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## ORIGINAL ARTICLE

# Expansion of lymph node metastasis in mixed-type submucosal invasive gastric cancer

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**KEYWORDS**

Mixed-type gastric cancer;  
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**Summary** *Background/Objective:* Mixed-type early gastric cancer (differentiated and undifferentiated components) incurs a higher risk of lymph node metastasis than pure-type early gastric cancer (only differentiated or only undifferentiated components). Therefore, we investigated the expansion of lymph node metastasis in mixed-type submucosal invasive gastric cancer in order to establish the most appropriate treatment for mixed-type cancer.

*Methods:* We retrospectively analyzed 279 consecutive patients with submucosal invasive gastric cancer who underwent curative gastrectomy for gastric cancer between 1996 and 2015. We classified the patients into the mixed-type and pure-type groups according to histologic examination and evaluated the expansion of lymph node metastasis.

*Results:* The rate of lymph node metastasis was 23.7% (66/279) in the total patients, 36.4% (36/99) in the mixed-type group, and 16.6% (30/180) in the pure-type group. The significant independent risk factors for lymph node metastasis were tumor size  $\geq 2.0$  cm ( $P = 0.014$ ), mixed-type gastric cancer ( $P < 0.001$ ), and lymphatic invasion ( $P < 0.001$ ). Lymphatic invasion and lymph node metastasis had a strong relationship in mixed-type group. The rates of no. 7 lymph node metastasis in the total patients and mixed-type group were 2.9% (8/279) and 5.1% (5/99), respectively; the rates of no. 8a lymph node metastasis were 1.4% (4/279) and 4.0% (4/99), respectively.

*Conclusion:* Mixed histological type is an independent risk factor for lymph node metastasis. Lymph node metastasis in mixed-type gastric cancer involves expansion to the no. 7 and no. 8a lymph nodes. Therefore, lymphadenectomy for mixed-type submucosal invasive gastric cancer requires D1+ or D2 dissection.

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## 1. Introduction

Patients with submucosal invasive gastric cancer have favorable prognosis after curative gastrectomy, with a 5-year survival rate exceeding 90%.<sup>1</sup> However, some patients experience recurrence of early gastric cancer after gastrectomy. Hematogenous metastasis and local recurrence are common. In order to prevent recurrence, it is important to understand the expansion of lymph node metastasis and determine the appropriate level of lymphadenectomy to be performed.

Gastric cancer can be classified as differentiated or undifferentiated according to the presence or absence of tubular structures.<sup>2</sup> There are several recent reports on the management and outcomes of mixed-type early gastric cancer, that is, gastric cancer with differentiated and undifferentiated components.<sup>3–6</sup> These reports indicate that early gastric cancer with a mixed-type histology incurs a higher risk of lymph node metastasis.

Because tumor with lymph node metastasis is not an indication for endoscopic treatment, risk factors for lymph node metastasis have been investigated. Although lymph node metastasis is present in approximately 25% of cases of mixed-type gastric cancer with submucosal invasion,<sup>5–7</sup> the expansion of lymph node metastasis in mixed-type cancer has scarcely been evaluated.

Therefore, in order to establish the most appropriate treatment for submucosal invasive gastric cancer, we investigated the histological type and lymph node metastasis of patients with submucosal invasive gastric cancer.

## 2. Materials and methods

### 2.1. Patients and clinicopathological evaluation

The study population consisted of 279 consecutive patients with primary gastric cancer invading the submucosa who underwent surgical resection at Fukuoka University Chikushi Hospital between 1996 and 2015. All cancers were diagnosed histopathologically as submucosal invasive cancer. All patients were restaged according to the 7th edition of the American Joint Commission on Cancer (AJCC) staging system.<sup>8</sup> We excluded patients if they received preoperative endoscopic submucosal dissection or chemotherapy, had multiple synchronous gastric cancers, had remnant stomach cancer, or had <15 dissected lymph nodes. We reviewed pathological reports and medical records, and collected the following: age, sex, tumor location, tumor size, gross type, histological type, depth of wall invasion, lymph node metastasis, lymphatic involvement, vascular involvement, presence of ulceration, and station of metastatic lymph node. We defined tumor location on the basis of the Japanese Classification of Gastric Carcinoma.<sup>2</sup> Because the treatment of tumors in the lower and middle thirds of the stomach is clinically the same, we classified lesions into two groups: upper third (U) and middle or lower third (ML). Furthermore, we classified lesions according to gross type: elevated and flat type (I, IIa, IIa + IIb, IIb, IIa + IIc, and IIb + IIc) or depressed type (IIc, IIc + IIa, IIc + IIb, III, and IIc + III). Because tumor size is a criterion for endoscopic treatment, we classified tumor size as <2.0

or  $\geq 2.0$  cm. Moreover, we classified submucosal invasive depth as SM1 or SM2: SM1 included tumors in which the tumor invasion was <500  $\mu\text{m}$  of the muscularis mucosae, and SM2 included tumors in which the tumor invasion was  $\geq 500$   $\mu\text{m}$  into the muscularis mucosae.

### 2.2. Histopathologic evaluation

We sectioned all lesions at intervals of 3–5 mm. We stained one section from each dissected lymph node with hematoxylin and eosin. To assess the histological type, we reviewed all specimens to determine the differentiated components (well- and moderately differentiated tubular adenocarcinoma, and papillary adenocarcinoma) or undifferentiated components (poorly differentiated adenocarcinoma, signet ring-cell carcinoma, and mucinous adenocarcinoma). We classified lesions as mixed-type gastric cancer (mixed differentiated and undifferentiated components) or pure-type gastric cancer (only differentiated or only undifferentiated components). We identified lymphatic invasion by cancer cells by using immunohistochemistry with anti-D2-40 antibody.

### 2.3. Statistical analysis

We performed all statistical analyses using SPSS version 15 (SPSS, Chicago, IL, USA). We evaluated the significance of differences between groups by the unpaired *t*-test or chi-squared test where appropriate. We performed logistic regression for multivariate analysis. *P* values < 0.05 were considered statistically significant.

This study followed the ethical principles for medical research involving human subjects as outlined by the Declaration of Helsinki. We obtained informed consent from each patient prior to participation.

## 3. Results

### 3.1. Patient characteristics

The study population consisted of 198 male and 81 female patients with a median age of 65.5 years (range: 18–91 years) (Table 1). Regarding lesion location, there were 45 lesions in the upper third of the stomach and 234 lesions in the middle or lower third of the stomach (113 in the middle third and 121 in the lower third). The median tumor size was 3.2 cm (range: 0.5–10.4 cm). The depressed type was predominant. There were 99 mixed-type lesions and 180 pure-type lesions. Regarding submucosal invasive depth, 61 cases were SM1 and 228 cases were SM2. The incidence rate of lymph node metastasis was 23.7% (66/279). The overall rates of lymphatic invasion, vascular invasion, and ulceration were 57.0%, 38.0%, and 72.0%, respectively.

### 3.2. Relationship between clinicopathological factors and lymph node metastasis

The clinicopathological factors in relation to the presence or absence of lymph node metastasis in all submucosal invasive cancer are summarized in Table 2. There were no

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