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Analysis of factors related to lymph node metastasis in undifferentiated early gastric cancer

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Background/aims: *This study was conducted to analyze the factors related to lymph node metastasis in undifferentiated early gastric cancer and to investigate whether endoscopic resection can be performed.* ***Methods:*** *Three hundred sixty-two early gastric cancer patients who were diagnosed with undifferentiated early gastric cancer and underwent surgery were divided into groups depending on their age, sex, location of tumor, macroscopic findings, presence of an ulcer, histological type, tumor size, depth of invasion, and lymphatic involvement, and the correlations between clinicopathological characteristics and lymph node metastasis were analyzed.* ***Results:*** *Lymph node metastasis was detected in 31 (8.5%) of the 362 patients. Univariate analysis revealed correlations between lymph node metastasis and various factors ranging from patient age, location of tumor, presence of an ulcer, and depth of invasion to lymphatic involvement. However, in multivariate analysis, presence of an ulcer and lymphatic involvement were found to be independent risk factors. After selecting and analyzing only patients with intramucosal early gastric cancer, we found that lymphatic involvement was the only independent risk factor.* ***Conclusions:*** *Though presence of an ulcer is an independent predictive factor for lymph node metastasis before operation in patients with undifferentiated early gastric cancer, caution is required in the interpretation. In addition, clinicopathological characteristics such as histological type and tumor size did not have a significant effect on lymph node metastasis. Therefore, we found that the evidence was insufficient to select endoscopic resection even when there is a small lesion, and we believe that the decision on the use of endoscopic resection for patients with undifferentiated early gastric cancer should be made more carefully when there is an ulcer.*

Key words: Lymph node metastasis, undifferentiated early gastric cancer, endoscopic resection, lymphatic involvement

Kötü differansiye erken gastrik kanserde lenf nodu metastazı ile ilişkili faktörlerin analizi

Amaç: *Bu çalışmada erken gastrik kanserde lenf nodu metastazı ile ilişkili faktörlerin araştırılması ve endoskopik rezeksiyona uygunluğun araştırılması amaçlanmıştır.* ***Yöntem:*** *Erken kötü differansiye gastrik kanseri olan ve cerrahi uygulanmış 362 hasta çalışmaya dahil edilmiş ve hastalar yaş, cinsiyet, tümör lokalizasyonu, makroskopik bulgular, ülser varlığı, histolojik tip, tümör boyutu, invazyon derinliği ve lenf nodu tutulumuna göre incelenmiş, klinikopatolojik bulgular ile lenf nodu metastazı arasındaki korelasyonlar araştırılmıştır.* ***Bulgular:*** *Hastaların 31'inde (%8,5) lenf nodu metastazı tespit edildi. Tek değişkenli analizde lenf nodu metastazı ile hasta yaşı, tümör lokalizasyonu, ülser varlığı, invazyon derinliği ve lenfatik tutulum arasında ilişki saptandı. Ancak çok değişkenli analizde ülser varlığı ve lenfatik tutulum varlığı, lenf nodu metastazı ile ilişkili bağımsız risk faktörleri olarak bulundu. İntramukozal erken gastrik kanser olan vakalar seçildiğinde ise lenfatik tutulumun tek önemli risk faktörü olduğu görüldü.* ***Sonuç:*** *Ülser varlığı kötü differansiye erken gastrik kanserli vakalarda lenf nodu metastazını öngörmekte prediktif olmasına rağmen, bu verinin değerlendirilmesinde dikkatli olunmalıdır. Ek olarak, tümörün histolojik tipi ve boyutu gibi klinikopatolojik karakteristiklerin lenf nodu metastazı üzerinde anlamlı etkisi olmadığı görülmüştür. Buna göre, küçük lezyonlarda dahi endoskopik rezeksiyonu tercih etmek için yeterli kanıt mevcut değildir. İnanıyoruz ki, ülserli kötü differansiye erken mide kanserli vakalarda endoskopik rezeksiyonu tercih ederken daha dikkatli olunmalıdır.*

Anahtar kelimeler: Lenf nodu metastazı, kötü differansiye erken gastrik kanser, endoskopik rezeksiyon, lenfatik tutulum

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INTRODUCTION

With the development of endoscopic devices and an increasing interest in cancer, detection of early gastric cancer (EGC) has been on the rise, and endoscopic resection, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), has played an important role in the treatment of EGC. Prediction of lymph node metastasis (LNM) in EGC has been an essential requirement for endoscopic resection [1]. Many studies have been conducted on patients with LNM to date, and accumulated experiences and the development of endoscopic devices have contributed to the expanded indication of endoscopic resection (1-3).

