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# Risk factors for lymph node metastasis of early gastric cancers in patients younger than 40

Tao Ji, MD[a], Fan Zhou, PhD[b], John Wang, MBBS (Hons)[c], Li Zi, MD[d,*]

**Abstract**

This research aims to explore the potential risk factors of lymph node metastasis (LNM) for early gastric cancers in young patients.

We retrospectively collected data from 4287 patients who underwent gastrectomy from January 2005 to December 2015 at Linyi People's Hospital. Of these, we enrolled 397 eligible consecutive patients who had early gastric cancer, then divided them into 2 groups according to age (≤40 years and >40 years). The association between the clinicopathological factors and LNM was analyzed by univariate and multivariate analysis.

Compared to older patients (>40 years), younger patients (≤40 years) with early gastric cancer had more diffuse and mixed types (51.1% and 37.8% vs 40% and 8.3%, respectively), less proximal gastric cancer (0% vs 33.8%, $P < .01$) and higher LNM (33.3% vs 13%, $P < .01$). Univariate analysis showed tumor invasion depth ($P < .01$), lymphovascular invasion ($P < .01$), and E-cadherin expression ($P = .024$) were associated with LNM in the younger cohort. Multivariate analysis revealed that lymphovascular invasion (OR = 17.740, 95% CI: 1.458–215.843) was an independent risk factor for LNM ($P = .024$). Further analysis showed 3 patients who were within expanded endoscopic resection indications were positive for LNM.

Given the high risk of lymph node involvement in young patients with early gastric cancer, both endoscopic and surgical resection procedures should be performed with caution, and active postoperative surveillance is warranted.

**Abbreviations:** EGC = early gastric cancer, OGC = old gastric cancer, YGC = young gastric cancer.

**Keywords:** early gastric cancer, endoscopic resection, lymph node metastasis, lymphovascular invasion, young population

## 1. Introduction

Although the prevalence and mortality rate of gastric cancer (GC) have decreased steadily in the last decade, it still remains the third leading cause of cancer death in the world. In 2012, about 952,000 new cases of GC were diagnosed, 42.5% of which were in China.[1,2] In recent years, many advances have been made in the treatment of GC, including establishment of endoscopic resection either by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), surgical resection of primary tumors and lymph nodes, and targeted monoclonal antibody therapy (trastuzumab), as demonstrated by the ToGA trial.[3–5] GC is commonly seen in patients above 50 years of age, and is rare in younger patients,[6] accounting for less than 10% of all GCs. The definition of young age varies among studies, but most research would define it as being younger than 40 years of age.[7,8] Reports have shown an increasing trend of GC in younger patients,[9,10] and the clinicopathological features in this group of patients showed more diffuse lesions and advanced tumor stage compared with older GC counterparts, although whether this translates into worse prognosis in this group remains controversial.[11,12]

Early gastric cancer (EGC) is defined by the Japanese Gastroenterological Endoscopy Society (JGES) as invasion confined to either mucosa or submucosa, irrespective of lymph node metastasis (LNM).[13] The 5-year survival rate is more than 90%, as demonstrated by both Eastern and Western studies.[3,14,15] LNM was recognized as a risk factor for worse prognosis.[16] The rate of positive LNM for all young GC patients ranges from 47% to 67%.[5,7] With the advantage of the ability to perform extensive en-bloc resection while being much less invasive compared to conventional surgical gastrectomy, endoscopic treatment has become an attractive alternative to surgical resection for EGC, especially in Japan and Korea.[17,18] However, although the criteria for endoscopic resection is based on surgically resected specimens,[19] the management of patients after endoscopic resection is based on the risk of LNM. Considering the more aggressive behavior and higher potential for metastasis, it is important to identify the risk factors of LNM of EGC in younger patients (YGC) when performing endoscopic resections for this specific group of patients.[20] To our knowledge, no studies have been published concerning this issue.

In our present study, we retrospectively reviewed our center's cases of EGCs in the younger cohort (≤40 years) from 2005 to 2015. By comparing the GC characteristics in this cohort with those in the older group (>40 years), we analyzed the unique features of this group of patients, and identified the risk factors for LNM in younger patients with GC.

