Extended Indication Criteria for Endoscopic Mucosal Resection of Early Gastric Cancer with Special Reference to Lymph Node Metastasis — Examination by Multivariate Analysis —

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Summary: The purpose of this study was to clarify extended indication criteria of endoscopic mucosal resection (EMR) for early gastric cancer (EGC) by analyzing the independent risk factors involved in lymph node metastasis (LNM). Subjects were 422 patients who underwent gastrectomy with lymph node dissection for EGC at the Kurume University Hospital from 1994 to 2001. The EGCs were mucosal cancers (M) in 252 cases and submucosal cancers (SM) in 170 cases. Twelve clinico-pathological factors were assessed for their possible association with LNM. On univariate analysis, EGC with LNM showed the following characteristics: size; 3.1 cm or more, ulceration; present, heterogeneity; present, differentiation; poor, lymphatic vascular invasion; present, and invasion depth; SM2 (cancer penetration of submucosal layer, 0.5 mm or more from the muscularis mucosa). On multivariate analysis, the following four factors were identified as independent risk factors; invasion depth: Odds Ratio (OR) 10.9, lymphatic vascular invasion: OR 10.6, size: OR 3.2, and ulceration: OR 3.2. The incidence of LNM was 0% (0/141) (95% confidence interval, 0-2.6%) when these risk factors met the following four conditions: invasion depth; M or SM1 (cancer penetration of submucosal layer, less than 0.5 mm), lymphatic vascular invasion; absent, size; 3.0 cm or less, and ulceration; absent. It is concluded that EMR is a suitable radical treatment for EGC, and that the indication criteria for EMR can be extended depending on the results of the histological evaluation of the en bloc/total resected specimen concerning the above four factors for LNM.

Key words early gastric cancer, lymph node metastasis, endoscopic mucosal resection, multivariate analysis

INTRODUCTION

Recently, there has been much discussion of whether the indications of endoscopic mucosal resection (EMR) for early gastric cancer (EGC) should be extended with respect to improving quality of life [1-9]. EGC is defined as gastric cancer in which tumor invasion is confined to the mucosa and submucosa, irrespective of the presence of regional lymph node

metastasis (LNM) [10]. For EMR to be considered an acceptable treatment for EGC, it must produce results similar to those obtained by surgery with respect to radicality, safety, and technique. Briefly, it will be necessary to demonstrate, by sufficient histological evaluation after treatment, that the risk of LNM is extremely low. In addition, it is essential that an en bloc/total resected specimen be collected, regardless of the location or size of the lesion [11-

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Abbreviations: 95%CI, 95% confidence interval; EGC, early gastric cancer; EMR, endoscopic mucosal resection; LNM, lymph node metastasis; M, mucosal cancer; OR, Odds Ratio; SM, submucosal cancer; SM1, cancer penetration of submucosal layer, less than 0.5mm; SM2, cancer penetration of submucosal layer, 0.5mm or more from muscularis mucosa.

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Previously, the size and location of EGCs in which en bloc/total resection was possible was limited due to technical issues with EMR [1,14,16]. Therefore, indication criteria for EMR were more strict in the past [1]. Currently, the accepted indications for EMR in Japan are well-differentiated mucosal lesions less than 2 cm in size without ulceration. However, the recent development of new endoscopic devices, such as the insulated-tip electrosurgical knife (IT knife) [11-14] and the Hooking knife [15], has resolved many of these technical issues.

In the present study we investigated the presence or absence of LNM, which is the most important factor related to extending the indication criteria of EMR in patients with EGC, clarified the clinico-pathological risk factors for LNM, and examined the conditions under which EMR can be selected as a suitable radical treatment for EGC.

PATIENTS AND METHODS

Patients

The study included 422 patients with EGCs, consisting of 252 mucosal and 170 submucosal lesions, who underwent surgery including lymph node dissection from 1994 to 2001, and whose stomach X-ray/Endoscopic and macroscopic/histological findings could be adequately examined. Patients who underwent local/segmental resection, laparoscopic surgery and EMR without lymph node dissection were excluded.

