

Estimating Postoperative Survival of Gastric Cancer Patients and Factors Affecting it in Iran: Based on a TNM-7 Staging System

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Abstract- Recently, reports have shown that gastric cancer has high abundance in Iran and is at the second level in men, and fourth in total. This study aimed to determine the 5-year survival of gastric cancer patients and to investigate factors affecting the performance, based on TNM-7 staging system. In this study, we investigated 760 patients with gastric cancer since the beginning of 1993 to the end of 2006 in the Iran Cancer Institute who underwent surgery. Survival of these patients was determined after surgery, and the effects of demographic characteristics such as age (during operation), sex, and information on diseases such as cancer site, pathologic type, stage of disease progress (Stage), metastasis and sites of metastases were evaluated. The 5-year survival probability of patients was 28 %, and median survival time was 25.69 months. Univariate tests showed that sex, cancer site, and pathologic type have no significant effects on patient's survival. But the probability of 5-year survival significantly decreases with increasing age, and as it is expected, those with metastases were significantly less likely to have 5-year survival, and disease stage was significantly effective on patients' life ($P < 0.001$). Simultaneous evaluation of different variables' effects on the probability of survival using the multiple Cox proportional hazards models showed that age and stage disease variables were effective on the survival of patients. The 5-year survival of patients with gastric cancer is low in Iran, although it is improved compared to the past. It seems that one of the main reasons for low survival rate of these patients is a late referral of patients for diagnosis and treatment. Most patients refer in the final stages of the disease, at this stage most patients are affected by lymph nodes metastases, liver and as the result, their treatment will be more difficult.

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Keywords: Survival; Gastric cancer; Cox proportional hazards model; TNM-7 staging system

Introduction

Cancer is increasingly becoming one of the main risks affecting the health of human society. It is predicted that in 2020, more than 15 million new cases of cancer will occur in the world, with more than 60% will be in less developed societies. In the last two decades, with the improvement of health indicators in Iran, and reduction of mortality due to infectious diseases, cancers have had more important role in Iranians' mortality. According to the reports of "Non-communicable Diseases Management Center of Iran Health Ministry", more than 40 thousand Iranian die each year due to the risk of these diseases (1). Gastric cancer is the leading cause of cancer mortality in the world. Currently, 10% of worldwide cancers and one of the most important one is gastric cancer (2). According

to the "National Report of the Cancer Registry", gastric cancer has the third highest level in Iran after skin and breast cancer (1). Unfortunately, patients with gastric cancer in Iran refer to more advanced stages of diseases for diagnosing and treatment, so the disease has a high degree of lethality (3-5).

Due to the risks of cancer, it is important to determine the probability of patients' survival. Several studies have been conducted in various countries in this regard. The 5-year survival of patients diagnosed with gastric cancer after surgery in China 29.6 percent, in Thailand 4.4 percent, in the U.S. 37 percent, in Switzerland 22 percent and in France 30 percent has been reported (6-10).

Effects of several factors on the survival of these patients were studied, and age, disease stage (Stage), and metastasis have been noted (6-22).

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This study aimed to determine the survival rates at 1, 3, and 5 years of old Iranian with gastric cancer who had surgery at main center for cancer treatment in the Iran (Cancer Institute) and was designed and implemented by examining some factors affecting them.

Materials and Methods

In this study, we followed up (median 21 months and 4 days) status of 760 patients with gastric cancer in a 14-year period from early 1993 to the end of 2006 at surgery parts of Iran Cancer Institute who had surgery. Survival of these patients was determined after surgery and those who were still alive at the end of study period from that date and those who, after a certain time, there was no information about them (Lost to follow-up) were considered as right censored. Five hundred and seventy-three patients died during the study period that 37 of them died due to causes other than the disease, and these 37 people were considered right censored after the date of death.

Effects of demographic characteristics such as age (at the time of surgery), sex (male-female) and information on diseases such as cancer site (cardia-antrum-other places), pathology type (Adenocarcinoma-other), stage of disease progression (I-II-III-IV), presence metastasis (positive-negative), site of metastases (lymph nodes-liver-other), and number of lymph nodes involved in survival were evaluated.

7th edition TNM (Tumor Node Metastasis) method

was used to determine the stage of disease, and methods of calculating life tables, Kaplan- Meier method, log - rank test, Cox proportional hazards model, and SPSS version 18 Software was used for statistical analysis and significance level of *P*-value less than 0.05 was considered.

