Risk factors for lymph node metastasis in histologically poorly differentiated type early gastric cancer

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Background: We retrospectively evaluated the predictive factors for lymph node metastasis in poorly differentiated early gastric cancer (poorly differentiated tubular adenocarcinoma, signet-ring cell carcinoma, mucinous adenocarcinoma) in order to examine the possibility of endoscopic resection for poorly differentiated early gastric cancer.

Methods: A total of 573 patients with histologically poorly differentiated type early gastric cancer (269 mucosal and 304 submucosal), who had undergone curative gastrectomy, were enrolled in this study. Risk factors for lymph node metastasis were evaluated by univariate and logistic regression analysis.

Results: Lymph node metastasis was observed in 74 patients (12.9%) (6 with mucosal cancer and 68 with submucosal cancer). By univariate analysis risk factors for lymph node metastasis were lymphovascular invasion (LVI) (presence), depth of invasion (submucosa), and tumor diameter (> 20 mm), ulcer or ulcer scar (presence), and histological type (mucinous adenocarcinoma). By multivariate analysis, risk factors for lymph node metastasis were LVI, depth of invasion, and tumor diameter. In mucosal cancers, the incidence of lymph node metastasis was 0% irrespective of LVI in tumors smaller than 20 mm, and 1.7% in tumors 20 mm or larger without LVI. In submucosal cancers, the incidence of lymph node metastasis was 2.4% in tumors smaller than 20 mm without LVI.

Conclusions: A histologically poorly differentiated type mucosal gastric cancer measuring less than 20 mm and without LVI may be a candidate for endoscopic resection. This result should be confirmed in a larger study with many patients.

Introduction

Early gastric cancer is defined as a tumor localized to the mucosa or submucosa, irrespective of lymph node metastasis. The incidence of early gastric cancer has been increasing worldwide as diagnostic techniques have advanced [1,2]. According to the Japanese guidelines for gastric cancer [3], there are two categories of treatment for early gastric cancer. One is endoscopic resection (endoscopic mucosal resection, EMR; endoscopic submucosal dissection, ESD), and the other is surgical resection. Surgical resection in its turn is divided into laparoscopy-assisted gastrectomy and conventional open gastrectomy.

Endoscopic resection has been widely performed as an alternative treatment to surgery in patients with mucosal tumors smaller than 20 mm that are of histologically differentiated type without ulceration, which is estimated to carry no risk lymph node metastasis [4,5]. This technique is advantageous for patients with mucosal gastric cancer because the stomach can be preserved. It is generally accepted that histologically undifferentiated type (poorly differentiated, signet-ring cell, mucinous) mucosal early gastric cancer more often has lymph node metastasis than does differentiated type early gastric cancer [6,7]. For this reason, EMR is contraindicated as a treatment for histologically undifferentiated type early gastric cancer.

ESD has been developed and can now dissect a larger portion of gastric mucosa containing a cancer as a single fragment with an adequate negative margin. With the improvements in this technique, some reports have argued that the indication for ESD could be extended to differentiated mucosal gastric cancers measuring less than 30 mm without lymphovascular invasion (LVI), which has a low probability of lymph node metastasis [8]. One report suggested that endoscopic resection might be extended to differentiated submucosal gastric cancer measuring less than 20 mm in extent [9]. However, few reports have

discussed the indication for endoscopic resection in patients with undifferentiated type early gastric cancer [10–12].

In this study, we retrospectively evaluated the predictive factors for lymph node metastasis in poorly differentiated early gastric cancer in order to examine the possibility of endoscopic resection for poorly differentiated early gastric cancer.