As undifferentiated EGC, including poorly differentiated (PD) adenocarcinoma, signet ring cell (SRC) carcinoma, and mucinous adenocarcinoma, is known to have a higher probability of LNM compared with differentiated EGC, the use of endoscopic resection for EGC is still controversial (4-8). Some have tried to include undifferentiated EGC in the expanded indication for endoscopic resection (9); however, since LNM has not been reported in most cases who underwent operation, uniform application of operation may be regarded as overtreatment (10).

In this study, risk factors affecting LNM in undifferentiated EGC were analyzed to know whether the expanded application of endoscopic resection would be advisable.

MATERIALS AND METHODS

This study was conducted on 362 patients finally diagnosed with undifferentiated cancer among 958 patients who underwent surgery for EGC (adenocarcinoma) between January 2002 and December 2006 at Kosin University Gospel Hospital. In this study, undifferentiated EGC was restricted to PD and SRC based on the World Health Organization (WHO) and Japanese classifications (11,12).

The surgical method was divided into open resection or laparoscopic procedure, and then open resection was subdivided into three categories: subtotal gastrectomy, total gastrectomy and wedge resection. Based on the patients' medical records and histopathologic records, we investigated and documented patient age, sex, location of tumor, macroscopic findings, presence of an ulcer, histological type, tumor size, depth of invasion, and lymphatic involvement (Figure 1) and analyzed the correlations between these factors and LNM.

Location and Macroscopic Findings of Tumor

Tumor location was divided into three categories based on the Japanese classification: upper third, middle third, and lower third. The macroscopic tumor findings were divided into three categories: elevated type, depressed (or ulcerative) type, and mixed type.

Presence of an Ulcer and Tumor Size

We confirmed the presence of an ulcer when endoscopic examination revealed an ulcer or scar within the lesion (Figure 2). Based on the gross or histological findings from the resected specimen, tumor size was measured by the longest diameter in formalin-fixed tissue.

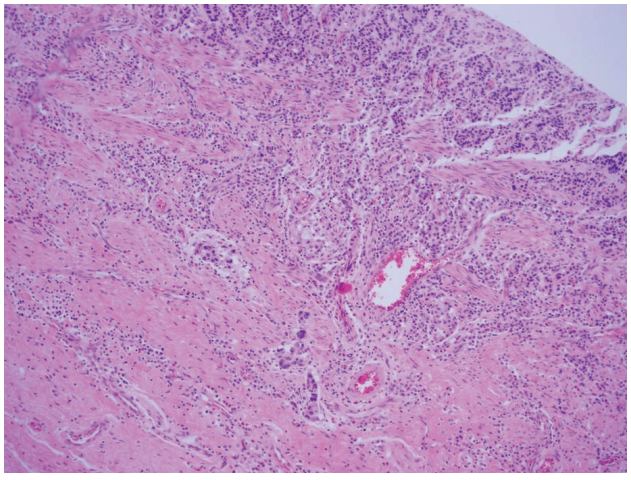

Figure 1. Microscopic image of early gastric cancer stained with hemetoxylen-eosin.

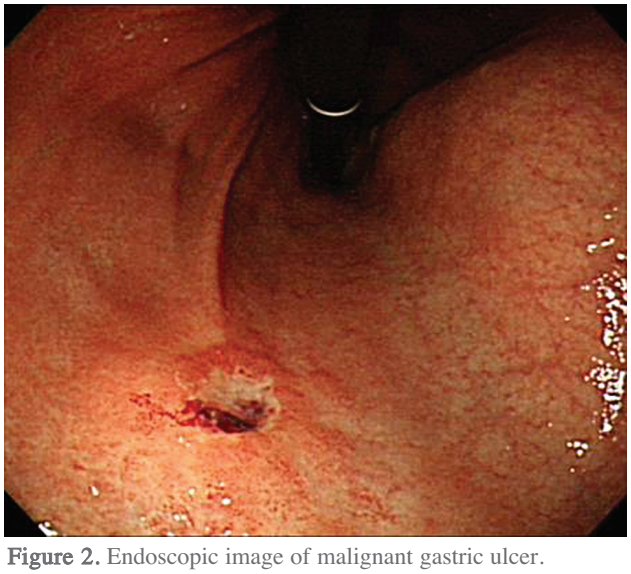

Figure 2. Endoscopic image of malignant gastric ulcer.

