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BRIEF ARTICLE

Predictive factors for lymph node metastasis in early gastric cancer

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Abstract

AIM: To analyze the predictive factors for lymph node metastasis (LNM) in early gastric cancer (EGC).

METHODS: Data from patients surgically treated for gastric cancers between January 1994 and December 2007 were retrospectively collected. Clinicopathological factors were analyzed to identify predictive factors for LNM.

RESULTS: Of the 2936 patients who underwent gastrectomy and lymph node dissection, 556 were diagnosed with EGC and included in this study. Among these, 4.1% of patients had mucosal tumors (T1a) with LNM while 24.3% of patients had submucosal tumors with LNM. Univariate analysis found that female gender, tumors ⩾ 2 cm, tumor invasion to the submucosa, vascular and lymphatic involvement were significantly associated with a higher rate of LNM. On multivariate analysis, tumor size, lymphatic involvement, and tumor with submucosal invasion were associated with LNM.

CONCLUSION: Tumor with submucosal invasion, size ⩾ 2 cm, and presence of lymphatic involvement are predictive factors for LNM in EGC.

Key words: Early gastric cancer; Lymph node metastasis; Endoscopic treatment; Endoscopic submucosa dissection; Depth of tumor invasion

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INTRODUCTION

The term early gastric cancer (EGC) describes gastric cancers involving the mucosa or submucosa irrespective of the presence of lymph node metastasis (LNM). Radical surgery including lymph node dissection has been the

standard treatment for early gastric cancer; however, LNM has only been associated with approximately 8% to 20% of EGC cases[1-3]. Unnecessary surgery could be avoided and endoscopic treatment might be a consideration in patients with EGC with negligible risk of LNM. Prior studies have demonstrated that the presence of LNM is the most significant factor for survival in patients with EGC[4,5] and usually constitutes the watershed between radical and endoscopic surgery. Identification of LNM cannot be achieved *via* endoscopic ultrasonography or computed tomography because the lymph node size is not a reliable parameter for detection of metastasis[1,2]. Many retrospective studies on EGC have established an indication for endoscopic treatment[6] and the probability of LNM in EGC has been estimated based on macroscopic-endoscopic tumor characteristics and histopathological findings.

According to the treatment guidelines for gastric cancer in Japan[7] the indication for endoscopic treatment such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) are patients with non-ulcerated tumors < 2 cm. Several investigators are currently attempting to extend the indication for endoscopic treatment to include: differentiated type, intramucosal cancer without ulcer, > 2 cm in size; differentiated type, intramucosal cancer, ≤ 3 cm in size if ulcerated; and, undifferentiated type, intramucosal tumor without ulcer, ≤ 2 cm in size (Table 1).

While endoscopic treatment for EGC is widely adapted in Japan and Korea using various criteria[4,8-10], it remains uncertain whether these guidelines for EMR/ESD are applicable to patients in areas outside of Japan and Korea. Japan and Korea have the highest gastric cancer rate in the world[11,12] and between 30% and 70% of all gastric cancers are diagnosed as EGCs. In other countries, EGCs account for only about 5% to 15% of all gastric cancers[13,14]. Japan and Korea have national screening programs in which the use of chromoendoscopy could increase the detection rate of EGC. Race, diet, and other factors such as pathologic diagnosis may explain differences in the diagnosis of EGC between Japan and other countries[15,16]; however, comparable data about EGC from other countries is rare or only involve a small case series[17]. The purpose of this study was to identify factors related to LNM in EGC and to elucidate which subgroup of EGC patients could be treated with EMR or ESD instead of radical surgery.

MATERIALS AND METHODS

Between January 1994 and December 2007, 2936 patients underwent gastrectomy for gastric cancer in the Department of Surgery, Chang Gung Memorial Hospital, Taipei, Taiwan, China. Clinicopathological data were obtained from a retrospectively constructed medical database, which had been reviewed by IRB, Chang Gung Memorial Hospital. In total, 556 of these patients were diagnosed with primary EGC and were included in this study. There were 330 men and 226 women with a median age of 62 years (range: 21-89 years).

