

RESEARCH COMMUNICATION

Prediction of Time to Recurrence and Influencing Factors for Gastric Cancer in Iran

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Abstract

Background: The patterns of gastric cancer recurrence vary across societies. We designed the current study in an attempt to evaluate and reveal the outbreak of the recurrence patterns of gastric cancer and also prediction of time to recurrence and its effected factors in Iran. **Materials and Methods:** This research was performed from March 2003 to February 2007. Demographic characteristics, clinical and pathological diagnosis and classification including pathologic stage, tumor grade, tumor site and tumor size in of patients with GC recurrent were collected from patients' data files. To evaluate of factors affected on the relapse of the GC patients, gender, age at diagnosis, treatment type and Hgb were included in the research. Data were analyzed using Kaplan-Meier and logistic regression models. **Results:** After treatment, 82 patients suffered recurrence, 42, 33 and 17 by the ends of first, second and third years. The mean (SD) and median (IQR) time to recurrence in patients with GC were 25.5 (20.6-30.1) and 21.5 (15.6-27.1) months, respectively. The results of multivariate analysis logistic regression showed that only pathologic stage, tumor grade and tumor site significantly affected the recurrence. **Conclusions:** We found that pathologic stage, tumor grade and tumor site significantly affect on the recurrence of GC which has a high positive prognostic value and might be functional for better follow-up and selecting the patients at risk. We also showed time to recurrence to be an important factor for follow-up of patients.

Keywords: Stomach neoplasia - recurrence - risk factors - logistic regression model

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Introduction

Gastric cancer (GC) is the fourth most common cancer and second important reason of cancer associated death worldwide. It is estimated that more than 930,000 new cases of GC are being detected annually and at least 700,000 deaths is correlated to the disease (Parkin et al., 2005). Following treatment, the patients usually experience periodic ultrasonography, computed tomography (CT) scan or CT-guided needle biopsy to observe for any probability of the disease recurrence. Nevertheless, these parameters of performance for detecting GC, do not identify recurrent GC all the time (Chopra, 2004). It is essential to distinguish the nature of recurrent gastric cancer by the occurrence of symptoms and evaluation the risk factors for planning further treatment (Kim et al., 2010). Validation and comparison of prognostic factors will indicate the effective models to predict the patterns of recurrence (Koo et al., 2011). Although several studies have been published on prognostic risk factors generally used in clinical practice for gastric cancer, the patterns of recurrence are still under debate in different societies. Moreover, without describe and interpreting all the risk

factors involved in cancer recurrence, it is difficult that GC be successfully prevented (Kosuga et al., 2011). The various risk factors such as gender, age at diagnosis, tumor size, site and grade, pathologic stage of disease, treatment type and Hgb have been the subject of study in the current research. Few studies to date have specifically addressed the role of risk factors implicated in probability of recurrence risk of GC patients in Iran. We designed the current study in an attempt to evaluate and reveal the outbreak of the recurrence patterns of gastric cancer and also prediction of time to recurrence in the gastric cancer patients in Iran using logistic regression model. This might provide predicting information to prognosis post-recurrence time (Kosuga et al., 2011).

We will also compare and explain the differences of the results obtained by logistic regression models to other researches and also to Cox proportional hazard (PH) model in our previous study.

Materials and Methods

We conducted a perspective cohort study of 471 patient's data in the cancer institute of Imam Khomeini

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hospital in Tehran, the capital of Iran. Out of 471 patients 320 cases were remained in the follow up and 151 patients were excluded from our research because of death or unavailability of patients during the period of research. The outbreak of recurrence was occurred only in 82 patients after treatment. This research was performed from March 2003 to February 2007. Demographic characteristics, clinical and pathological diagnosis and classification including pathologic stage, tumor grade, tumor site and tumor size in of patients with GC recurrent were collected from patients' data files. To evaluate of factors affected on the relapse of the GC patients, gender, age at diagnosis, treatment type and Hgb were included in the research. The stage of disease before surgery was determined by CT scan and endosonography and after surgery was determined by pathologic reports. Time of relapse in patients with GC after performing of different treatments including surgery, chemotherapy, radiotherapy or combination methods of therapy was determined according to month unit. We evaluated the effects affected on the recurrence outbreak so that the outcome of our research was recurrence or non recurrence. The data of this research in the case of prediction of time to recurrence were analyzed by Kaplan-Meier and the factors affected on the outbreak of gastric cancer recurrent were analyzed by logistic regression models utilizing STATA and SPSS16 statistical software with setting P-value as 0.05.