Patients and methods

Between April 1985 and March 2000, 1857 consecutive patients with a preoperative diagnosis of early gastric cancer (T1: mucosa, submucosa) underwent curative gastrectomy with lymph node dissection (D1 plus lymph nodes along the left gastric artery, the common hepatic artery, and the celiac axis: D2) at the Department of Surgery, Gastroenterological Center, Department of Gastroenterological Surgery, Yokohama City University, Japan, and its related institutions. Of these, 573 patients with histologically poorly differentiated type early gastric cancer were enrolled in this study. In this study, histological classification was based on the World Health classification of tumors [13]. Histologically poorly differentiated type gastric cancer included poorly differentiated tubular adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma. The participants were 309 men and 264 women, who were aged 21–85 years (mean age ± standard deviation = 56.5 ± 12.3 years). All patients also underwent a barium swallow study and computed tomography (CT) scans. Ultrasonography of the abdomen (US) was performed in some patients. Patient data were retrieved from the operative and pathological reports.

The staging and definition of lymph node status were principally based on the UICC TNM classification of malignant tumors [14]. Experienced pathologists ensured a high quality of pathological diagnosis. Surgery was performed after all possible alternative procedures and treatments had been explained to each patient, and his or her informed consent had been obtained.

Of the 573 registered patients, mucosal cancer was observed in 269, and submucosal cancer in 304. Submucosal cancer was classified into two groups: SM1, where the depth of invasion was less than 500 µm from the muscularis mucosae; and SM2, in which it was 500 µm or more from the muscularis mucosae. A total of 174 patients had tumors located in the lower third of the stomach, 337 had tumors in the middle third, 57 had tumors in the upper third, and 5 had tumors occupying the entire stomach. Depressed-type tumors were macroscopically observed in 480 patients, mixed-type (depressed plus elevated) tumors were observed in 67 patients, and elevated type or flat-type tumors were observed in the remaining 26 patients. The tumor diameter was measured at the maximum microscopic length of the tumor, irrespective of its depth. Tumors less than 20 mm were observed in 149 patients, and tumors measuring 20 mm or more were observed in 424 patients. Lymph node metastasis was observed in 74 patients (12.9 %). Among these, pN1 disease was observed in 65 patients, and pN2 in 9 patients.

The distribution of pathological stages among the patients was as follows: IA, 499 patients; IB, 65 patients; and II, 9 patients.

Gastrectomy was performed in accordance with the Japanese Classification of Gastric Carcinoma [15]. Distal gastrectomy was performed in 466 patients, total gastrectomy in 93 patients, and proximal gastrectomy in 14. Distal gastrectomy was performed for tumors located in the lower third of the stomach. Distal or total gastrectomy was performed for tumors in the middle third, depending on the direction of tumor invasion. Total gastrectomy was employed for tumors in the upper third of the stomach or those occupying the entire stomach.

D1 gastrectomy (complete dissection of the first-tier lymph nodes) plus removal of the lymph nodes along the left gastric artery and the common hepatic artery was employed in 304 patients without metastasis-suspicious lymph nodes. D2 gastrectomy (complete dissection of the first-tier and second-tier lymph nodes) was performed in 279 patients with metastasis-suspicious lymph nodes. In each case, 15 or more lymph nodes were dissected according to the UICC/TNM classification. Surgery was performed after all possible alternative procedures or treatments had been explained to the patient, and informed consent had been obtained. The study was retrospective and neither randomized nor controlled. The institutional review board approved this study.

Follow-up of patients was performed according to our standard protocol (every 8–12 weeks for at least 2 years, and every 12–24 weeks for the next 3 years), which included blood counts, biochemical examinations, and tumor marker studies. In addition, endoscopic examinations, US, CT, and chest radiography were performed annually. The median follow-up time (mean ± SD) was 63.5 ± 44.9 months.

Statistical analysis

Data were analyzed using SPSS software version 10.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Disease-specific survival was calculated using the Kaplan–Meier estimation, and was examined by the log-rank test. The χ^2 test was used to evaluate the difference in proportions. The logistic regression analysis for lymph node metastasis was applied using the following nine variables: age (< 75 vs. ≥ 75 years), sex (female vs. male), tumor location (lower third vs. middle third vs. upper third vs. entire of the stomach), macroscopic appearance (flat vs. elevated versus depressed mixed), tumor diameter (< 20 vs. ≥ 20 mm), ulcer or ulcer scar (absence vs. presence), histological type (poorly differentiated vs. signet-ring cell vs. mucinous), depth of invasion (M vs. SM1 vs. SM2), and LVI (absence vs. presence).

