RESEARCH COMMUNICATION

Effect of Demographic and Clinicopathologic Factors on Prognosis of Early Gastric Cancer in Iran

Bijan Moghimi-Dehkordi*, Azadeh Safaee, Mohamad Amin Pourhoseingholi, Mohammad Reza Zali

Abstract

<u>Background</u>: The aim of this study was to estimate some prognostic factors that affect on overall survival of patients with early gastric cancer. <u>Methods</u>: A retrospective study had been done on patients diagnosed with early gastric cancer who registered in cancer registry center, Tehran-Iran, between December 21, 2001 and December 21, 2006 and all patients were followed by telephone contacts. The Kaplan-Meier method was performed to describe survival curves and log-rank test to compare the survival rate in subgroups. Cox regression was used to determine the prognosis factors. <u>Results</u>: The mean age was 57.9 ± 11.9 years and 72.6% of patients were male. Tumor size (>35mm) and lymph node metastasis were established as significant factors for survival of patients with EGC in both univariate and multivariate analysis. <u>Conclusion</u>: The findings of this study indicate that lymph node metastasis and tumor size are the most independent prognostic factors in these patients.

Key Words: Early gastric cancer - prognosis - clinicopathologic factors

Introduction

Early gastric cancer (EGC) is defined as a lesion in which the depth of invasion is limited to the mucosa, submucosa, or both, regardless of whether regional lymph node metastasis is evident on histologic examination, is now recognized as a curable malignancy (Dent et al., 1988; Robertson et al., 1994; Baba et al., 1995; Miwa et al., 1995; Cuschieri et al., 1996; Kitamura et al., 1997; Bonenkamp et al., 1999; Maehara et al., 2000; Miyata et al., 2000; Seto et al., 2001). This is equivalent to the pT1 category in the pTNM (pathologic tumor/node/metastasis) system of the UICC (Union International Contra Cancrum) classification (Wang et al., 1997). EGC and invasive gastric carcinoma have 5-year survival rates higher than 90% and 46%, respectively (Ohta et al., 1987; Nakamura et al., 1992), after surgery compared with 82% to 87% for EGC and of 5% to 25% following surgery for invasive gastric carcinoma in Western countries (Green et al., 1988; Msika et al., 1989; Lawrence and Shiu, 1991). Many studies have focused on identifying EGC prognostic factors (Guadagni et al., 1993; Maehara et al., 1993; Kim et al., 1995; Ranaldi et al., 1995). Because of its low specific mortality, methodologically sound identification of EGC prognostic factors requires a large number of cases and long-term follow-up.

Published reports have focused on tumor recurrence and none has considered outcome with respect to other causes of death (Health and Welfare Statistics Association,
2002). The aim of the present study was to estimate some prognostic factors that affect on overall survival of patients with early gastric cancer.

Materials and Methods

Subjects

The study included a total of 161 patients with EGC that registered in cancer registry center of Research Center for Gastroenterology and Liver Disease(RCGLD), Shaheed Beheshti University M.C., Tehran, Iran, in the period from December 21, 2001 to December 21, 2006. All patients were followed from their diagnostic date up to December 21, 2006 (as failure time). Deaths were confirmed through the contact to family patients with telephone. All deaths during this period were considered as a consequence of the gastric cancer. Survival time was calculated in months. EGC was defined as pT1 and pT2 according to pathology reports. The clinicomorphologic factors consist of sex, age at diagnosis (<60>years), tumor size (<35>mm), histologic grade of tumor, histologic type (Adenocarcinoma, Signet Cell Carcinoma&Mucin-producing adenocarcinoma & Mucinous adenocarcinoma and other type of histology), lymph nodes involvement (present or absent) and distant metastasis (present or absent) were included in the analysis as prognostic factors. Histologic grade of tumor was classified according to the World Health Organization classification (1977): well- , moderately-, and poorly-differentiated.

*Research Center of Gastroenterology and Liver Diseases, Shaheed Beheshti University, M.C., Tehran, Iran *For correspondence: b_moghimi_de@yahoo.com*

Statistical analysis

Overall and disease-specific survival rates were calculated. Kaplan-Meier product limit-estimates were used to describe survival curves (Kaplan and Meier, 1958) and the log-rank test was performed to compare survival rates among subgroups (Kalbfleisch and Prentice, 1980).

Multivariate Cox stepwise regression analyses were performed to determine the most independent predictive factors for patients with EGC (Cox, 1972). The 95 percent confidence interval (CI) was calculated for all hazard ratios (HRs) in Cox regression analyses. The accepted level of significance was p<0.05. All calculations were carried out by SPSS (version13.0) statistical software.

