



Original article

Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers

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Abstract

Background. The presence of lymph node metastasis (LNM) is the most important prognostic factor for patients with early gastric cancer (EGC). A D2 gastrectomy has been the gold standard treatment. Strict criteria for endoscopic mucosal resection have been widely accepted in Japan. There are some trials aimed at expanding the indications for local treatment, although there has not been a comprehensive review of the risk of LNM with the lesions of EGC.

Methods. We investigated 5265 patients who had undergone gastrectomy with lymph node dissection for EGC at the National Cancer Center Hospital and the Cancer Institute Hospital. Nine clinicopathological factors were assessed for their possible association with LNM.

Results. None of the 1230 well differentiated intramucosal cancers of less than 30 mm diameter regardless of ulceration findings, were associated with metastases (95% confidence interval [CI], 0–0.3%). None of the 929 lesions without ulceration were associated with nodal metastases (95% CI, 0–0.4%) regardless of tumor size. Similarly to findings for intramucosal cancers, for submucosal lesions, there was a significant correlation between tumor size larger than 30 mm and lymphatic-vascular involvement with an increased risk of LNM. None of the 145 differentiated adenocarcinomas of less than 30-mm-diameter without lymphatic or venous permeation were associated with LNM, provided that the lesion had invaded less than 500 μm into the submucosa (95% CI, 0–2.5%).

Conclusion. Based on our large series of cases, we have been able to clarify the risks associated with EGC and to propose expansion of the criteria for local treatment. However, accurate histological evaluation of the resected specimens is essential to avoid recurrence for such EGCs that should be cured.

Key words Early gastric cancer · Local treatment · Endoscopic mucosal resection · Incidence of lymph node metastasis

Introduction

Endoscopic mucosal resection (EMR) is an accepted treatment for those early gastric cancers (EGC) associated with a minimal risk of regional lymph node (LN) metastasis [1,2]. EMR is currently considered appropriate for well differentiated lesions less than 2 cm in diameter without central ulceration. It is recognised that lymphatic-vascular involvement, ulcer formation, and tumor size above 3 cm are independent risk factors for LN metastasis in EGCs limited to the mucosa [3]. Several institutions have suggested that the indications for gastric EMR should be widened [4–6]. However, any revision of the indications must be based on the evaluation of a large number of cases to provide sufficient statistical power. We reviewed a large series of gastrectomies to propose a revised list of indications for local treatment, including EMR, of EGC.

Patients and methods

A total of 5265 patients who had undergone gastrectomy with LN dissection for EGC at the National Cancer Center Hospital and the Cancer Institute Hospital were studied; 3016 lesions (57.2%) were intramucosal cancers and 2249 (42.8%) penetrated the submucosa. Only 65 (2.2%) intramucosal cancers were associated with regional lymph node metastases. In comparison, 402 cancers invading the submucosa (17.9%) were associated with nodal metastases. The clinical and pathological features of the lesions were assessed by univariate analysis to determine which factors predicted the presence of nodal metastases.

The following features were looked at: sex; age; and tumor (location, macroscopic appearance, size, presence or absence of ulceration of the lesion, the two major histological types [differentiated or undifferentiated lesions], lymphatic-vascular involvement, and de-

Table 1. Relationship between clinicopathological factors and lymph node (LN) metastasis in intramucosal cancer; univariate analysis results

	Total	Status of LN metastasis			P value
		Negative	Positive	Percent	
Sex					
M	1676	1638	38	2.3	0.4087
F	894	869	25	2.8	
Tumor location					
U	248	243	5	2.0	0.7974
M	1492	1453	39	2.6	
L	830	811	19	2.3	
Macroscopic type					
Elevated	390	388	2	0.5	0.0083
Depressed	2048	1992	56	2.7	
Tumor size					
≤ 10 mm	357	353	4	1.1	<0.0001
≤ 20 mm	767	763	4	0.5	
≤ 30 mm	927	917	10	1.1	
> 31 mm	965	918	47	4.9	
Histological type					
Differentiated	1647	1640	7	0.4	<0.0001
Undifferentiated	1369	1311	58	4.2	
Ulcer findings					
Absence	1284	1278	6	0.5	<0.0001
Presence	1732	1673	59	3.4	
Lymphatic-vascular involvement					
Absence	2997	2937	60	2.0	<0.0001
Presence	19	14	5	26.3	

Differentiated type includes papillary and tubular adenocarcinoma. Poorly differentiated adenocarcinoma and signet-ring cell carcinoma are classified as undifferentiated type