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*[a] Department of Gastroenterology, Linyi People's Hospital, Linyi, Shandong Province, [b] Department of Gastroenterology, Drum Tower Hospital Affiliated to Nanjing University Medical School, Nanjing, Jiangsu Province, China, [c] Department of Gastroenterology and Hepatology, Royal Prince Alfred Hospital, Sydney, NSW, Australia, [d] Department of General Surgery, Linyi People's Hospital, Linyi, Shandong Province, China.*

*[*] Correspondence: Li Zi, Department of General Surgery, Linyi People's Hospital, Linyi 276003, Shandong Province, China (e-mail: ppcrab@163.com).*

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## 2. Patients and methods

### 2.1. Patients' characteristics

We retrospectively identified 4287 consecutive surgical GC resections with sufficient lymph node dissections through our center's electronic pathology database from January 2005 to December 2015 at Linyi People's Hospital. Among them, 428 (9.98%) were EGCs. We excluded gastric stump cancer (n=4), esophageal cancers extending into the stomach (n=4), and cancers with unclear invasion depth (n=23). EGC is defined as invasion confined to mucosal or submucosal layer regardless of LNM. Besides, the eligible cases (n=397) were divided into 2 groups: young gastric cancer (YGC) (n=45), defined as patients younger than 40 years; and old gastric cancer (OGC) (n=352), for patients older than 40 years old. This observational study was in accordance with the Declaration of Helsinki (1964), and was approved by institutional review board of Linyi People's Hospital. Informed consent was obtained from all of the involved patients.

### 2.2. Data

For each patient, we collected data on clinical features, endoscopic findings, and histopathology results. Clinical features of each patient, obtained from the medical record, included age, gender, symptoms, and durations. Living status and family history of each patient were acquired at follow-up. Endoscopic findings were obtained from our endoscopic center, including tumor location (proximal, including gastroesophageal junction and proximal third of the stomach; middle [gastric body]; distal stomach, from the incisura, antrum to pylorus), site (lesser or greater curvature, anterior or posterior), size, gross type according to the Paris classification (protruded [type 0–I], superficially elevated [type 0–IIa], superficially flat [type 0–IIb], superficially depressed [type 0–IIc], and excavated [type 0–III] patterns). Pathology characteristics were assessed using Lauren classification,[21] which included atrophy (defined as decreased or loss of normal gastric glands and replacement with interglandular extracellular matrix or metaplastic changes of gastric glands)[22] and/or intestinal metaplasia of noncancerous mucosa, *Helicobacter pylori* (*Hp*) infection (confirmed by both rapid urease test and histopathology), invasion depth and tumor staging (based on the seventh edition of the American Joint Committee on Cancer [AJCC7]),[23] lymphovascular invasion (LVI) (defined as tumor embolus in lymphatic and vascular ducts), perineural invasion (PNI) (defined as the process of neoplastic invasion of nerves). Patients' immunohistochemistry results for p53 and E-cadherin were also drawn from the pathology report. For p53, negative staining was defined as less than 10% positive neoplastic cells on the slide. While the score for E-cadherin was based on the area-intensity-score method,[24] which multiplies intensity score (from 0 to 3, indicating absent, weak, moderate, and strongly positive) and area score (from 0 to 4, where 0=<5%, 1=5–24%, 2=25–49%, 3=50–74%, 4=≥75%, respectively), and the total score of 0 was absent staining, 2 to 7 for aberrant, and 8 to 12 for normal staining. The entire study population was interviewed and followed-up through telephone, mainly focused on living status and family history. Follow-up period was defined as procedure date to death or the study cutoff date (March 31, 2016).

### 2.3. Treatments

EGC patients underwent either endoscopic resection or surgery based on indications and patient's choice. If within absolute indications, endoscopic resection was performed. While for patients within expanded indications, endoscopic resectability was discussed in GI weekly meetings. Prior to endoscopic treatment or surgery no patients received neoadjuvant chemotherapy. Monthly physical examination with CT imaging and laboratory tests were performed in all patients during follow-up.

### 2.4. Statistical analysis

Descriptive data, such as age and tumor size, are presented as mean ± SD, and was compared using Student *t* test. Categorical variables were compared with Pearson chi-square ($\chi^2$) test or Fisher exact test. Associations between various factors and LNM were assessed by univariate and multivariate logistic regression analysis. Variables found to be statistically significant by the univariate analysis were further scrutinized backward stepwise by the multivariate analysis, in which the least significant variable was excluded sequentially. Independent risk factors were presented as odds ratio (OR) with 95% confidence interval (CI). All 2-tailed *P* values of $<.05$ were considered statistically significant. All statistical analyses were performed using SPSS Statistics Version 23 (SPSS Inc, Chicago, IL).

