The predictive prognostic factors and risk factors of lymph node metastasis in patients with early gastric cancer

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Research article

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Abstract

Background: Determining the prognosis of early gastric cancer (EGC) is very important for the selection of preoperative treatment strategies. The purpose of this paper was to investigate the clinicopathological features and prognostic factors in EGC and the related risk factors of lymph node metastasis (LNM).

Methods: From March 2007 through December 2010, 1004 patients who underwent gastrectomy at Harbin Medical University were retrospectively identified; 120 patients were diagnosed with EGC. The clinicopathological features and prognostic factors were analysed by univariate and multivariate analyses. Multivariate logistic regression analysis was used to discern risk factors for LNM in EGC.

Results: The incidence of EGC was 11.96%. A univariate analysis showed that age, preoperative haemoglobin (Hb) level, prealbumin level, tumour size and LNM were significant prognostic factors. A multivariate analysis showed that the preoperative Hb level and LNM were independent prognostic factors. A multivariate logistic regression analysis revealed that age, Ca-199 level and macroscopic tumour type were independent risk factors for LNM in EGC. **Conclusions:** Preoperative Hb level and LNM were both independent prognostic factors for EGC. These factors may help surgeons implement appropriate treatment strategies during the perioperative period.

Background

Approximately 989,000 people worldwide are diagnosed annually with gastric cancer (GC), and approximately 738,000 of them die of the disease [1]. GC remains the second leading cause of cancer-related death worldwide and is the most common cancer in Eastern Asia [2]. Over 70% of cases occur in developing countries, mainly in China [3]. Of all patients, most are at an advanced stage at the time of diagnosis, and the incidence of early gastric cancer (EGC) is nearly 10% [4]. At present, the treatment of EGC primarily includes endoscopic mucosal resection (EMR) [5], endoscopic submucosal dissection (ESD) [6] and open or laparoscopic radical gastrectomy [7,8,9]. Radical gastrectomy is usually used to treat patients with EGC; although this treatment can achieve adequate oncological resection margins and lymphadenectomy, it is still associated with some postsurgical complications [10]. On the other hand, although endoscopic treatment has been widely used in the treatment of EGC [11,12], higher recurrence rates and metachronous cancer are still concerns [13]. This study retrospectively analysed the clinicopathological characteristics and prognosis of EGC patients and related risk factors of lymph node metastasis (LNM) and provided information for the choice of optimal therapies for EGC.

Patients And Methods

Between 2007 and 2009, 1004 patients with histologically proven primary gastric adenocarcinoma underwent gastrectomy at the Department of Surgical Gastroenterology, Affiliated Tumour Hospital of Harbin Medical University, Harbin, China. Among the patients, 120 patients were diagnosed with EGC. According to the WHO classification [14,15], the diagnosis of EGC refers to a tumour confined to the mucosa or the submucosa, irrespective of the presence of regional LNMs. None of these patients received neoadjuvant chemotherapy or radiotherapy before surgery. This retrospective study was approved by the

Ethics Committee of Harbin Medical University, and all patients provided informed consent before enrolment in the study. The stomach was divided into three portions, which were defined by subdividing the lesser and greater curvatures into three equal lengths, as described in the Japanese Classification of Gastric Cancer [16]: proximal, middle and distal. The following clinicopathological parameters were collected: sex (male or female); age (mean, SD); preoperative haemoglobin (Hb) (mean, SD); prealbumin (Pre-ALB) (mean, SD); tumour size (mean, SD); carcinoembryonic antigen (CEA) level (mean, SD); Ca-199 level (mean, SD); macroscopic tumour type (elevated, flat, depressed, mixed, X) [17]; degree of differentiation (well differentiated, moderately differentiated, poorly differentiated, mucinous carcinoma or signet ring cell carcinoma; if two or more histological types were present, the histological type was defined by the predominant type in the tumour); depth of tumour invasion (T1a: tumour has invaded the mucosal layer; T1b: tumour has invaded the submucosal layer); and the 7th American Joint Committee on Cancer (AJCC) lymph node status (N0, N1, N2, N3a, or N3b, as shown Table 1). Moreover, we evaluated the clinicopathologic features in patients with early gastric carcinoma with and without LNM.

