Int J Clin Exp Med 2019;12(10):12487-12493
www.ijcem.com /ISSN:1940-5901/IJCEM0098944

Original Article

The risk factors for lymph node metastasis in mucosal gastric cancer: a single institutional analysis

Jinggui Chen[1,2], Guangfa Zhao[1,2], Yanong Wang[1,2]

[1]*Department of Gastric Surgery, Fudan University Shanghai Cancer Center, Shanghai, People's Republic of China;* [2]*Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, People's Republic of China*

Received June 26, 2019; Accepted September 4, 2019; Epub October 15, 2019; Published October 30, 2019

Abstract: Background: Lymph node metastasis (LNM) is a major factor influencing the prognosis of early gastric cancer. The aim of this study was to evaluate the risk factors for LNM in mucosal gastric cancer. Methods: Patients who underwent curative gastrectomy with lymphadenectomy for mucosal gastric cancer between March 2011 and August 2016 were retrospectively analyzed. Univariate and multivariate analyses were performed to identify the clinicopathological characteristics that were risk factors for LNM. Results: A total of 530 patients with mucosal gastric cancer were enrolled. Forty-six (8.7%) patients had LNM, including 3 of the 223 with the differentiated-type and 43 of the 307 with the undifferentiated-type. A univariate analysis revealed that age, sex, tumor size, differentiation type, lymphovascular invasion, and Lauren's classification showed a significant association with LNM. Sex, tumor size, differentiation type, and lymphovascular invasion were independent risk factors for LNM according to a multivariate analysis. Conclusions: Our study revealed a relatively high incidence of LNM and identified several risk factors for LNM in mucosal gastric cancer. Endoscopic resection should be considered carefully in the management of mucosal gastric cancer.

Keywords: Mucosal gastric cancer, lymph node metastasis, differentiation type

Introduction

Early gastric cancer (EGC) is defined as gastric cancer with the tumor confined to the mucosa or submucosa, regardless of the presence of lymph node metastasis (LNM) [1]. The 5-year survival rate in patients with EGC is above 90%, with LNM being the most critical prognostic factor [2-5]. Previous studies indicated an incidence of LNM in a range of 5-15% among EGC patients [6-9]. The incidence of LNM, which differs by invasion depth, was reported to range from 2% to 10% in mucosal gastric cancer (MGC) and 8% to 25% in submucosal gastric cancer, respectively [10-13].

Nowadays, endoscopic resection (ER) has become accepted worldwide as an alternative curative treatment for EGC, to reduce operative complications after traditional surgery and improve quality of life. ER is regarded as the standard procedure for differentiated-type MGC with no ulcerative findings, of which the tumor size ≤ 2.0 cm [14]. Meanwhile, rapid development in endoscopic techniques and instrumentation have prompted an increasing number of patients with MGC to be treated by ER. The indication of ER was expanded to include patients with tumors clinically diagnosed as T1a and as follows: differentiated-type, without ulceration, tumor size > 2 cm; differentiated-type, with ulceration, and tumor size ≤ 3.0 cm; undifferentiated-type, without ulceration, and tumor size ≤ 2.0 cm [2]. This guideline is now being followed, especially in Japan and Korea. However, the expansion of the reasonable indication for EGC should be based on a full consideration of the balance between the benefits and potential risks. It is definitely important to accurately predict LNM when deciding whether patients with MGC are suitable for ER.

This study involved a relatively large number of patients with MGC, and we retrospectively evaluated the association between the clinicopath-

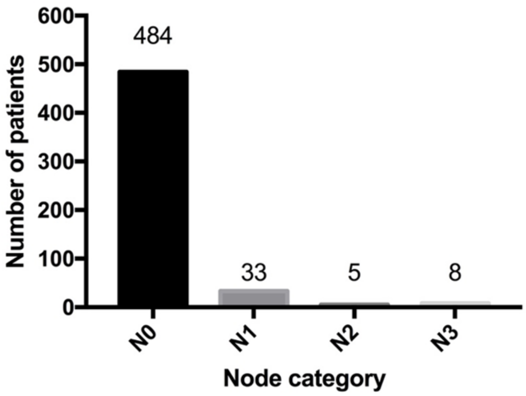

Figure 1. Lymph node category histogram for patients with mucosal gastric cancer.

ologic features and LNM. Our study aimed to identify the risk factors for LNM and to guide the management of patients with MGC.