U, Upper-third of stomach; M, middle-third of stomach; L, lower-third of stomach

gree of submucosal penetration). The *Japanese classification of gastric carcinoma* was used to classify the endoscopic appearance of the lesions [7]. Well and moderately differentiated tubular adenocarcinomas and papillary adenocarcinomas were grouped together as “differentiated lesions”. Poorly differentiated adenocarcinomas and signet-ring cell carcinomas were classified as “undifferentiated histological types” [7]. Lesions with ulceration or scarring from previous ulceration (converging folds or deformity of the muscularis propria, or fibrosis in the submucosal or deeper layer) within them were regarded as “ulcerated lesions”. The depth of submucosal invasion was measured from the muscularis mucosa to the point of deepest penetration. The depth of submucosal penetration was classified into two subgroups: SM1 ($\leq 500\mu\text{m}$ penetration into submucosa) and SM2 ($> 500\mu\text{m}$). All histological sections were examined by three pathologists (Y.K., A.Y., and T.S.).

Statistical analysis was carried out using the SAS program (SAS Institute, Cary, NC, USA). The association of LN metastasis with clinicopathological variables was assessed using the simple χ test, with $P < 0.01$ considered significant. The probability of LN metastasis was

estimated with 95% confidence intervals (95% CI), based on the exact binominal distribution.

Results

Intramucosal cancer

The relationship between different clinical and pathological factors and the risk of LN metastases is summarized in Table 1. Depressed or ulcerated lesions, larger than 30 mm, of the undifferentiated histological type, with invasion into lymphatics or venules, were associated with an increased risk of nodal metastases. In contrast, none of the 1230 differentiated less than 30 mm in size, regardless of ulceration, were associated with metastases (95% CI, 0–0.3%) (Table 2). None of the 929 lesions without ulceration were associated with nodal metastases (95% CI, 0–0.4%) regardless of the size of the lesion.

The overall risk of LN metastases in histologically undifferentiated lesions was 4.2%. However, none of the 141 undifferentiated lesions without ulceration, less than 20 mm in size, were associated with positive lymph nodes (95% CI, 0–2.6%).

Table 2. Lymph node metastasis in intramucosal cancer by tumor size and histological type^a

All intramucosal cancers									
	Total	LNM	%	Diff.	LNM	%	Undiff.	LNM	%
≤10 mm	357	4	1.1	257	0	0.0	100	4	4.0
≤20 mm	767	4	0.5	455	0	0.0	312	4	1.3
≤30 mm	927	10	1.1	518	0	0.0	409	10	2.4
>31 mm	965	47	4.9	417	7	1.7	548	40	7.3
Total	3016	65	2.2	1647	7	0.4	1369	58	4.2
Intramucosal cancer without ulcer findings									
	Total	LN	%	Diff.	LNM	%	Undiff.	LNM	%
≤10 mm	206	0	0.0	163	0	0.0	43	0	0.0
≤20 mm	372	0	0.0	274	0	0.0	98	0	0.0
≤30 mm	422	2	0.5	305	0	0.0	117	2	1.7
>31 mm	284	4	1.4	187	0	0.0	97	4	4.1
Total	1284	6	0.5	929	0	0.0	355	5	1.4

LNM, Lymph node metastasis; Diff, differentiated histological type; Undiff, undifferentiated histological type

^a Lesions of differentiated type, limited to the mucosa, of size ≤30 mm, have minimal risk of LNM; incidence, 0/1230; 95% confidence interval (CI), 0–0.3%

Lesions of differentiated type, limited to the mucosa, without ulcerative findings, have little possibility of LNM; incidence, 0/929; 95% CI, 0–0.4%

Lesions of undifferentiated type, limited to the mucosa, without ulcerative findings, and a size of ≤20 mm, have a small risk of LNM; incidence 0/141; <95% CI, 0–2.6%

Submucosal invasive cancer

Similarly to the findings for intramucosal cancers, there was a significant correlation between tumor size larger than 30 mm and lymphatic-vascular involvement with an increased risk of LN metastases. In addition, those cancers penetrating deeply into the submucosa were the most likely to be associated with regional LN metastases (Table 3). The relationship between LN metastasis and tumor characteristics such as size, depth of submucosal invasion, presence of ulceration, differentiation, and lymphatic or vascular permeation is shown in Table 4. For well differentiated tumors, subgroup analysis based on the pairing of individual factors such as tumor size, depth of submucosal penetration, and lymphatic-vascular involvement failed to yield a subgroup entirely free of nodal metastasis. However, the subgroup of 145 lesions with a size less than 30 mm, well differentiated histology, lack of lymphatic-vascular invasion, and submucosal penetration of less than 500 μm was entirely free of nodal metastasis (95% CI, 0–2.5%).