Histological Type of Tumor

The WHO standard was used in the evaluation of histological findings, and SRC was defined as a carcinoma in which malignant cells containing intracellular mucin accounted for 50% or more (Figure 3).

Statistical Analysis

The SAS (version 9.1; SAS Institute, Cary, NC, USA) statistical program was used as the analysis tool. In univariate analysis, a cross-tabulation analysis (chi-square test) of LNM was performed for each category of individual variables. To identify independent risk factors for LNM, multivariate logistic regression analysis was used. A finding of $p \leq 0.05$ was considered significant.

RESULTS

Characteristics of Material

The operation methods were subtotal gastrectomy (321 cases), total gastrectomy (27 cases), wedge resection of the stomach (10 cases), and laparoscopic gastrectomy (4 cases) with D1 dissection (143 cases), D2 dissection (206 cases), and D2+ dissection (13 cases). The mean number of resected lymph nodes was 22.4 (1-76). There were 248 cases (68.5%) younger than 60 and 114 cases (31.4%) aged 60 or older. The gender ratio of male to female was 201 cases (55.5%): 161 cases (44.4%). Tumors were located in the upper third in 33 cases (9.1%), middle third in 234 cases (64.6%), and lower third in 95 cases (26.2%), and the depth of invasion was the mucous layer in 200 cases (55.2%) and the submucous layer in 162 cases (44.7%). Macroscopic findings were elevated type in 19 cases (5.3%), depressed (or ulcerative) type in 301 cases (83.2%), and mixed type in 42 cases (11.6%). Ulcers were observed in 120 cases (33.2%) and not observed in 242 cases (66.9%). The tumor was <10 mm in 63 cases (17.4%), 11-20 mm in 143 cases (39.5%), and >20 mm in 156 cases (43.1%). The histological type of tumor was PD in 158 cases (43.6%) and SRC in 204 cases (56.3%), and lymphatic involvement was positive in 51 cases (14.1%) and negative in 311 cases (85.9%).

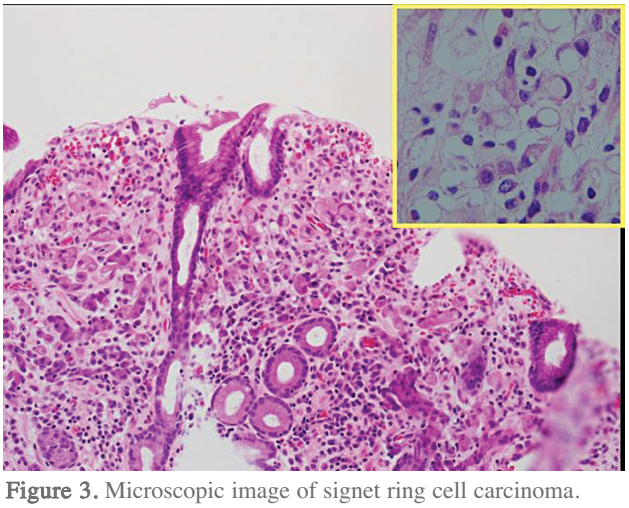

Figure 3. Microscopic image of signet ring cell carcinoma.

Correlations between Clinicopathological Characteristics and LNM

Among 362 cases diagnosed with undifferentiated EGC, LNM occurred in 31 cases (8.5%). Among 200 cases of intramucosal EGC, LNM was observed in 7 cases (3.5%), while among 162 cases of submucosal EGC, 24 cases (14.8%) had LNM. Our analysis of the correlations between LNM and clinicopathological characteristics such as patient age, sex, location of tumor, macroscopic findings, presence of an ulcer, histological type, tumor size, depth of invasion, and lymphatic involvement found that the statistically significant factors were patient age ($p=0.007$), tumor location ($p=0.011$), presence of an ulcer ($p=0.009$), depth of invasion ($p<0.001$), and lymphatic involvement ($p<0.001$). The rate of LNM in patients older or younger than 60 years was 14.91% (17/114) and 5.65% (14/248), respectively. The LNM rate classified by tumor location was 3.03% (1/33) in the upper third, 6.41% (15/234) in the middle third, and 15.79% (15/95) in the lower third, showing a higher rate of LNM in tumors that occurred in the lower third of the stomach. The LNM rate was 5.79% (14/234) in cases without ulcers and 14.17% (17/120) in cases with ulcers. The LNM rate in intramucosal and submucosal EGC was 3.50% (7/200) and 14.81% (24/162), respectively, showing a higher LNM rate in submucosal EGC. The LNM rate was 52.94% (27/51) in cases with lymphatic involvement and 1.29% (4/311) in cases without lymphatic involvement (Table 1).

