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Original Article

Estimating the Net Survival of Patients with Gastric Cancer in Iran in a Relative Survival Framework

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Abstract

Background: Iran is an Eastern Mediterranean region country with the highest rate of gastric cancer. The present study aimed to evaluate the 5-year net survival of patients with gastric cancer in Iran using a relative survival framework.

Methods: In a cross-sectional study, using life-table estimation of relative survival, we reported 1- to 5-year relative survival regarding age, sex, disease stage, pathology, and adjuvant therapies via modeling excess mortality. All the analyses were done applying Stata 11.2 with a confidence level of 95%.

Results: Data on 330 patients (aged 32–96 y), who were comprised of 228 (69.1%) men and 102 (30.1%) women with gastric cancer and were followed up for 10 years, were analyzed. Adenocarcinoma was the most common malignancy (281 [85.2%] patients), and 248 (75.1%) patients were at stage 3 or stage 4. The 1- and 5-year net survival rates after surgery were 67.96 (95% CI: 62.35–72.98) and 23.35 (95% CI: 17.94–29.28), respectively. Higher stages (P=0.001), older ages (P=0.007), and less use of adjuvant therapies (P<0.001) were independently associated with excess mortality.

Conclusion: It is recommended to use the relative survival framework to analyze the survival of cancer patients as an alternative approach not only to eliminate biases due to competing risks and their dependencies but also to estimate the cure at the population level concerning the most important individual characteristics. Our findings showed that the survival rate of gastric cancer in Iran is lower than that in most developed countries in terms of net survival.

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Keywords ● Survival analysis ● Epidemiology ● Stomach Neoplasms

What's Known

- In cancer survival analysis, it is necessary to adjust the effects of competing risks.
- In the real world, accommodation of competing risks requires exact determination of the cause of death.
- Assumption that the competing risks are independent of cancer is not true and can create bias.

What's New

- Net survival represents a ratio of patients expected to survive after a period of follow-up in a hypothetical scenario of the absence of competing risks.
- Using the relative-survival framework addressing either the probable effects of the competing risks or their dependencies, the 5-year net survival of our gastric cancer patients after surgery was 23.35 (95% CI: 17.94–29.28).

Introduction

Gastric cancer is one of the most common cancers worldwide.[1] A total of 22,220 people in the United States of America are annually affected by the disease, of which 10,990 people die.[2] Until 1980s, gastric cancer was the primary cause of mortality from cancers all over the world; since then, it has been ranked second, subsequent to lung cancer. Adenocarcinoma is the most common pathologic type of the cancer.[1,3]

Iran is one of the countries with a relatively high incidence and prevalence of the disease and suffers from a relatively high

annual mortality from the disease.[4] According to the GLOBOCAN database of the World Health Organization, Iran is one of the countries in the Eastern Mediterranean region with the highest rate of the disease.[4] The high prevalence of the disease in Iran is mainly attributed to 3 environmental factors: *Helicobacter pylori* infection, high salt intake, and smoking.[5]

Fortunately, in recent decades, in addition to a significant decrease in the prevalence and incidence of gastric cancer in the world, patient survival has also improved. According to a report by the Cancer Research Center in the United Kingdom, over the last 40 years the 10-year survival of patients in that region has increased from 4% to 15%.[6]

In a study by Moghimi-Dehkordi et al.,[3] the 5-year survival rate of the patients was estimated to be 29.7% using an actuarial life-table method. According to the results of a systematic review and meta-analysis of 22 studies carried out in Iran in a period from 1990 to 2011, the 5-year survival rates estimated based on the data obtained from hospitals and cancer registry centers were 15% and 16%, respectively. As was reported by these studies, the minimum and maximum 5-year survival rates were between 6% and 30%, with the rates having a significant increasing trend over time.[7]

In studies which evaluate the survival of cancer patients, it is expected to consider the death from the disease (cancer) to estimate the survival. However, after diagnosis the patient may die due to other reasons, seemingly independent of the cancer (e.g., due to myocardial infarction). In such a case, where the data are in a competing risks setting, it is common to exactly determine the cause of death for every individual. Accordingly, only the death that occurs due to cancer is taken into account as the main outcome. In such a condition, the analysis is carried out in a cause-specific framework and it is called "cause-specific survival".[8] Although it is assumed that the reasons for the death, other than the cancer, are independent of the cancer, this assumption is not true and can create a bias in the estimations because the data in a context of cause-dependent competing risks can be better defined. In addition, the factor of cure and the variable of frailty should also be considered in the analysis. The relative-survival framework is another method for the analysis of survival. In this method, all-cause mortality as the primary outcome in cancer patients is compared with the mortality in the reference population. In fact, this method does not require knowledge of the cause of death in the studied patients. Studies on population data have shown that when the incidence of a cancer in the reference population is not high, the net survival estimated via the relative-survival framework is less affected by the above-mentioned biases. This method is used to measure the patients' survival and compare it with the survival of the matched population in terms of age, sex, and calendar time.[8]