Follow-up and statistical analysis

Patient follow-up lasted until death or the cut-off date of March 30, 2016. For patients who survived, data were censored at the date of last contact. Only cases in which patients died of GC were classified as tumour-related deaths. Continuous variables were expressed as the mean±standard deviations. Chi-squared and Fisher exact tests were used to analyse the associations between categorical variables, and the t-test was used to compare continuous variables. Survival data were estimated using the Kaplan-Meier method; the log-rank test was used to analyse the significant prognostic factors in EGC and to compare the different survival rates of patients with or without LNM. A multivariate analysis of prognostic factors related to overall survival was performed using a Cox proportional hazards model. A multivariate logistic regression model was used to analyse the multivariate predictors of LNM. The criterion for statistical significance was $p < 0.05$. All data analyses were performed using SPSS for Windows, Version 22.0 software (SPSS Inc., Chicago, IL, USA).

Results

Clinicopathological features

Table 1 describes the clinicopathological features and prognostic single-factor analysis of the EGC cases. In these patients, 73 were men and 47 were women, and the male to female sex ratio was approximately 1.55. The average age was 54.74 ± 11.68 years (range, 28 to 78 years). The average preoperative Hb level was 135.09 ± 22.76 g/l, and the average prealbumin level was 280.34 ± 67.36 mg/dl. The mean tumour size was 2.81 ± 2.11 cm. The average Ca-199 level was 11.94 ± 16.38 U/ml. Most patients were diagnosed with distal tumours (78.3%). Macroscopically, the flat type tumour was the most common (38.33%), followed by the depressed type (33.33%), elevated type (17.5%), and mixed type (5%). According to the differentiation, 12 (10%) were well-differentiated adenocarcinomas, 55 (45.8%) were moderately differentiated adenocarcinomas, 44 (36.7%) were poorly differentiated adenocarcinomas, and 7 (5.8%)

were signet ring cell carcinomas. LNM was detected in 19 patients; the incidence of node-positive EGC was 11.96% (19/120). Twenty-eight patients (23.3%) had mucosal cancers and 92 patients (76.7%) had submucosal cancers. The incidence of node-positive EGC was 17.8% in patients with mucosal tumours and 15.2% in those with submucosal tumours.

The univariate analysis revealed a close relationship between age and Ca-199 level and LNMs ($p = 0.014$; $p = 0.043$). No significant correlation was observed among LNM and sex, Hb, prealbumin, CEA, tumour size, tumour location, macroscopic type, differentiation and T stage ($p = 0.451$; $p = 0.095$; $p = 0.864$; $p = 0.393$; $p = 0.35$; $p = 0.671$; $p = 0.959$; $p = 0.057$; $p = 0.77$, respectively) (Table 3). A multivariate logistic regression analysis for variables associated with lymph node metastasis in EGC showed that age, Ca-199 level and macroscopic tumour type were independent prognostic factors (Table 4).

Univariate and multivariate survival analyses

A univariate survival analysis showed that age, preoperative Hb level, prealbumin level, tumour size and N stage were significant prognostic factors in EGC (as shown in Table 1). The Kaplan-Meier survival curve indicated that more LNMs were predictive of a worse prognosis compared with fewer LNMs in EGC (as shown in Fig. 1). A multivariate analysis showed that the preoperative Hb level and LNM were independent prognostic factors (as shown in Table 2).

Discussion

The incidence of EGC was 11.96% in our 1004 patients, which is similar to that in another study in China [18]. In the western hemisphere, EGC accounts for 4–16% of all gastric carcinoma cases [19]. In South Korea, the proportion of EGC accounts for 47.4% of all diagnosed GCs in 2004 [20], while in Japan, the proportion of EGC accounts for approximately 30–50% of all GCs [21]. The differences in incidence may be related to screening strategies and various economic and health levels in different countries.

In our study, the LNM rate in EGC was 15.8%. Shen L et al [18] reported that LNM was observed in 12.20% of EGC patients. In another study [22], LNM was reported in 19.7% of EGC cases. The reported rates range from 5.7–20% of patients [23–28]. In our study, the node-positive rate of patients with EGC was 17.8% in those with tumours in the mucosal layer and 15.2% in those with tumours in the submucosal layer. As previously reported [28–29], once the tumour has invaded the submucosal layer, the rate of LNM increases significantly. However, we did not obtain the same result.

