RESEARCH COMMUNICATION

Assessment of Risk Factors Affecting Recurrence of Patients with Gastric Cancer in the Presence of Informative Censoring in Iran

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Abstract

Background: In some survival studies, several events are taken into consideration. If the events are independent then the ordinary methods such as Kaplan-Meier, Cox or parametric models can be used. If one of the events dependently (informatively) censors the other, the results are biased. The present study was designed to assess the risk factors for recurrence of patients with gastric cancer in the presence of informative censoring using parametric models with a semi-competing risk approach. Materials and Methods: In a retrospective study, 408 cases of gastric cancer were selected from the patients referred to the Tehran Cancer Institute from March 2003 to March 2007. Gender, age at diagnosis, distant metastasis, tumor size, histology type, tumor grade, pathologic stage, tumor site, and type of treatment were studied as prognostic factors and used in the models. Parametric models such as Weibull, exponential, log-logistic were used with informative right censoring using Akaike Information Criteria (AIC) as criteria to compare models. The data were analyzed using R statistical software. A p-value of less than 0.05 was considered as statistically significant. Results: Based on Akaike information criteria (AIC), the Weibull model best fitted to data. The effect of tumor size and pathologic stage were significant on recurrence in both univariate and multivariate analyses. Tumor site and tumor grade were significant only in univariate analysis. Conclusions: The results showed that semi-competing risk methods perform well in determining risk factors for disease recurrence.

Key words: Gastric cancer - informative censoring - parametric model - risk factors - semi-competing risk

Asian Pacific J Cancer Prev, **12**, 2443-2446

Introduction

It has been reported that recurrence of gastric cancer (GC) occurred in some patients after gastrectomy and recurrence rate in this patient is 1.4–7 percent (Ichiyoshi et al., 1990; Furusawa et al., 1991; Craddock, 1992; Ikeda et al., 2005; Lo et al., 2007). In survival analysis, competing risk method is used to investigate several events and related risk factors. In this kind of data only the time and type of the first event are recorded. For these types of studies, each of the events may censor each other. Thus, each event is considered as a terminal event. When the first event occurs, the follow up method is ended or in the end of the study of the desired events do not occur of.

In the literature of survival, these types of competing risks are called classical competing risks (Hougaard, 2000). In contrast, there are other types of competing risk in which some of the events such as death and dropout are terminal (with occurrence of the event follow-up ends) and other events are non-terminal (with occurrence of the event follow-up is continued) such as relapse and progression. These types of the risks were first introduced as semi-competing risks. In semi-competing risk problem, a terminal event can censor non-terminal event but not vice versa. The first time this method has been applied to leukemia patients. This study aimed to determine the relapse distribution (Fine et al., 2001; Jiang et al., 2005).

Unlike competing risk method in which events are mutually independent, in semi-competing risk method the occurrence of the terminal events following non-terminal events is allowed. Thus, there is extra information about terminal events. Semi-competing risk data must consist of at least two events, one of terminal event (might be death or informative dropout), while the other is non-

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terminal event (relapse, distance metastasis, progression of disease, non-fatal disease) (Jiang et al., 2003; 2005). There is a special order in occurrence of events in semi-competing risks data which is not noticed in competing risks data. Using this information and special structure of data in analysis can produce the convenient results (Dignam et al., 2007b). Inference in semi-competing risks often focuses on non-terminal events. Distribution of the terminal event can be determined by cumulative incidence and cause-specific risks. However, the analysis of marginal distribution of non-terminal event, with removing the terminal event, leads to biased estimation. Also, due to the structure of correlation among events, using of Cox proportional hazards analysis and Kaplan-Meier curve is not valid.

Therefore, in survival studies of multiple events under independent assumption can be used Kaplan-Meier and Nelson-Allen, cumulative incidence, cause-specific risks and Cox proportional hazards, but using these methods with dependent structure between two events provide biased estimation (Gred, 2006). Many studies have been performed to evaluate of affecting risk factors on recurrence in gastric cancer patients which were implemented Cox regression and logistic regression models for analysis of data. The majority of these studies showed that the number of patients with relapse is low (Lee et al., 2003; Roviello et al., 2003; Lo et al., 2007; Takenaka et al., 2008c). Although clinicopathological findings have been used to assess the risk factor of recurrence, however, they are sometimes inadequate and improper for predicting recurrence(Moriguchi et al., 1992a). Previous studies were performed with typical statistical methods and non-informative censoring assumption. But the aim of the present study was to use survival parametric models to determine the marginal distribution of recurrence in patients with gastric cancer and prediction of related prognostic factors in the presence of informative censoring and to verify which model is the most efficient.