Several factors are associated with the survival of patients with gastric cancer. The most important factor is the stage of the disease. When taking into account the stage of the disease, the 5-year survival of patients may vary between 5% and 80%.[9] The 1- and 5-year net survival rates of patients with gastric cancer in England are 41.8% and 18.9%, respectively.[6]

A review of studies conducted in Iran shows that researchers have paid less attention to the measurement of net survival. The present study drew upon hospital data obtained from a cancer diagnosis and treatment referral center in Iran to evaluate the 5-year net survival of patients with gastric cancer after surgery as the primary treatment modality. The evaluation was performed using the relative-survival framework to introduce and apply this method for survival analysis.

Patients and Methods

In this study, after obtaining approval from the Ethics Committee of Tehran University of Medical Sciences, we used and reanalyzed the data collected by an important study carried out in Iran aiming at evaluating the survival of patients with gastric cancer after surgery.[10] The mentioned study collected the data on patients referring to the Cancer Institute of Imam Hospital in Tehran, which is one of the central hubs for cancer diagnosis and treatment in the country, in a period from 1996 to 2000. So far, the mentioned data have been analyzed by different researchers and the results have been published.[10-15] More detailed information on what characteristics of the patients were evaluated and how the variables were measured can be found in the original article.[10]

First, considering the objectives of the study, the data were redefined using Stata 11.2. The data were described through reporting the numbers and percentages presented in the frequency distribution table. To perform the analysis, we utilized the strs command for life-table estimation of relative survival.[8]

To estimate the expected survival in different sex and age groups and calendar time, we employed the data on mortality in the Iranian population obtained from the Cancer Research Center of the Cancer Institute of Iran (Imam

Khomeini Hospital) applying the Ederer II method.[8] Relative survival was estimated and reported in the 2 forms of interval-specific relative survival and cumulative relative survival. Via the Hakulinen method, the confidence interval was calculated for 5-year relative survival.[16] In addition, 1-year to 5-year relative survival was reported by underlying factors in the studied patients including gender, age group, site of involvement, pathology, metastasis, site of metastasis, lymph node involvement, hepatic involvement, distant metastasis, disease stage, and therapeutic interventions.

The effects of the most important underlying factors on survival (including age, sex, disease stage, pathology, and adjuvant therapies) were determined using modeling excess mortality through a full-likelihood approach.[8] Because of collinearity, the rest of the variables were excluded from the model.

Results

We analyzed data on a total of 330 patients, consisting of 228 (69.1%) men and 102 (30.1%) women with gastric cancer. The study population was followed up for a maximum of 10 years. Adenocarcinoma was the most common type of malignancy in that it affected 281 (85.2%) patients. Concerning the stage of the disease, 248 (75.1%) patients referred to the center when they were at stage 3 or stage 4 of the disease. The patients were aged between 32 and 96 years.

Table 1 presents the life-table estimation of net survival using interval-specific relative survival and cumulative relative survival. According to the life-table estimation of point- and interval-specific survival, the 1- and 5-year net survival rates of the patients after surgery, respectively, were 67.96 (95% CI: 62.35–72.98) and 23.35 (95% CI: 17.94–29.28) (figure 1). The lowest index value for interval-specific relative survival was 79.12%, which was related to the time interval between 1 and 1.5 years: it represents the greatest risk of death from the disease. When the value reaches 100% (or more), it represents the statistical cure of the patients from the seventh year onwards.