Table 1 Extended indications for endoscopic mucosal resection/endoscopic submucosal dissection according to the treatment guidelines for gastric cancer in Japan

Differentiated type, mucosal cancer, ulcer (-), > 2 cm
Differentiated type, mucosal cancer, ulcer (+), ≤ 3 cm
Undifferentiated type, mucosal cancer, ulcer (-), ≤ 2 cm

Additional lymph node resection is not necessary when lymphovascular invasion is absent and also when it is not deeper than SM1 (-500 μm).

Poorly differentiated adenocarcinomas, signet ring cell carcinomas, and mucinous adenocarcinomas were classified as undifferentiated tumors. Well and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma were grouped together as differentiated tumors. Associations between the various clinicopathological factors and the presence of LNM were analyzed to identify risk factors of LNM. These factors included: gender; age (< 65 years or ≥ 65 years), carcinoembryonic antigen (CEA, < 5 ng/mL or ≥ 5 ng/mL), gross appearance, presence of an ulcer, histological type, depth of invasion (mucosa or submucosa), lymphatic involvement, and vascular involvement. Endoscopic macroscopic appearance was evaluated based on the Japanese Classification of Gastric Carcinoma established by the Japanese Research Society for Gastric Cancer[18]. Gross tumor findings were classified into five groups: type I (protruded); Ⅱa (superficially elevated); Ⅱb (flat); Ⅱc (superficially depressed); or Ⅲ (excavated). Macroscopic findings were defined as elevated types (type Ⅰ, Ⅱa, and combined Ⅰ or Ⅱa with Ⅱb), flat type (type Ⅱb), or depressed types (type Ⅱc, Ⅲ, and any combination of Ⅱb, Ⅱc or Ⅲ). When both elevated and depressed types were observed in one lesion, the lesion was defined as mixed type. An ulcer was identified based on the presence of an ulcer or ulcer scar defined endoscopically as converging folds and recognized histologically as a deformity of the muscularis propria or fibrosis in the submucosal layer[19].

Specimens were fixed in 5% formaldehyde and the tumor area and surrounding normal tissue were completely embedded in paraffin. The size (largest diameter) of each carcinoma was measured by the pathologist after fixation. From each block, 2 μm thick sections were cut and stained with hematoxylin and eosin. The depth of infiltration was measured at the deepest point of penetration of the cancer cells[20]. The pT1 category was confirmed as well as the subdivision in pT1a (limited to the mucosa or muscularis mucosa) and pT1b (submucosa).

All dissected lymph nodes were analyzed microscopically for metastatic disease. When necessary, additional lymph node sections were analyzed and special staining was applied. Immunohistochemistry for micrometastasis was not performed.

Statistical analysis

Calculations were performed using SPSS for Windows

Table 2 Clinicopathological features of 556 patients diagnosed with early gastric cancer and univariate analysis of potential risk factors of regional lymph node metastasis

Variables	Positive rate of lymph node metastasis (%)	*P* value
Age (yr)		0.876
< 65	40/288 (13.9)	
⩾ 65	36/268 (13.4)	
Gender		0.012
Male	35/330 (10.6)	
Female	41/226 (18.1)	
Size (cm)		< 0.001
< 2	34/352 (9.7)	
⩾ 2	42/204 (20.6)	
Endoscopic appearance		0.993
Elevated	9/65 (13.8)	
Depressed	43/307 (14.0)	
Flat	16/123 (13.0)	
Mixed	8/61 (13.1)	
Serum CEA (ng/mL)		0.152
< 5	43/336 (12.8)	
⩾ 5	7/32 (21.9)	
Depth of invasion		< 0.001
T1a	12/293 (4.1)	
T1b	64/263 (24.3)	
Histology differentiation		0.759
Differentiated	41/309 (13.3)	
Undifferentiated	35/247 (14.2)	
Vascular invasion		< 0.001
Absence	68/546 (12.5)	
Presence	8/10 (80.0)	
Lymphatic involvement		< 0.001
Absence	44/517 (8.5)	
Presence	32/39 (8.2)	
Ulcer		0.449
Absence	22/182 (12.1)	
Presence	54/374 (14.4)	

(version 11.5K, Chicago, Illinois). The χ^2 test was used to assess potential risk factors of LNM by bivariate comparisons of the categorical variables. Significant factors noted by univariate analysis were subsequently entered into a multivariate logistic regression model for analysis. *P* values < 0.05 were considered to be statistically significant.

