



Risk Factors for Lymph Node Metastasis in Undifferentiated Early Gastric Cancer

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Abstract

The indication for endoscopic resection is differentiated gastric cancer ≤ 2 cm in size without an ulcer, of which the depth of invasion is clinically diagnosed as tumor confined to the mucosa. Endoscopic resection is not indicated for undifferentiated gastric intramucosal carcinoma, which is associated with a high rate of lymph node metastasis. This study aimed to analyze the factors associated with lymph node metastasis and to determine the validity of endoscopic resection in patients with undifferentiated early gastric cancer (EGC). This study included 141 patients who underwent gastrectomy with lymph node dissection for undifferentiated EGC. The clinicopathological findings were retrospectively analyzed to identify the factors associated with lymph node metastasis. According to the depth of tumor invasion, lymph node metastasis was observed in 13 patients (9.2%), including three with intramucosal carcinoma (3.6%) and ten with submucosal invasive carcinoma (17.2%). Univariate analysis identified tumor size ($p = 0.038$), depth of tumor invasion ($p = 0.008$), and lymphovascular invasion (LVI) ($p = 0.0002$) as risk factors for lymph node metastasis. On multivariate analysis, LVI ($p = 0.002$) was identified as the only independent risk factor for lymph node metastasis. The use of endoscopic resection for the undifferentiated EGC should be considered carefully for patients with LVI because of the risk for lymph node metastasis.

Keywords Endoscopic resection · Lymph node metastasis · Risk factor · Undifferentiated early gastric cancer

Introduction

Gastric cancer lesions confined to the mucosa or submucosa, irrespective of the presence or absence of lymph node metastasis, are referred to as early gastric cancer (EGC) [1]. Gastrectomy with lymph node dissection results in a 5-year survival rate of approximately 99% in cases of intramucosal carcinoma, except in cases of death from intercurrent disease [2]; thus, endoscopic resection must also achieve comparable therapeutic outcomes. Therefore, in order to achieve a radical cure comparable

to surgical resection, it is important to select lesions with $\leq 1\%$ probability of lymph node metastasis in performing endoscopic resection.

In Japan, the indication for endoscopic resection is differentiated cancer ≤ 2 cm in size without an ulcer, of which the depth of invasion is clinically diagnosed as tumor confined to the mucosa [3]. Meanwhile, endoscopic resection is not indicated for undifferentiated gastric intramucosal carcinoma, which is associated with a significant rate of lymph node metastasis ranging from 2.9 to 7.3% [4, 5].

However, in cases of undifferentiated gastric intramucosal carcinoma ≤ 2 cm in size without an ulcer and lymphovascular invasion (LVI), the probability of lymph node metastasis is as low as 0% [6, 7]. Therefore, endoscopic resection could become a standard treatment for this type of cancer.

This study aimed to retrospectively analyze the factors associated with lymph node metastasis and to determine the validity of endoscopic resection in patients with undifferentiated EGC. The factors in question were identified from the clinicopathological features of patients who underwent surgical resection for undifferentiated EGC.

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Table 1 Univariate analysis of risk factors for lymph node metastasis in patients with undifferentiated EGC

Variables	Lymph node metastasis		p value
	Positive (n = 13)	Negative (n = 128)	
Median age, years (range)	54 (27–81)	63.5 (27–83)	0.118
Sex			0.565
Male	9	76	
Female	4	52	
Median tumor size, mm (range)	50 (21–100)	34 (5–145)	0.019*
Tumor size (mm)			0.038*
≤ 20	0	35	
> 20	13	93	
Main tumor location			0.683
Upper third	2	11	
Middle third	7	68	
Lower third	4	49	
Macroscopic type			0.793
Elevated	0	3	
Flat	0	3	
Depressed	11	110	
Mixed	2	12	
Histological type			0.067
Por	7	51	
Sig	5	76	
Muc	1	1	
Depth of tumor invasion			0.008*
Mucosa	3 (3.6%)	80 (96.4%)	
Submucosa	10 (17.2%)	48 (82.8%)	
Lymphovascular invasion			0.0002*
Positive	9 (29.0%)	22 (71.0%)	
Negative	4 (3.6%)	106 (96.4%)	
Ulcer findings			0.464
Positive	3 (12.5%)	21 (87.5%)	
Negative	10 (8.5%)	107 (91.5%)	
Median dissected lymph node (range)	28 (10–49%)	23.5 (0–82%)	0.465

