



## Original article

# Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer

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### Abstract

**Background.** Endoscopic resection (ER) has been accepted as minimally invasive treatment in patients with early gastric cancer (EGC) who have a negligible risk of lymph node metastasis. It has already been determined which lesions in differentiated-type EGC present a negligible risk of lymph node metastasis, and ER is being performed for these lesions. In contrast, no consensus has been reached on which lesions in undifferentiated-type (UD-type) EGC present a negligible risk for lymph node metastasis, nor have indications for ER for UD-type EGC been established.

**Methods.** We investigated 3843 patients who had undergone gastrectomy with lymph node dissection for solitary UD-type EGC at the Cancer Institute Hospital, Tokyo, and the National Cancer Center Hospital, Tokyo. Seven clinicopathological factors were assessed for their possible association with lymph node metastasis.

**Results.** Of the 3843 patients, 2163 (56.3%) had intramucosal cancers and 1680 (43.7%) had submucosal invasive cancers. Only 105 (4.9%) intramucosal cancers compared with 399 (23.8%) submucosal invasive cancers were associated with lymph node metastases. By multivariate analysis, tumor size 21 mm or more, lymphatic-vascular capillary involvement, and submucosal penetration were independent risk factors for lymph node metastasis ( $P < 0.001$ , respectively). None of the 310 intramucosal cancers 20 mm or less in size without lymphatic-vascular capillary involvement and ulcerative findings was associated with lymph node metastases (95% confidence interval, 0–0.96%).

**Conclusion.** UD-type intramucosal EGC 20 mm or less in size without lymphatic-vascular capillary involvement and ulcerative findings presents a negligible risk of lymph node metastasis. We propose that in this circumstance ER could be considered.

**Key words** Undifferentiated-type early gastric cancer · Lymph node metastasis · Risk factor · Endoscopic resection

### Introduction

Early gastric cancer (EGC) is defined as gastric cancer in which tumor invasion is confined to the mucosa or submucosa (T1 cancer), irrespective of the presence of lymph node metastasis [1]. A complete cure can almost always be achieved by conventional gastrectomy with lymph node dissection. Therefore, this treatment has been the gold standard, providing an excellent prognosis in patients with EGC in Japan [2–4]. On the other hand, endoscopic resection (ER) is beneficial, as it is minimally invasive and conserves the whole stomach, and postoperative quality of life is good provided the survival results do not differ from those obtained by surgical procedures [5–8]. ER has been accepted as a minimally invasive means of local resection for EGC with a negligible risk of lymph node metastasis [9, 10].

Because ER involves only local treatment without lymph node dissection, as a rule it is performed only if lymph node metastasis is not present. We previously investigated a large number of gastrectomies performed for EGC and reported the risk of lymph node metastasis [11]. In histologically differentiated-type (D-type) EGC, it has been determined which lesions are associated with a negligible risk of lymph node metastasis, and such lesions have been included in both the guideline criteria and expanded criteria for ER [12]. As a result, ER has been performed for D-type EGC in Japan in recent years [13]. In contrast, for undifferentiated-type (UD-type) EGC, a consensus could not be reached on which lesions present a negligible risk of lymph node metastasis, because of the small sample size. If it were possible

to identify those patients in whom the risk of lymph node metastasis was negligible, it might be possible to avoid surgery. During the 9 years since our previous publication [11], we have prospectively accumulated data on surgical cases of UD-type EGC and here we review the validity of expanded criteria for ER.

## Patients and methods

A total of 3843 patients who had undergone gastrectomy with standard lymph node dissection for solitary UD-type EGC at the Cancer Institute Hospital, Tokyo, and the National Cancer Center, Tokyo, between January 1969 and December 2007 were studied. Seven clinicopathological factors were evaluated, by means of univariate analysis, for their possible association with lymph node metastasis. Furthermore, multivariate analysis was performed using a logistic model with a stepwise method. The factors analyzed, according to the Japanese classification of gastric carcinoma, were age, sex, tumor location, depth of tumor invasion, tumor diameter, presence or absence of intratumoral peptic ulceration, and lymphatic-vascular capillary involvement. Histologically, well- and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma were classified as D-type adenocarcinoma and poorly differentiated adenocarcinoma, and signet-ring cell carcinoma was classified as UD-type adenocarcinoma [1]. Positive ulcer findings included the presence of a pathological peptic ulcer or peptic ulcer scar within a cancerous lesion. The size of the lesion was histologically measured the largest portion of the tumor on the formalin-fixed specimen.