Independent prognostic factors were evaluated by Cox proportional regression analysis using the following nine variables: age (< 75 vs. ≥ 75), sex (female vs. male), tumor location (lower third vs. middle third vs. upper third vs. entirety of the stomach), macroscopic appearance (flat vs. elevated vs. depressed mixed), tumor diameter (< 20 vs. ≥ 20), histological type (poorly differentiated vs. signet-ring cell vs. mucinous), lymph node metastasis (absence vs. presence), depth of invasion (M vs. SM1 vs. SM2), and LVI (absence vs. presence). Probability (P) values were considered statistically significant at the 0.05 level.

To verify the accuracy of the independent predictive factors for lymph node metastasis, selected predictive factors were tested in a second population. This consisted of 183 patients with histologically proven undifferentiated type early gastric cancer who underwent curative gastrectomy at the Department of Surgery, Fujisawa Municipal Hospital, in the same time period. Twenty-two patients (12 %) had lymph node metastasis.

Table 1 Univariate and multivariate analysis of risk factors for lymph node metastasis in patients with undifferentiated early gastric cancer.

	Lymph node metastasis					Logistic regression model		
	Presence, n = 74		Absence, n = 499		*P*-value	Odds ratio	95 % CI	*P*-value
	n	%	n	%				
Age (y)					0.9534	–		
< 75	69	93.2	464	93.0				
≥ 75	5	6.7	35	7.0				
Sex					0.7845	–		
Female	33	44.6	231	46.3				
Male	41	55.4	268	53.7				
Tumor location					0.3119	–		
Lower third	24	32.4	150	30.1				
Middle third	41	55.4	296	59.3				
Upper third	7	9.5	50	10.0				
Entire of the stomach	2	2.7	3	0.6				
Tumor diameter (mm)					0.0005			0.007
< 20	7	9.5	142	28.5		1		
≥ 20	67	90.5	357	71.5		3.336	1.390 – 8.007	
Macroscopic appearance					0.2307			
Flat	1	1.4	8	1.6				
Elevated	2	2.7	15	3.0				
Depressed	57	77.0	423	84.8				
Mixed	14	18.9	53	10.6				
Depth of invasion*					< 0.0001	–		0.011
M	6	8.1	263	52.7		1		
SM1	13	17.6	105	21.0		2.956	1.026 – 8.518	
SM2	55	74.3	131	26.3		4.534	1.687 – 12.184	
Ulcer or ulcer scar					< 0.0001	–		
Absence	11	14.9	235	47.1				
Presence	63	85.1	264	52.9				
Histological type					0.0304	–		
Poorly differentiated	32	43.2	150	30.1				
Signet-ring cell	39	52.7	339	67.9				
Mucinous	3	4.1	10	2.0				
Lymphovascular invasion					< 0.0001			< 0.0001
Absence	20	27.0	426	85.4		1		
Presence	54	73.0	73	14.6		9.369	4.777 – 18.372	

* M, mucosa; SM1, submucosa, depth of invasion < 500 µm from the muscularis mucosae; SM2, submucosa, depth of invasion ≥ 500 µm from the muscularis mucosae.

Results

Survival

The 5-year overall survival rates were 98.3 % in patients with M cancer, 97.2 % in patients with SM1 cancer, and 92.4 % in patients with SM2. There was a significant difference in survival between the M and SM2 groups ($P = 0.0100$), whereas no significant difference was observed between M and SM1 ($P = 0.6349$), or between SM1 and SM2 ($P = 0.1204$). The 5-year disease-specific survival rates were 100 % in patients with M cancer, 98.1 % in patients with SM1 cancer, and 96.1 % in those with SM2 cancer. There were significant differences in survival between the M and SM1 groups ($P = 0.0366$), and between M and SM2 ($P = 0.0008$), whereas no significant difference was observed between SM1 and SM2 ($P = 0.2420$).