Statistical analysis

All analysis was done with the Stat View software package for Macintosh (version 5.0). The chi square test, Fisher's direct test, the Mann-Whitney U test and Logistic regression analysis were performed. $P < 0.05$ was regarded as significant (paired test).

Examination of EGC with LNM

Univariate analysis was performed to compare the following 12 clinico-pathological factors between 30 lesions with and 392 lesions without LNM. Clinico-pathological factors were classified into the following categories in accordance with the Japanese Classification of Gastric Carcinoma [10].

- 1) Age: year (Mean $\pm$ SD).
- 2) Gender: 2 categories; male and female.
- 3) Location: 3 categories; U: upper third of stomach, M: middle third of stomach, and L: lower

third of stomach.

- 4) Regional wall: 4 categories; the lesser curvature, greater curvature, anterior wall, and posterior wall.
- 5) Macroscopic type: 3 categories; depressed type, protruded type, and mixed type.
- 6) Size: 2 categories; 3.0 cm or less and 3.1 cm or more.
- 7) Histological type: 2 categories; undifferentiated type (poorly differentiated adenocarcinoma, signet-ring cell carcinoma) and differentiated type (tubular adenocarcinoma, papillary adenocarcinoma).
- 8) Heterogeneity: 2 categories; absent and present. When the above 2 histological types were mixed, lesions were defined as "present".
- 9) Differentiation: 3 categories; well, moderate, and poor. Differentiation was defined as representing not the quantitatively predominant histological type but the most poorly differentiated areas.
- 10) Ulceration: 2 categories; absent and present. Lesions in which macroscopic and histological findings showed fold convergence or submucosal fibrosis were defined as "present".
- 11) Lymphatic vascular invasion: 2 categories; absent and present.
- 12) Invasion depth: 3 categories; M, SM1 and SM2. Among lesions infiltrating the submucosal layer, those in which the infiltration distance from the muscularis mucosa was less than 0.5 mm were evaluated as SM1, while those in which the distance was 0.5 mm or more were evaluated as SM2.

Examination of risk factors for LNM

Multivariate analysis (logistic regression analysis) was performed using the presence or absence of LNM as an objective variable and the above factors selected by univariate analysis as explanatory variables. To select variables that may be risk factors for LNM, the variable-increasing method using the likelihood ratio test was used. Explanatory variables with a correlation coefficient of 0.9 or more or with multiple commensal linearity were excluded. The odds ratio (OR) in each factor and 95% confidence interval (95%CI) were calculated.

Examination of indication criteria for EMR

Stratified analysis was performed based on risk factors for LNM selected by multivariate analysis. We investigated conditions showing the lowest risk

of LNM.

RESULTS

Examination of EGC with LNM

EGC with LNM showed the following characteristics in comparison to EGC without LNM; size: 3.1 cm or more, ulceration: present, heterogeneity: present, differentiation: poor, lymphatic vascular invasion: present, and invasion depth: SM2. There were no significant differences in age, gender, location, regional wall, macroscopic type, or histological type (Table 1).

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Examination of risk factors for LNM

The following four factors were identified as independent risk factors for LNM among the above six factors, namely invasion depth: $P=0.0311$, OR10.85, lymphatic vascular invasion: $P<0.0001$,