Materials and methods

Patients

Among the patients who underwent curative gastrectomy with lymphadenectomy for gastric cancer in the Department of Gastric Surgery, Fudan University Shanghai Cancer Center between March 2011 and August 2016, the patients with MGC (tumor invasion confined to mucosa) were enrolled. Following a retrospective review of the clinical and pathological data for these patients, only patients with a pathological diagnosis of mucosal EGC were considered for inclusion in the present study. The inclusion criteria for this study were: a histologically confirmed gastric adenocarcinoma; lymph node dissection beyond D1 dissection; the resected specimens and lymph nodes were pathologically analyzed, and mucosal gastric cancer was diagnosed; newly diagnosed cancer without previous treatment, and the patient's medical record was available in the database. The exclusion criteria for the study were as follows: patients with multiple lesions; patients without intact clinical data or precise pathological records; cancers from the remnant stomach; patients receiving preoperative treatment such as endoscopic resection, and neoadjuvant chemotherapy. The ethical committee of Fudan University Shanghai Cancer Center approved this study. The study was performed in accordance with the Declaration of Helsinki and its revisions.

Histopathologic evaluation

The primary gastric adenocarcinoma and retrieved LNs were routinely examined by experienced pathologists. Papillary adenocarcinoma and well or moderately differentiated adenocarcinoma were classified as the differentiated-type. Poorly or undifferentiated adenocarcinoma, signet ring cell carcinoma, and mucinous carcinoma were classified as the undifferentiated-type. The maximum diameter was recorded as the tumor size. The analyses were based on a postoperative pathology of the specimens. Pathological staging was performed according to the American Joint Committee on Cancer, 7th edition. The relationships between the clinicopathological characteristics and LNM were examined to identify the risk factors. These clinicopathological parameters were analyzed: sex, age, location of the tumor, tumor size, number of retrieved LNs, lymphovascular invasion, perineural invasion, Lauren's classification, and differentiation type.

Statistical analysis

The risk factors for LNM were identified by performing Student's *t* test, a Chi squared test, or Fisher's exact test. A multivariate analysis of risk factors was performed using logistic regression. The statistical analysis was carried out using SPSS software (version 22.0, IBM Inc., Armonk, NY), and a P value < 0.05 was considered statistically significant.

Results

Patient characteristics

Five hundred and thirty patients with MGC were studied. Among these patients, 328 (61.9%) were male, and 202 (38.1%) were female, ranging in age from 19 to 80 years (mean 55.8 ± 11.3 years). LNM was detected in 46 (8.7%) patients (**Figure 1**). Thirty-nine (7.4%) of the patients with MGC were located in the upper third, 104 (19.6%) were located in the middle, and 387 (73%) were located in the lower third of the stomach.

Univariate analysis of risk factors for LNM in MGC

The relationship between LNM and the clinicopathological characteristics were analyzed by univariate analysis (**Table 1**). There were no sig-

Table 1. Univariate analysis of the risk factors for lymph node metastasis in mucosal gastric cancer

Variables	LN Negative (n=484)	LN Positive (n=46)	*P*
Age, yrs	56.2 ± 11.1	49.7 ± 11.4	< 0.001
Sex, n (%)			< 0.001
Male	313 (95.4)	15 (4.6)	
Female	171 (84.7)	31 (15.3)	
Location, n (%)			0.232
Upper	38 (97.4)	1 (2.6)	
Middle	92 (88.5)	12 (11.5)	
Lower	354 (91.5)	33 (8.5)	
Tumor size, cm	1.9 ± 1.1	2.6 ± 1.4	< 0.001
Retrieved LN	24.3 ± 8.1	25.8 ± 9.1	0.229
Lymphovascular invasion, n (%)			< 0.001
Negative	475 (92.4)	39 (7.6)	
Positive	9 (56.2)	7 (43.8)	
Perineural invasion, n (%)			NA
Negative	484 (91.3)	46 (8.7)	
Positive	0 (0.0)	0 (0.0)	
Differentiation, n (%)			< 0.001
D-type	220 (98.7)	3 (1.3)	
UD-type	264 (86.0)	43 (14.0)	
Lauren classification*, n (%)			< 0.001
Intestinal	208 (97.2)	6 (2.8)	
Diffuse	138 (85.7)	23 (14.3)	
Mixed	68 (88.3)	9 (11.7)	

