

RESEARCH ARTICLE

Survival Analysis of Patients with Gastric Cancer Undergoing Surgery at the Iran Cancer Institute: A Method Based on Multi-State Models

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Abstract

Background: Gastric cancer is one of the most common causes of cancer deaths all over the world and the most important reason for its high rate of death is its belated diagnosis at advanced stages of the disease. Events occur in patients which are regarded not only as themselves factors affecting patients' survival but also which can be affected by other factors. This study was designed and implemented aiming to identify these events and to investigate factors affecting their occurrence. **Materials and Methods:** Data from 330 patients with gastric cancer undergoing surgery at the Iran Cancer Institute from 1995-1999 were analyzed. The survival time of these patients was determined after surgery and the effects of various factors including demographic, diagnostic and clinical as well as medical, and post-surgical variables on the occurrence of death hazard without relapse, hazard of relapse, and death hazard with a relapse were assessed. **Results:** The median survival time for these patients was 16.3 months and the 5-year survival rate was 21.6%. Based on the results of multi-state model, age and distant metastases affected relapse whereas disease stage, type and extent of surgery, lymph nodes metastases, and number of renewed treatments affected death hazard without relapse. Moreover, age, type and extent of surgery, number of renewed treatments, and liver metastases were identified as factors affecting death hazard in patients with relapse. **Conclusions:** Most cancer studies pay heed to factors which have effect on death occurrence, but some events occur which should be taken into consideration to better describe the natural process of the disease and provide researchers with more accurate data.

Keywords: Gastric cancer - intermediate event - multi-state model - proportional hazards model - survival rate

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Introduction

Gastric cancer is one of the most common causes of cancer deaths all over the world. Now, gastric cancer includes 10% of cancers in the world and is one of the most prevalent kinds of cancers (Parkin, 1998). According to the latest statistics of Iran Cancer Research Center, gastric cancer is the most common cancer among Iranian men and the third most common cancer among Iranian women after breast cancer (Mohagheghi et al., 1998; Mohagheghi, 2004).

The primary treatment of gastric cancer in initiative stages is surgery; so it is regarded as the best treatment for cancer. Radiotherapy and chemotherapy will be used as renewed treatments, if necessary. Unfortunately, more than 80% of patients with gastric cancer are diagnosed at a stage when common treatments such as gastrectomy, chemotherapy, or radiation therapy are not effective in increasing the patients' survival (Sadighi et al., 2005; Samadi et al., 2007). For this reason, the 5-year survival

rate is low in patients with gastric cancer after surgery. This rate has been reported to be 29.6% in China, 4.4% in Thailand, 37% in the US, 22% in Switzerland, 30% in France and 21% in Iran (Thong-Ngam et al., 2001; Triboulet et al., 2001; Schwarz and Zagala-Nevarez, 2002; Adachi et al., 2003; Ding et al., 2004; Zeraati et al., 2005c). The increase in these patients' survival after surgery involves identifying various factors, including demographic, clinical and diagnostic, therapeutic, and post-surgical. Some of these variables may undergo no change over time, e.g. patient's sex, or just their obtained measurements calculated and recorded at the commencement of study are presented in modeling. But in many survival studies, the sample subjects may be subjected to monitoring and follow-ups for several times during the study, and in the meantime their variable-based data are systematically measured, recorded and collected. Such data depend on time and therefore they are often called Time-dependent covariates. In some studies we are faced with a class of time-dependent covariates

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which are not only effective in patients' survival but their occurrence also is influenced by various factors. Relapse is an obvious example for these variables. Not only does it affect patients' survival as a time-dependent variable but its occurrence is also influenced by different factors. Such variables, in fact, are events that occur in patients during the study and are among factors affecting survival. Besides, they affect treatment process and death event.

One of the statistical models designed to consider such events is to take such variables into account as time-dependent variables and to model survival data based on them (Andersen, 1993; Andersen and Keiding, 2002; Collett, 2003; Klein and Moeschberger, 2003; Zeraati et al., 2006; Kalbfleisch and Prentice, 2011). This approach has limitations because the effect of these variables on death occurrence can only be studied in this situation and it will not be likely to identify the factors affecting their occurrence.