Results

Descriptive findings

Of 161 patients, 117 were male. The age (mean ± SD) was 57.9±11.9 years, ranges between 27-83 years, (58.7 ± 12.8 years for males; 55.8 ± 9.2 years for females; p>0.05). Considering the age distribution, 80 patients were < 60 years, 81 patients were >60 years. According to histology grade of tumor, most of patients were diagnosed with moderately differentiated lesions. Also, the most common histology type of tumor was adenocarcinoma (68.9%) (see Table 1).
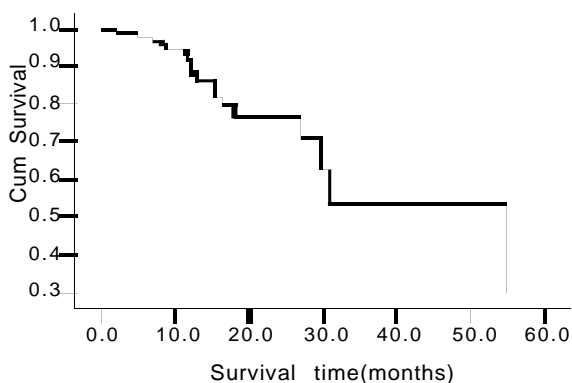

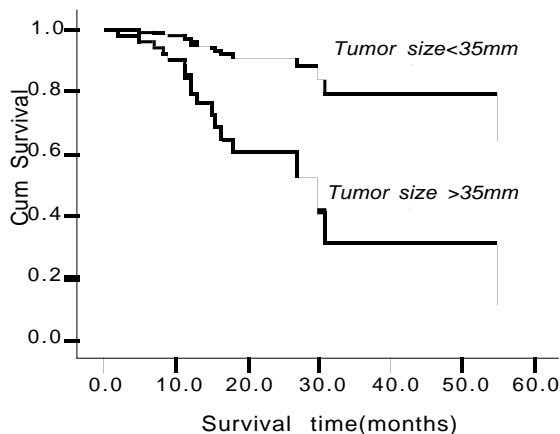**Figure 1. Overall Survival Curve for Patients with EGC by the Cox Proportional Hazard Model**

Figure 1. Overall Survival Curves According to Tumor Size as a Prognostic Factor for Patients with EGC by the Cox Proportional Hazard Model

Table 1. Demographic and Clinical Characteristics of Patients and Log-rank Test

Variable		Count n (%)	Log-rank test
Age n=161	<60	80 (49.7)	0.580
	>60	81 (50.3)	
Sex n=161	Male	117 (72.7)	0.954
	Female	44 (27.3)	
Grade n=131			
	Well differentiated	41 (25.5)	0.757
	Moderately diff	46 (28.6)	
	Poorly differentiated	44 (27.3)	
Tumor size n=120	<35mm	47 (29.2)	**0.027**
	>35mm	73 (45.3)	
Histology type n=161			
	Adenocarcinoma NOS	111 (68.9)	0.880
	Signet cell carc*	24 (14.9)	
	Other type of histology	25 (15.5)	
Regional Lymph Node Metastasis			
n=149	N1	105 (65.2)	**0.014**
	N2	42 (28.2)	
	N3	2 (1.2)	
Pathologic Distant Metastasis			
n=122	M0	120 (74.5)	0.778
	M1	2 (1.2)	

*Signet cell carc.+mucin-producing adenocarc. + mucinous adeno.

Univariate analysis of prognostic factors

Kaplan-Meier method indicated that tumor size (>35mm) and lymph node metastasis were prognostic factors in patients with EGC. Also, variables such as: age at diagnosis, sex, grade of tumor, histology type of tumor and distant metastasis did not have statistically significant affects on survival rate of these patients (P>0.05) (see Table 1).

Multivariate analyses of prognostic factors

Overall survival curves by multivariate analysis are shown in Figure 1. Cox stepwise regression analyses identified that tumor size >35mm as an independent prognostic indicator of greater value than <35mm (see Table 2). Patients who in time of diagnosis those tumor size was higher than 35 mm have about five-fold hazard of death from EGC (Figure 2). Also, metastasis of tumor to regional lymph nodes was another prognostic factor
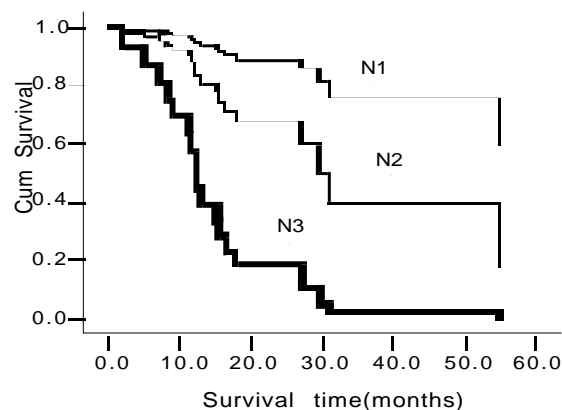

Figure 3. Overall Survival Curves According to Lymph Node Metastasis as a Prognostic Factor for Patients with EGC by the Cox Proportional Hazard Model

Table 2. Multivariate Cox Stepwise Proportional Hazard Model for Overall Survival

Variable	Subgroups	p value	Hazard rate
Tumor size	<35mm	-	-
	>35mm	**0.014**	5.08
Regional Lymph Node Metastasis			
	N1	-	-
	N2	0.054	3.33
	N3	0.181	4.32

that affect on survival of EGC patients, for example; cases with N2 regional lymph node metastasis had a 3.3-fold increased risk of death (Figure 3).