D-type, differentiated-type; LN, lymph node; LNM, lymph node metastasis; NA, not available; UD-type, undifferentiated-type. *There are some patients with unknown information about their Lauren classification.

Table 2. Multivariate analysis of the risk factors for lymph node metastasis in mucosal gastric cancer

Variables	Odds Ratio	95% Confidence Interval	*P*
Age	0.980	0.952-1.009	0.172
Male sex	0.386	0.191-0.79	0.008
Tumor size	1.355	1.056-1.740	0.017
Undifferentiated-type	7.096	2.056-24.491	0.002
Lymphovascular invasion	9.146	2.713-30.835	< 0.001

nificant differences between patients with and without LNM in terms of tumor location or number of retrieved LNs. The age, sex, tumor size, lymphovascular invasion, tumor differentiation, and Lauren classification showed an association with LNM. Patients with LNM were younger (49.7 ± 11.4 vs 56.2 ± 11.1, *P* < 0.001). The proportion of patients with LNM was higher in female patients (15.3% vs 4.6%, *P* < 0.001). A greater tumor size (2.6 ± 1.4 cm vs 1.9 ± 1.1 cm, *P* < 0.001) and lymphovascular invasion positive (43.8% vs 7.6%, *P* < 0.001) were associated with more frequent LNM. In patients with the undifferentiated-type cancer, the incidence of LNM was higher than it was in patients with the differentiated-type (14.0% vs 1.3%, *P* < 0.001).

Multivariate analysis of risk factors for LNM in MGC

Age, sex, tumor size, lymphovascular invasion, and tumor differentiation showed a significant association with LNM in the univariate analysis, so these factors were then included in the multivariate analysis. The sex, tumor size, type of differentiation and lymphovascular invasion had significant effects on LNM in MGC based on the multivariate analysis using logistic regression (**Table 2**).

Clinicopathologic characteristics of undifferentiated-type cancer compared with differentiated-type cancer

Table 3 shows the relationships between the clinicopathological characteristics and differentiation type. Age, sex, location of tumor, tumor size, number of retrieved LNs, Lauren classification, and LNM status differed significantly between the two types. Patients with undifferentiated-type cancer were younger (52.3 ± 11.4 vs 60.3 ± 9.3, *P* < 0.001), had a higher proportion of females (49.8% vs 22.0%, *P* < 0.001), had a higher proportion of lower lesions (75.2% vs 70.0%, *P* < 0.001), had larger tumor sizes (2.1 ± 1.2 cm vs 1.7 ± 1.1 cm, *P* < 0.001), and had more retrieved LNs (25.1 ± 8.2 vs 23.5 ± 8.0, *P*=0.021) and more LNM (14.0% vs 1.3%, *P* < 0.001) than patients with the differentiated-type cancer. In terms of Lauren's classifica-

Table 3. Clinicopathologic characteristics of the undifferentiated-type compared with the differentiated-type in mucosal gastric cancer

Variables	D-type (n=223)	UD-type (n=307)	*P*
Age, yrs	60.3 ± 9.3	52.3 ± 11.4	< 0.001
Sex, n (%)			< 0.001
Male	174 (78.0)	154 (50.2)	
Female	49 (22.0)	153 (49.8)	
Location, n (%)			< 0.001
Upper	30 (13.4)	9 (3.0)	
Middle	37 (16.6)	67 (21.8)	
Lower	156 (70.0)	231 (75.2)	
Tumor size, cm	1.7 ± 1.1	2.1 ± 1.2	< 0.001
Retrieved LN	23.5 ± 8.0	25.1 ± 8.2	0.021
LNM, n (%)			< 0.001
Negative	220 (98.7)	264 (86.0)	
Positive	3 (1.3)	43 (14.0)	
Lymphovascular invasion, n (%)			0.373
Negative	218 (97.8)	296 (94.4)	
Positive	5 (2.2)	11 (3.6)	
Perineural invasion, n (%)			NA
Negative	223 (100.0)	307 (100.0)	
Positive	0 (0.0)	0 (0.0)	
Lauren classification*, n (%)			< 0.001
Intestinal	185 (97.9)	29 (11.0)	
Diffuse	0 (0.0)	161 (61.2)	
Mixed	4 (2.1)	73 (27.8)	