According to previous reports, anaemia is closely correlated with worse outcomes in cancer patients. For example, some studies have shown that anaemic patients with laryngeal [30], cervical [31], ovarian [32] and lung cancers exhibit worse survival [33,34]. A Korean study has shown that pretreatment anaemia is associated with poorer survival in patients with stage I and II GC [35]. Xuechao Liu et al found that preoperative anaemia, even mild anaemia, was an important predictor of postoperative survival of patients with TNM III GC [36]. Our study showed that the preoperative Hb level was an independent

prognostic factor in EGC. This is a unique finding compared with the findings in previous reports. The Hb level may affect the prognosis of early-stage GC. These results may provide information used in the treatment of EGC. In the future, we will study the exact mechanism by which the preoperative Hb level influences EGC.

Many studies have evaluated LNM in EGC and have confirmed that LNM is the most crucial prognostic factor for EGC [37–40]. We also obtained this result. LNM and preoperative Hb level were independent prognostic factors in EGC. Fig. 1 shows that the prognosis of EGC patients with different N stages was significantly different ($p = 0.000$). Patients who were lymph node-positive were younger and had higher Ca-199 values than those who were lymph node-negative. A multivariate logistic analysis for variables associated with LNM in EGC showed that age, Ca-199 and macroscopic tumour type were independent prognostic factors. In a study of 376 patients with EGC who underwent gastrectomy, Lim et al [41] found that macroscopic tumour type was related to LNM. Another publication [18] also revealed that macroscopic tumour type and other factors were independent risk factors for LNM. These studies suggest that macroscopic tumour type is important for predicting LNM in EGC. Moreover, Roviello et al [42] analysed 652 EGC patients with LNM and confirmed age ($p = 0.012$, $RS = 0.97$) as an independent predictor of nodal involvement. Fukuhara [43] also showed that younger age (OR, 1.11; 95% CI, 1.01–1.12; $p = 0.046$) was a significant predictor of LNM. Thus, younger patients with EGC may have more LNMs than older patients.

Limitations of this study include an inability to obtain a specific cut-off value for the preoperative Hb for predictive prognosis. We anticipate larger databases for further validation in the future. Another limitation was that this study analysed data originating from a single centre. In the future, we expect to perform a multi-centre and large-scale collaborative study to further demonstrate the prognostic significance of the preoperative Hb level in EGC.

In conclusion, we found that the preoperative Hb level and LNM were independent prognostic factors in EGC. Age, Ca-199 level and macroscopic tumour type were independent prognostic factors of LNM in EGC. The preoperative Hb level and LNM may help surgeons make better treatment decisions in the perioperative period.

Abbreviations

EGC: early gastric cancer; LNM: lymph node metastasis; Ca-199: cancer antigen-199; CEA: carcino-embryonic antigen; SD: standard deviation; Hb: haemoglobin; X: unknown type; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; Pre-ALB: prealbumin

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Hongliang Zu: analysis and interpretation of data, Study conception and design

Huiling Wang: data collection, drafting of article

Yan Ma: critical revision, drafting of article

Yingwei Xue: Study conception and design, analysis and interpretation of data; critical revision

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Harbin Medical University, and all patients provided informed consent before enrolment in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Race/Ethnicity is predictive of lymph node status in patients with early gastric cancer. [J Gastrointest Surg.](#)2014 Oct;18(10):1744-51.