## 3. Results

### 3.1. Patient's characteristics

To figure out the unique characteristics of EGCs in the young population, we compared the clinicopathological features of EGC according to age (Table 1). In terms of demographics, early

**Table 1**

**Clinicopathological characteristics of EGCs in young (≤40 y) and older (>40 y) population.**

| Characteristics | YGC (n=45) | OGC (n=352) | *P* value* |
|---|---|---|---|
| Gender | | | |
| M | 16 (35.6) | 246 (69.9) | <.01 |
| F | 29 (64.4) | 106 (30.1) | |
| Family history | 15 (33.3) | 38 (10.8) | <.01 |
| *Hp* infection | 34 (75.6) | 245 (69.6) | .411 |
| Lauren classification | | | |
| Diffuse | 23 (51.1) | 133 (37.8) | <.01 |
| Intestinal | 4 (8.9) | 192 (54.5) | |
| Mixed | 18 (40.0) | 29 (8.3) | |
| Tumor location | | | |
| Proximal | 0 | 119 (33.8) | <.01 |
| Middle | 17 (37.8) | 74 (21) | |
| Distal | 28 (62.2) | 159 (45.2) | |
| Atrophy | 37 (82.2) | 332 (94.3) | .007 |
| Intestinal metaplasia | 38 (84.4) | 332 (94.3) | .031 |
| Tumor size | 2.6 ± 1.42 | 2.3 ± 1.01 | .0481 |
| Invasion depth | | | |
| M1-M2 | 10 (22.2) | 79 (22.4) | .186 |
| M3 | 18 (40) | 97 (27.6) | |
| >SM1 | 17 (37.8) | 176 (50) | |
| LVI | 7 (15.6) | 37 (10.5) | .446 |
| PNI | 1 (2.2) | 45 (12.8) | .037 |
| LNM | 15 (33.3) | 46 (13) | <.01 |
| Recurrence | 1 (2.22) | 15 (4.26) | .801 |
| Survival rate | | | |
| 3 y | 100 | 98.6 | .069† |
| 5 y | 100 | 96.6 | |
| 10 y | 97.8 | 94.3 | |
| Overall survival (months after surgery) | 120.9 ± 1.6 | 98.1 ± 2.6 | .167‡ |

EGC = early gastric cancer, *Hp*=*H pylori*, LNM=lymph node metastasis, LVI=lymphovascular invasion, M1=epithelium, M2=lamina propria, M3=muscularis mucosa, OGC=old gastric cancer, PNI=perineural invasion, SM1=<500 μm submucosa, YGC=young gastric cancer.

* $\chi^2$ test.

† Log-rank test.

‡ *t* test.