D-type, differentiated-type; LN, lymph node; LNM, lymph node metastasis; NA, not available; UD-type, undifferentiated-type. *There are some patients with unknown information about their Lauren classification.

Table 4. The lymph node metastasis rate assessed by combining differentiation type, lymphovascular invasion, sex, and tumor size in mucosal gastric cancer

Variables	Tumor size (cm)			
	≤ 1	> 1, ≤ 2	> 2, ≤ 3	> 3
D-type (n=223)				
Lymphovascular invasion (-), Male	0/54	0/67	1/31	1/18
Lymphovascular invasion (-), Female	0/17	0/19	0/10	0/2
Lymphovascular invasion (+), Male	0/0	1/4	0/0	0/0
Lymphovascular invasion (+), Female	0/0	0/0	0/1	0/0
UD-type (n=307)				
Lymphovascular invasion (-), Male	0/31	1/58	5/42	5/18
Lymphovascular invasion (-), Female	4/35	11/56	7/34	4/22
Lymphovascular invasion (+), Male	0/0	0/1	1/3	0/1
Lymphovascular invasion (+), Female	0/1	1/1	1/1	3/3

D-type, differentiated-type; UD-type, undifferentiated-type.

tion, the diffuse or mixed histologic type was observed significantly more often in the undifferentiated-type than in the differentiated-type.

The LNM rate assessed by combining sex, tumor size, lymphovascular invasion, and differentiation type in MGC

The patients were divided into two groups according to differentiation type. In both subgroups, the LNM rate was assessed by further subdividing by the presence or absence of lymphovascular invasion, female or male sex, and tumor size (**Table 4**). In the differentiated-type group, no LNM was detected in the 157 patients without lymphovascular invasion, and tumor size ≤ 2 cm; of the 52 differentiated-type patients with tumor size > 2 cm, 2 (3.8%) patients showed LNM. In the undifferentiated-type group, 17 (9.3%) of the 183 patients with tumor size ≤ 2 cm showed LNM.

Discussion

Despite the prevalence of gastric cancer in the Chinese population, most patients are diagnosed at an advanced stage, resulting in a relatively low incidence of ECG in China, compared with Japan and Korea. In recent years, the proportion of EGC has increased along with the advances in diagnostic technologies and more screening programs in China. Previous studies indicated LNM as one of most pivotal prognostic factors for EGC [12, 15-17]. It was reported that the 5-year survival rate was 87.3% and 94.2% respectively in ECG for those patients with LNM and those without LNM [18]. When EGC was subdivided into mucosal and submucosal EGC according to the invasion depth, the overall survival in MGC patients was significantly better than those of the submucosal cancer patients, owning to the lower incidence of LNM in MGC. Therefore, ER has become an alternative option for MGC. The status of LNM is the most important factor when determining the optimum treatment in patients with MGC. The selection of ER is decided by the absence of LNM.

For MGC, the rate of LNM is relatively low and has been reported as approximately 2-4% [19-23]. In a recent study, only 18 (1.8%) patients out of 1003 patients with MGC had LNM [24]. However, our study indicated a LNM incidence of 8.7% in patients with MGC, which is notably higher than those reported by other East Asian countries. Among the 530 patients in our cohort, LM metastasis was detected in 46 patients. 33 patients (71, 7%) were N1, 5 (10.9%) were N2, and 8 (17.4%) were N3. Some reasons should be taken into account for this discrepancy. It might be interpreted by the differences in the diagnostic criteria. In Japan, structural or cellular atypia is sufficient to make a diagnosis of gastric carcinoma irrespective of the presence of invasion. However, these lesions could be diagnosed instead as high-grade dysplasia in our institution. This difference might result in a higher incidence of LNM in patients with MGC in this study than in the Japanese cohort.