*Statistically significant at $p < 0.05$

Por poorly differentiated adenocarcinoma, Sig signet-ring cell carcinoma, Muc mucinous adenocarcinoma

Patients and Method

This study included 141 patients (85 men and 56 women with a median age of 63 years, ranging from 27 to 83 years) who underwent gastrectomy with lymph node dissection for solitary undifferentiated EGC (poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma) in the Department of Surgery, The Jikei University School of Medicine Kashiwa Hospital, between January 2002 and December 2014. Patients with multiple cancers involving other organs or gastric carcinoma in the remnant stomach were excluded.

Age, sex, maximum tumor size, location of primary lesion, macroscopic type, histological type, depth of tumor invasion,

the presence or absence of LVI, the presence or absence of intratumoral ulcers, and the number of dissected lymph nodes were retrospectively compared between patients with and without lymph node metastasis to identify the factors associated with lymph node metastasis.

Table 2 Relationship between tumor size, depth of tumor invasion, and lymph node metastasis in undifferentiated EGC

Depth of tumor Invasion	Tumor size (mm)					Total
	≤ 5	≤ 10	≤ 20	≤ 30	30 <	
Mucosa	0/1	0/3	0/14	0/13	3/52	3/83
Submucosa	–	0/2	0/15	2/14	8/27	10/58

Table 3 Multivariate analysis of risk factors for lymph node metastasis in patients with undifferentiated EGC

Variables	Odds ratio	95% CI	<i>p</i> value
Tumor size (> 20 mm)	4.11	0.86–19.7	0.077
Depth of tumor invasion (submucosa)	1.26	0.19–8.16	0.812
Lymphovascular invasion (positive)	16.8	2.85–99.0	0.002*

*Statistically significant at $p < 0.05$. *CI* confidence interval

The clinicopathological findings were documented according to the Japanese Classification of Gastric Carcinoma published by the Japanese Gastric Cancer Association [1]. Histological examinations including the diagnosis of LVI were performed with routine hematoxylin and eosin staining.

Statistical Analysis

Continuous variables were expressed as the median value (range) and were compared by the Mann-Whitney *U* test. Categorical variables were compared using the Fisher exact test or χ^2 test. Factors found to be significant by univariate analysis were included in subsequent multivariate logistic regression analysis to determine variables independently associated with risk factors for lymph node metastasis. The statistical analysis was performed with the Microsoft Excel software program. $p < 0.05$ was regarded as statistically significant.

Results

According to the depth of tumor invasion, lymph node metastasis was observed in 13 patients (9.2%), including three with

intramucosal carcinoma (3.6%) and ten with submucosal invasive carcinoma (17.2%). Univariate analysis identified tumor size, depth of tumor invasion, and LVI as risk factors for lymph node metastasis (Table 1).

In terms of the association of wall invasion depth and tumor size with lymph node metastasis, the tumor size exceeded 30 mm in all three intramucosal carcinoma patients with lymph node metastasis (Table 2).

Among the three factors showing a significant difference by univariate analysis, LVI (positive; $p = 0.002$) was identified by multivariate analysis as an independent risk factor for lymph node metastasis (Table 3).

Discussion

The rate of lymph node metastasis in undifferentiated EGC is reported to range from 8.5 to 18.3% [5, 8], and the rate in this study was 9.2%. In this study, the rate of lymph node metastasis in intramucosal carcinoma was 3.6%, which was almost comparable to previously reported rates [4, 7, 8, 10]. While many studies [4, 5, 7–12], like ours, found that univariate analysis identified tumor size, depth of tumor invasion, and LVI as risk factors for lymph node metastasis in undifferentiated EGC, many others found that multivariate analysis identified these variables as independent risk factors for lymph node metastasis. However, some reports indicated that tumor size, depth of tumor invasion, and ulcerative findings were not independent risk factors for lymph node metastasis, as found in our study (Table 4) [4, 5, 7–12].

