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Original Article

Acquisition of histologic diversity contributes to not only invasiveness but also lymph node metastasis in early gastric cancer

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ABSTRACT

Background: As more endoscopic resections are performed in early gastric cancer, the pretreatment prediction of lymph node metastasis (LNM) becomes more important. Some tumor characteristics including histologic type, invasion depth, ulceration, size, and lymphovascular invasion have been used to determine the endoscopic resectability of early gastric cancer; however, a more detailed analysis between clinicopathologic factors and lymph node metastasis is needed.

Methods: We analyzed the correlation between the clinicopathological findings and LNM with 310 cases of early gastric cancer by dividing invasion depths in detail.

Results: LNM occurred in 3.2% and 16.2% of the T1a and T1b tumors, respectively. LNM was associated with invasion depth ($p = 0.002$) and lymphatic ($p < 0.001$) and perineural ($p = 0.013$) invasion. Among them, lymphatic invasion was the most powerful factor associated with LNM and significantly constant in T1a and T1b. The rate of LNM increased gradually as the tumor invaded deeper, and invasion of the muscularis mucosae layer was associated with an increased mixed adenocarcinoma incidence, suggesting that histologic diversity was associated with tumor invasiveness.

Conclusions: We demonstrated that lymphatic invasion was the most important and powerful parameter for LNM in early gastric cancers. In addition, tumor invasiveness into the muscularis mucosae was accompanied by tumor histologic diversity.

1. Introduction

Early gastric cancer (EGC) is defined as gastric cancer that is confined to the mucosa or submucosa, irrespective of the presence of regional lymph node metastasis (LNM). Reported rates of LNM in EGC range from 5.7% to 20%, based on the analysis of surgically resected specimens of EGC [1–6]. As endoscopic resection becomes a major treatment modality for early gastric cancers without risks of LNM, the prediction of LNM is the most important factor to determine the endoscopic resectability and to predict the patients' prognosis [7–9].

Owing to the failure in the accurate pretreatment evaluation of LNM by currently available imaging modalities, endoscopic resectability of EGCs has been determined through tumor characteristics: histologic type, invasion depth, ulceration, size, and lymphovascular invasion [9–11]. Therefore, numerous studies were performed to assess the pathologic parameters to predict LNM precisely in resected specimens [12–21]. Some ancillary markers were also proposed for LNM prediction, and these include the overexpression of P53 and ki-67, abnormal expression of beta-catenin, and Epstein-Barr virus positivity [13,14]. Among the numerous revealed parameters, lymphatic invasion was the main risk factor predicting LNM in EGCs; however, it was reported as an insignificant factor in one study with submucosa-invading EGCs [20]. Therefore, the risk factors for LNM needed to be further evaluated, especially in accordance with detailed invasion depths.

We analyzed the correlation between the clinicopathological parameters and LNM in EGCs and demonstrated the microscopic changes according to detailed invasion depths with gastrectomy specimens.

2. Materials and methods

2.1. Patients and clinical data

This retrospective study was approved by the Institutional Review Board of Kangbuk Samsung Hospital. Initially, we included 330 consecutive gastrectomy specimens with EGC, which were resected at Kangbuk Samsung Hospital between January 2011 and December

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2014. Among them, 20 cases with previous endoscopic resections were excluded for an accurate comparison of invasion depth. Finally, we analyzed 310 gastrectomy cases. The clinical information, including age, sex, and follow-up findings was obtained from the electronic medical records.

2.2. Gross examination and microscopic evaluation of the gastrectomy specimens

The gastrectomy specimens were fixed in a 10% buffered formalin solution overnight after opening the lumen. Gross characteristics, including tumor location, tumor size, and EGC type were recorded. All gastrectomy cases were microscopically reviewed to determine their histological classifications according to the 2010 World Health Organization (WHO) Tumor Classification [22]. The invasion depth of the tumors was recorded as lamina propria (LP), muscularis mucosae (MM), sm (submucosa) 1, sm 2, and sm 3. Tumor stage was assigned in accordance with the 2010 AJCC Tumor Node Metastasis Staging System [23]. Tumor differentiation, resection margin status, lymphovascular invasion, and perineural invasion were also evaluated. In cases with more than 2 EGC lesions, we used the tumor characteristics (including histologic type and invasion depth) of the lesion with the deepest tumor invasion.

2.3. Statistical analysis

Data were analyzed using the PASW Statistics 18 (SPSS Inc., Chicago, IL, USA) software. Crosstabs, Pearson's chi-square test, and Fisher's exact test were used as needed. To obtain the odds ratios, binary logistic regression tests were performed. Differences were regarded as statistically significant at $p < 0.05$.

3. Results

The median age of the patients was 61 years (range: 29–87 years). Subtotal and total gastrectomies were performed in 264 (85.2%) and 45 (14.5%) patients, respectively. One patient (0.3%) underwent a proximal gastrectomy. LNM occurred in 30 patients (9.7%), and the N stage was N1, N2, and N3 in 23 (7.4%), 6 (1.9%), and 1 (0.3%) patients, respectively. All 310 patients have lived for a mean post-operative month of 34.7 (range: 0.3–61.4 months) without tumor recurrence or distant metastasis, although the tumor involved the proximal resection margin in 1 case.