RESULTS

EGCs were diagnosed in 18.9% of the gastric cancer cases (556 cases). Of these 556 diagnosed with EGC, 76 (13.7%) had LNM. As shown in Table 2, 293 (52.7%) were intramucosal tumors and 4.1% of these had LNM. In addition, 263 lesions (47.3%) penetrated the submucosa and 24.3% of submucosal tumors had LNM.

Univariate analysis identified that female gender, size ⩾ 2 cm, tumor invasion to the submucosa, presence of lymphatic involvement, and presence of vascular involvement were significantly associated with a higher rate of LNM (Table 2). Tumor size ⩾ 2 cm ($P < 0.008$), deep penetration into the submucosa ($P < 0.001$), and lymphatic involvement ($P < 0.001$) remained significant in multivariate analysis (Table 3).

Table 4 demonstrates the incidence of LNM of our patients fulfilled the criteria used for endoscopic treatment in EGD Japan[7]. In patients without lymphovascular invasion, 42 (tumor size ⩽ 2 cm) and 77 (any tumor size) patients with differentiated intramucosal cancers and no ulceration did not have LMN; intramucosal lesions with ulcer, size ⩽ 3 cm were found in 78 patients, who had no LNM; 3 of 35 patients with undifferentiated intramucosal tumors, no ulceration and size ⩽ 2 cm had LNM.

Table 3 Multivariate analysis of potential risk factors for regional lymph node metastasis

Variables	Odds ratio (95% CI)	*P* value
Gender (female/male)	1.49 (0.35-1.1)	0.163
Tumor size (⩾ 2 cm/< 2 cm)	2.28 (1.20-4.17)	0.008
Vascular invasion (yes/no)	1.86 (0.23-12.65)	0.598
Lymphatic invasion (yes/no)	27.2 (10.3-74.8)	< 0.001
Depth of invasion (T1b/T1a)	4.91 (2.44-9.89)	< 0.001

Table 4 Incidence of lymph node metastasis in our patients fulfilled the criteria used in endoscopic treatment for early gastric cancer in Japan

Criteria	Patient number with lymph node metastasis/total patient	Incidence (%)
Non-ulcerated, differentiated, intramucosal tumor without lymphovascular invasion, ⩽ 2 cm	0/42	0
Non-ulcerated, differentiated, intramucosal tumor without lymphovascular invasion, any size	0/77	0
Ulcerated, intramucosal tumor, without lymphovascular invasion, ⩽ 3 cm	0/78	0
Non-ulcerated, undifferentiated intramucosal tumor without lymphovascular invasion, ⩽ 2 cm	3/35	8.6

DISCUSSION

The incidence of LNM in EGC ranges from 2.6% to 4.8% in mucosal cancers and 16.5% to 23.6% in submucosal cancers[21,22]. In this study the positive rates of LNM in intramucosal and submucosal lesions were 4.1% and 24.3%, respectively, in line with the previous reports[21,22]. Endoscopic treatment for gastric cancer not only preserves gastric function but also helps maintain the patient's quality of life. For patients with EGC, "early" treatment is advocated as the best option for obtaining a complete cure. At present, a correct diagnosis of LNM is impossible during either EMR or ESD. This means that if LNM exists at the time of EMR or ESD, recurrence is very likely. For this reason, multiple patient- and tumor-related variables are currently under investigation as predictors of lymph node involvement[23], particularly in Japan and Korea. Many investigators have suggested possible extended criteria for local treatment[4].

In areas outside of Japan and Korea, the possibility

of using the above-described criteria remains problematic. Japan and Korea have the highest rate of gastric cancer rate in the world[11,12] and that in these countries, between 30% and 70% of all gastric cancers are diagnosed as EGCs. In other areas or countries, EGCs account for only about 5% to 15% of all gastric cancers[13,14,24].