Gotoda et al reported that no lymph node metastasis was observed in 141 patients with undifferentiated gastric intramucosal carcinoma ≤ 20 mm in size without an ulcer [6]. Hirasawa et al also reported that no lymph node metastasis

Table 4 Reports of lymph node metastasis rate in undifferentiated early gastric cancer

Authors	Number of Patients	Incidence of lymph node metastasis (%)		Risk factors related to lymph node metastasis
		Mucosa	Submucosa	
Abe N et al. [5]	175	7.3	27.9	tumor size, LI
Nasu J et al. [9]	332	5.0	24.0	LVI
Ye BD et al. [4]	591	2.9	27.4	tumor size, depth, LI
Li C et al. [10]	646	4.2	15.9	tumor size, depth, LVI
Hirasawa T et al. [7]	3843	4.9	23.8	tumor size, depth, LVI
Kunisaki C et al. [11]	573	2.2	22.4	tumor size, depth, LVI
Li H et al. [12]	108	5.0	28.0	tumor size, depth, LVI
Kim KJ et al. [8]	362	3.5	14.8	LI, ulcer
Our study	141	3.6	17.2	LVI

LI lymphatic invasion, LVI lymphovascular invasion

was observed in 310 patients with the same clinical conditions (95% confidence interval, 0–0.96%), suggesting that endoscopic resection might also achieve therapeutic outcomes comparable to surgical resection in these patients [7]. In addition, no lymph node metastasis was observed in any of the 13 patients in our study. However, there are also reports of lymph node metastasis in undifferentiated intramucosal carcinoma \leq 20 mm in size without an ulcer or LVI. For example, lymph node metastasis was reported in one patient each with a 13-mm tumor by Nasu et al [13], with a 15-mm tumor by Odagaki et al [14], and with a 17-mm tumor by Park et al [15]. Early signet-ring cell carcinoma is reportedly associated with a lower rate of lymph node metastasis than other undifferentiated types of cancer [16–19]. However, our study showed no statistically significant difference according to the histological type; all three patients with intramucosal carcinoma associated with lymph node metastasis were histologically diagnosed as having signet-ring carcinoma. In conclusion, only LVI was an independent risk factor of lymph node metastasis for undifferentiated EGC in this study. Thus, in this study the undifferentiated EGC which undifferentiated early gastric cancer is a mucosal depth. Currently, the LVI can be revealed only by the histopathological examination of the excision lesion. So it is difficult to estimate the LVI before treatment. As the evidence is still insufficient for undifferentiated EGC, the following resections are regarded as non-curative for the time being [20]. Therefore, it was thought that it should perform endoscopic resection for the undifferentiated EGC as diagnostic treatment. The use of endoscopic resection for the undifferentiated EGC should be considered carefully for patients with LVI because of the risk for lymph node metastasis.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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References

