Tumori, 96: 433-437, 2010

Parametric model to analyse the survival of gastric cancer in the presence of interval censoring

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ABSTRACT

Aims and background. The objective of the study was to assess the impact of prognostic factors on survival of patients with gastric cancer in the presence of interval censoring using parametric models.

Methods and study design. In a retrospective cohort study, 178 patients with gastric cancer were studied from February 2003 to January 2008. Gender, age at diagnosis, distant metastasis, tumor size, histology type, tumor grade, lymph node metastasis and pathologic stage were selected as prognostic and entered in the models. Weibull, exponential, log-logistic and log-normal analyses with interval censoring were performed as parametric models, and Akaike Information Criterion (AIC) was used to compare the efficiency of models.

Results. The risk of death for patients at an older age, with tumor size greater than 35 mm, distant metastasis and advanced stage of disease was statistically higher. Other clinical and demographic factors were not significant. According to AIC, the log logistic model is the most efficient of all the models in multivariable analysis.

Conclusions. The results indicated that the early detection of a cancer at a young patient age and in primary stages is important to increase survival from gastric cancer. According to statistical criteria, a parametric model can also be a useful statistical model to find prognostic factors in the presence of interval censoring. Although it seems that all models in this analysis fit well, AIC supported the log logistic regression as the best option. Free full text available at www.tumorionline.it

Introduction

Survival analysis is the modeling of time to event of death to evaluate the effects of treatment on survival. Two major regression models are used for right censored data: proportional hazards model (Cox) as a semiparametric method[1] and accelerated failure time model or linear model representation in log time as a parametric model. However, in some cases the time of the event is not exactly known. In this mechanism, we cannot observe the interesting event directly, and it is only known to have occurred during a random interval of time, the censored item called interval censoring[2].

Although Cox regression is the most favored technique in the case of interval censoring, the parametric model[3] also leads to some benefit. Researchers in medical science often tend to prefer semiparametric over parametric models because they requires less assumptions, but some comments recommend that under certain circumstances, parametric models estimate the parameters more efficiently than Cox[4,5]. In a parametric model, we use a maximum likelihood procedure to estimate the unknown parameters, and the technique and its interpretation is well-known by researchers.

Gastric cancer is one of the important causes of mortality due to cancer[6], and is predicted to be the eighth leading cause of all deaths worldwide in the year 2010[7].

Key words: gastric cancer, interval censoring, parametric model.

Acknowledgments: We are thankful to the Cancer Registry Center of the Research Center for Gastroenterology and Liver Diseases, Shaheed Beheshti Medical University, for data gathering and collaboration in the study.

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Received November 16, 2009;
accepted January 13, 2010.

The aim of the present study was to use parametric models to evaluate the prognostic factors of gastric cancer in the presence of interval censoring and to verify which is the most efficient.

Methods

This is a historical cohort study of patients treated from February 2003 through January 2008, between 178 patients whom were admitted to the Taleghani hospital with a diagnosis of gastric cancer. The hospital is a referral center for gastrointestinal cancers, and all of the patients were diagnosed by endoscopy and biopsies. The exclusion criteria were the patients who had not completed document at hospital registry or treated out of the time February 2003 to January 2008 and the start point for survival time was the time of diagnosis which extracted from the patient's document. The study protocol was approved by the ethics committee of the Research Center for Gastroenterology and Liver Disease of Shaheed Beheshti Medical University. In the research center, all patients who register with gastrointestinal cancer are annually followed for survival. The a patient's death was confirmed by contact with the patient's family by telephone, and clinical information was extracted from hospital documents. Since for some patients there was no information regarding the exact time of death, we supposed that type of censoring is interval censoring.

Age at diagnosis, sex, histologic type, tumor grade, tumor size, pathologic stage, lymph node metastasis and distant metastasis were categorized according to the SEER summary staging manual[8] and entered in the parametric model, such as Weibull, exponential log-logistic and log-normal censored regression in the presence of interval censoring. The analysis was carried out using S-plus and relative risk (RR), which are used to interpret the risk of death in parametric results. The term of Akaike Information Criterion (AIC) was employed to compare the efficiency of models. The proposed AIC is a measure of the goodness of fit of an estimated statistical model[9]. It is based on the concept of entropy. The AIC is an operational way of trading off the complexity of an estimated model against how well the model fits the data. A lower AIC indicates better model. All *P* values less than 0.05 were considered as statistically significant.

Results

A total number of 178 patients with gastric cancer entered the study – 30 males (73%) and 48 females (27.0%). The mean age at diagnosis was 58.5 ± 12.7 years. Up to 80% of patients survived during the first year of follow-up, 52.2% during the second year, and 35.3% during third year.

Overall, 7.9% had pathologic distant metastasis, 73% had a tumor size of more than 35 mm, 60.1% were diagnosed at an advanced stage, 38.2% had a poorly differentiated tumor grade, 74.2% had adenocarcinoma NOS, and 11.8% had N3 grade of regional lymph nodes metastasis (Table 1). Mean and median overall survival were 48.31 ± 7.07 and 25.3 months, respectively.