As is shown in table 2, the 5-year net survival rates for the men and women, correspondingly, were 26.11% and 17.97% (figure 2). This index had changed for disease stages 1 to 4 and decreased from 48.42% to 16.44% (figure 3). Net survival in the patients with the most common pathological form of the disease

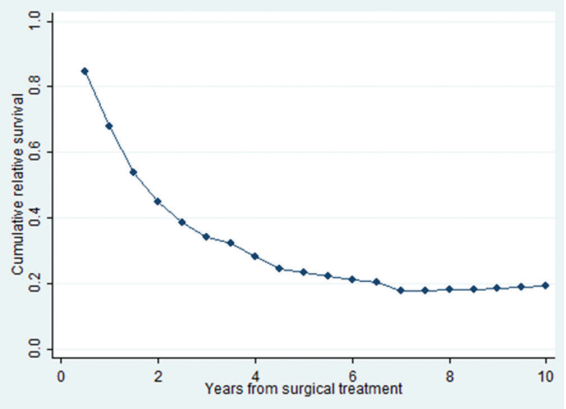

Figure 1: Cumulative relative survival of the patients with gastric cancer.

Table 1: Life-table net survival estimation of interval-specific and cumulative relative survival

Interval (y)	n	d	w	Observed p	Expected p	r	Observed cs	Expected cs	Relative cs	95% CI for Relative cs	
0-.5	330	55	5	83.21	98.48	84.49	83.21	98.48	84.49	79.91	88.18
0.5-1	270	55	8	79.32	98.62	80.43	66.00	97.12	67.96	62.35	72.98
1-1.5	207	44	13	78.05	98.65	79.12	51.52	95.82	53.77	47.85	59.37
1.5-2	150	26	7	82.25	98.76	83.28	42.37	94.63	44.78	38.87	50.57
2.2.5	117	17	6	85.09	98.69	86.22	36.06	93.39	38.61	32.77	44.46
2.5-3	94	12	2	87.10	98.72	88.23	31.40	92.19	34.06	28.34	39.93
3-3.5	80	5	3	93.63	98.77	94.80	29.40	91.05	32.29	26.59	38.19
3.5-4	72	9	8	86.76	98.78	87.83	25.51	89.95	28.36	22.79	34.25
4-4.5	55	8	5	84.76	98.75	85.84	21.62	88.82	24.35	18.93	30.22
4.5-5	42	2	5	94.94	98.98	95.92	20.53	87.91	23.35	17.94	29.28
5-6	35	3	13	89.47	97.73	91.55	18.37	85.91	21.38	15.87	27.55
6-7	19	3	5	81.82	98.20	83.32	15.03	84.36	17.81	12.03	24.65
7-8	11	0	6	100.00	98.04	102.00	15.03	82.71	18.17	12.28	25.15
8-9	5	0	4	100.00	97.92	102.13	15.03	80.98	18.56	12.54	25.68
9-10	1	0	0	100.00	96.24	103.91	15.03	77.94	19.28	13.03	26.69

N: Number alive at start; d: Number of deaths during the interval; w: Withdrawals (censorings) during the interval; p: Interval-specific survival (percentage); r: Interval-specific relative survival (percentage); cs: Cumulative survival (percentage); CI: Confidence interval

Table 2: One to 5-year net survival of gastric cancer by underlying characteristics

Characteristics	Group	Count (%)	1 y	2 y	3 y	4 y	5 y
Sex	Male	228 (69.1)	69.59	46.75	36.49	30.40	26.11
	Female	102 (30.1)	64.43	40.64	29.08	24.15	17.97
Age	≤60	87 (26.4)	76.12	56.61	46.21	42.22	39.27
	61-70	123 (37.3)	75.43	51.30	40.28	31.95	23.91
	>70	120 (36.3)	54.12	28.41	17.17	12.10	7.53
Site	Cardia	145 (43.9)	64.31	38.85	29.51	24.58	22.07
	Antrum	63 (19.1)	69.73	52.13	42.82	38.03	26.89
	Other sites	122 (37.0)	71.30	48.34	35.67	28.71	23.81
Pathology	Adenocarcinoma	281 (85.2)	68.27	43.77	32.90	27.62	22.17
	Other types	49 (14.8)	66.21	50.53	40.57	32.46	29.55
Metastasis	Yes	192 (58.2)	66.40	40.16	29.96	21.52	16.60
	No	138 (41.8)	70.10	51.26	39.83	38.46	33.48
Lymph node involvement	Yes	143 (43.3)	66.72	40.53	33.06	25.43	19.92
	No	187 (56.7)	68.90	48.01	34.83	30.68	26.08
Liver involvement	Yes	24 (7.3)	52.78	48.48	21.46	14.69	15.31
	No	306 (92.7)	69.11	44.62	34.91	29.26	23.92
Other organs involvement	Yes	43 (13.0)	71.03	30.50	21.66	12.59	8.49
	No	287 (87.0)	67.49	47.03	36.01	30.93	25.78
Stage	I	22 (6.7)	70.06	62.30	53.68	54.86	48.42
	II	60 (18.2)	78.17	53.83	41.35	39.58	36.36
	III	54 (16.4)	59.37	42.51	32.87	30.85	25.21
	IV	194 (58.8)	66.83	40.34	29.66	21.30	16.44
Treatment	S	67 (20.3)	32.27	21.96	15.90	16.35	16.81
	SC	76 (23.0)	53.61	26.92	17.27	15.50	13.34
	SCR	101 (30.6)	74.91	48.82	41.84	33.58	32.35
	SCRA	86 (26.1)	98.49	70.85	51.61	41.98	27.65