Statistical analysis was carried out using the statistical computing software R version 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria). The association of lymph node metastasis with clinicopathological variables was assessed using Fisher's exact test. Factors found to be significant by univariate analysis were included in subsequent multivariate logistic regression analysis to identify those variables independently associated with lymph node metastasis. *P* values of less than 0.01 were considered to be statistically significant. The probability of lymph node metastasis was estimated with 95% confidence intervals (95% CI) based on binominal distribution.

## Results

The mean age of the 3843 patients studied was 55.0 years (range, 20 to 87 years), the mean tumor size was 36.0 mm, and the incidence of lymph node metastasis was 13.1%. Of these patients, 2163 (56.3%) had intramu-

cosal cancers and 1680 (43.7%) had submucosal invasive cancers. Only 105 (4.9%) intramucosal cancers were associated with regional lymph node metastases, while 399 (23.8%) submucosal invasive cancers were associated with lymph node metastases. The relationship between different clinicopathological factors and the risk of lymph node metastases is summarized in Table 1. Univariate analysis revealed that the presence of lymph node metastasis had a significant correlation with tumor size of 21 mm or more, lymphatic-vascular capillary involvement, submucosal penetration, and tumor location (lower third of stomach [L], upper third [U], middle third [M]). Among the four factors that were found to be significantly correlated with the presence of lymph node metastasis by univariate analysis, tumor size 21 mm or more, lymphatic-vascular capillary involvement, and submucosal penetration were shown by multivariate analysis to have a significant correlation with lymph node metastasis ( $P < 0.001$ , respectively), while tumor location was not correlated with lymph node metastasis (Table 2). To identify the criteria for a negligible risk of lymph node metastasis, the relationship between lymph node metastasis and tumor characteristics such as size, presence of ulceration, and lymphatic-vascular capillary involvement in intramucosal cancer was analyzed (Table 3). None of the 310 UD-type intramucosal cancers that were 20 mm or less in size and without lymphatic-vascular capillary involvement and ulcerative findings was associated with lymph node metastases (95% CI, 0–0.96%).

## Discussion

The presence of lymph node metastasis is the most important prognostic factor in EGC [14–17]. Radical surgery with lymph node dissection has provided an excellent therapeutic outcome; the 5-year survival rate after curative resection is more than 90%, including findings in recent European series [4, 14, 16–21]. In Japan, analyses of databases containing a large number of pathology reports, patients' histories, and long-term survival data from major leading hospitals have demonstrated that the 5-year cancer-specific survival rates of EGC limited to the mucosa or the submucosa are 99% and 95%, respectively [4]. In patients with cancer limited to the mucosa, the incidence of lymph node metastasis is less than 3%. By comparison, this risk increases to around 20% when the cancer invades the submucosa.

Currently accepted indications for ER of EGC include the resection of small intramucosal EGCs of the histological intestinal type [22, 23]. The rationale behind this recommendation is that larger lesions or lesions with a diffuse histological type may extend into the submucosal layer and present a higher risk of lymph node metas-

**Table 1.** Relationship between clinicopathological factors and lymph node metastasis (LNM) in UD-type EGC; results of univariate analysis

