Identification of clinicopathological factors predicting lymph node metastasis in differentiated submucosal gastric cancer: Impact on surgical strategy

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Abstract. The aim of this study was to identify the clinicopathological factors predictive of lymph node metastasis (LNM) in differentiated submucosal gastric cancer (SGC), and to establish a simple criterion which may be useful in selecting the optimal treatment for cases with SGC. A total of 70 patients with differentiated and surgically treated SGC were retrospectively examined, and the association between the clinicopathological factors and the presence of LNM was retrospectively analyzed by univariate and multivariate logistic regression analyses. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. In the univariate analysis, tumor size, lymphatic vessel involvement and the presence of intermingled components of undifferentiated cancer cells were significantly associated with a higher rate of LNM (all $P<0.05$). In the multivariate analysis, lymphatic vessel involvement (OR=392.269; 95% CI 1.380-1115.032; P=0.038) and presence of intermingled components of undifferentiated cancer cells (OR=98.515; 95% CI 2.687-3612.400; P=0.012) were found to be independent pathological risk factors for LNM. LNM was observed in 75.0% (3/4) of patients with the two risk factors, but in none of the 45 patients without the two risk factors. Lymphatic vessel involvement and presence of intermingled components of undifferentiated cancer cells are independently associated with the presence of LNM in differentiated SGC. Thus, these two risk factors may be used to establish a simple criterion to guide further surgical procedures in cases with SGC revealed after endoscopic mucosal resection (EMR).

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Introduction

Due to an increased rate in the accurate diagnosis of early gastric cancer (EGC), in which invasion is confined to either the mucosa or submucosa, regardless of the presence or absence of regional lymph node metastasis (LNM), and subsequently improved prognosis, increased interest has focused on improving the quality of life and minimizing invasive procedures. Endoscopic mucosal resection (EMR) has been widely used for the treatment of ECG (1,2). EMR is now considered to be sufficient treatment for histopathologically differentiated, non-ulcerated intramucosal gastric cancer smaller than 2 cm (3), as such cancer rarely metastasizes to the lymph nodes (4,5). However, in certain cases of EGC, submucosal gastric cancer (SGC) is later revealed upon histopathological examination of the specimen obtained by EMR (6-8). In such cases, additional gastrectomy with lymphadenectomy is considered the standard therapy (9,10), even if the gastric tumor lesion has been completely excised by EMR in consideration of the high rate (approximately 20%) of LNM (11,12). However, LNM is not present in approximately 80% of surgical cases of SGC (11,12), thus gastrectomy with lymphadenectomy may be overtreatment for these cases.

Therefore, we conducted a retrospective study to determine the clinicopathological characteristics predictive of LNM in differentiated SGC. Furthermore, we established a simple criterion to indicate additional surgical treatment in differentiated SGC cases revealed following EMR.

Patients and methods

Patients. In this retrospective study, patients who had undergone radical surgery due to EGC in the Department of Surgical Oncology of the Affiliated Xingtai People's Hospital of Hebei Medical University, Xingtai, China, between January 1985 and December 2006 were screened for the identification of SGC cases revealed following EMR.

The inclusion criteria for this study were: i) lymph node dissection beyond limited (D1) dissection (D1 dissection and dissection of lymph nodes along the left gastric artery, D1 dissection and dissection of lymph nodes along the common hepatic artery, D1 dissection and dissection of lymph nodes

Table I. Univariate analysis of potential risk characteristics for lymph node metastasis.

Characteristics	No. of cases	Positive no. (%) of lymph node metastasis	P-value
Gender			
Male	60	8 (13.3)	0.180
Female	10	3 (30)	
Age (years)			
<60	33	3 (9.1)	0.150
≥60	37	8 (21.6)	
Family medical history			
Positive	13	3 (23.1)	0.419
Negative	57	8 (14.0)	
No. of tumors			
Single	67	10 (14.9)	0.391
Multitude	3	1 (33.3)	
Location			
Upper	4	1 (25)	0.419
Middle	11	3 (27.3)	
Lower	55	7 (12.7)	
Tumor size in diameter (cm)			
<2	35	2 (5.7)	0.022
≥2	35	9 (25.7)	
Macroscopic type			
I	3	1 (33.3)	0.514
II	41	5 (12.2)	
III	26	5 (19.2)	
Histological type			
Well-differentiated	33	5 (15.2)	0.450
Moderately differentiated	31	4 (12.9)	
Papillary adenocarcinoma	6	2 (33.3)	
Lymphatic vessel involvement			
Negative	61	5 (8.2)	<0.001
Positive	9	6 (66.7)	
Undifferentiated component[a]			
Absence	51	3 (5.9)	<0.001
Presence	19	8 (42.1)	

[a]Intermingled components of undifferentiated cancer cells within a cancer lesion.

along the celiac artery), or extended (D2) dissection was performed; ii) resected specimens and lymph nodes that had been pathologically analyzed and diagnosed as SGC; iii) histopathologically-classified SGC as the differentiated type, according to the Japanese Classification of Gastric Carcinoma (JCGC) (13); and iv) availability of the patient's medical records.