TABLE 1.
Characteristics of EGC with LMN by univariate analysis

Clinico-pathological factors		LMN: absent	LMN: present	P-value
Age	Mean±SD	64.32±10.81	66.47±8.31	$P=0.2605$
Gender	Male	269 (68.6%)	20 (66.7%)	$P=0.8241$
	Female	123 (31.3%)	10 (33.3%)	
Location	U	76 (19.4%)	5 (16.7%)	$P=0.4276$
	M	101 (25.8%)	11 (36.7%)	
	L	215 (54.8%)	14 (46.7%)	
Regional wall	Posterior wall	95 (24.2%)	7 (23.3%)	$P=0.3770$
	Anterior wall	83 (21.2%)	8 (26.7%)	
	Lesser curvature	157 (40.1%)	8 (26.7%)	
	Greater curvature	57 (14.5%)	7 (23.3%)	
Macroscopic type	Depressed type	273 (69.6%)	17 (56.7%)	$P=0.3154$
	Protruded type	51 (13.0%)	5 (16.7%)	
	Mixed type	68 (17.3%)	8 (26.7%)	
Size	3.0 cm or less	263 (67.1%)	8 (26.7%)	$P<0.0001$
	3.1 cm or more	129 (32.9%)	22 (73.3%)	
Histological type	Undifferentiated type	142 (36.2%)	8 (26.7%)	$P=0.2918$
	Differentiated type	250 (63.8%)	22 (73.3%)	
Heterogeneity	absent	311 (79.3%)	14 (46.7%)	$P<0.0001$
	present	81 (20.7%)	16 (53.3%)	
Differentiation	well	153 (39.0%)	1 (3.3%)	$P=0.0004$
	moderate	58 (14.8%)	8 (26.7%)	
	poor	181 (46.2%)	21 (70.0%)	
	absent	220 (56.1%)	5 (16.7%)	
Ulceration	present	172 (43.9%)	25 (83.3%)	$P<0.0001$
	absent	349 (89.0%)	6 (20.0%)	
Lymphatic vascular invasion	present	43 (11.0%)	24 (80.0%)	$P<0.0001$
	M	251 (64.0%)	1 (3.3%)	
Invasion depth	SM1	42 (10.7%)	3 (10.0%)	$P<0.0001$
	SM2	99 (25.3%)	26 (86.7%)	

TABLE 2.
Risk factors for LNM in EGC by multivariate analysis

Clinico-pathological factors		P-value	Odds ratio	95%CI
Invasion Depth	SM1 vs M	$P=0.1580$	5.66	0.51-62.7
	SM2 vs M	$P=0.0311$	10.85	1.24-94.8
Lymphatic vascular invasion	present vs absent	$P<0.0001$	10.56	3.64-30.6
Size	3.1 cm- vs -3.0 cm	$P=0.0175$	3.22	1.23- 8.42
Ulceration	present vs absent	$P=0.0394$	3.21	1.06- 9.73

TABLE 3.
Stratified analysis of 4 risk factors for LMN in EGC

Risk Factors		M or SM1				SM2			
		Lymphatic vascular invasion absent		Lymphatic vascular invasion present		Lymphatic vascular invasion absent		Lymphatic vascular invasion present	
		LNM		LNM		LNM		LNM	
		absent	present	absent	present	absent	present	absent	present
-3.0 cm	Ulceration absent	141	0	3	0	19	0	8	0
	present	61	1	4	0	18	1	9	6
3.1 cm-	Ulceration absent	34	0	2	1	8	1	5	3
	present	47	1	1	1	21	2	11	13
Total		283	2	10	2	66	4	33	22

Fig. 1. The percentages of cases in which EMR is indicated among the EGC patients who underwent surgery.

TABLE 4.
Extended indication criteria for EMR of EGC

Invasion depth	: M or SM1
Lymphatic vascular invasion	: absent
Size	: 3.0 cm or less
Ulceration	: absent
Lymph node metastasis	: 0% (0/141), 95% CI: 0-2.6%

OR10.56, size: $P=0.0175$, OR3.22, and ulceration: $P=0.0394$, OR3.21 (Table 2).

Concerning the overall adaptability of multivariate analysis, the likelihood ratio was $P<0.0001$. When likelihood ratio tests for individual variables were conducted, the following values were obtained; invasion depth: $P=0.0294$, lymphatic vascular

invasion: $P<0.0001$, size: $P=0.0139$, and ulceration: $P=0.0284$. These variables were essential for analysis.

Examination of the indication criteria for EMR

The four conditions with the lowest risk of LNM were: invasion depth; M or SM1, lymphatic vascular invasion; absent, size; 3.0 cm or less, and ulceration; absent. When lesions met these conditions the incidence of LNM was 0% (0/141) (95%CI, 0-2.6%) (Tables 3, 4).

Among EGC lesions surgically resected in our hospital, 53.2% met the four conditions (134/252, 95%CI: 46.8-59.5%) in the case of M and 15.6% (7/45, 95%CI: 6.4-29.5%) for SM1. Overall, the rate was 33.4% (141/422, 95%CI: 28.9-38.1%) (Fig. 1).