Results

Of total 320 patients with GC, 237 cases were male (74.1%) and the rest of them (25.9%) were female. After treatment, 82 patients had recurrent. Of totally 82 patients with recurrence, 42, 33 and 17 patients had recurrence in the end of first, second and third years. The mean (SD) and median (IQR) time to recurrence in patients with GC were 25.5 (20.6-30.1) and 21.5 (15.6-27.1) months respectively (Figure 1). Evaluation of sex and age in GC patients under the current study showed that 46% of patients less than 60 years old were male while 67.5% were female (Table 1). Table 2 shows demographic and pathologic data in the patients under study. In order to assess the effects of risk factors affecting the recurrent of GC in the outbreak of patients following therapy, univariate logistic regression was used first to evaluate the risk factors independently. The results of univariate logistic regression analysis showed that age at diagnosis, tumor grade, tumor site, radiotherapy, pathologic stage

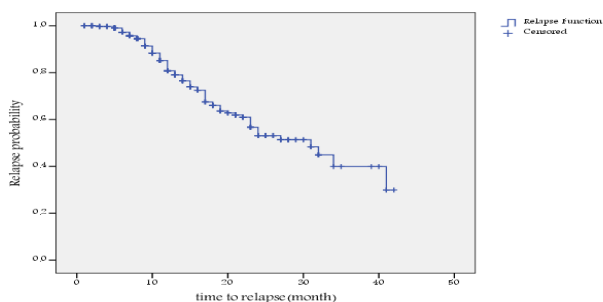


Figure 1. The Mean (SD) and Median (IQR) Time of Recurrence in the GC Patients were 25.5 (20.6-30.1) and 21.5 (15.6-27.1) Months.

Table 1. Evaluation of Sex and Age in GC Patients

Variable	Age (N/%)		
	< 60	> 60	Total
Sex Male	109 (46.0)	128 (54.0)	237 (100)
Female	56 (67.5)	27 (32.5)	83 (100)
Total	165 (51.6)	155 (48.4)	320 (100)

Table 2. Assessment of Affected Factors on Relapse in Gastric Cancer Patients using of Univariate Logistic Regression

Variable	P value	OR (95% CI)
Sex	0.12	1.62 (0.88-2.82)
Age at diagnosis	0.018 ^a	1.2 (0.7-1.96)
Tumor grade	0.034 ^a	1.62 (1.07-2.53)
Tumor site	0.043 ^a	0.75 (0.54-0.98)
Radiotherapy	0.03 ^a	2 (1.1-3.7)
Pathologic stage	0.002 ^a	1.76 (1.24-2.5)
Tumor size (mm)	0.43	1.2 (0.79-1.74)
Chemotherapy	0.16	3.1 (0.6-7.2)
Surgery	0.001 ^a	2.8 (1.53-5.1)
Hgb	0.9	1.1 (0.5-1.74)

*Significant (p-value <0.05)

Table 3. Assessment of Factors on Relapse using of Multivariate Logistic Regression

Variable	OR (95% CI)	
Gender	Female	1 ^a
	MALE	1.3 (0.6-2.7)
Age at diagnosis (Year)	< 60	1 ^a
	> 60	1.3 (0.7-2.4)
Pathologic stage	II	1 ^a
	III	1.9 (1.03-4) ^b
	IV	1.93 (1.1-5.9) ^b
Tumor grade	Well	1 ^a
	Moderate	2.1 (1.05-4.8) ^b
	Poor	2.3 (1.4-6.7) ^b
Radiotherapy	Yes	1 ^a
	No	1.43 (0.6-2.5)
Surgery	Yes	1 ^a
	No	1.4 (0.71-1.74)
Tumor size	Cardia	1
	Body	0.7 (0.4-0.9) ^b
	Other	0.56 (0.3-0.92) ^b

^aReference group, ^bSignificant (p-value <0.05)

and surgery were significantly affected on the recurrence of GC (p-value <0.05) (Table 2). However, evaluation of the significant risk factors together using multivariate analysis showed that only pathologic stage, tumor grade and tumor site were significantly (p-value <0.05) affected on the recurrence of GC (Table 3).

Discussion

This study was undertaken in order to determine the variables that influences the onset of GC recurrence in an independent manner after treatment. A combination of subjective and objective evaluation is necessary for the early prediction of recurrence in cases of GC patients after treatment. Thus, it is vital to distinguish the nature of

recurrent GC. The present study was planned to observe the effectiveness of different patterns of recurrence in GC in Iran and also to use logistic regression model, a generalized linear model to estimate the odds ratio.

Based on our finding, evaluation of sex and age at diagnosis in GC patients showed that 46% of patients less than 60 years old were male while 67.5% of patients located in this age category were female (Table 1). We estimate that the higher numbers of females under 60 in the current research is due to multiple refers of females for check up which results in early diagnosis and in turns early treatment of cancer that leads to lower results of recurrence outcome.