Discussion

EGC is defined as that in which tumor invasion is confined to the mucosa or submucosa, irrespective of the

presence of regional LN metastasis [7]. Because it is recognized that the presence of LN metastasis has a strong adverse influence on the prognosis of patients with EGC [8–10], radical surgery with the complete removal of the first and second tier LNs has become the gold standard treatment for patients with EGCs [11–12], with 5-year survival rates being in excess of 90%, including recent European series [10–16]. In our own series from the National Cancer Center in Japan, the 5-year survival rates in patients with intramucosal and submucosal invasive cancers, excluding noncancerous deaths, were 99% and 96%, respectively [14]. However, the incidence of LN metastasis in intramucosal and submucosal EGCs has been reported as approximately 3% and 20%, respectively [17–23]; therefore, surgery may be excessive in many patients with these lesions. Considering the risks of gastrectomy and the negative effect on the patient's quality of life [24–29], if a group of patients with a negligible risk of LN metastasis can be defined, it is sensible to offer a local treatment for them.

EMR for selected intramucosal EGC, for which the possibility of LN metastasis is almost zero, has been widely accepted as a therapeutic strategy for cure in Japan. Currently, the accepted indications for EMR are: (1) well differentiated elevated lesions less than 20 mm in size, and (2) small (≤10 mm) depressed well differentiated tumors without ulceration [30]. However, these

Table 3. Relationship between clinicopathological factors and lymph node metastasis in submucosal invasive cancer; univariate analysis results

	Total	Status of LN metastasis			<i>P</i> value
		Negative	Positive	Percent	
Sex					
M	1424	1173	251	17.6	0.0215
F	629	491	138	21.9	
Tumor location					
U	619	501	118	19.1	0.9402
M	1028	836	192	18.7	
L	406	327	79	19.5	
Macroscopic type					
Elevated	440	331	109	24.8	0.0003
Depressed	1505	1247	258	17.1	
Tumor size					
≤10 mm	114	105	9	7.9	<0.0001
≤20 mm	512	444	68	13.3	
≤30 mm	677	572	105	15.5	
>31 mm	946	726	220	23.3	
Histological type					
Differentiated	1277	1060	217	17.0	0.2110
Undifferentiated	972	787	185	19.0	
Ulcer findings					
Absence	790	640	150	19.0	0.9712
Presence	1263	1024	239	18.9	
Lymphatic-vascular involvement					
Absence	1350	1218	132	9.8	<0.0001
Presence	703	446	257	36.6	
Degree of submucosal penetration					
SM1	364	333	32	8.8	<0.0001
SM2	1272	971	301	23.7	

SM1, Penetration of submucosal layer less than 500µm from muscularis mucosa; SM2, penetration of 500µm or more

criteria are rather strict, and currently, many patients may be subjected to unnecessary surgery. Therefore many Japanese investigators have suggested possible extended criteria for local treatment (Table 5 [3,5,31–35]). The upper limit of the 95% CI calculated from these reports, because of the small sample size, was too large to exclude the possibility of LN metastasis. Previous reviews have been based on smaller series, providing large confidence intervals when the risk of lymph node metastasis is being calculated. Based on our larger series of cases, we have been able to clarify the risks associated with different lesions further, and we propose an expansion of the criteria for local treatment (Table 6).

These criteria are based on complete histological examination of the resected specimen. The findings for some factors, especially lack of lymphatic-vascular involvement, or SM1 grade, which are associated with a minimal risk of LN metastasis, are available only after histological examination of the entire resected specimen. Therefore, it is of paramount importance that the specimen is resected in such a way that an accurate histological examination can be carried out.

When expansion of local treatment for patients with EGC is considered, it is essential to accurately evaluate the resected specimen to determine whether an additional surgical procedure is warranted. The method of local treatment varies among institutions, depending on the techniques used to make such evaluations.

There are several techniques for endoscopic mucosal resection. Korenaga et al. [17] reported that depth of penetration was difficult to assess correctly in lesions larger than 15 mm resected piecemeal. At the National Cancer Center, a new technique, using an insulated-tipped (IT) needle knife has been invented to allow the endoscopic en-bloc resection of larger lesions [36]. If resected en-bloc, even lesions larger than 15 mm can be examined as accurately as surgically resected material. With the IT knife, we are now offering EMR for many patients who would have been treated by surgical intervention.