	Total	Status of LNM			P value
		Positive	Negative	Percentage positive	
Mean age (years)		55.7 ± 11.7	54.9 ± 11.7		NS
Sex					
M	2057	254	1803	12.3	NS
F	1786	250	1536	14.0	
Tumor location					
U	345	49	296	14.2	0.009
M	2586	310	2276	12.0	
L	912	145	767	15.9	
Depth					
M	2163	105	2058	4.9	<0.0001
SM	1680	399	1281	23.8	
Tumor size					
≤20 mm	1107	77	1030	7.0	<0.0001
≥21 mm	2736	427	2309	15.6	
Ulcer finding					
Absence	1319	167	1152	12.7	NS
Presence	2524	337	2187	13.4	
Lymphatic-vascular involvement					
Absence	3266	249	3017	7.6	<0.0001
Presence	577	255	322	44.2	

UD, undifferentiated-type; EGC, early gastric cancer; U, upper third of stomach; M, middle third of stomach; L, lower third of stomach; NS, not significant

**Table 2.** Relationship between clinicopathological factors and lymph node metastasis (LNM) in UD-type EGC; results of multivariate analysis

	Odds ratio	95% CI	P value
Tumor location			NS
Depth (M versus SM)	3.21	2.49–4.14	<0.0001
Tumor size (≤20 mm versus ≥21 mm)	2.05	1.57–2.69	<0.0001
Lymphatic-vascular involvement (absence versus presence)	4.82	3.82–6.09	<0.0001

M, mucosal; SM, submucosal; NS, not significant

tasis. Therefore, the accepted indications for ER include well-differentiated elevated cancers less than 2 cm and small (≤1 cm) depressed lesions without ulceration. From clinical observations, it has been suggested that the accepted indications for ER can be too strict and can lead to unnecessary surgery. Therefore, an expanded set of criteria for ER has been proposed. The upper limit of the 95% CI calculated from these early studies, however, was too broad for clinical use, because of the small sample size in those studies [24–33].

More recently, however, we investigated 5265 patients who had undergone gastrectomy with lymph node dissection for EGC, and we reported the risk of lymph node metastasis [11]. In D-type EGC, lymph node metastasis was not found in intramucosal cancer when lesions were 30 mm or less in size and there was no lymphatic-vascular capillary involvement, regardless of ulcerative findings (0/1230; 95% CI, 0–0.3%) or when there was no ulceration, regardless of tumor size (0/929;

95% CI, 0–0.4%). The upper limit of the 95% CI in both cases was 1% or less. These groups of patients were shown to have no or lower risks of lymph node metastasis compared with the risks of mortality from surgery. The results of this study have allowed the development of an expanded candidate list for ER (Fig. 1) [12].

In UD-type EGC, in contrast to D-type EGC, lymph node metastasis was not found in intramucosal cancer when the lesion was 20 mm or less in size without lymphatic-vascular capillary involvement and ulcerative findings (0/141). Because the majority of UD-type EGCs are associated with intratumoral ulcerative findings, the number of cases in this category was small, even in our large series; the 95% CI was 0–2.6% and the upper limit 1% or more. In the present study, we added to the previous report the cases of UD-type EGC resected at our institutions over the past 9 years; the number of cases in the category of intramucosal cancer with a lesion 20 mm or less in size without lymphatic-

**Table 3.** Lymph node metastasis in UD-type intramucosal EGC

Lymph node metastasis by tumor size in all UD-type intramucosal EGC

Tumor size	LNM rate (%)
≤10 mm	2.2 (4/185)
11–20 mm	1.4 (7/512)
21–30 mm	2.7 (13/484)
≥31 mm	8.2 (81/982)
Total	4.9 (105/2163)

Lymph node metastasis by tumor size and lymphatic-vascular involvement (LVI) in UD-type intramucosal EGC

Tumor size	LNM rate (%); LVI (-)	LNM rate (%); LVI (+)
≤10 mm	2.2 (4/185)	0.0 (0/0)
11–20 mm	1.4 (7/510)	0.0 (0/2)
21–30 mm	2.3 (11/477)	28.6 (2/7)
≥31 mm	7.5 (72/962)	45.0 (9/20)
Total	4.4 (94/2134)	37.9 (11/29)

Lymph node metastasis by tumor size and ulcerative findings (UL) in UD-type intramucosal EGC