According to univariate analysis (Table 2), the risk of death increased slightly but significantly with patient age. Patients with distant metastasis were also at a higher risk of death, followed by larger tumor size and advanced pathologic stage. Sex, histologic type, tumor grade and lymph node metastasis were not significant as prognostic factors in univariate analysis.

Table 3 shows the results for all the models in multivariate analysis for the 178 cases. According to the multivariate results, the risk of death for patients with tumor size greater than 35 mm was statistically higher in all the models. The presence of pathologic distant metastasis and tumor grade were found to be prognostic factors only in the Weibull model. Other clinical and demographic factors were not significant.

The values of parametric models were compared using the AIC. Based on AIC, log logistic is the most efficient of all the models in multivariate analysis.

Discussion

The purpose of the study was to assess the association between survival of patients with gastric cancer and prognosis factors using parametric models. The results showed that age, metastasis, tumor size and advanced

Table 1 - Demographic characteristics of gastric cancer patients

Variable	Subgroup	Frequency No.	%
Tumor grade	Well differentiated	49	27.5
	Moderately differentiated	61	34.3
	Poorly differentiated	68	38.2
Tumor size (mm)	<35	48	27
	>35	130	73
Histologic type	Adenocarcinoma NOS	132	74.2
	SCC, MPA, MA	24	13.5
	Other type of histology	22	12.4
Regional lymph node metastasis	N1	52	29.2
	N2	105	59
	N3	21	11.8
Pathologic distant metastasis	Absent	164	92.1
	Present	14	7.9
Pathologic stage	I (0,IA,IB), II	71	39.9
	III (IIIA,IIIB), IV	107	60.1

SCC, signet cell carcinoma; MPA, mucin-producing adenocarcinoma; MA, mucinous adenocarcinoma.
N1, Metastasis in 1-6 regional lymph nodes; N2, metastasis in 7-15 regional lymph nodes; N3, metastasis in more than 15 regional lymph nodes (According to SEER Summary Staging Manual 2000).

Table 2 - Univariate model of parametric regression with prognostic factors

Prognostic factors	Weibull RR (95% CI)	Exponential RR (95% CI)	Log-Logistic RR (95% CI)	Log-Normal RR (95% CI)
Age at diagnosis	1.02* (1.01-1.04)	1.02* (1.01-1.04)	1.02* (1.01-1.05)	1.01* (1.01-1.03)
Sex				
Male	1.69 (0.95-3.01)	1.55 (0.87-2.77)	1.66 (0.79-3.48)	1.40 (0.91-2.14)
Female	1.00	1.00	1.00	
Distant metastasis				
Absent	1.00	1.00	1.00	
Present	2.23* (1.05-4.72)	2.22* (1.06-4.66)	3.16* (1.07-9.33)	1.89* (1.01-3.60)
Tumor size (mm)				
<35	1.00	1.00	1.00	
>35	1.94* (1.03-3.28)	1.94* (1.04-3.63)	3.01* (1.39-6.51)	1.95* (1.24-3.07)
Histologic type				
Adenocarcinoma	0.59 (0.3-1.16)	0.63 (0.32-1.24)	0.6 (0.23-1.52)	0.63 (0.36-1.09)
Signet ring cell°	0.41 (0.14-1.21)	0.42 (0.14-1.22)	0.36 (0.09-1.45)	0.48 (0.22 -1.04)
Other	1.00	1.00	1.00	1.00
Tumor grade				
WD	0.84 (0.46-1.53)	0.85 (0.47-1.56)	0.76 (0.35-1.67)	0.83 (0.52-1.32)
MD	0.73 (0.41-1.3)	0.78 (0.44-1.38)	0.89 (0.42-1.87)	0.88 (0.57-1.36)
PD	1.00	1.00	1.00	1.00
Lymph node metastasis				
N1	0.81 (0.33-1.98)	0.81 (0.33-1.96)	0.54 (0.17-1.72)	0.70 (0.37-1.33)
N2	0.91 (0.41-2.03)	0.95 (0.43-2.12)	0.74 (0.26-2.16)	0.86 (0.48-1.54)
N3	1.00	1.00	1.00	1.00
Pathologic stage				
Early	1.00	1.00	1.00	1.00
Advanced	1.73* (1.01-2.94)	1.69 (0.99-2.86)	2.03* (1.03-3.99)	1.54* (1.04-2.28)

RR, relative risk; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.
*Statistically significant.
°Signet ring cell, mucin-producing adenocarcinoma, and mucinous adenocarcinoma.