LNM was associated with tumor invasion depth ($p = 0.002$) and lymphatic ($p < 0.001$) and perineural ($p = 0.013$) invasion as well as with histologic classifications (Table 1). The rate of LNM increased gradually as the tumor invaded deeper. Histologically, mixed adenocarcinoma showed the highest metastasis rate (19.0%), whereas poorly cohesive carcinoma showed a lower metastasis rate than tubular adenocarcinoma. The Lauren classification showed similar patterns to the 2010 WHO classification with the highest LNM rate in the mixed type (18.5%). However, the previous (2000) WHO classification was not a significant factor for LNM. The rate of LNM was slightly higher in the female patients, but not significant statistically. The rate of LNM changed on the basis of the cut-off value of 2 cm.

With only tumors confined to the mucosa, the most noteworthy finding was that LNM occurred only in cases invading into the MM in spite of a statistical insignificance and only in poorly differentiated adenocarcinoma cases according to the previous 2000 WHO classification (Table 2). The 2010 WHO classification was not a significant factor for LNM in the analysis with only the mucosa-invading cases. Only lymphatic invasion showed a significantly constant correlation with LNM when the tumors were divided into 2 groups by invasion depth (Table 2). Vascular invasion was one of the significant factors for LNM; however, its incidence was too low in the mucosa-invading cases. Further, perineural invasion was not identified in the mucosa-invading cases. With only the submucosa-invading tumors, lymphatic invasion was the only significant factor associated with LNM. The sub-division of submucosal invasion depths and histologic classifications had no significant correlation with LNM. In both univariate and multivariate regression analyses, lymphatic invasion was the most powerful parameter for LNM (Table 3).

Since LNM increased gradually in accordance with tumor invasion depth and factors associated with LNM were different between the mucosa- and submucosa-invading EGCs, we analyzed the correlation between the detailed invasion depth and other clinicopathologic parameters (Table 4). Lymphatic invasion was strongly correlated with invasion depth, with a gradually increased rate according to invasion depth, showing a pattern similar to LMN. However, lymphatic invasion was rarely identified in the mucosa with an incidence rate of 2.9%. Perineural invasion was also a significant factor for LNM; however, it was observed only in the submucosa, especially in the deep areas. The rate of the N1 stage increased with invasion depth; N stages 2 and 3 were not correlated with invasion depth. In addition, the abrupt increase in the elevated type and decrease in the flat type were noted at the sm 3 (Table 4 and Fig. 1).

Table 1
Clinicopathologic features associated with lymph node metastasis in all 310 early gastric cancers.

Variables	Cases without LNM (%)	Cases with LNM (%)	*p* value
Sex			0.312
male	193 (91.5)	18 (8.5)	
female	87 (87.9)	12 (12.1)	
Size			0.051
≤2	99 (96.1)	4 (3.9)	
2.1–3.0	68 (87.2)	10 (12.8)	
> 3	113 (87.6)	16 (12.4)	
Gross type			0.427
Elevated	48 (85.7)	8 (14.3)	
Flat	111 (91.7)	10 (8.3)	
Depressed	121 (91.0)	12 (9.0)	
Invasion depth			0.002
Lamina propria	53 (100.0)	0 (0)	
Muscularis mucosae	98 (95.1)	5 (4.9)	
sm 1	40 (87.0)	6 (13.0)	
sm 2	40 (85.1)	7 (14.9)	
sm 3	49 (17.5)	12 (19.7)	
2000 WHO classification			0.125
Well-differentiated	56 (96.6)	2 (3.4)	
Moderately differentiated	80 (87.9)	11 (12.1)	
Poorly differentiated	85 (85.9)	14 (14.1)	
Signet ring cell carcinoma	55 (94.8)	3 (5.2)	
Others[a]	4 (100.0)	0 (0)	
2010 WHO classification			0.037
Tubular adenocarcinoma	147 (91.9)	13 (8.1)	
Poorly cohesive carcinoma	78 (94.0)	5 (6.0)	
Mixed adenocarcinoma	51 (81.0)	12 (19.0)	
Others[a]	4 (100.0)	0 (0)	
Lauren classification			0.026
Intestinal	146 (93.0)	11 (7.0)	
Diffuse	81 (92.0)	7 (8.0)	
Mixed	53 (81.5)	12 (18.5)	
Lymphatic invasion			< 0.001
Absent	255 (96.6)	9 (3.4)	
Present	25 (54.3)	21 (45.7)	
Vascular invasion			0.075
Absent	277 (90.8)	28 (9.2)	
Present	3 (60.0)	2 (40.0)	
Perineural invasion			0.013
Absent	277 (91.1)	27 (8.9)	
Present	3 (50.0)	3 (50.0)	
Adenomatous background			0.377
Absent	265 (89.8)	30 (10.2)	
Present	15 (100.0)	0 (0)	

LNM: lymph node metastasis; WHO: World Health Organization; sm: submucosa.
[a] Others includes mucinous adenocarcinoma and carcinoma with lymphoid stroma.