% and the anterior in 20.6% of patients. Metastases were found in 166 (59.1%) patients; 77.7% of these patients had metastases in the lymph nodes, 10.8% in the liver and 21.7% had distant metastases. The surgical procedure was total gastrectomy in 52.3%, and subtotal gastrectomy in 27.0%, while distal, partial, and proximal gastrectomy was performed in 2.8%, 8.5%, and 9.3%, respectively. For reconstruction, esophagojejunostomy was the choice in 50.9% of patients, 27.6% received gastrojejunostomy, in 13.6% esophagogastrostomy was performed, while colon bypass, Billroth II, and colostomy were carried out in 3.3%, 3.1%, and 1.5%, respectively. Affected nodes were found in 45.9% of patients with a median positive node count of 8 (range, 2 to 18). Pathologic stage distribution included stages IA (2.8%), IB (3.6%), II (17.4%), IIIA (13.9%), IIIB (2.8%), and IV (59.4%). All stage IV assignments were due to an N3 category, a T4 classification, or a T3 classification with M1. While 19.2% of patients had received no secondary treatment, such treatments were tried three times in another 26.0% of them. Relapse was reported in 56.9% of patients, and the median disease-free interval was 11.63 months (range, 10.27 to 12.99 mo). Using the method of Kaplan Meier, the five, three, and one year survival rates were

computed as 22.6% (SE=.0294), 32.5% (SE= 0303), 66.8%(SE=.0284), respectively, and the median life span was 19.00 mo.

The effects of the variables on patient survival were simultaneously measured. This showed that variables of age, lymph node metastasis, disease stage, and relapse related to patients' life expectancy (Table 1). The risk of death for patients afflicted with stage 2, 3, and 4 of the disease was respectively 1.47 (95% confidence interval: 0.68 to 3.15), 2.78 (95% confidence interval: 1.32 to 5.85), and 4.08 (95% confidence interval: 1.92 to 8.67) times greater than those with stage 1. Lymph node metastasis and relapse increased this risk 1.79 (95% confidence interval: 1.19 to 2.69), and 2.52 (95% confidence interval: 1.86 to 3.42) times. The risk of death also increased with age; 1.023 (95% confidence interval: 1.01 to 1.04) times per year.

In the next stage, considering the time-dependent covariate related to the interval before relapse,

We found that chance of survival was not only affected by variables of age, distant metastases, disease stage, and disease-free interval before relapse, but also by this time-dependent covariate, and a longer survival without relapse decreased the risk of death. This analysis (Table 2) showed that the risk of death for patients afflicted with stage 2, 3, and 4 of the disease was respectively 1.38 (95% confidence interval: 0.38 to 4.99), 2.68 (95% confidence interval: 0.77 to 9.38), and 2.84 (95% confidence interval: 0.86 to 9.31) times greater than those with stage 1. Being free of cancer relapse for less than 6 mo, compared to more than one year, increased the risk of death 3.39 (95% confidence interval: 1.95 to 5.88) times. When relapse occurred between 6 to 12 mo, this risk was 1.54 (95% confidence interval: 0.95 to 2.49) times greater in comparison to relapse after one year. The increase in risk of death was 1.03 (95% confidence interval: 1.01 to 1.06) times greater per year with aging (Table 2). This is strong evidence to consider an intermediate situation for analyzing survival.

Table 1: Estimated effects in a Cox model for the total mortality

Variable	Regression coefficient	Standard error	Wald	Degree of freedom	*P*	Relative risk	95% C. I. for relative risk
Age (year)	.023	.008	8.552	1	.003	1.023	1.008- 1.039
Stage**			21.667	3	.000		
Stage(2)	.382	.391	.957	1	.328	1.465	.682- 3.150
Stage(3)	1.023	.379	7.290	1	.007	2.783	1.324- 5.849
Stage(4)	1.406	.385	13.363	1	.000	4.079	1.919- 8.667
Lymph Node Metastases	.580	.208	7.785	1	.005	1.787	1.188- 2.686
Relapse	.925	.155	35.564	1	.000	2.522	1.861- 3.419

*Variable(s) Entered at Step Number 1: Sex, Age, Tumor site, Lymph Node Metastases, Liver Metastases, Distant Metastases,
Stage, Relapse, Smoking History, Type of Gastrectomy
Variable Removed at Step Number 2: Liver Metastases
Variable Removed at Step Number 3: Smoking History
Variable Removed at Step Number 4: Distance Metastases
Variable Removed at Step Number 5: Sex
Variable Removed at Step Number 6: Tumor site
Variable Removed at Step Number 7: Type of Gastrectomy
** Baseline is Stage=1