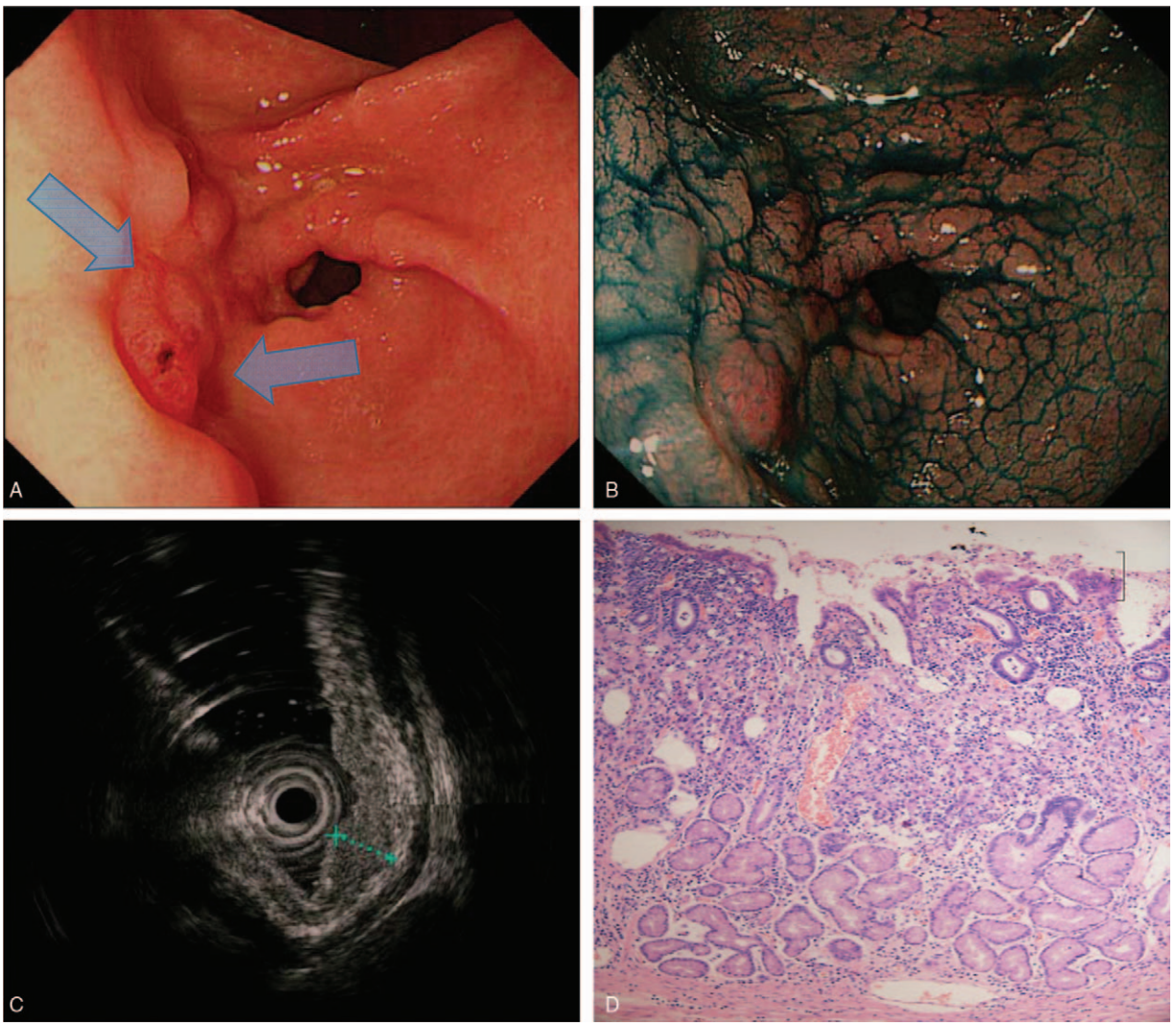


**Figure 1.** A case of early YGC (T1aN1M0). (A) Gastrointestinal endoscopy with white light reveals a rough appearance in anterior antrum. (B) Indigo Carmine staining shows the demarcation. (C) Thickening of mucosa in endoscopic ultrasound image. (D) HE staining demonstrates poorly differentiated-type adenocarcinoma located in the muscularis mucosa of the stomach. Blue arrow here indicates the lesion. YGC = young gastric cancer.

YGC had more female patients (64.4% vs 30.1%) and positive family history (33.3% vs 10.8%) ($P < .01$). Regarding tumor location, no early proximal GC was seen in YGC group, while middle GC and distal GC accounted for 37.8% and 62.2% of YGC, respectively. In OGC group, 33.8% were located at proximal, 21% at middle, and 45.2% at distal part ($P < .01$). In terms of histopathology, diffuse GC (undifferentiated GC according to Japanese guidelines) or mixed-type GC were more frequently seen in the young group (51.1% and 37.8% vs 40.0% and 8.3%, respectively, $P < .01$), in which less gastric atrophy or intestinal metaplasia (IM) of noncancerous mucosa was observed (82.4% and 84.4% vs 94.3% and 94.3% in OGC). No difference in invasion depth or LVI was seen in the 2 groups, while LNM did happen more frequently in early YGC (33.3% vs 13%, $P < .01$). And interestingly, early OGC had more perineural invasion than their counterparts (12.8% vs 2.2%, $P = .037$). Due to the small sample size, Kaplan-Meier curve was not drawn. However, there was a trend toward improved survival in the younger cohort compared to the older cohort (10-year survival rate: 97.8% vs 94.3%, $P = .069$). In fact, only 1 patient out of the 45 early YGCs died of cancer recurrence. Endoscopic and pathologic images of an early YGC were shown in Figure 1.

### 3.2. Risk factors of lymph node metastasis in early YGC

To identify LNM risk factors in the younger cohort, we conducted a comparison between LN positive and LN negative group (Table 2) and a multivariate analysis (Table 3) to summarize the independent risk factors. Firstly, Pearson chi-square test showed that LN positive group had a higher LVI rate (40% vs 3.3%, $P < .01$) and aberrant or absent E-cadherin expression ($P = .024$). No difference was seen in age, gender, family history, Lauren classification, tumor location, size, site, noncancerous mucosal status (IM or atrophy), or PNI. In the multivariate analysis, only LVI was an independent risk factor for LNM in the younger cohort (OR = 17.740, 95% CI: 1.458–215.843, $P = .024$).