- (2011) Japanese classification of gastric carcinoma. 3rd English Edition. Japanese gastric cancer association. *Gastric Cancer* 14: 101–112
- Sasako M, Kinoshita T, Maruyama K (1993) Prognosis of early gastric cancer (in Japanese with English abstract). *Stomach and Intestine* 28(Suppl):139–146
- Japanese gastric cancer treatment guidelines 2010 (ver. 3). Japanese gastric cancer association (2011). *Gastric Cancer* 14:113–123
- Ye BD, Kim SG, Lee JY, Kim JS, Yang HK, Kim WH, Jung HC, Lee KU, Song IS (2008) Predictive factors for lymph node metastasis and endoscopic treatment strategies for undifferentiated early gastric cancer. *J Gastroenterol Hepatol* 23:46–50
- Abe N, Watanabe T, Sugiyama M, Yanagida O, Masaki T, Mori T, Atomi Y (2004) Endoscopic treatment or surgery for undifferentiated early gastric cancer? *Am J Surg* 188:181–184
- Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, KY (2000) Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 3:219–225
- Hirasawa T, Gotoda T, Miyata S, Kato Y, Shimoda T, Taniguchi H, Fujisaki J, Sano T, Yamaguchi T (2009) Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. *Gastric Cancer* 12:148–152
- Kim K-J, Park SJ, Moon W, Park MI (2011) Analysis of factors related to lymph node metastasis in undifferentiated early gastric cancer. *Turk J Gastroenterol* 22:139–144
- Nasu J, Nishina T, Hirasaki S, Moriwaki T, Hyodo I, Kurita A, Nishimura R (2006) Predictive factors of lymph node metastasis in patients with undifferentiated early gastric cancers. *J Clin Gastroenterol* 40:412–415
- Li C, Kim S, Lai JF, Oh SJ, Hyung WJ, Choi WH, Choi SH, Zhu ZG, Noh SH (2008) Risk factors for lymph node metastasis in undifferentiated early gastric cancer. *Ann Surg Oncol* 15:764–769
- Kunisaki C, Takahashi M, Nagahori Y, Fukushima T, Makino H, Takagawa R, Kosaka T, Ono HA, Akiyama H, Moriwaki Y, Nakane A (2009) Risk factors for lymph node metastasis in histologically poorly differentiated type early gastric cancer. *Endoscopy* 41:498–503
- Li H, Lu P, Lu Y, Liu C, Xu H, Wang S, Chen J (2010) Predictive factors of lymph node metastasis in undifferentiated early gastric cancers and application of endoscopic mucosal resection. *Surg Oncol* 19:221–226
- Nasu J, Hori S, Asagi A, Nishina T, Ikeda Y, Tanimizu M, Iguchi H, Aogi K, Kurita A, Nishimura R (2010) A case of small undifferentiated intramucosal gastric cancer with lymph node metastasis. *Gastric Cancer* 13:264–266
- Odagaki T, Suzuki H, Oda I, Yoshinaga S, Nonaka S, Katai H, Taniguchi H, Kushima R, Saito Y (2013) Small undifferentiated intramucosal gastric cancer with lymph-node metastasis: case report. *World J Gastroenterol* 19:3157–3160
- Park YD, Chung YJ, Chung HY, Yu W, Bae HI, Jeon SW, Cho CM, Tak WY, Kweon YO (2008) Factors related to lymph node metastasis and the feasibility of endoscopic mucosal resection for treating poorly differentiated adenocarcinoma of the stomach. *Endoscopy* 40:7–10
- Ha TK, An JY, Youn HK, Noh JH, Sohn TS, Kim S (2008) Indication for endoscopic mucosal resection in early signet ring cell gastric cancer. *Ann Surg Oncol* 15:508–513
- Park JM, Kim SW, Nam KW, Cho YK, Lee IS, Choi M-G, Chung I-S, Song KY, Park CH, Jung CK (2009) Is it reasonable to treat early gastric cancer with signet ring cell histology by endoscopic resection? Analysis of factors related to lymph-node metastasis. *Eur J Gastroenterol Hepatol* 21:1132–1135
- Tong J-h, Sun Z, Wang Z-n, Zhao Y-h, Huang B-j, Li K, Xu Y, Xu H-m (2011) Early gastric cancer with signet-ring cell histologic type: risk factors of lymph node metastasis and indications of endoscopic surgery. *Surgery* 149:356–363
- Kim HM, Pak KH, Chung MJ, Cho JH, Hyung WJ, Noh SH, Kim CB, Lee YC, Song SY, Lee SK (2011) Early gastric cancer of signet ring cell carcinoma is more amenable to endoscopic treatment than is early gastric cancer of poorly differentiated tubular adenocarcinoma in select tumor conditions. *Surg Endosc* 25:3087–3093
- (2018) Japanese gastric cancer treatment guidelines (ver. 5) (in Japanese). Japanese gastric cancer association