Independent Risk Factors Affecting LNM

According to multivariate analysis, the statistically significant variables were the presence of an ulcer [odds ratio (OR) 3.816, 95% confidence interval (CI) 1.342-10.845, $p=0.012$] and lymphatic involvement [OR 98.970, 95% CI 30.284-323.439, $p<0.0001$], both of which were independent predictive factors for LNM (Table 2).

Table 1. Univariate analysis of potential risk factors for lymph node metastasis

Variable	LN metastasis Positive n = 31	Negative n = 331	% positive	p-value
Age (years)				0.007
≤ 60	14	234	5.65	
> 60	17	97	14.91	
Sex				0.707
Male	16	185	7.96	
Female	15	146	9.32	
Tumor location				0.011
Middle third	15	219	6.41	
Upper third	1	32	3.03	
Lower third	15	80	15.79	
Macroscopic type				0.903
Elevated	2	17	10.53	
Depressed	26	275	8.64	
Mixed	3	39	7.14	
Ulcer				0.009
Negative	14	228	5.79	
Positive	17	103	14.17	
Histologic type				0.057
PD	19	139	12.03	
SRC	12	192	5.88	
Size				0.185
1-10 mm	3	60	4.76	
11-20 mm	10	133	6.99	
≥21 mm	18	138	11.54	
Depth				<0.001
Mucosa	7	193	3.50	
Submucosa	24	138	14.81	
Lymphatic involvement				<0.001
Negative	4	307	1.29	
Positive	27	24	52.94	

PD: Poorly differentiated. SRC: Signet ring cell.

Table 2. Multivariate analysis of potential risk factors for lymph node metastasis

Variable	Odds ratio	95% CI	p-value
Ulcer			
Negative	1		
Positive	3.816	1.342~10.845	0.0120
Lymphatic involvement			
Negative	1		
Positive	98.970	30.284~323.439	<0.0001

CI: Confidence interval.

Predictive Factors for LNM in Undifferentiated Intramucosal EGC

In our univariate analysis of the selected undifferentiated intramucosal EGC (200 cases), tumor location (lower third) and lymphatic involvement were found to be the factors associated with LNM. However, multivariate analysis revealed that lymphatic involvement was the only independent risk factor for LNM (Tables 3 and 4).

DISCUSSION

Based on histological characteristics, gastric cancer can be classified into differentiated carcinoma (DC) and undifferentiated carcinoma (UDC). UDC includes PD, SRC, and mucinous adenocarcinoma (11,12). Endoscopic resection, such as EMR and ESD, has still not been indicated for undifferentiated EGC (4). As tumor margins tend to be unclear, it is difficult to set a lateral margin, and tumors are known to have a higher rate of LNM than differentiated EGC, even when the lesion is as small as 2 cm (13). In addition, the LNM rate is relatively higher in patients with undifferentiated intramucosal EGC (4.2-7.3%) than in patients with differentiated intramucosal EGC (0.4%) (4-8). In this study, we found that the LNM rate of undifferentiated intramucosal EGC was 3.5% (7/200 cases), similar to that of other studies.

Recently, with the development of techniques and endoscopic devices, some have tried to expand the guidelines of endoscopic resection to include undifferentiated EGC within the scope of indication. However, as the number of studies was small and the studies had limitations, controversy remains (14). Some have asserted that outcome and long-term prognosis were equivalent to those of the standard indication group as long as several conditions are met, and therefore endoscopic resection can be performed (15). In our study, the LNM rate of undifferentiated EGC was 8.5%, that is, 3.5% in mucosal EGC and 15% in submucosal EGC, which is similar to other studies (10). Undifferentiated EGC has a higher LNM rate than differentiated EGC as described above, but approximately 97% of patients with mucosal EGC without LNM have been receiving unnecessary surgery, which can reduce their quality of life. Though various examinations have been performed using computed tomography (CT), endoscopic ultrasonography (EUS), and multidetector row computed tomography (MDCT) to clinically identify LNM before resection, these are not satisfactory (16). Thus, some studies have tried to identify the conditions for predicting LNM in patients with undifferentiated EGC for application in endoscopic resection. Abe et al. (17) analyzed 175 cases of undifferentiated EGC and reported that tumor size and lymphatic involvement were independent risk factors.