Discussion

Prognostic factors in early gastric cancer (EGC) are a source of controversy in many series. The aim of this study was to identify several demographical and clinicopathological variables that influence the prognosis of patients with early gastric adenocarcinoma. Some studies (Guadagni et al., 1993; Isozaki et al., 1999; Pacelli et al., 1999; Basili et al., 2003; Bando et al., 2004) have shown that age has a significant influence on patients outcome. In our study, age did not influence long-term survival in both univariate and multivariate analysis, in agreement in one previous report regarding survival of EGC patients (Tuech et al., 1999).

Several studies shown that sex could be found as prognostic factor for EGC (Yokota et al., 2000; Basili et al. 2003). Isozaki et al (1999) reported that prognosis was better in women. Another study carried out in Italy (Pacelli et al., 1999) reported no differences in survival rates regarding sex in EGC patients. In this present study, a sex-related difference was not observed.

Using univariate analysis, several authors have identified lymph node metastasis (Lawrence and Shiu, 1991; Moriguchi et al., 1991; Guadagni et al., 1993; Folli et al., 1995; Fujimura et al., 1995; Ranaldi et al., 1995; Skoropad et al., 2005), tumor size (Lawrence and Shiu, 1991; Moriguchi et al., 1991; Shiozawa et al., 1994; Ranaldi et al., 1995) and histological type (Moriguchi et al., 1991) as important prognostic factors in patients with EGC. In our study, significant differences in survival rate were found with respect to tumor size and lymph node metastasis.

Previous multivariate analyses have demonstrated that depth of invasion (Ranaldi et al., 1995), lymph node metastasis (Moriguchi et al., 1991; Maehara et al., 1993; Fujimura et al., 1995; Ranaldi et al., 1995), histological type (Lawrence and Shiu, 1991; Moriguchi et al., 1991; Maehara et al., 1993), tumor size (Ranaldi et al., 1995), lymph node dissection (Fujimura et al., 1995) are independent prognostic factors that influence survival. Our results indicated that tumor diameter and regional lymph nodes metastasis are independent prognostic factors for EGC patients.

Comparison of results from previous studies and the present investigation with regard to prognostic factors is difficult, due to differences in statistical methods and patient populations. However, the present findings indicate that tumor size and lymph node metastasis are two independent prognostic factors when analyzed by cancer-related survival.

In conclusion, the findings of this study indicate that lymph node metastasis and tumor size represent independent prognostic factors in these cases.

Acknowledgements

References

Baba H, Maehara Y, Takeuchi H, et al (1995). Effect of lymph node dissection on the prognosis in patients with node-negative early gastric cancer. *Surgery*, **117**, 165-9.

Bando E, Kojima N, Kawamura T, et al (2004). Prognostic value of age and sex in early gastric cancer. *Br J Surg*, **91**, 1197-201.

Basili G, Nesi G, Barchielli A, Manetti A, Biliotti G (2003). Pathologic features and long-term results in early gastric cancer: report of 116 cases 8-13 years after surgery. *World J Surg*, **27**, 149-52.

Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ (1999). Extended lymph-node dissection for gastric cancer. Dutch Gastric Cancer Group. *N Engl J Med*, **340**, 908-14.

Cox DR (1972). Regression models and life tables. *J R Stat Soc B*, **34**, 187-220.

Cuschieri A, Fayers P, Fielding J, et al (1996). Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomized controlled surgical trial. The Surgical Cooperative Group. *Lancet*, **347**, 995-9.

Dent DM, Madden MV, Price SK (1988). Randomized comparison of R1 and R2 gastrectomy for gastric carcinoma. *Br J Surg*, **75**, 110-2.

Folli S, Dente M, Dell'amore D, et al (1995). Early gastric cancer: prognostic factors in 223 patients. *Br J Surg*, **82**, 952-6.

Fujimura T, Yonemura Y, Noguchi M, Falla R (1995). Rationale for extensive lymphadenectomy in early gastric carcinoma. *Br J Cancer*, **72**, 1518-24.