Analysis of risk factors for lymph node metastasis in patients with poorly differentiated early gastric cancer

Univariate analysis showed that there were significant differences in tumor diameter, depth of invasion, histological type, and LVI. A tumor larger than 20 mm, submucosal invasion, histologically poorly differentiated type tumor, and LVI significantly predicted lymph node metastasis in patients with poorly differentiated early gastric cancer (**Table 1**). Logistic regression analysis using eight clinicopathological factors revealed that LVI, submucosal invasion, and larger tumor diameter (≥ 20 mm) independently predicted lymph node metastasis (**Table 1**). In this study, histological type was not selected as an independent predictive factor for lymph node metastasis.

Correlation of the two predictive factors (tumor diameter and LVI) and lymph node metastasis

Of 85 patients with poorly differentiated type mucosal gastric cancer measuring less than 20 mm, no lymph node metastasis was detected, irrespective of LVI status. By contrast, among 184 patients with tumors measuring 20 mm or more, 3 of the 179 patients without LVI (1.7 %) had lymph node metastasis and 3 of the 5 with LVI (60 %) had lymph node metastasis. Moreover, among 64 patients with submucosal gastric cancer measuring less than 20 mm, only 1 of the 41 without LVI (2.4 %) had lymph node metastasis, and 6 of the 23 with LVI (26.1 %) had lymph node metastasis. Of 240 patients with tumors measuring 20 mm or more, 14 of those without LVI (10 %) had lymph node metastasis, and 47 of those with LVI (47 %) also had lymph node metastasis (**Fig. 1**).

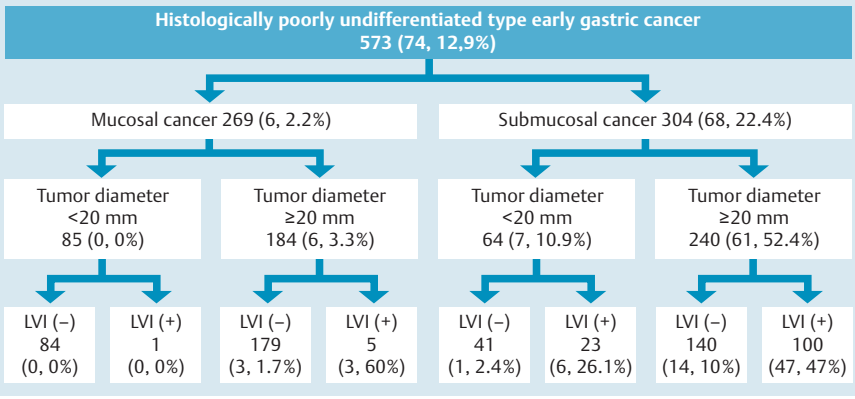

Fig. 1 Correlation of the two predictive factors (tumor diameter and lymphovascular invasion, LVI) and lymph node metastasis. Statistics are given in the form: total number in group (number with lymph node metastasis, percentage with lymph node metastasis).

Estimation of independent predictive factors for lymph node metastasis in a second population

In the second population of 183 patients, the incidence of lymph node metastasis in patients with mucosal cancer was 2.4% (2 of 85): in those with tumors smaller than 20 mm, it was 0% (0 of 24); in those with tumors measuring 20 mm or larger, it was 3.3% (2 of 61). Of 61 patients with mucosal cancer measuring 20 mm or more, the incidence of lymph node metastasis was 0% among those without LVI (0 of 58); in those with LVI, it was 66.7% (2 of 3). The incidence of lymph node metastasis in patients with submucosal cancer was 20.4% (20 of 98): in those with tumors smaller than 20 mm, it was 10.3% (3 of 28); in those with tumors measuring 20 mm or larger, it was 24.3% (17 of 70). Of 28 patients with tumors measuring less than 20 mm, the incidence of lymph node metastasis in those without LVI was 5.6% (1 of 18); in those with LVI, it was 40% (2 of 10). Of 17 patients with tumors measuring 20 mm or more, the incidence of lymph node metastasis in those without LVI was 11.8% (6 of 51); in those with LVI, it was 57.9% (11 of 19).