During the period mentioned, radical surgery was performed in 293 patients with EGC. Of these patients, 163 patients were histologically diagnosed as SGC; 73 as differentiated SGC and 90 as undifferentiated SGC. Among the 73 patients with differentiated SGC, medical records were not completely available for three cases. Thus, 70 patients (60 males and 10 females; mean age, 59 years; range, 33-80 years) with histopathologically differentiated-type SGC met the inclusion criteria for the study. The study protocol was approved by the Ethics Committee of Hebei Medical University.

Surgical dissection of lymph nodes. The lymph nodes of each case were meticulously dissected from the en bloc specimens, and the classification of the dissected lymph nodes was determined by a surgeon following examination of the excised specimens based on the JCGC (13). The resected lymph nodes were then sectioned, stained with hematoxylin and eosin, and examined by pathologists for metastasis and lymphatic vessel involvement.

Association between clinicopathological parameters and LNM. Clinicopathological parameters investigated in this study were selected according to the JCGC (13). These characteristics

Table II. Multivariate analysis of potential risk factors for lymph node metastasis.

Characteristics	Hazard ratio	95% Confidence interval	P-value
Tumor size (cm)			
<2 vs. ≥2	1.375	0.146-12.980	0.781
Lymphatic vessel involvement			
Negative vs. positive	392.269	1.380-1115.032	0.038
Undifferentiated component			
Absence vs. presence	98.515	2.687-3612.400	0.012

included, gender (male and female), age (<60 years and ≥60 years), family medical history of gastric cancer, number of tumors (single or multitude), location of the tumor (upper, middle or lower section of the stomach), tumor size (maximum dimension, <2 or ≥2 cm), macroscopic type [protruded (type I)], superficial elevated (type IIa), flat (type IIb), superficial depressed (type IIc) or excavated (type III)], histopathological type (well-differentiated, moderately differentiated or papillary adenocarcinoma), lymphatic vessel involvement, presence of intermingled components of undifferentiated cancer cells (poorly differentiated adenocarcinoma, signet-ring-cell carcinoma or mucinous adenocarcinoma).

Statistical analysis. Data were analyzed using SPSS 13.0 statistical software (SPSS Inc., Chicago, IL, USA). The differences in the clinicopathological parameters between patients with and without LNM were determined by the χ^2 test. A multivariate stepwise logistic regression analysis was performed to identify independent risk factors of LNM. The hazard ratio and 95% confidence interval (CI) were calculated. P<0.05 was considered to indicate a statistically significant difference.

Results

Association between the clinicopathological parameters and LNM. The association between various clinicopathological characteristics and LNM was first analyzed using the χ^2 test (Table I). Tumor size, lymphatic vessel involvement and presence of intermingled components of undifferentiated cancer cells were significantly associated with a higher rate of LNM (P<0.05). However, gender, age, family medical history of gastric cancer, number of tumors, location, macroscopic type and histological type of the tumor were not found to be associated with LNM.

Multivariate analysis of potential independent clinicopathological risk factors for LNM. Of the three characteristics that were significantly associated with LNM by univariate analysis, lymphatic vessel involvement and presence of intermingled components of undifferentiated cancer cells were found to be significant and independent risk factors for LNM by multivariate analysis (P<0.05) (Table II).

LNM in differentiated SGC. Of the 70 cases, LNM was histologically confirmed in 11 (15.7%) patients. The correlation between the two positive risk clinicopathological characteristics and LNM were studied in differentiated SGC. There was no LNM in 45 patients without the two pathological risk factors, whereas LNM was present in 38.1% (8/21) of patients with only one pathological risk characteristics. LNM occurred in 75.0% (3/4) of the patients with two risk factor characteristics (Fig. 1).