Many efforts have been made to evaluate the clinicopathologic factors that might be used to predict the possibility of LNM. Numerous studies have been done to identify the risk factors for LNM. Several clinicopathologic factors, including sex, tumor size, histological differentiation, and lymphovascular invasion have been reported to be tightly associated with LNM in EGC [2, 20, 25-29]. In our study, age, sex, tumor size, differentiation type, Lauren's classification, and lymphovascular invasion were related to LNM in MGC according to our univariate analysis. Furthermore, sex, tumor size, differentiation type, and lymphovascular invasion were independent risk factors for LNM according to our multivariate analysis. The present study identified female sex as an independent risk factor, which has been demonstrated previously, but the mechanism of the relationship between sex and LNM remains unknown [30, 31]. Levels of endogenous estrogen might be involved in this association.

Differentiation type is also closely associated with LNM. In the present study, the incidence of LNM in undifferentiated-type cancer was higher than in differentiated-type cancer, 14% vs 1.3%, respectively. Undifferentiated-type was identified as an independent risk factor for LNM. Undifferentiated-type cancer showed more aggressive clinical features than did the differentiated-type cancer [24]. In our study, age, sex, tumor location, size, number of retrieved LNs, Lauren's classification and LNM status differed significantly between the two types. Patients with the undifferentiated-type cancer had a younger age, a higher proportion of females, lower tumor location, larger tumor size, and more LNM than patients with the differentiated-type cancer. In the differentiated-type group, no LNM was detected in the 157 patients without lymphovascular invasion, and with tumor size ≤ 2 cm; In the undifferentiated-type group, 17 of 183 patients with tumor size ≤ 2 cm still showed an LNM. In our study, LNM was observed in 14% of the undifferentiated-type cancer patients. In view of the high risk of LNM in the undifferentiated-type cancer patients, ER has generally been limited to patients with the differentiated-type MGC.

In order to reduce morbidity and improve the patients' quality of life after conventional surgery, it is reasonable to consider less-invasive treatments for patients with EGC. In recent years, ER has been deemed one of the standard treatments, and it is indicated for patients with MGC and with tumor size ≤ 2 cm and for those without LNM [14]. ER provides reliable outcomes in most selected patients with MGC. The most important critical factor in considering to choose ER is determining whether the patient has LNM. Considering the indications for ER in MGC, the absolute indication has been accepted worldwide [32, 33]. However, available studies that address the application of the expanded indication for ER in MGC are limited. In patients with the undifferentiated-type MGC, even if the indication of ER is satisfied, the risk of LNM is clearly higher than it is with the differentiated-type cancer. Our study also showed that LNM was observed in MGC that satisfied the expanded indication for ER. The risk of LNM should never be ignored, even if the indication for ER was satisfied. Therefore, we suggest more studies on evaluating the risk factors associated with LNM and reappraising the expanded indication of ER in MGC.

There are some limitations to this study. First, the present study was retrospectively designed in a single center. Second, only patients who underwent surgery were included. Thus, a possible selection bias as a result of excluding patients who received ER for MGC was unavoidable. Therefore, the incidence rate for LNM might have been overestimated. Third, a further histologic distinction beyond the differentiated and undifferentiated-type, and their association with LNM were not specifically assessed.