Independent prognostic factors

Cox proportional regression analysis showed that lymph node metastasis was an independent prognostic factor in patients with poorly differentiated type early gastric cancer [hazard ratio (95% confidence interval) = 10.401 (2.547 – 42.470), $P = 0.001$].

Discussion

This study showed that predictive factors for lymph node metastasis in patients with histologically poorly differentiated type early gastric cancer were presence of LVI, submucosal invasion, and tumor diameter measuring more than 20 mm. Mucosal tumors measuring more than 20 mm together with presence of LVI, and submucosal tumors measuring more than 20 mm together with presence of LVI were similarly selected as predictive factors for lymph node metastasis by univariate analysis and by logistic regression analysis, respectively. Therefore, histologically poorly differentiated type mucosal tumors measuring less than 20 mm and without LVI can be treated endoscopically.

The incidence of lymph node metastasis of mucosal gastric cancer is extremely low in histologically differentiated type gastric cancer [16,17]. Endoscopic treatments have therefore been recommended for mucosal cancers with certain clinicopathological features, i.e., tumors smaller than 20 mm and without any ulcer scar [3]. This technique preserves patients' quality of life by preserving the stomach. It would be beneficial if the indications for endoscopic treatment of early gastric cancer could be extended.

Table 2 Prevalence of lymph node metastasis in patients with poorly differentiated early gastric cancer.

Authors	Number of patients	Incidence of lymph node metastasis, %	
		Mucosa	Submucosa
Gotoda et al. [8]	2124	4.2	15.1
Abe et al. [18]	175	7.3	27.9
Nasu et al. [19]	332	5.0	24.0
Li et al. [10]	646	4.2	15.9
Ye et al. [20]	591	2.9	27.4
Park et al. [11]	234	3.4	21.6

On principle, endoscopic treatments are allowed for histologically differentiated type early gastric cancer. However, some reports have argued for the possibility of endoscopic treatment for poorly differentiated type early gastric cancer. In these studies, the incidence of lymph node metastasis of mucosal cancer was also low [10 – 12]. In the current study, the incidence of lymph node metastasis in patients with poorly differentiated type mucosal cancer was 2.2%. Although the incidence of lymph node metastasis in our study is lower than those in other reports [8,10,11,18 – 20] (**Table 2**), it is possible that the diagnosis might change after precise pathological evaluation of the depth of invasion. On this basis, some mucosal cancer in the other studies could be rediagnosed as submucosal cancer, and then the incidence of lymph node metastasis with mucosal cancer would be lower and come down closer to that in the current study.

Most patients with poorly differentiated type mucosal gastric cancer as well as those with differentiated type mucosal gastric cancer do not need to undergo surgical treatment. In our study, lymph node metastasis was not observed in patients with mucosal tumors smaller than 20 mm irrespective of LVI status, and in another report lymph node metastasis was found in patients with LVI in spite of their having smaller tumors [10]. Therefore, histologically poorly differentiated type mucosal cancer measuring less than 20 mm and with no LVI can be curatively treated endoscopically. LVI is identified only by pathological evaluation. Therefore, endoscopic treatment should be definitely performed on clinical suspicion of a histologically poorly differentiated type

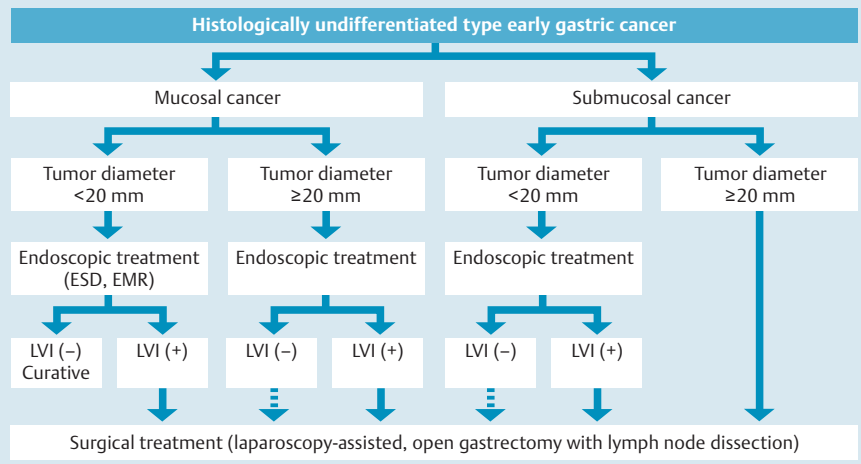

Fig. 2 Treatment algorithm for poorly differentiated early gastric cancer.