Materials and Methods

From March 2003 to March 2007, 408 patients with gastric cancer were retrospectively studied in the cancer institute of Tehran Medical University, Iran. The staging of disease before surgery was based on CT-Scan and andosonography and after surgery was based on pathologic reports. At the time of the last follow-up, 89 patients (21.8%) had recurrence of gastric cancer. Recurrence time was calculated from time of diagnosis to the recurrence according per unit month. To identify the independent risk factors, sex, age at diagnosis, tumor grade, tumor site, distant metastasis, tumor size, pathologic stage and type of treatment are evaluated on time to recurrence, univariate and multiple model were performed using a parametric model. All of the significant predictors in univariate analysis were entered in parametric multiple models, such as exponential, Weibull, log-normal and log-logistic to investigate the influence of risk factors on recurrence in two situation. In the first situation, by using competing risk method and assuming that occurrence of two events, recurrence and death, are independent. In the second condition, which our main interest was the determination of the distribution of recurrence time and its related factors, we used semi-competing risk approach. This method was performed with non-informative censoring assumption. The analysis was carried out using R software. The Akaike Information Criterion (AIC) was used to compare the models. All p-values less than 0.05 were considered as statistically significant.

Results

Out of 408 patients, 304 (74.5 %) were male. The mean (SD) age of patients was 57.9 (12.2) years old and the median age 61.9. 89 (21.8%) out of patients had recurrence during the follow-up period. The median time to recurrence was 42.5 months. A total of 89 patients with gastric cancer, the cumulative number of recurrence in 1th, 2th, 3th, 4th and 6th years respectively were 45, 80, 83, 85 and 89 cases. Demographic characteristics and assessment of risk factors on the recurrence, in univariate analysis, showed that tumor grade, tumor site, pathologic stage and tumor size were statistically significant on recurrence (Table 1). The results of multiple analyses, with first situation, indicated that the effects of all variables were not significant (Table 2).

The results of evaluation of risk factors on time to recurrence, using of semi-competing risk approach showed that the Weibull model according to AIC criteria has well fitted the data. Table 3 shows that the tumor size and stage of disease are significant.

Table 1. Demographic Characteristics and Univariate Analysis of Prognostic Factors on Recurrence of Gastric Cancer Patients

P-value	N (%)	Subgroup	Variable
0.21	304 (75.8)	Male	Gender
	104 (24.2)	Female	
0.1	205 (50.2)	<=60	Age at diagnosis
	203 (49.8)	>60	
0.045	40 (10.9)	well	Tumor grade
	110 (30)	moderate	
	217(59.1)	poor	
0.02	119(32.8)	cardia	Tumor site
	99(27.2)	body	
	145(40)	other	
0.16	272(57.7)	negative	Distance metastasis
	199(42.3)	positive	
0.45	150 (38.2)	Chemotherapy	Type of treatment
	243 (61.8)	Chemo & surgery	
0.006	61 (15)	II	Pathologic stage
	141 (34.5)	III	
	206 (50.5)	IV	
0.036	138 (65.4)	<25	Tumor size(mm)
	32 (15.2)	25-45	
	41 (19.4)	>45	

Table 2. Multiple Parametric Model with Risk Factors on Recurrence in Gastric Cancer Patients in a Competing Risk Approach (non-informative censor assumption)

Prognostic factors		Exponentialβ (SE)	Weibullβ (SE)	Log-Logistic β (SE)	Log-Normal β (SE)
Tumor size (mm)	25-45	0.13(0.2)	0.1(0.055)	0.1(0.06)	0.16(0.1)
	>45	0.32(0.21)	0.34(0.23)	0.4(0.23)	0.35(0.2)
Tumor grade	MD	0.41(0.22)	0.4(0.22)	0.39(0.25)	0.39(0.21)
	PD	0.6(0.34)	0.59 (0.29)	0.62(0.4)	0.6(0.38)
Pathologic stage	III	0.18(0.12)	0.14(0.8)	0.17(0.1)	0.1(0.06)
	IV	0.29(0.17)	0.29(0.17)	0.32(0.18)	0.27(0.15)
Tumor site	Body	-0.1(0.07)	-0.07(0.04)	-0.03(0.02(	-0.12(0.07(
	Antrum & Diffuse	-.22(0.14)	-0.17(0.11)	-0.25(0.15)	-0.16(0.11)
Median †	42	41	38	40	
AIC§	317	309	312	314	