Table 3. Univariate subgroup analysis of potential risk factors for lymph node (LN) metastasis in patients with intramucosal undifferentiated EGC

Variable	LN metastasis Positive n = 7	Negative n = 193	% positive	p-value
Age (years)				0.402
≤ 60	4	140	2.78	
> 60	3	53	5.36	
Sex				0.053
Male	1	105	0.94	
Female	6	88	6.38	
Tumor location				0.001
Middle third	1	132	0.75	
Upper third	0	14	0.00	
Lower third	6	47	11.32	
Macroscopic type				0.261
Elevated	0	7	0.00	
Depressed	5	167	2.91	
Mixed	2	19	9.52	
Ulcer				0.402
Negative	4	140	2.78	
Positive	3	53	5.36	
Histologic type				0.237
PD	4	65	5.80	
SRC	3	128	2.29	
Size				0.796
1-10 mm	2	38	5.00	
11-20 mm	3	80	3.61	
≥21 mm	2	75	2.60	
Lymphatic involvement				<0.001
Negative	2	192	1.03	
Positive	5	1	83.33	

PD: Poorly differentiated. SRC: Signet ring cell.

Table 4. Multivariate subgroup analysis of potential risk factors for lymph node metastasis in patients with intramucosal undifferentiated EGC

Variable	Odds ratio	95% CI	p-value
Ulcer			
Negative	1		
Positive	3.660	0.269~49.763	0.330
Lymphatic involvement			
Negative	1		
Positive	511.118	27.320~	<0.0001

CI: Confidence interval.

In our study, the undifferentiated EGC was mainly located in the middle third of the stomach, and depressed-type cancer was the dominant macroscopic finding. In univariate analysis, patient age (60 years or older), tumor location (lower third), presence of an ulcer (positive), depth of invasion (submucosa), and lymphatic involvement (positive) were associated with LNM. However, in multivariate analysis, ulcer and lymphatic involvement were found to be the only independent risk factors for LNM. Unlike the previous studies, depth of invasion was not included in the independent risk factors, probably because many cases of SM1 cancers in which tumor cell invasion is limited to the upper third of the SM were included in the submucosal EGC cases of this study (16).

In general, the presence of an ulcer is determined from endoscopic and pathological findings. The pathological definition of an ulcer is the existence of fibrosis in the submucosal layer and damage to the muscularis mucosa (13). We used endoscopic findings to determine the presence of an ulcer, and slightly depressed lesions covered with exudates or lesions situated on the converged fold were considered ulcers. However, in the concept of the malignant cycle, the presence of an ulcer can be determined differently depending on the time of observation and individual observers. In addition, when a small converged fold may occur due to a previous biopsy, determining the presence of an ulcer through endoscopic findings becomes even more difficult.

In our selection and subsequent analysis of cases with intramucosal EGC, tumor location (lower third) and lymphatic involvement (positive) were associated with LNM, and there was no significant correlation between LNM and factors such as patient age, sex, macroscopic findings, presence of an ulcer, histological type, and tumor size. In multivariate analysis, lymphatic involvement was found to be the only independent risk factor.

In our study, lymphatic involvement was the independent risk factor for predicting LNM in both EGC and intramucosal EGC, and the results were similar to those of previous studies. However, as the study has a limitation in that lymphatic involvement cannot be determined until surgery or endoscopic resection is performed, lymphatic involvement cannot be used in determining whether to perform endoscopic resection.

In conclusion, although an ulcer is thought to be an independent predictive factor for LNM before resection, caution is required in the interpretation. In addition, clinicopathological characteristics such as histological type and tumor size did not have a significant effect on LNM. Therefore, we found that the evidence was insufficient to select endoscopic resection even when the lesion is small, and we believe that the decision to use endoscopic treatment should be made more carefully, especially when there is an ulcer.

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