mucosal cancer measuring less than 20 mm. When a tumor is diagnosed by pathological analysis as confined to the mucosa and without LVI, endoscopic treatment could be curative. This treatment is optimal.

By contrast, the incidence of lymph node metastasis was 1.7% in patients with mucosal tumors measuring 20 mm or more and without LVI. Therefore, endoscopic treatment may be contraindicated in these patients. Endoscopic treatment is basically contraindicated even in differentiated type submucosal gastric cancer. However, Gotoda et al. proposed an extension of the indications for endoscopic treatment [8], and one of the extended indications was histologically differentiated type SM1 tumor measuring less than 30 mm. In our previous study, we reported that the incidence of lymph node metastasis was 1.8% in patients with submucosal gastric cancer measuring less than 20 mm and without LVI. Moreover, the site of lymph node metastasis was restricted to the paragastric lymph nodes. We therefore concluded that D1 gastrectomy may be sufficient for submucosal gastric cancer of this type [9]. In contrast to this, the incidence of lymph node metastasis in poorly differentiated type submucosal gastric cancer is 2.4% in patients with tumors measuring less than 20 mm and without LVI. Therefore, endoscopic treatment basically is not indicated for histologically poorly differentiated type submucosal tumors, but less extensive gastrectomy may be feasible. We confirmed similar results in a second population in the current study. However, the number of patients in this study was not large, and therefore these results should be confirmed in a larger population.

At present, it is mandatory to exclude histologically poorly differentiated type submucosal gastric cancer from the indications for endoscopic treatment, whereas histologically differentiated type submucosal gastric cancer can be curatively resected endoscopically. However, endoscopic treatment may be feasible for histologically poorly differentiated type mucosal gastric cancer 20 mm in size or more and without LVI, for submucosal cancer less than 20 mm and without LVI in elderly patients with severe co-morbid disease, because the incidence of lymph node metastasis is low in these patients.

On the basis of the results of this study, an algorithm of the treatment for poorly differentiated early gastric cancer has been made (**Fig. 2**). Patients with mucosal cancer have a chance to be treated endoscopically. If a patient has LVI, surgical treatment such as laparoscopy-assisted or open gastrectomy with lymph node dissection should be added. Although for mucosal tumors measuring 20 mm or more and submucosal tumors measuring 20 mm or less without LVI the basic indication is for gastrectomy with lymph node dissection, endoscopic treatment of these tumors may have the possibility to cure as the incidence of lymph node metastasis is low. To clarify the optimal therapeutic strategy for these tumors, overall survival should be compared between endoscopic treatment and gastrectomy with lymph node dissection for these tumors in a well-designed randomized trial. For other submucosal cancer, surgical treatment should be performed.

Laparoscopy-assisted gastrectomy, which provides satisfactory lymph node dissection for early gastric cancer, has become more prevalent and has been used for patients in whom endoscopic treatment for early gastric cancer has been noncurative [21,22]. With this useful technique, patients whose tumors are not cured endoscopically can have less invasive surgery.

In conclusion, even histologically poorly differentiated type early gastric cancer has a possibility to be cured by endoscopic treatment alone. Mucosal cancer less than 20 mm in size and without LVI may be regarded as cured by endoscopic treatment on the basis of pathological examination of the endoscopically resected specimens. A randomized controlled trial (endoscopic treatment vs. gastrectomy with lymph node dissection) should be conducted to decide the optimal treatment for mucosal tumors measuring 20 mm or more, and submucosal tumors measuring 20 mm or less without LVI.

Competing interests: None

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