It is difficult to determine clinically whether lesions are confined to the mucosa or whether they are likely to penetrate the submucosa. Reported series have indicated that the endoscopic assessment of depth of pen-

Table 4. Lymph node metastasis by submucosal invasive cancer^a

All submucosal invasive cancers

	Total	LNM	%	Diff.	LNM	%	Undiff.	LNM	%
≤10mm	99	8	8.1	70	6	8.6	29	2	6.9
≤20mm	437	56	12.8	266	32	12.0	171	24	14.0
≤30mm	567	106	18.7	344	56	16.3	223	50	22.4
>31mm	743	130	17.5	411	92	22.4	332	38	11.4
Total	1846	300	16.3	1091	186	17.0	755	114	15.1

Lymph node metastasis by tumor size and depth of submucosal penetration in tumors with differentiated histological type

	SM1	LNM	%	SM2	LNM	%
≤10mm	31	1	3.2	39	5	12.8
≤20mm	71	4	5.6	195	28	14.4
≤30mm	71	4	5.6	273	52	19.0
>31mm	92	6	6.5	319	86	27.0
Total	265	15	5.7	826	171	20.7

Lymph node metastasis by tumor size and ulcer findings in tumors with differentiated histological type

	ul-	LNM	%	ul+	LNM	%
≤10mm	42	3	7.1	28	3	10.7
≤20mm	140	13	9.3	126	19	15.1
≤30mm	158	27	17.1	186	29	15.6
>31mm	188	44	23.4	223	48	21.5
Total	528	87	16.5	563	99	17.6

Lymph node metastasis by tumor size and lymphatic-vascular involvement in tumors with differentiated histological type

	Negative	LNM	%	Positive	LNM	%
≤10mm	56	3	5.4	14	3	21.4
≤20mm	181	14	7.7	85	18	21.2
≤30mm	202	14	6.9	142	42	29.6
>31mm	231	21	9.1	180	71	39.4
Total	670	52	7.8	421	134	31.8

Lymph node metastasis by tumor size in SM1 differentiated tumors without lymphatic-vascular involvement

	Number	LNM	%
≤10mm	28	0	0.0
≤20mm	59	0	0.0
≤30mm	58	0	0.0
>31mm	78	2	2.6
Total	223	2	0.9

LNM, Lymph node metastasis; Diff, differentiated histological type; Undiff, undifferentiated histological type; ul, histological ulcer findings

^aWhen the tumor is of differentiated type, submucosal, showing no lymphatic-vascular permeation, and size is 30mm or less, the incidence of LNM is 0% (0/145; 95% CI, 0–2.5%). Only this subgroup should be considered for local treatment

etration is inaccurate in up to 20% of lesions [37,38]. Biopsies are too superficial to provide this information, but EMR provides a larger specimen, which allows assessment of depth of invasion and lymphatic-vascular involvement. Considering that the pretreatment diag-

nosis could be incorrect for 20% of the tumors that are candidates for local treatment, it is essential to make an accurate histological evaluation of the resected specimens to avoid recurrence of such early lesions that should be cured.

Table 5. Investigation of extended EMR criteria

Author	Criteria	Incidence	95% CI
Yamao [3]	Intramucosal cancer, no lymphatic-vascular invasion, without ulcer findings, tumor less than 3 cm in size	1/277; 0.36%	0.009%–1.99%
Hiki [31]	Intramucosal elevated lesion, tumor less than 2.5 cm in size	0/21; 0%	0–16.1%
	Intramucosal depressed lesion, without ulcer findings, tumor less than 2 cm in size	0/113; 0%	0–3.2%
Ohgami [32]	Intramucosal protruded lesion, tumor less than 2.5 cm in size	0/67; 0%	0–5.4%
Yasuda [5]	Submucosal invasive cancer less than 300 μm in depth, tumor less than 1 cm in size	0/12; 0%	0–26.5%
Oizumi [33]	Submucosal invasive cancer, tumor less than 1 cm in size	0/28; 0%	0–12.3%
Fujii [34]	Submucosal invasive cancer, tumor less than 1 cm in size	0/14; 0%	0–23.2%
Gotoda [35]	Differentiated adenocarcinoma, no lymphatic-vascular invasion, tumor less than 3 cm in size, submucosal invasive cancer less than 500 μm in depth	0/117; 0%	0–3.1%

EMR, Endoscopic mucosal resection

Table 6. Criteria for expansion of local treatment, derived from our results

Criteria	Incidence	95% CI
Intramucosal cancer differentiated adenocarcinoma, no lymphatic-vascular invasion, irrespective of ulcer findings, tumor less than 3 cm in size	0/1230; 0%	0–0.3%
Intramucosal cancer differentiated adenocarcinoma, no lymphatic-vascular invasion, without ulcer findings, irrespective of tumor size	0/929; 0%	0–0.4%
Undifferentiated intramucosal cancer no lymphatic-vascular invasion, without ulcer findings, tumor less than 3 cm in size	0/141; 0%	0–2.6%
Minute submucosal penetration (SM1) differentiated adenocarcinoma, no lymphatic-vascular invasion, tumor less than 3 cm in size	0/145; 0%	0–2.5%

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