Green, PHR, O Toole, KM, Slonim, D, et al (1988). Increasing incidence and excellent survival of patients with early gastric cancer: experience in a United States medical center. *Am J Med*, **85**, 658-61.

Guadagni S, Reed PI, Johnston BJ, et al (1993). Early gastric cancer: follow-up after gastrectomy in 159 patients. *Br J Surg*, **80**, 325-8.

Health and Welfare Statistics Association (2002). *J Health and Welfare Statistics*, **49**, 68 (in Japanese).

Isozaki H, Tanaka N, Okajima K (1999). General and specific prognostic factors of early gastric carcinoma treated with curative surgery. *Hepatogastroenterology*, **46**, 1800-8.

Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. John Wiley: New York, 1980.

Kaplan EL, Meier P (1958). Nonparametric estimation for incomplete observations. *J Am Stat Assoc*, **53**, 457-81.

Kim JP, Hur YS, Yang HK (1995). Lymph node metastasis as a significant prognostic factor in early gastric cancer: analysis of 1,136 early gastric cancers. *Ann Surg Oncol*, **2**, 308-13.

Kitamura K, Yamaguchi T, Sawai K, et al (1997). Chronologic

changes in the clinicopathologic findings and survival of gastric cancer patients. *J Clin Oncol*, **15**, 3471-80.

Lawrence M, Shiu MH (1991). Early gastric cancer: twenty-eight-year experience. *Ann Surg*, **213**, 327-34.

Maehara Y, Kakeji Y, Oda S, et al (2000). Time trends of surgical treatment and the prognosis for Japanese patients with gastric cancer. *Br J Cancer*, **83**, 986-91.

Maehara Y, Okuyama T, Oshiro T, et al (1993). Early carcinoma of the stomach. *Surg Gynecol Obstet*, **177**, 593-7.

Miwa K, Miyazaki I, Sahara H, et al (1995). Rationale for extensive lymphadenectomy in early gastric carcinoma. *Br J Cancer*, **72**, 1518-24.

Miyata M, Yokoyama Y, Okoyama N, et al (2000). What are the appropriate indications for endoscopic mucosal resection for early gastric cancer? Analysis of 256 endoscopically resected lesions. *Endoscopy*, **32**, 773-8.

Moriguchi S, Odaka T, Hayashi Y, et al (1991). Death due to recurrence following curative resection of early gastric cancer depends on age of the patients. *Br J Cancer*, **64**, 555-8.

Msika S, Chastang C, Houry S, et al (1989). Lymph node involvement as the only prognostic factor in curative resected gastric carcinoma: a multivariate analysis. *World J Surg*, **13**, 118-23.

Nakamura K, Ueyama T, Yao T et al (1992). Pathology and prognosis of gastric carcinoma: findings in 10,000 patients who underwent primary gastrectomy. *Cancer*, **70**, 1030-7.

Ohta H, Noguchi Y, Tagagi, K et al (1987). Early gastric carcinoma with special reference to macroscopic classification. *Cancer*, **60**, 1099-106.

Pacelli F, Doglietto GB, Alfieri S, et al (1999). Survival in early gastric cancer: multivariate analysis on 72 consecutive cases. *Hepatogastroenterology*, **46**, 1223-8.

Ranaldi R, Santinelli A, Verdolini R, et al (1995). Long-term follow-up in early gastric cancer: evaluation of prognostic factors. *J Pathol*, **177**, 343-51.

Robertson CS, Chung SC, Woods SD, et al (1994). A prospective randomized trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer. *Ann Surg*, **220**, 176-82.

Seto Y, Shimoyama S, Kitayama J, et al (2001). Lymph node metastasis and preoperative diagnosis of depth of invasion in early gastric cancer. *Gastric Cancer*, **4**, 34-8.

Shiozawa N, Kodama M, Chida T, et al (1994). Recurrent death among early gastric cancer patients: 20-years' experience. *Hepatogastroenterology*, **41**, 244-7.

Skoropad V, Berdov B, Zagrebin V (2005). Clinicopathological features and outcome of surgical treatment of 149 patients with early (pT1) gastric cancer. *Onkologie*, **28**, 247-52.

Tuech JJ, Cervi C, Pessaux P, et al (2000). Early gastric cancer: univariate and multivariate analysis for survival. *Hepatogastroenterology*, **46**, 3276-80.

Wang, CS, Hsueh, S, Chao TC, et al (1997). Prognostic study of gastric cancer without serosal invasion: reevaluation of the definition of early gastric cancer. *J Am Coll Surg*, **185**, 493-8.

World Health Organization (1977). Types histologiques des tumeurs gastriques et oesophagiennes. In Classification Histologique Internationale des Tumeurs, Geneva.

Yokota T, Kunii Y, Teshima S, et al (2000). Significant prognostic factors in patients with early gastric cancer. *Int Surg*, **85**, 286-90.