Another statistical model designed to consider such events is the multi-state model. According to this model, patients experience different states during the study from the beginning to death event. The time reaching each state and factors affecting its occurrence play a fundamental role in patients' survival. Considering these states (often called intermediate events) has developed a novel approach in survival studies, because the natural trend of disease in such cases can be considered as a stochastic process in which patients can be placed in various states throughout the study.

Standard models of survival which are the simplest of multi-state model focus solely on factors affecting time to occurrence of death event. In these models, the patient is "alive" at the beginning of the study and then his/her state may change to "death". This is the only transition which is considered for patients during the study. This transition can be illustrated (Figure 1).

Models more complex than two-state, provide the patients with the possibility of more transition during the study. These models are used when the initial state of the patient, i.e. "being alive", is itself divided to two or more other states. The number of division depends on the type of disease. In the process of gastric cancer disease, the survival time of patient is recorded since the patient has undergone surgery. After surgery the patient enters the study and is subjected to death hazard. In these studies, the occurrence of death is considered as the end point of the study. But there is no difference between patients who have experienced a relapse and those who have not suffered a relapse event. It seems very unlikely that death hazard be the same between the two groups. Moreover, factors affecting the occurrence of death are also different in these two groups. Therefore, separation of the patient's state of "being alive" based on relapse is proposed (Figure 2).

Most studies on cancer take factors affecting time to the occurrence of death into account, but in many cases, events occur in patients during the study period which may affect



Figure 1. Standard Models

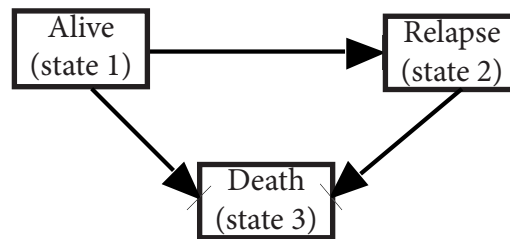


Figure 2. Three Transitions for Patients During the Study in the Above Model. Death hazard without a relapse (state 1→state 3); Relapse hazard (state 1→state 2); Death hazard with a relapse (state 2→state 3)

the final results (Yagi et al., 2000; Adachi et al., 2003; Buonadonna et al., 2003; Chau et al., 2004; Zeraati et al., 2005; Dehkordi and Tabatabaee, 2007; Pourhoseingholi et al., 2007; Biglarian et al., 2009). Disregarding these states or intermediate events and the time of their occurrence can influence the results of study and bias the data analysis (Kay, 1986; Andersen, 1988; Andersen and Keiding, 2002). Considering these intermediate states, of course, as time-dependent covariates has been proposed as an alternative approach. In this state, however, the effect of these variables can only be investigated on the occurrence of death and there is no chance to identify factors affecting their occurrence. Taking intermediate events into account, multi-state models provide a better description of disease process. In addition, it helps cancer researchers identify factors affecting the occurrence of these events. This study aims to identify factors affecting various events during the study which occur in patients with gastric cancer undergone surgery. The study has been designed and implemented based on a multi-state model.

Materials and Methods

In this study, 330 patients with gastric cancer with the following data were studied: *i*) the patients had been hospitalized and had undergone surgery from 1995-1999 in surgical wards of Cancer Institute of Iran; *ii*) they had records in the archives of the hospital, and in their files their addresses and phone numbers were available for subsequent follow-ups. The survival time of patients was determined after surgery and those patients who were still alive at the end of study period or the ones whose data were not available after a specific time-period were considered right censored.

The effect of demographic variables such as age (at the time of surgery), sex, and smoking history, as well as clinical data of the disease including tumor location (Cardia - Anterior - other), type of pathology (Adenocarcinoma - other), disease stage (I-II-III-IV) , location of metastases (lymph nodes - Liver - other), and the type and extent of gastrectomy (T.G-S.G-D.G-PT.G-PX.G) was studied. Moreover, the effect of post-surgical and treatment variables including number of renewed treatments (chemotherapy - radiotherapy - surgery or a combination of them) on the occurrence death hazard without a relapse, relapse hazard, and death hazard with a relapse was evaluated. To examine the effect of different variables on patients' survival, a multi-state model with

three states of patient's being alive without a relapse (state 1), relapse (state 2) and death (state 3) was considered. Moreover, based on Cox proportional hazards model, the effect of different variables on these transitions was studied. A significance level of 5% was considered and the data were analyzed using R 2.15.1 software.