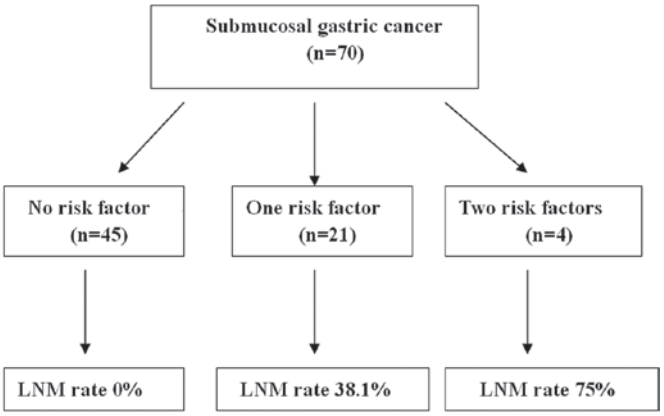

Figure 1. Association between the two identified risk factors and lymph node metastasis (LNM) in submucosal gastric cancer

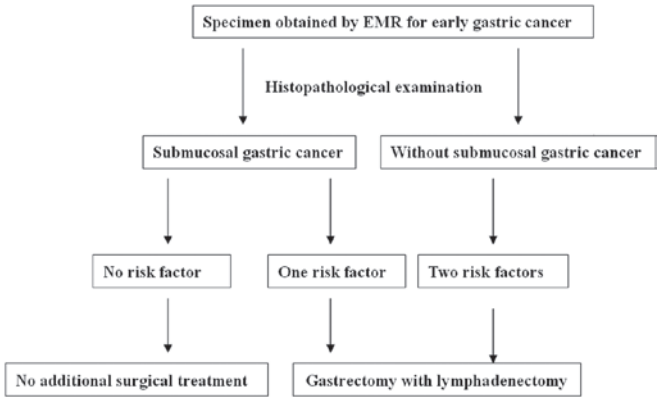

Figure 2. Proposed therapeutic strategy for differentiated submucosal gastric cancer revealed following endoscopic mucosal resection (EMR) according to the identified pathological risk factors.

Discussion

Several studies have been conducted to evaluate predictive factors for LNM in SGC and to establish the most appropriate

treatment strategy (13-16). Factors including depth of invasion, tumor size, gross appearance and histological type have been observed to be predictors of LNM in SGC (17,18). In the present study, lymphatic vessel involvement and presence of intermingled components of undifferentiated cancer cells were significantly associated with differentiated LNM.

A significant issue is whether additional treatment, including gastrectomy with lymph node dissection, is necessary when SGC is revealed by pathological examination following EMR since LNM is known to occur in approximately 20% of SGC cases. In the present study, LNM was not observed in the patients without the two pathological risk characteristics. This finding may indicate that EMR is sufficient in treating these cases, and that additional surgery is unnecessary. However, 38.1 and 75.0% of patients with one or two of the pathological risk factors had LNM, respectively, and the survival rate of patients with one or two of the pathological risk factors was significantly lower than that of the patients without any of the risk factors. Therefore, gastrectomy with lymphadenectomy is inevitable for patients with the risk factors.

In addition to conventional open gastrectomy with lymphadenectomy, laparoscopic gastrectomy with lymphadenectomy may be an alternative approach (19). When compared with conventional open gastrectomy, laparoscopic gastrectomy has several clinical advantages, including less pain, milder inflammatory response, faster recovery of the gastrointestinal function, shorter hospital stay and improved quality of life (20). Moreover, over the past 17 years significant advances in laparoscopic surgical techniques and instruments, such as laparoscopic coagulating shears, have been observed (21). It is now possible to perform total gastrectomy and extended lymph node dissection (D2) laparoscopically (22,23).

In this study, all cases underwent conventional open gastrectomy and all metastatic lymph nodes were within N2. Thus, for patients with pathological risk characteristics laparoscopic gastrectomy coupled with lymph node dissection simultaneously may enable curability and improve the quality of life. However, this hypothesis requires further clinical verification.

Based on our findings, we propose a treatment strategy for patients with SGC that is revealed after EMR for EGC. For patients without any of the risk factors, EMR without lymphadenectomy is sufficient. However, for patients with a pathological risk factor, additional radical gastrectomy should be recommended (Fig. 2).

Lymphatic vessel involvement and presence of intermingled components of undifferentiated cancer cells are independently associated with LNM in differentiated SGC. Thus, the two risk factors may be used to establish a simple criterion to guide further surgical procedures in cases with SGC revealed by EMR. EMR alone may be sufficient for the majority of cases without the two risk factors. However, for patients with either of these pathological risk factors, additional radical gastrectomy is recommended.

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