Table 2: Estimated effects in a Cox model for the total mortality with a Time-Dependent Variable (Time to Relapse)

Variable	Regression coefficient	Standard error	Wald	Degree of freedom	*P* value	Relative risk	95% C. I. for relative risk
Age (year)	.033	.011	8.726	1	.003	1.033	1.011 – 1.056
Stage**			7.097	3	.041		
Stage(2)	.323	.656	.243	1	.622	1.382	.382 – 4.994
Stage(3)	.986	.639	2.381	1	.123	2.681	.766 – 9.383
Stage(4)	1.042	.606	2.955	1	.086	2.836	.864 – 9.309
Distant Metastases	.666	.273	5.970	1	.015	1.946	1.141 - 3.320
Time to Relapse (months)***			19.198	2	.000		
Waiting time≤6 months	1.221	.281	18.843	1	.000	3.391	- 5.884
6 months≤waiting time≤12 months	.432	.245	3.120	1	.077	1.541	.954 - 2.490

*Variable(s) Entered at Step Number 1: Sex, Age, Tumor site, Lymph Node Metastases, Liver Metastases, Distant Metastases,
Stage, Smoking History, Type of Gastrectomy, Time to Relapse
** Baseline is Stage=1
*** Baseline is Time to relapse ≥ 12 months

Discussion

The five-year survival rate in this study was 22.6% which is lower than that of many other countries such as the United States, Switzerland, France, and China (4, 6-9). This may be explained by the fact that Iranian patients generally seek medical attention when the disease has reached an advanced stage. Therefore, diagnosis is made when the chance of a full cure is slim. In this study, comparison of survival and median life span between genders showed that men survived longer, although the difference was not statistically significant. This finding agreed with results of studies carried out in other countries, and the life span difference between male and female gastric cancer patients was not statistically significant (27-29).

As we expected, life expectancy significantly decreased with age (P<0.001). A study performed in the United States also showed that older age groups have a shortened life expectancy in comparison to the young (15). This fact has been verified by studies performed in Japan and Italy as well (16, 27).

One hundred and sixty six patients (59.1%) were afflicted with metastasis and their survival was much shorter compared to other patients. Presence of metastases usually indicates an advanced disease and therefore a smaller chance of survival. This finding has been confirmed by all studies performed in this regard (4-6, 9, 10, 29-31). Of these patients, 45.9% had metastasis to the lymph nodes and in 6.4% the liver was involved. The site of metastasis did not influence life expectancy, however, distant metastasis significantly decreased survival; this was expected because these patients are classified in stage IV.

The disease stage greatly affected life expectancy; the five-year survival rate for patients in stage 1 was 52.96 %, while it was only 16.72% for those in stage 4. Unfortunately 59.4% of patients were first seen with a stage 4 disease and therefore the life expectancy was shortened in general. In Thailand, 68.9% of patients were initially diagnosed with a stage 4 cancer, and so the five-year survival rate was as low as 4.4%, and in Malaysia, where 82% of patients were

first diagnosed with a stage 4 disease, only 16% were operable or curable (5, 13). The effect of disease stage on life expectancy has been reflected in reports concerning Western and developed countries as well (3, 19, 28).

Multivariate analysis for detecting the simultaneous effect of different variables on life expectancy showed that age, lymph node metastasis, cancer stage, and cancer relapse influenced survival significantly. Advancing age and a more advanced stage proved to lower the chance of survival, just as lymph node metastasis and relapse did, while gender and cancer site had no significant effect. These findings have been confirmed by studies performed in Japan (10, 29) and Switzerland (7). In addition to these variables, metastasis to the liver and tumor site were found related in studies carried out respectively in China (9) and the United States (19).

In the past decade, a considerable amount of literature concerning the time-dependent covariates model has been published. However, time-dependent covariates model has been limited due to their complexity. In the analysis of multiple events, when the interval between events is the subject of attention, it is important to find out whether the events follow a sequence, or such sequential order is lacking. An example of non-sequential events is the competing risks model. In the present study, cancer relapse and death are two events that compete in time of occurrence. In such analyses, counting processes provides the researcher with a valuable tool to investigate not only sequential or non-sequential events, but also a combination of them simultaneously (26).

In the present study, we first see that variables such as age, disease stage, relapse, and lymph node metastases affect patients' survival. However, further careful analyses showed that time to relapse can be considered to have an effect. We suggest that in future works interaction between variables (e.g. time to relapse by stage) should be incorporated into modeling.

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