National screening programs and chromoendoscopy could improve the detection rate of EGC; however, race, diet, and other factors such as pathological diagnosis may explain differences in the diagnosis of EGC between Japan and other countries. For example, there are some intestinal-type mucosal cancers in Japan that are not regarded as cancer in Western countries[15,16]. Hölscher *et al*[17] reported that the rate of LNM in mucosal cancer in one European series (6.5%) is higher than reported in Asian countries (2.7%). These differences are even greater if study data are limited to Japan and Korea; however, no difference in submucosal cancer exists (23.9% *vs* 22.1%). Therefore, whether the standard treatment employed in Japan and Korea can be used in other countries remains unknown. Compared with the data generated in this study, the rate of EGC was 18.9%, which is lower than that previously reported in Japan and Korea and similar to the reports from the United States and Europe. Our results revealed that the rate of LNM in intramucosal cancer was 4.1%, higher than the value published from Japan and Korea[17]. This might be explained due to the bias of histology criteria employed in our study (similar to those used in Western countries) and Japan and Korea.

In this study, various clinicopathological factors including gender, age, CEA levels, gross appearances, histological type, invasion depth, lymphatic involvement, and vascular involvement were analyzed for LNM in EGC. Our results showed that female gender was a significant factor in univariate analyses, but was not evident in multivariate analyses. Other research teams reported that being female was associated with LNM in both depressed EGCs and differentiated submucosally invasive EGC[10,25], possibly related to estrogen level[26]. At present, the precise link between gender and LNM remains unclear and further biologic studies are required to explain this effect.

Many studies suggest that serum CEA is an independent risk factor for hematogenous recurrence of gastric carcinoma[27]. Ikeda *et al*[28], for example, reported that stage Ⅱ and Ⅲ gastric cancer patients with higher preoperative CEA levels had frequent liver metastasis. This analysis, however, included all stages of gastric cancer. In the subgroup analysis of EGC in our studies, serum CEA levels were not a significant risk factor for LNM. Whether increased CEA levels have any impact on survival in patients with EGC needs further study.

Some studies have indicated that histological differentiation and ulceration had no significant association with LNM[25,26,29-31]. In contrast, Gotoda *et al*[4] performed a large study including 5265 patients with EGC. They reported that undifferentiated EGC and ulceration were independent factors. Moreover, Ye *et al*[32] assessed 591 patients with undifferentiated EGC and found that poorly differentiated EGCs had higher rates of LNM ($P < 0.001$). In the current study, histological differentiation was not a predictor of LNM, consistent with previous reports[25,26,29-31]. Nonetheless, our results showed that 3 of 35 cases (8.6%) with undifferentiated intramucosal tumors, which were not ulcerative and ⩽ 2 cm in size, had LNM. It is well accepted that in the presence of LNM, only radical gastrectomy provided a chance for curing patients with EGC. Therefore, we suggest that surgical resection with lymphadenectomy instead of endoscopic management should be the treatment choice for undifferentiated EGC.

Many researchers have accepted that depth of tumor invasion is the major factor relating to regional LNM[4,26,30,31] and endoscopic treatment is considered in EGC even if there is minimal submucosal invasion. Nonetheless, some of these researchers still advise against the use of extended criteria even if minimal submucosa invasion is present because rare cases had LNM that met the extended criteria for EMR/ESD[33].

In summary, tumor with submucosal invasion, size ⩾ 2 cm, and presence of lymphatic involvement appear to be significant factors for LNM. Endoscopic treatment might be an alternative in carefully selected EGC patients without predictors for LNM.

COMMENTS

Background

Endoscopic treatment for early gastric cancer (EGC) has been widely adapted in Japan and Korea to avoid unnecessary gastric resection. However, the presence of lymph node metastasis (LNM) which affects patient survival is considered a contraindication of endoscopic management in this situation. This study was designed to analyze the predictive factors for LNM in early gastric cancer.

Research frontiers

Studies have established an indication for endoscopic treatment for EGC and the probability of LNM in EGC is extremely low based on endoscopic and histopathological findings.

Innovations and breakthroughs

Guidelines for endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) remains uncertain in areas outside of Japan and Korea. The authors identify the predictive factors related to LNM in EGC and test the guideline.

Applications

Endoscopic treatment might be an alternative in carefully selected EGC patients without risk factors for LNM.

Terminology

EMR is an endoscopic technique of resection of a lesion that requires the separation of the submucosa using normal saline solution. ESD is a new method of resection, allowing the dissection of the lesion within the thickness of the submucosa or the interface between the submucosa and the muscularis propria.

Peer review

Excellent contribution highlighting the appropriate selection indicators for endoscopic treatment of early gastric cancer indicating that not all early cancers are the same.

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