In conclusion, our study revealed a relatively high incidence of LNM in patients with MGC. Sex, tumor size, differentiation type, and lymphovascular invasion were identified as independent risk factors for LNM. ER might be acceptable as curative treatment for highly selective MGC patients with a negligible risk of LNM. The application of ER should be considered carefully. Radical gastric resection with lymphadenectomy is still the standard treatment in patients with a high risk of LNM.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yanong Wang, Department of Gastric Surgery, Fudan University Shanghai Cancer Center, No. 270 Dongan Road, Shanghai 200032, People's Republic of China. Tel: +86-2164175590; Fax: +86-2164430130; E-mail: wyfuscc@163.com

References

[1] Kajitani T. The general rules for the gastric cancer study in surgery and pathology. part I. clinical classification. Jpn J Surg 1981; 11: 127-139.
[2] Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T and Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000; 3: 219-225.
[3] Seto Y, Nagawa H and Muto T. Impact of lymph node metastasis on survival with early gastric cancer. World J Surg 1997; 21: 186-189.
[4] Ahmad R, Setia N, Schmidt BH, Hong TS, Wo JY, Kwak EL, Rattner DW, Lauwers GY and Mullen JT. Predictors of lymph node metastasis in western early gastric cancer. J Gastrointest Surg 2016; 20: 531-538.
[5] Choi AH, Nelson RA, Merchant SJ, Kim JY, Chao J and Kim J. Rates of lymph node metastasis and survival in T1a gastric adenocarcinoma in western populations. Gastrointest Endosc 2016; 83: 1184-1192.
[6] Ryu KW, Choi IJ, Doh YW, Kook MC, Kim CG, Park HJ, Lee JH, Lee JS, Lee JY, Kim YW and Bae JM. Surgical indication for non-curative endoscopic resection in early gastric cancer. Ann Surg Oncol 2007; 14: 3428-3434.
[7] Ito H, Inoue H, Ikeda H, Odaka N, Yoshida A, Satodate H, Onimaru M, Takayanagi D, Santi EG and Kudo SE. Surgical outcomes and clinicopathological characteristics of patients who underwent potentially noncurative endoscopic resection for gastric cancer: a report of a single-center experience. Gastroenterol Res Pract 2013; 2013: 427405.
[8] Yang HJ, Kim SG, Lim JH, Choi J, Im JP, Kim JS, Kim WH and Jung HC. Predictors of lymph node metastasis in patients with non-curative endoscopic resection of early gastric cancer. Surg Endosc 2015; 29: 1145-1155.
[9] Kim ER, Lee H, Min BH, Lee JH, Rhee PL, Kim JJ, Kim KM and Kim S. Effect of rescue surgery after non-curative endoscopic resection of early gastric cancer. Br J Surg 2015; 102: 1394-1401.
[10] Pelz J, Merkel S, Horbach T, Papadopoulos T and Hohenberger W. Determination of nodal status and treatment in early gastric cancer. Eur J Surg Oncol 2004; 30: 935-941.
[11] Borie F, Millat B, Fingerhut A, Hay JM, Fagniez PL and De Saxce B. Lymphatic involvement in early gastric cancer: prevalence and prognosis in France. Arch Surg 2000; 135: 1218-1223.
[12] Roviello F, Rossi S, Marrelli D, Pedrazzani C, Corso G, Vindigni C, Morgagni P, Saragoni L, de Manzoni G and Tomezzoli A. Number of lymph node metastases and its prognostic significance in early gastric cancer: a multicenter Italian study. J Surg Oncol 2006; 94: 275-280.
[13] Kwee RM and Kwee TC. Predicting lymph node status in early gastric cancer. Gastric Cancer 2008; 11: 134-148.
[14] Kodera Y and Sano T. Japanese gastric cancer treatment guidelines (JGCTG) version 4, 2014. Gastric Cancer 2017; 20: 1-19.
[15] Saka M, Katai H, Fukagawa T, Nijjar R and Sano T. Recurrence in early gastric cancer with lymph node metastasis. Gastric Cancer 2008; 11: 214-218.
[16] Sano T, Sasako M, Kinoshita T and Maruyama K. Recurrence of early gastric cancer. Follow up of 1475 patients and review of the Japanese literature. Cancer 1993; 72: 3174-3178.
[17] Kim DY, Joo JK, Ryu SY, Kim YJ and Kim SK. Factors related to lymph node metastasis and surgical strategy used to treat early gastric carcinoma. World J Gastroenterol 2004; 10: 737-740.
[18] Noh SH, Hyung WJ and Cheong JH. Minimally invasive treatment for gastric cancer: approaches and selection process. J Surg Oncol 2005; 90: 188-193.