Results

68.3% of these patients were male, and their median age was 67 years (range was 32 to 96 years). Investigations revealed that in 44.9% of patients cardia was involved and in 19.7% of patients anterior part was involved. Pathology results reported Adenocarcinoma in 88.4% of patients and in the rest of them (squamous cell carcinoma, small cell carcinoma, carcinoid tumor, sarcoma, stromal tumor, malignant lymphoma, tumor spindle cell). A total of 439 patients (57.8) had metastatic disease that among metastatic patients 68.3 percent had only lymph nodes metastasis. Lymph nodes involved in 44.2% of patients with a median number of involved lymph nodes, 8 nodes were observed. Assessment of the disease stage distribution showed that IA (3.4%), IB (4.6%), IIA (21.2%), IIB (13.7%), IIIA (3.6%), IIIB (6.4%), IIIC (28.8%) and IV (18.3%) existed. The probability of survival at 1, 3 and 5 years of patients was 75, 39, and 28 percent, respectively, and median lifetime in this study was 25.69 months (Table 1).

Table 1. Life Table of Patient Survival

Interval Start Time (Month)	Number Entering This Interval	Number Withdrawn During Interval	Number Exposed To Risk	Number of Terminate Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End	Probability Density	Hazard Rate	SE of Probability Density
0.0	760	21	749.500	190	0.25	0.75	0.75	0.021	0.02	0.001
12.0	549	36	531.000	163	0.31	0.69	0.52	0.019	0.03	0.002
24.0	350	21	339.500	81	0.24	0.76	0.39	0.010	0.02	0.002
36.0	248	33	231.500	43	0.19	0.81	0.32	0.006	0.01	0.001
48.0	172	33	155.500	22	0.14	0.86	0.28	0.004	0.01	0.001
60.0	117	28	103.000	12	0.12	0.88	0.24	0.003	0.01	0.001

** These calculations for the last interval are meaningless.
The median survival time is 25.69 (months)

Comparison of survival probability in both sexes showed that 5-year survival probability is 27% for men while the 5-year survival probability is 28% for women, and median life expectancy is 25.23 and 25.67 months,

but this difference was not statistically significant (Table 2).

The studies showed that 5-year survival probability decreases significantly with increasing age ($P < 0.001$),

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and it is for over 70 years group only 8% (Table 2).

It was observed that the least likely 5-year survival is related to patients whose cardia (25%) was involved, and then patients with antrum involvement (28%) and other points (31%) were considered, although these differences were not statistically significant (Table 2).

The 5-year probability of survival in patients with

Adenocarcinoma pathology was significantly ($P<0.01$) lower than others (26% vs. 40%) (Table 2).

As might be expected, those with metastases were significantly less likely to have 5-year survival (19% vs. 39%, $P<0.001$) and median life expectancy were 22.50 and 30.00 months, respectively (Table 2).

Table 2. Univariate analysis of prognostic factors

Prognostic factor		No. of patient (%)	5-Year survival rate (%)	Median Survival Time (Month)	95% Confidence Interval for Median	Log-Rank test P-value
Sex	Male	519(68.3)	27.0	25.23	21.56-28.90	0.661
	Female	241(31.7)	28.0	25.67	22.06-29.28	
Age	<61	184(24.2)	48.0	52.70	30.37-75.03	<0.001
	61-70	363(47.8)	27.0	28.23	23.15-33.32	
	>70	213(28.0)	08.0	14.80	11.61-17.99	
Location	Cardia	341(44.9)	25.0	22.50	19.27-25.73	0.072
	Antrur	150(19.7)	28.0	29.83	21.74-37.93	
Pathology	Other	269(35.4)	31.0	27.70	21.88-33.52	0.008
	Adenocarcinoma	672(88.4)	26.0	24.60	21.90-27.30	
Metastases	Other*	88(11.6)	40.0	46.13	27.76-64.51	<0.001
	Positive	439(57.8)	19.0	22.50	19.29-25.71	
Lymph node Metastases	Negative	321(42.2)	39.0	30.00	18.36-41.64	0.002
	Positive	336(44.2)	22.0	21.87	18.70-25.03	
Liver Metastases	Negative	424(55.8)	33.0	28.53	23.52-33.54	0.063
	Positive	57(7.5)	20.0	19.43	07.98-30.88	
Distance Metastases**	Negative	703(92.5)	28.0	25.23	22.20-28.26	0.001
	Positive	90(11.8)	11.0	22.50	16.67-28.33	
Stage(TNM System)	IA	26(3.4)	77.0	172.23	--	<0.001
	IB	35(4.6)	66.0	77.70	61.31-94.09	
	IIA	161(21.2)	40.0	36.63	19.76-53.51	
	IIB	104(13.7)	16.0	20.63	13.62-27.65	
	IIIA	27(3.6)	17.0	20.80	07.51-34.09	
	IIIB	49(6.4)	08.0	18.47	12.86-24.08	
	IIIC	219(28.8)	27.0	24.97	20.17-29.76	
	IV	139(18.3)	11.0	22.00	16.48-27.52	

*squamous cell carcinoma (SCC), small-cell carcinoma, carcinoid tumor, spindle cell tumor, sarcoma, malignant lymphoma, stromal tumor

**diaphragm, spleen, pancreas, lungs, bone

Disease stage significantly influenced the probability of 5-year survival of patients ($P<0.001$) and reached from 77% for stage IA to 11% for IV stage.