DISCUSSION

Many previous retrospective studies reported on clinico-pathological conditions regarding LNM in EGC and extended criteria for EMR [1-9]. However, the statistical limitations of univariate analysis in these retrospective studies include randomization, selection bias, survey omission, and confounding factors. Therefore, it has been pointed out that study design and analytic evaluation should be performed more carefully than in prospective studies [17]. Multivariate analysis has recently been used as a more appropriate statistical procedure. However, previous studies have mainly analyzed LNM with respect to the histological type [18], macroscopic type [19], size [20], or have investigated submucosal invasive cancer alone [21-23].

In the present study, we investigated the risk factors for LNM using multivariate analysis in patients with EGC (mucosal and submucosal cancers) who underwent surgery. Initially, univariate analysis revealed that EGC with LNM showed a larger lesional diameter, a higher incidence of ulceration, more marked heterogeneity, poorly differentiated areas, and deeper infiltration (Table 1). Considering these characteristics, multivariate analysis was performed to adjust confounding factors among individual clinico-pathological factors. As a result, the following four factors were extracted as the independent risk factors for LNM: invasion depth; OR10.85, lymphatic vascular invasion; OR10.56, size; OR3.22, and ulceration; OR3.21. It was shown that the risk of LNM increased with the odds ratio (Table 2).

In addition, we investigated the conditions for adoption of EMR. In resected EGC lesions the incidence of LNM was 0% (0/141) (95%CI: 0-2.6%) (Tables 3,4) when the four independent risk factors identified above met the following conditions: invasion depth; M or SM1, lymphatic vascular invasion; absent, size; 3.0 cm or less, and ulceration; absent. The results of this study were similar to those reported by several other investigators with respect to these four factors [1-9,18-23]. However, multivariate analysis showed that the above four factors independently and markedly influenced LNM, and that the histological type was not a risk factor for LNM. There was no significant difference in invasion depth between SM1 and M cancers among EGCs. This is an important finding with regard to extended adoption of EMR.

With respect to size and ulceration, the possibility of SM invasion is higher and ulceration develops more readily in larger lesions. In addition, from the technical perspective of en bloc/total resection, a condition of 3 cm or less may be considered safe.

As for lymphatic vascular invasion, this may be the most important direct route to the lymph nodes. However, it is impossible to evaluate the presence or absence of lymphatic vascular invasion preoperatively, therefore postoperative histological evaluation is essential.

With respect to histological type, EMR has previously been indicated only for differentiated cancers [1]. However, this study suggested that EMR is applicable for lesions meeting the above four conditions regardless of whether they were differentiated or undifferentiated. In clinical practice, non-serial infiltration sometimes makes it difficult to identify the extent of infiltration and to evaluate the stump in undifferentiated type, and this is a diagnostic issue [7]. Currently, careful local treatment is indicated, and sufficient investigation of this issue should be performed in the future.

As described in the Introduction, to more accurately evaluate the status of these four risk factors, an EMR procedure must be employed, in which an en bloc/total resected specimen can be obtained, thereby facilitating evaluation similar to that of surgery [3,11-15]. When resection is fragmented, the bruised margin makes it difficult to evaluate the stump, and the degree of radical treatment cannot be adequately evaluated. This issue is particularly important in lesions for which local treatment is indicated. When en bloc/total resection is technically impossible, indications of EMR should not be readily extended.

In approximately 30% (Fig. 1) of patients with EGC who underwent surgery in our hospital, it was suggested that EMR was a suitable radical treatment. However, a large-scale prospective study should be carried out to determine whether the extended criteria for EMR in this study (Table 4) can be applied in clinical practice. Furthermore, not only treatment techniques but also the accuracy of preoperative diagnosis must be further improved in order to promote this treatment in clinical practice.

In conclusion, EMR is a suitable radical treatment for EGC. Based on the extended criteria identified in this study, it is expected that EMR can replace surgery in more EGC cases that had previously been indicated.

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