[19] Sano T, Kobori O and Muto T. Lymph node metastasis from early gastric cancer: endoscopic resection of tumour. Br J Surg 1992; 79: 241-244.

[20] Kitamura K, Yamaguchi T, Taniguchi H, Hagiwara A, Sawai K and Takahashi T. Analysis of lymph node metastasis in early gastric cancer: rationale of limited surgery. J Surg Oncol 1997; 64: 42-47.

[21] Yamao T, Shirao K, Ono H, Kondo H, Saito D, Yamaguchi H, Sasako M, Sano T, Ochiai A and Yoshida S. Risk factors for lymph node metastasis from intramucosal gastric carcinoma. Cancer 1996; 77: 602-606.

[22] Tsujitani S, Oka S, Saito H, Kondo A, Ikeguchi M, Maeta M and Kaibara N. Less invasive surgery for early gastric cancer based on the low probability of lymph node metastasis. Surgery 1999; 125: 148-154.

[23] Folli S, Morgagni P, Roviello F, De Manzoni G, Marrelli D, Saragoni L, Di Leo A, Gaudio M, Nanni O, Carli A, Cordiano C, Dell'Amore D and Vio A; Italian Research Group for Gastric Cancer (IRGGC). Risk factors for lymph node metastases and their prognostic significance in early gastric cancer (EGC) for the Italian research group for gastric cancer (IRGGC). Jpn J Clin Oncol 2001; 31: 495-499.

[24] Oh SY, Lee KG, Suh YS, Kim MA, Kong SH, Lee HJ, Kim WH and Yang HK. Lymph node metastasis in mucosal gastric cancer: reappraisal of expanded indication of endoscopic submucosal dissection. Ann Surg 2017; 265: 137-142.

[25] Wu CY, Chen JT, Chen GH and Yeh HZ. Lymph node metastasis in early gastric cancer: a clinicopathological analysis. Hepatogastroenterology 2002; 49: 1465-1468.

[26] Boku T, Nakane Y, Okusa T, Hirozane N, Imabayashi N, Hioki K and Yamamoto M. Strategy for lymphadenectomy of gastric cancer. Surgery 1989; 105: 585-592.

[27] Maehara Y, Orita H, Okuyama T, Moriguchi S, Tsujitani S, Korenaga D and Sugimachi K. Predictors of lymph node metastasis in early gastric cancer. Br J Surg 1992; 79: 245-247.

[28] 28. Yamada T, Sugiyama H, Ochi D, Akutsu D, Suzuki H, Narasaka T, Moriwaki T, Endo S, Kaneko T, Satomi K, Ikezawa K, Mizokami Y and Hyodo I. Risk factors for submucosal and lymphovascular invasion in gastric cancer looking indicative for endoscopic submucosal dissection. Gastric Cancer 2014; 17: 692-696.

[29] Abe N, Watanabe T, Suzuki K, Machida H, Toda H, Nakaya Y, Masaki T, Mori T, Sugiyama M and Atomi Y. Risk factors predictive of lymph node metastasis in depressed early gastric cancer. Am J Surg 2002; 183: 168-172.

[30] Jin EH, Lee DH, Jung SA, Shim KN, Seo JY, Kim N, Shin CM, Yoon H and Jung HC. Clinicopathologic factors and molecular markers related to lymph node metastasis in early gastric cancer. World J Gastroenterol 2015; 21: 571-577.

[31] Abe N, Sugiyama M, Masaki T, Ueki H, Yanagida O, Mori T, Watanabe T and Atomi Y. Predictive factors for lymph node metastasis of differentiated submucosally invasive gastric cancer. Gastrointest Endosc 2004; 60: 242-245.

[32] Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T and Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001; 48: 225-229.

[33] Pyo JH, Lee H, Min BH, Lee JH, Choi MG, Lee JH, Sohn TS, Bae JM, Kim KM, Ahn JH, Carriere KC, Kim JJ and Kim S. Long-term outcome of endoscopic resection vs. surgery for early gastric cancer: a non-inferiority-matched cohort study. Am J Gastroenterol 2016; 111: 240-249.