Other types: Squamous cell carcinoma, small-cell carcinoma, carcinoid tumor, spindle-cell tumor, sarcoma, and lymphoma; Other sites: fundus, body, and pylorus ; Other organs: lungs, diaphragm, spleen, pancreas, and bone; S, Surgery; SC, Surgery+ chemotherapy; SCR, Surgery+ chemotherapy+ radiotherapy; SCRA, Surgery+ chemotherapy+ radiotherapy+ adjuvant surgery

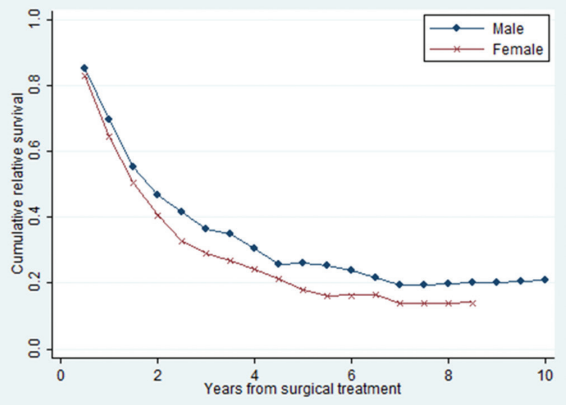

Figure 2: Cumulative relative survival of the patients with gastric cancer by gender.

(i.e., adenocarcinoma) was 22.17%, which was lower than that of the other forms (29.55%).

With increasing the number of adjuvant therapies, relative survival increased too. We estimated the expected hazard ratio in a multiple model within the first 5 years of follow-up, and the results showed that higher stages of the disease (P=0.001), older ages (P=0.007), and less use of adjuvant therapies (P<0.001) were independently associated with excess mortality (table 3)

Discussion

One of the main advantages of relative survival estimations is that it does not need determination of the exact cause of death among the patients to analyze their survival. However, it is necessary to have information regarding the expected mortality in the community.[8,16] It is also essential to select the sample from the same community. As a result, it is recommended to use this method for the analysis of cancer registry data. When the data are not directly obtained from the same community, this procedure should be conducted with caution and prudence. In this study, the data were obtained from a medical center. Nonetheless, as the Cancer Institute is one of the major referral centers in Tehran and the country, it can be assumed that the composition of its clients is very close to that of the Iranian population.

Table 3: Modeling excess mortality using a full-likelihood approach for 5 years' follow-up

End of year	EHR	SE for EHR	z	P	95% CI for EHR	
2	1.35	0.22	1.84	0.065	0.98	1.87
3	0.93	0.21	-0.30	0.763	0.58	1.47
4	0.65	0.21	-1.30	0.193	0.34	1.23
5	0.68	0.27	-0.93	0.351	0.31	1.51
Characteristics						
Female	1.18	0.18	1.09	0.277	0.87	1.59
Elder age group	1.30	0.13	2.68	0.007	1.07	1.58
Adenocarcinoma (vs. other types)	0.90	0.19	-0.46	0.646	0.59	1.37
Higher stage	1.29	0.10	3.32	0.001	1.11	1.51
More adjuvant therapies	0.63	0.04	-6.36	<0.001	0.55	0.73

EHR: Expected hazard ratio; SE: standard error; CI: Confidence interval; Other types: squamous cell carcinoma, small-cell carcinoma, carcinoid tumor, spindle-cell tumor, sarcoma, and lymphoma; Adjuvant therapies: chemotherapy, radiotherapy, and adjuvant surgery