Results

Two hundred twenty-eight patients were male (69.1%) and 100 (30.3%) had a history of smoking. The mean and median age of patients at diagnosis time were 65.61 11 and 68 years (range: 32-96 years). The mean of age diagnosis was 65.7 11.22 years for men and 65.41 10.56 years for women. 239 patients (72.4%) died by the end of the study and the rest were censored. The survival mean and median of these patients were 24.86 23.73 and 16.33 months, respectively. The patients' one-year, three-year, and five-year survival rates were 66%, 31%, 21.6%, consecutively. Analyses showed that 43 patients (13.03%) had a relapse, and in 43.9% of patients Cardia and in 19.1% of them Anterior was involved. In the pathology of 85.2% of patients Adenocarcinoma and for the rest of patients other pathologies (squamous cell carcinoma, small cell carcinoma, carcinoid tumor, carcinoma, malignant lymphoma, stromal tumor, and spindle tumor) have been reported. 192 patients (58.2%) had metastases out of which 66.67% suffered from lymph nodes metastases only. 52.42% of patients had undergone Total Gastrectomy, 27.27% had undergone Subtotal Gastrectomy, 3.03% had undergone Distal Gastrectomy, 8.79% had undergone Partial Gastrectomy and 8.48% had undergone Proximal Gastrectomy. The analysis of disease stage revealed that 6.67% of patients were in stage I, 18.18% in stage II, 16.36% in stage III and 58.79% in stage IV. 20.3% of patients had not received any renewed treatments whereas 26.06% of the patients had received three renewed treatments.

The effect of different variables on death hazard without a relapse, hazard of relapse, and death hazard with a relapse has been shown in Table 1. Variables of age (at diagnosis time) and distance metastases were factors affecting the occurrence of relapse. Based on these results, distance metastases increases the hazard of relapse by 3.20 (95%CI: 1.28-7.96) times and with each year increase in patients' age, the hazard of relapse rises by 1.07 (95%CI: 1.04-1.11) times. Furthermore, male (sex), smoking history, receiving renewed treatment, lymph nodes metastases, liver metastases, as well as Adenocarcinoma pathology, location of Cardia involvement, surgeries (D.G-PT.G-PX.G), and disease stage (II-III-IV), were not statistically significant but were among the factors which would increase the hazard of relapse.

Regarding factors affecting the hazard of transition from state 1 to state 3 (death hazard without a relapse), only variables of disease stage, type and extent of gastrectomy, lymph nodes metastases, and number of received renewed treatments were significant. These analyses showed that the increase in the number of renewed treatments minimized the hazard of patients' death to 0.44 (95%CI: 0.34-0.57) times. In addition,

death hazard was 0.27 (95%CI: 0.08-0.91) times less in patients who were at stage II of the disease compared to patients who were in stage I. But for patients in stages III and IV, death hazard maximized to 1.19 (95%CI: 0.46-3.09) and 6.60 (95%CI: 1.02-42.85) times respectively. The analysis of type and extent of surgery also showed that only S.G surgery maximizes death hazard to 2.60 (95%CI: 1.26-5.39) times in these patients and other surgeries (D.G-PT.G-PX.G) reduce the probability of patients' death. Among other metastases, only lymph nodes metastases had significant effect on death hazard without a relapse so that this metastases maximized death hazard to 5.86 (95%CI: 1.13-30.53) times. Although many of the factors were not statistically significant in this transition, the analyses showed that female (sex), advanced age at the time of diagnosis, Adenocarcinoma pathology, and distance and liver metastases were among factors maximizing death hazard in patients without a relapse.