Tumor size	LNM rate (%); UL (-)	LNM rate (%); UL (+)
≤10 mm	0.0 (0/105)	5.0 (4/80)
11–20 mm	0.0 (0/205)	2.3 (7/307)
21–30 mm	2.4 (4/166)	2.8 (9/318)
≥31 mm	6.6 (17/257)	8.8 (64/725)
Total	2.9 (21/733)	5.9 (84/1430)

Lymph node metastasis by tumor size without UL and LVI in UD-type intramucosal EGC

Tumor size	LNM rate (%); UL (-) and LVI (-)
≤10 mm	0.0 (0/105)
11–20 mm	0.0 (0/205)
21–30 mm	1.9 (3/162)
≥31 mm	5.2 (13/249)
Total	2.2 (16/721)

LNM, lymph node metastasis; LVI, lymphatic-vascular capillary involvement; UL, ulcerative findings

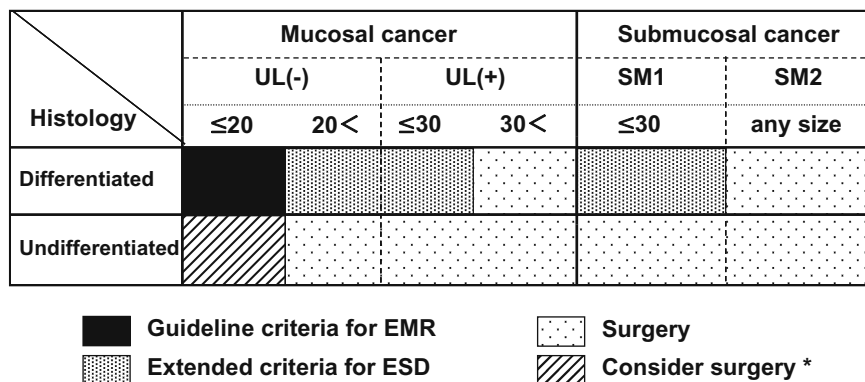
vascular capillary involvement and ulcerative findings reached 310, and no lymph node metastasis was found in any of these patients. The 95% CI is now 0–0.96% and the upper limit 1% or less. We believe that we can expand the criteria for ER in UD-type EGC.

The criteria for ER are based on complete histological examination of specimens resected en bloc, because sometimes an accurate histological examination cannot be performed on a specimen resected in multiple fragments. The tumor size is also difficult to assess in the multifragment specimens. Mucosal tumors may have shrunk during the process of formalin-fixation and the recorded size in our database may not accurately represent the pretreatment size of the tumor. Moreover, the rate of shrinkage is not constant and we cannot accurately estimate it in each case. Nevertheless, after endoscopic submucosal dissection (ESD) also, as the tumor size is measured in the formalin-fixed specimen, the shrinkage will not influence the assessment of the suitability of this procedure.

Because the absence of ulcerative findings is a crucial factor for an ER of UD-type EGC to be considered curative, careful histological evaluation of specimens completely resected en bloc is essential. ESD is a new method of ER developed for achieving en-bloc resection and for this reason it is particularly useful for the ER of UD-type EGCs [34–38].

As the accurate diagnosis of EGC is difficult even for experienced endoscopists, careful histological examination of the specimen resected by en-bloc ESD is essential to determine whether the tumor satisfies the criteria in our proposal. Furthermore, ESD itself is technically demanding and requires a learning curve; thus, we believe that ESD for UD-type EGC should be first attempted at high-volume centers with sufficient experience.

In conclusion, UD-type intramucosal EGC that is 20 mm or less in diameter without lymphatic-vascular capillary involvement and ulcerative findings could be considered suitable for curative ER due to the negligible risk of lymph node metastasis.



**Fig. 1.** Extended criteria for endoscopic resection (Tumor size is shown in millimeters). \*We propose in this report that this category should be revised and included in the extended criteria for ESD. EMR, Endoscopic mucosal resection; ESD, endoscopic submucosal dissection; UL, ulcerative findings; SM, submucosal

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