Table 3 - Multivariate model of parametric regression with prognostic factors

Prognostic factors	Weibull RR (95% CI)	Exponential RR (95% CI)	Log-Logistic RR (95% CI)	Log-Normal RR (95% CI)
Age at diagnosis	1.02 (0.99-1.4)	1.01 (0.99-1.04)	1.02 (0.99-1.05)	1.01 (0.99-1.02)
Sex				
Male	1.77 (0.94-3.35)	1.6 (0.85-2.98)	1.88 (0.84-4.22)	1.43 (0.9-2.26)
Female	1.00	1.00	1.00	
Distant metastasis				
Absent	1.00	1.00	1.00	
Present	2.51* (1.06-5.97)	2.243 (0.97-5.16)	3.0 (0.94-9.57)	1.82 (0.92-3.59)
Tumor size (mm)				
<35	1.00	1.00	1.00	
>35	2.24* (1.14-4.38)	2.08* (1.08-4.30)	3.29* (1.44-7.53)	2.09* (1.28-3.42)
Histology type				
Adenocarcinoma	0.57 (0.28-1.16)	0.61 (0.3-1.25)	0.46 (0.17-1.22)	0.57 (0.33-1.01)
Signet ring cell°	0.34 (0.11-1.08)	0.38 (0.12-1.19)	0.27 (0.06-1.25)	0.45 (0.2 -1.02)
Other	1.00	1.00	1.00	1.00
Tumor grade				
WD	0.68 (0.36-1.29)	0.71 (0.38-1.33)	0.57 (0.25-1.3)	0.74 (0.46-1.19)
MD	0.51* (0.27-0.97)	0.59 (0.31-1.1)	0.55 (0.24-1.25)	0.70 (0.44-1.12)
PD	1.00	1.00	1.00	1.00
Lymph node metastasis				
N1	2.19 (0.68-7.02)	1.9 (0.61-5.88)	1.46 (0.35-6.06)	1.23 (0.55-2.78)
N2	1.22 (0.47-3.18)	1.24 (0.5-3.1)	0.98 (0.31-3.1)	0.99 (0.53-1.83)
N3	1.00	1.00	1.00	1.00
Pathologic stage				
Early	1.00	1.00	1.00	1.00
Advanced	1.9 (0.92-3.92)	1.75 (0.86-3.59)	1.89 (0.73-4.87)	1.52 (0.88-2.62)
AIC	569.8	576	564.2	566

RR, relative risk; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.*Statistically significant. °Signet ring cell, mucin-producing adenocarcinoma, and mucinous adenocarcinoma.

stage of disease were significant for the prognosis. Age at diagnosis was a prognostic factor, and our findings in univariate analysis were similar to those of previous reports showing a better survival for young patients[10-12].

Metastasis is another important prognostic factor for gastric cancer[13]. Many authors have shown that survival depends on the presence of metastasis. Our findings are in agreement with these observations in univariate analysis and according to the Weibull model, indicating an association with distant metastasis, which was maintained in the multivariate analysis[14,15].

Size and tumor grade were also significant factors which affected the survival probability of patients in the parametric analysis. The finding is similar to those of other studies which reported a high hazard ratio of death for patients with large tumors or high tumor grade[16]. Another study[14] also reported the same conclusion for tumor size in univariate analysis.

Some studies have reported better survival for females than for males[17]. Our results indicated no relation between sex and risk of death. A study carried out by the Rotterdam Cancer Registry on 2773 patients reported similar results, finding that the death rate in males and females was similar[18]. Li *et al.*[12] found no association between sex and survival for patients with advanced gastric cancer[12].

Histologic type, tumor grade and lymph node metastasis did not seem to be significant in our analysis.

A limitation of the study is missing data due to incomplete patient documents. Surgical curability is one of the most important prognostic factors. Unfortunately, there was no information regarding the results of curative operations because most of the patients had been referred from other cities or hospitals and we only had access to registry information and not to their original documents. This was also true for regional lymph node metastases. Up to 60% of patients had a history of lymph node metastases according to the registry data (categorized as N1, N2 and N3), but no information existed for others (lymph node metastases or not). This incomplete covariate can thus seriously influence the results of this prognostic factor.

Nardi and Schemper[19] compared Cox and parametric models in three clinical studies. They used normal-deviate residuals[20] to verify the parametric model assumptions. In their study in which there were some parameters far from zero, the Weibull regression produced standardized variability. In our study, this case holds true, but the model also supports interval censoring.

Moghimi-Dehkordi *et al.*[21] compared Cox and parametric models in the survival of patients with gastric cancer in southern Iran. They showed that although the hazard ratio in the Cox model and parametric models is similar, according to AIC parametric models are the most favorable for survival analysis.

Even though the Cox parameter estimations are familiar for researchers in the field of medical sciences, the results in accelerated failure times can be interpreted as the relative risk, which is not unknown for medical scientists. These parameters can thus be interpreted as accelerating or decelerating factors similarly in interpretation of the Cox hazard ratio, not only for right censored data but also for the interval-censored data base.

In conclusion, the log logistic is the most efficient model for multivariable analysis.

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