The analysis of the effect of different variables on transition hazard from state 2 to state 3 (death hazard with a relapse) also revealed that the variables of patient's age at the time of diagnosis, number of renewed treatments, type and extent of surgery, and liver metastases were significant. These analyses indicated that with each year increase in patient's age, death hazard increases by 1.06 (95%CI: 1.01-1.11) times in patients. With an increase in the number of renewed treatments, death hazard decreases by 0.55 (95%CI: 0.40-0.74) times in these patients. Among surgeries, only S.G and PX.G reduce death hazard 0.33 (95%CI: 0.12-0.94) and 0.22 (95%CI: 0.09-0.54) times respectively. Other surgeries (D.G-PT.G) have cumulative effect on death hazard. The analyses also showed that liver metastases increases death hazard in patients with a relapse up to 7.36 (95%CI: 1.30-41.61) times. In this transmission, variables of female (sex), Adenocarcinoma pathology, advanced stages of disease, lymph nodes metastases, distance metastases, and location of Cardia involvement were among the factors increasing death hazard in patients with a relapse. None of the above factors, of course, were statistically significant in the present study.

Discussion

In the current study, the 5-year survival rate of patients with gastric cancer undergone surgery based on multi-state model was estimated 21.6%. The estimation achieved in this study was lower compared to many studies conducted in America, Switzerland, France, and China (Thong-Ngam et al., 2001; Triboulet et al., 2001; Schwarz and Zagala-Nevarez, 2002; Wang et al., 2002; Adachi et al., 2003; Ding et al., 2004). Unfortunately, most patients with gastric cancer are diagnosed at a stage when common treatments such as gastrectomy, chemotherapy, or radiation therapy are not effective in increasing the patients' survival. For this reason, the 5-year survival rate is low in these patients after surgery. Increasing the survival rate in these patients after the surgery requires identifying various factors e.g. demographic, clinical and diagnostic, and medical, and post-surgical. There are various statistical methods to investigate the effect of

different factors on the survival of patients with gastric cancer. The identification of factors affecting the survival of patients with gastric cancer, however, is mostly done by standard models of survival (Yagi et al., 2000; Adachi et al., 2003; Buonadonna et al., 2003; Chau et al., 2004; Zeraati et al., 2005c; Dehkordi and Tabatabaee, 2007; Pourhoseingholi et al., 2007; Biglarian et al., 2009). These models generally focus on the effective factors on time to occurrence of the death event. But in many cases, events occur for patients during the study which may affect the final results. Disregarding these states or intermediate events and the time of their occurrence, can also affect the results and cause bias to creep into data analysis. Using multi-state models, perhaps at first glance, may cause statistical analysis to become more complex but these models have advantages vis-à-vis standard methods. The first advantage of these models is considering intermediate events like relapse in a survival study which leads to differentiation in the impact of different variables on patients' survival so that the effect of some variables can be direct and without interference of intermediate events or can be produced with indirect effect on intermediate events. In fact, many of the factors affecting the patients' survival have direct effect on death event, while for another group of variables, they have effect on patients' survival through affecting the occurrence of intermediate events such as relapse. Certainly in such cases, the analysis results based on multi-state models will be more accurate. In the present study, the effect of different variables on patients' survival was studied according to a multi-state model with three states of patient's 'being alive' without a relapse (state 1), relapse (state 2), and death (state 3). Based on the results of Table 1, the analysis of the effect of different variables showed that patient's age at the time of diagnosis was one of the effective factors on relapse (state 1→state 2) as well as death hazard with a relapse (state 2→state 3). This variable, however, had no significant effect on death hazard without a relapse (state 1→state 3). Most studies on patients with gastric cancer which have been designed based on standard models of survival, though, indicate that the survival rate of patients does decrease with age (Zeraati et al., 2005a; 2005b; 2006; Dehkordi and Tabatabaee, 2007; Pourhoseingholi et al., 2007; Akbari et al., 2009; Maroufizadeh et al., 2011; Roshanaei et al., 2011; Haidari et al., 2012). But the analysis based on multi-state model shows that age does not have a direct impact on the survival of patients, but its effect is indirect and through the occurrence of a relapse only. Number of received renewed treatments and the type and extent of surgery are also factors affecting death hazard with a relapse (state 2→state 3) and death hazard without a relapse (state 1→state 3). But as you can see in Table 1, these variables have no impact on relapse (state 1→state 2). Therefore, number of received renewed treatments and the type and extent of surgery have direct impact on the survival of patients. These findings are congruent with those reported by studies conducted on standard models of survival whose reason is the direct effect of these variables on the survival of patients (Zeraati et al., 2005a; 2005b; Zeraati et al., 2005c; 2006; Pourhoseingholi et al., 2009; Roshanaei et al., 2011). Another advantage of these models