Reference group, <25, WD, II, cardia WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; †time-to-recurrence, §Akaike Information Criteria

Table 1. Parametric Model with Risk Factors on Recurrence in Gastric Cancer Patients in a Semi-competing Risk Approach

Variable		RR	(95%CI)
Tumor size(mm) †	<25	1*	
	45-25	1.42#	(1.1-1.82)
	>45	2.02#	(1.6-2.6)
Tumor grade§	WD	1*	
	MD	1.95	(0.8-4.8)
	PD	3.82	(0.6-6.4)
Pathologic stage‡	II	1*	
	III	1.73#	(1.53-1.94)
	IV	2.96#	(2.2-3.7)
Tumor site*	Cardia	1*	
	Body	0.9	(1.2-0.7)
	Other	0.87	(0.5-1.83)
Median †	14.5(8.3-23.5)		
AIC§	284		

*Reference group;†time-to-recurrence (month); §Akaike Information Criteria; #Statistically significant

Discussion

The main purpose of this study was to assess risk factors for recurrence of patients with gastric cancer using parametric models and semi-competing risk approach. Identifying risk factors affecting recurrence can lead to prevention of recurrence and increase longevity of patient. In this study, mean (SD) age of 89 patients with recurrence was 59 12 years.

Univariate analysis in Table 1 indicated that tumor grade, pathologic stage, tumor size and tumor site were associated with recurrence, whereas gender, age at diagnosis, distance metastasis and type of treatment were not significant (Table1). The competing risk method, with independence assumption between recurrence and death, showed that median time to recurrence was 41 months and no significant relationship was found between recurrence and variables (Table 2). The results of this method, because of independent assumption of censoring, may be biased (Gred, 2006).

Semi-competing risk approach was employed to determine distribution of time to recurrence and the result showed that the median time to relapse was 14.5 months. Our research similar to the other studies showed that more than 70 percent of patients recurred in less than two years after treatment and median time to recurrence was estimated between 12 to 22 months (Moriguchi et al., 1992; Ahn et al., 2001; Lee et al., 2003; Buzzoni et al., 2006; Takenaka et al., 2008; Esther, 2009; Cidon, 2010; Park et al., 2010).

Another significant factor in univariate method but not in multiple analyses was tumor grade. Some reports has been indicated significant effect of this variable on recurrence (Hyung et al., 2003; Jiang et al., 2003; Ikeda et al., 2005; Gred, 2006; Dignam et al., 2007; Lai et al., 2009). Whereas the study of 1013 patients (Fumiro et al., 2000) with 24 recurred patients identified a non-significant effect.

We identified that tumor size has a significant relationship with recurrence and patients with tumor size of more than 25 mm had high risk to recurred (table 3). Many authors have shown that same results (Fumiro et al., 2000; Lee et al., 2003; Ohno et al., 2003; Takenaka et al., 2008) the discrepancy of the results obtained in this study with other similar studies can be due to the limited number of relapses in those studies that the number of recurrence cases in these studies was less than 30 (Hyung et al., 2003; Ohno et al., 2003; Buzzoni et al., 2006; Li et al., 2008; Lai et al., 2009; Park et al., 2010).

Although tumor site in univariate analysis was significant but in multiple analyses was not significant. Some studies showed no relation between tumor site and recurrence (Lee et al., 2003; Park et al., 2010; Ahn et al., 2001; Buzzoni et al., 2006; Hyung et al., 2003; Lai et al., 2009; Li et al., 2008) but there are some reports showing that tumor site has significant effect on recurrence (Pacelli et al., 2001; Ohno et al., 2003; Talamonti et al., 2003; Takenaka et al., 2008). Stage of disease is another significant risk factor on recurrence both in univariate and multiple analyses. The risk of recurrence in patients with stages 3 and 4 of disease, 1.73 and 2.96 fold respectively increased with respect to stage 2 (Table3). Some studies indicated similar results (Roderich and Zagala, 2002; Buzzoni et al., 2006) whereas, the result of another (Cidon, 2010) showed that the effect of disease stage was not significant on recurrence. This is because the

patients in that study were in stage of 2 and 3 while in our study more than 50 percent of patients were in stage 4.

In conclusion, we were able to predict the risk factors of recurrence by analyzing of related risk factors on recurrence using semi-competing risk. However, identifying the risk factors is important for increasing survival and quality of life in patients.

Acknowledgements

The Authors thank of Research Centre of Cancer Iinstitute of Imam Khomeini Hospital and Research Department of Tehran Medical University for data gathering and collaboration in this study..

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