The presence of symptomatic recurrence is accounted as a new predictive marker to assess biologic factors, which is an essential determinant of survival at the time of recurrence diagnosis in a GC (Bilici et al., 2012). We identified in our research that the mean (SD) and median (IQR) time to recurrence in patients with GC were 25.5 (20.6-30.1) and 21.5 (15.6-27.1) months respectively (figure 1). It is in consistent with the previous study, which report the average time to recurrence after primary surgery in gastric patients as 26.4 2.8 months (Nunobe et al., 2011). Another research also reports median time to recurrence as 20.5 months (Lai et al., 2009). But there is a discrepancy between our results and the results published by another study which declare the median time from post operation to the recurrence process as 13 months (range, 5–25 months) (Chan et al., 2005). It seems that time to recurrence in patients with GC needs paying attention in this part of Iran but we evaluated time to recurrence as an important factor which can be effective in proper treatment and follow-up the patients.

From the data obtained in univariate logistic regression analysis, it could be inferred that age at diagnosis, tumor grade, tumor site, radiotherapy, pathologic stage and surgery were significantly affect on recurrence of GC (Table 2). Nevertheless, assessment of the significant risk factors together using multivariate analysis model showed that only pathologic stage, tumor grade and tumor site were significantly (p -value <0.05) affect on the recurrence of GC (Table 3).

The finding of univariate analysis regarding to age at diagnosis is in line with another research that showed significant correlation between age at diagnosis and recurrent GC (Roviello et al., 2003; Lai et al., 2009). Thus, it showed older age was significantly related to the progress of GC recurrent. However, it is not in agreement with previous study which reported age at diagnosis as an independent factor for recurrence of early gastric cancer (Ikeda et al., 2005). Marrelli et al., also showed the age at diagnosis as a significant risk factor affected on the GC recurrence (Marrelli et al., 2005).

The assessment criteria in the univariate and multivariate analysis indicated that the role of tumor site in recurrence after treatment was a significant factor (p -value <0.05). Several authors have also demonstrated the significant association between tumor site and GC recurrent after treatment (Marrelli et al., 2005; An et al., 2008; Park et al., 2010; Wu et al., 2010). Nevertheless, it was not in agreement with the previous study (Park et

al., 2010). Also, a research which performed by Lai et al, in South Korea using logistic regression showed no significant correlation between tumor site and occurrence of GC. The discrepancy of results may be due to the role of ethnics and cultures in different societies. However, it remains to be elucidated (Lai et al., 2009). Moreover, tumor site was significant only in univariate analysis in our previous report using Cox analysis model (Roshanaei et al., 2011). It should be noted that it is not abnormal for different or even paradoxical conclusions to be reported for similar subjects in the identical field of study, because it may be due to the different analytical models used in different studies and also we evaluated the effects affected on the recurrence outbreak while they assessed the effects affected to time to recurrence (Table 3).

In this research evidence was presented that in terms of conventional tumor grading (well, moderate, poor differentiation) of gastric cancer, the results of both univariate and multivariate logistic regression model (Tables 2 and 3) showed that the moderate and poor tumor grades variables should be considered as significant predictors at recurrent risk (p -value <0.05). In contrast, tumor grade was significant only in univariate analysis in our latest study using Cox model of analysis (Roshanaei et al., 2011). The difference can be explained by combination of various factors such as various statistical models and also different total numbers of patients used in that study.

In conclusion, we found that pathologic stage, tumor grade and tumor site were significantly (p -value <0.05) affect on the recurrence of GC which has a high positive prognostic value and might be functional for better follow-up and selecting the patients at risk of GC recurrent. We also showed time to recurrence as an important factor which can be effective in proper treatment and follow-up the patients.

It can also partially fulfill the need for evaluating the therapeutic strategies and performing proper treatment policy for GC patients. A large prospective research must be undertaken in future years to establish such system to investigate a combination of various factors such as pathologic stage, tumor site and tumor grade, affecting significantly on the recurrence of GC to confirm our findings in other parts of Iran and also in this part of geographical region which provides a plausible plan to establish the best treatment modality for recurrence. Nevertheless, the results obtained in the current study recommend a complex interplay between different risk factors and GC recurrent. Thus, a number of questions await further research. One question has to do with defining the detailed mechanisms by which risk factors differ in diverse investigations. Although, the role of ethnics and cultures may be considered as interfering factors in this case. Are the results obtained in the current study attributable to other parts of Iran and other countries? What is the role of different analytical models applied in diverse studies on the accuracy of determining the risk factors affecting on GC recurrent? Why do some risk factors not achieve statistical significance in some analytical models but achieve significant in others? Further studies have to be conducted to answer these questions clearly.

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