Table 1. The effect of Different Variables on Hazard of Relapse, Death Hazard without a Relapse and Death Hazard with a Relapse (Hazard ratio with 95% confidence interval)^a

Risk factor	state1-state2	state1-state3	state2-state3
Sex			
Male			
Female	0.93(0.52-1.65)	1.32 (0.71-2.46)	1.37 (0.67-2.79)
Age	1.07 (1.04-1.11)	1.00 (0.98-1.03)	1.06(1.01-1.11)
Smoking History			
NO			
Yes	1.11 (0.58-2.14)	0.92 (0.49-1.74)	0.54 (0.21-1.40)
Location			
Cardia			
Anterior	0.83 (0.32-2.15)	0.42 (0.17-1.05)	0.71(0.22-2.25)
Other**	0.99 (0.57-1.73)	0.54(0.30-0.97)	0.92 (0.41-2.07)
Pathology			
Adenocarcinoma			
Other*	0.94 (0.43-2.07)	0.65 (0.34-1.25)	0.82 (0.23-2.98)
Lymph node Metastases			
Negative			
Positive	2.33(0.69-7.84)	5.86(1.13-30.53)	2.32(0.45-11.83)
Liver Metastases			
Negative			
Positive	1.65 (0.45-6.01)	1.43(0.71-2.84)	7.36 (1.30-41.61)
Distance Metastases			
Negative			
Positive	3.20(1.28-7.96)	1.39 (0.67-2.88)	1.05 (0.58-1.91)
Stage			
I			
II	3.34(0.83-13.40)	0.27(0.08-0.91)	6.08(0.45-81.99)
III	2.76(0.65-11.62)	1.19 (0.46-3.09)	6.51(0.45-94.84)
IV	1.20 (0.18-8.02)	6.60(1.02-42.85)	2.63 (0.13-53.36)
Number of Renewed Treatment			
	1.14(0.85-1.53)	0.44 (0.34-0.57)	0.55(0.40-0.74)
Type of Gastrectomy			
Total			
Subtotal	0.82 (0.36-1.90)	2.60 (1.26-5.39)	0.33 (0.12-0.94)
Distal	1.12 (0.38-3.34)	0.09(0.00-2.42)	5.54 (0.75-86.82)
Partial	1.32(0.52-3.34)	0.47 (0.15-1.47)	1.02(0.28-3.66)
Proximal	1.48(0.71-3.06)	0.15(0.04-0.51)	0.22(0.09-0.54)

*Squamous cell carcinoma (SCC), small-cell carcinoma, carcinoid tumor, spindle cell tumor, sarcoma, malignant lymphoma, **Diaphragm, spleen, pancreas, lungs, bone, *First category is considered as a reference group

is that the data analysis of patients' survival derived from multi-state model reveals interesting results compared to common analysis because based on the analysis of multi-state model, the behavior of variables under study can be studied in different transitions the patients go through during the study and arrive at more accurate understanding of their effect on the survival of patients. On this basis, most studies have shown that disease stage, lymph nodes metastases, distance metastases, and liver metastases are among factors affecting patients' survival (Zeraati et al., 2006; Shiraiishi et al., 2007; Pourhoseingholi et al., 2009; Maroufizadeh et al., 2011; Roshanaei et al., 2011). But more detailed analyses based on multi-state models in this study showed that lymph nodes metastases and disease stage variables are among the factors affecting death hazard without a relapse (state 1→state 3), whereas distance metastases is among factors affecting relapse (state 1→state 2), while liver metastases is among factors affecting death hazard with a relapse (state 2→state 3).

Applying such a complex model instead of the standard models of survival makes us have better understanding of the natural process of the disease. Not only will we be able to identify factors affecting the occurrence of death

event, we will be able to identify different events which occur in patients during the study, hence factors affecting them. Multi-state models take a closer look at the behavior of the variables and provide the researchers with more accurate data.

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