In the end, all variables were included simultaneously in a multiple Cox proportional hazards models, and their effect was measured on the probability of survival and the results indicated that age and stage of

disease variables have influenced on the survival of patients (Table 3). This study showed that the risk of death in patients with stages II, III, and IV is 2.24 times (CI 95%: 1.47- 3.41), 2.57 times (CI 95%: 1.70- 3.91), 3.85 times (CI 95%: 2.49- 5.97) compared with patients in stage I. Also, each year increase in the age of death risk is 1.06 times (CI 95%: 1.05- 1.07).

Table 3. Multivariate analysis of prognostic factors by Backward Stepwise* (Likelihood Ratio) Method Cox Proportional Hazard Model

Variable	Regression coefficient	Standard error	Wald	Degree of freedom	P-value	Hazard Ratio	95% CI. for Hazard Ratio
Age	0.053	0.006	106.454	1	0.000	1.059	1.047 – 1.070
Stage**	--	--	43.372	3	0.000	--	--
Stage(2)	0.805	0.216	13.931	1	0.000	2.236	1.465 – 3.411
Stage(3)	0.945	0.213	19.765	1	0.000	2.574	1.697 – 3.905
Stage(4)	1.349	0.223	36.575	1	0.000	3.853	2.489 – 5.966

*Variable(s) Entered at Step Number 1: Sex, Age, Location, Pathology, Lymph Node Metastases, Liver Metastases, Distance Metastases, Stage

Variable Removed at Step Number 2: Sex

Variable Removed at Step Number 3: Lymph Node Metastases

Variable Removed at Step Number 4: Distance Metastases

Variable Removed at Step Number 5: Liver Metastases

Variable Removed at Step Number 6: Location

Variable Removed at Step Number 7: Pathology

** Baseline is Stage=1

Discussion

5-year survival probability of the patients in this study was approximately 28%, compared to the previous study (23) that was reported 23.6 percent, shows improvement, still, compared to many countries, including the U.S., Switzerland, France and China is lower (6,8-11).

Comparison of survival probabilities and median survival in both sexes revealed that women have a longer life (although this difference was not statistically significant), and this finding is consistent with studies in other countries and life expectancy of men and women with gastric cancer are not significantly different from each other (24-26).

With increasing age of patients, their life expectancy is significantly reduced ($P < 0.001$). In studies conducted in U.S., Japan and Italy, the same pattern has been reported (17,18, and 24).

A total of 439 (57.8%) of patients had afflicted metastasis and survival of these patients are far less than other patients. Metastasis usually means having more advanced disease, and thereby reducing the chances of patients' survival. This finding has been confirmed in all studies (6-8,11-12, and 24-26). Among these 439 patients, 336 patients had lymph nodes metastasis and 34 patients' liver was involved.

Disease stage strongly influences survival, and while the 5-year survival of patients at stage I is 71 percent, in patients at IV stage, 5-year survival is only 11% and unfortunately, 18.3% of patients have referred at this stage, and thus the chances of patients survival have decreased. In Thailand, the 68.9% of patients who have referred at stage IV, 5-year survival of patients was very

small (4.4 percent) and in Malaysia, where 82 percent of patients who have referred at stage 4, only 16 percent of them have had surgery and treatment (7,15). Effect of disease stage on life expectancy in studies on developed and western countries have been seen (5,21,25). It is important to note that in all above studies (except present study) TNM-6 system was used for staging of the disease, whereas we used TNM-7 system, and, therefore, comparisons may not be accurate in some cases.

Multiple analysis for the simultaneous effect of variables assessment on survival showed that age and stage of disease variables have a significant effect on survival, with increasing age and stage of disease, the chance of survival is reduced. However, gender, pathology, site effects variables are not significant. These results are validated by studies in Japan (12,26), and Switzerland (8), but in a study conducted in China, liver metastases (11), and in U.S. the tumor site (21) are effectively detected in addition to the foregoing factors.

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