Tables

Table 1 Baseline characteristics and prognostic single-factors analysis in EGC patients. (N = 120)

Variable	Mean,SD/n	5-survival rate	χ^2	P /t value
Gender			0.792	0.373
Male	73(71.9%)	91.3%		
Female	47/(28.1%)	86.6%		
Age(years)	54.74±11.68	90%	99.357	0.000
Mean,SD✖ Hb g/l	135.09±22.76	90%	197.586	0.000
Mean,SD Pre-albumin(mg/dl)	280.34±67.36	92%	264.163	0.000
Mean,SD Ca-199(u/ml)	11.94±16.38	90.7%	113.39	0.096
Mean,SD CEA(ng/ml)	1.78±1.72	90%	99.82	0.164
Mean,SD Tumor size(cm)	2.81±2.11	90%	25.32	0.021
Mean,SD Tumor location			0.387	0.824
Upper	3(2.5%)	100%		
Middle	23(19.2%)	91.3%		
Lower	94(78.3%)	88.5%		
Macroscopic type			3.717	0.446
Elevated	21 (17.5%)	95.2%		
Flat	46(38.3%)	83.8%		
Depressed	40 (33.3%)	89.1%		
Mixed	6(5%)	100%		
x	7			
Differentiation			1.044	0.959

Well	12(10%)	83.3%		
moderate	55(45.8%)	92%		
poor	44(36.7%)	88.3%		
signet	7(5.8%)	85.7%		
mucinous	1			
x	1			
Stage N+			36.008	0.000
N0	101(84.2%)	92.7%		
N1	10(8.3%)	78.8%		
N2	8(6.7%)	71.4%		
N3a	1(0%)			
Stage T*			0.041	0.84
T1a	28(23.3%)	92.6%		
T1b	92(76.7%)	88.5%		

*T1a tumor has invaded mucosa layer ;T1b tumor has invaded submucosa layer;+N0 no regional lymph node metastasis;N1 1-2 regional lymph node metastasis;N2 3-6 regional lymph node metastasis;and N3a 7-15 regional lymph node metastasis;N3b ≥15 regional lymph node metastasis.

※SD standard deviation;□Hb haemoglobin;;X unknow type.

Table 2 Multivariate Cox stepwise proportional hazard model for overall survival in EGC.

Variables	χ^2	P	hazard ratio (95% CI)
Hb	8.463	0.004	0.967–0.945–0.989
Lymph node metastasis	17.280	0.000	3.650–1.973, 6.719

Table 3 Clinicopathologic findings in patients with early gastric carcinoma with and without lymph node metastasis

Variables	Node-negative n= 109	Node-positive n=19	P /t value
Age(years)	55.87±11.29	48.73±12.14	0.014
Mean,SD sex			0.451
Male	63 (62.4%)	10 (52.6%)	
Female	38 (37.6%)	9 (47.4%)	
Hb g/l	133.5±23.61	143.10±15.68	0.095
Mean,SD Pre-albumin(mg/dl)	279.8±66.91	282.7±71.56	0.864
Mean,SD CEA(ng/ml)	1.84±1.81	1.47±1.15	0.393
Mean,SD Ca-199(u/ml)	10.63±11.74	18.90±30.78	0.043
Mean,SD Tumor size(cm)	2.289±2.24	2.39±1.17	0.350
Mean,SD Tumor location			0.671
Upper	3 (3%)	0 (0)	
Middle	20 (19.8%)	3 (15.8%)	
Lower	78 (77.2%)	16(84.2%)	
Macroscopic type			0.136
Elevated	16 (15.8 %)	5 (26.3 %)	
Flat	37 (36.6 %)	9 (47.4 %)	
Depressed	36 (35.6 %)	4 (21.1 %)	
Mixed	5 (5.0 %)	1 (5.3 %)	
x	0	1(5.3 %)	
Differentiation			0.057

Well	12(11.9%)	0
moderate	47 (46.5 %)	8(42.1 %)
poor	34 (33.7 %)	10(52.6 %)
signet	7 (6.9 %)	0
mucinous	1(1%)	0
x	0	1(5.3%)
Stage T		0.770
T1a	23(22.8 %)	5(26.3 %)
T1b	78 (77.2 %)	14(73.7 %)

Table 4 Multivariate logistic regression analysis for variables associated with lymph node metastasis in EGC.

Variables	Risk ratio	95% CI	x2	P value
Age	0.910	0.867-0.956	14.418	0.000
Ca-199	1.043	1.018-1.069	11.867	0.001
Macroscopic typ	0.551	0.321-0.949	4.622	0.032

Figures

Figure 1

The Kaplan-Meier survival curve indicated that more LNMs were predictive of a worse prognosis compared with fewer LNMs in EGC.