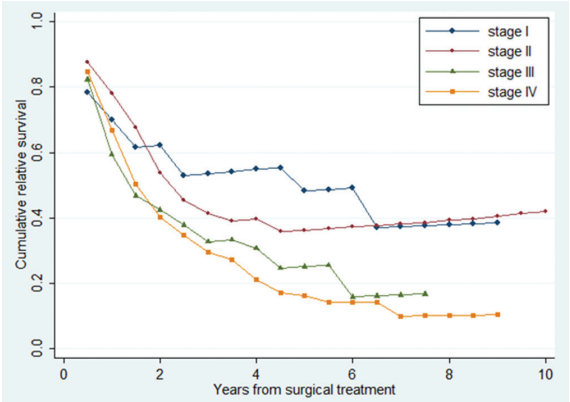

Figure 3: Cumulative relative survival of the patients with gastric cancer by stage.

Net survival represents a ratio of the patients in a hypothetical scenario (in which cancer is the only possible reason for the death) that are expected to survive after a defined period of follow-up. In survival analysis, it is necessary to eliminate or accommodate the effects of competing risks. In the real world, accommodation of competing risks requires that the cause of death from cancer be exactly separated from those of other types of death. The most important sources for determining the cause of death are medical records and death certificates, which are not exact in many cases.[17] Even when such documents report that the cause of death is something other than cancer, we cannot be sure that the preliminary cause of death is not associated with the main disease (cancer). At least, we cannot say with confidence that cancer played no role in the death.[18] This is the most important reason for the use of net survival because when we accept the aforementioned hypothetical scenario, the issue of competing risks is completely eliminated.

As one of the main biases associated with the use of net survival, when cancer (e.g., lung cancer) is highly associated with one of the prevalent risk factors (e.g., smoking), excess mortality will be overestimated. However, previous studies have shown that this type of bias is low.[19] Given the problems associated with recording the cause of death in the national and legal registry systems in Iran and because of the low bias due to common risk factors in the community, this method is appropriate for analyzing the survival of patients with gastric cancer.

Clinical cure occurs when all signs of the cancer are removed. In fact, it is the definition of survival at the individual level. Nevertheless, at the population level, cure occurs when the mortality of the patients approaches the rate of mortality among the general population. (It is also called statistical cure.) In the present study, as the values of interval-specific relative survival reached 1 and an interval-specific relative survival ratio of unity became stable, statistical cure was reported from the seventh year. Despite the increase in interval-specific relative survival over time, a reduction was observed in the net survival of the patients; however, because of the significant effect of age in the multivariate model, the observed changes were not significant.

Based on the estimates obtained from this study and previous analyses, the 5-year survival rate in Iran is lower than that in most developed countries.[20-23] Although in this study the difference between the women and the men in terms of 5-year survival was not significant, it was numerically in line with our knowledge about the better prognosis of disease in men.[24-27] In the study of Moghimi-Dehkordi et al.[3] on 746 patients with gastric cancer in Iran, no gender-related difference was observed between the participants.

Consistent with available studies and scientific resources which indicate that disease stage is

the most decisive factor in cancer prognosis after treatment, in this study we observed a significant correlation between disease stage and net survival among the patients, such that with every stage of the progress of cancer, the expected hazard ratio increased by 29%. In addition, aging was also an important factor associated with reduced patient survival, which chimes in with the findings of other studies.[28,29] Zeraati et al.[15] analyzed the same data in a real-world construct in a cause-specific setting. In that study, the crude survival measure was calculated and the 5-year survival rate in these patients was estimated to be 23.6%. In the analysis of the same data using the competing risks method to estimate the cumulative incidence functions, the 5-year survival rate was estimated at 20.4%.[14] Through a multi-state model and the Weibull cure model, the same value was reported to be 21.6%[11] and 24%,[12] respectively. As was shown, the confidence interval of 5-year net survival estimated in this study not only covers all the aforementioned estimates but also its point estimate is placed within the range of the point estimates obtained from previous analyses (between 20.4% and 24%). Additionally, it shows that the model with hypothetical scenarios is consistent with models derived from a real-world construct.

Conclusion

According to our life-table estimation of interval-specific survival, the 1- and 5-year net survival rates of the patients after surgery were 67.96 and 23.35, correspondingly. It is recommended to use the net survival index within a relative survival framework to analyze the survival of cancer patients as an alternative approach not only to eliminate biases due to competing risks and their dependencies but also to estimate the cure at population level regarding the most important individual characteristics such as age, sex, and calendar time.

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Conflict of Interest: None declared.

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