### 3.3. LNM in cases fulfilling absolute or extended indication for endoscopic resection

To evaluate the efficacy and safety of endoscopic resection in this group of patients, we categorized our cohorts according to the Japanese Endoscopic Resection Guidelines[25] listed indications. As shown in Table 4, altogether 13 YGC patients fulfilled both

**Table 2**

**Comparison of clinicopathological features between lymph node positive and negative early YGCs.**

| Characteristics | N positive | N negative | *P* value* |
|---|---|---|---|
| Age | 33.4 ± 6.09 | 34.5 ± 4.37 | .490 |
| Gender | | | |
| M | 4 (26.7) | 12 (40) | .378 |
| F | 11 (73.3) | 18 (60) | |
| Family history | 5 (33.3) | 10 (33.3) | |
| *Hp* infection | 10 (66.7) | 24 (80) | .540 |
| Lauren classification | | | |
| Diffuse | 5 (33.3) | 18 (60.0) | .230 |
| Intestinal | 2 (13.3) | 2 (6.7) | |
| Mixed | 8 (53.3) | 10 (33.3) | |
| Tumor location | | | |
| Proximal | 0 | 0 | .384 |
| Middle | 7 (46.7) | 10 (33.3) | |
| Distal | 8 (53.3) | 20 (66.7) | |
| Atrophy | 11 (73.3) | 26 (86.7) | .491 |
| Intestinal metaplasia | 12 (80) | 26 (86.7) | .884 |
| Tumor size | 2.8 ± 1.31 | 2.5 ± 1.48 | .422† |
| Invasion depth | | | |
| M1-M2 | 0 | 10 (33.3) | .002 |
| M3 | 8 (53.3) | 10 (33.3) | |
| >SM1 | 7 (46.7) | 10 (33.3) | |
| LVI | 6 (40) | 1 (3.3) | <.01 |
| PNI | 1 (6.7) | 0 | .333 |
| P53 positive | 3 (20) | 3 (10) | .642 |
| E-cadherin expression | | | |
| Normal | 5 (33.3) | 18 (60) | .024 |
| Aberrant | 7 (46.7) | 3 (10) | |
| Absent | 3 (20) | 9 (30) | |

*Hp* = *H pylori*, LVI = lymphovascular invasion, M1 = epithelium, M2 = lamina propria, M3 = muscularis mucosa, PNI = perineural invasion, SM1 = <500 μm submucosa, YGC = young gastric cancer.
* $\chi^2$ test.
† *t* test.

the absolute and extended indications for endoscopic resection. However, all of these patients were referred to surgery because of patient's concerns. In the absolute group, both of the patients were LNM negative. But in the expanded group, we can see that each group had 1 LNM positive patient, and detailed clinicopathological characteristics of 13 patients are shown in Table 5.

## 4. Discussion

In this study, we compared the clinicopathological features of EGC in patients younger than 40 years of age to those older than 40 years of age. YGC patients were further divided into 2 groups based on LNM. In the LN positive group, deeper invasion depth, more LVI, and decreased E-cadherin expression were observed. Multivariate analysis revealed that LVI was the only independent risk factor for LNM in the younger cohort. In terms of endoscopic treatment indications in this group, we confirmed that YGC patients fulfilling absolute indications for endoscopic resection had no LNM risk, whereas for those within extended indications, appropriate treatment should be cautiously chosen due to a potentially increased risk of LNM.

**Table 3**

**Multivariate analysis of LNM risk factors for early YGCs.**

| Factors | Odds ratio (95% CI) | *P* value* |
|---|---|---|
| LVI | 17.740 (1.458–215.843) | .024 |
| Invasion depth | 1.549 (0.557–4.312) | .402 |
| E-cadherin expression | 1.328 (0.516–3.420) | .556 |

LVI = lymphovascular invasion, YGC = young gastric cancer.
* Multivariate logistic regression analysis.

**Table 4**

**LNM in cases fulfilling absolute or expanded indication for endoscopic treatment.**

| Categories | Indication | LNM rate |
|---|---|---|
| Differentiated, UL (−), T1a, ≤2 cm | Absolute | 0/2 |
| Differentiated, UL (−), T1a, >2 cm | Expanded | 1/4 (case 4*) |
| Differentiated, UL (+), T1a, ≤3 cm | Expanded | 1/1 (case 7) |
| Undifferentiated, UL (−), T1a, ≤2 cm | Expanded | 1/6 (case 13) |

LNM = lymph node metastasis, LNM rate = numbers of patients with LNM/number of overall patients.
* Case number was indicated as in Table 5.

Previous reports showed the overall risk of LNM ranged from 1.4% to 5.2% for mucosal cancers, and 15% to 21.4% for submucosal cancers.[26–28] Although in our cohort, the LNM rate of early YGC rose up to 27.6% (8/29) for T1a lesions and 43.7% (7/16) for T1b lesions, which is much higher than that have been reported, the overall LNM risk in the older cohort was 13%, which is in agreement with previous studies.[29] Takatsu et al[5] reported that more YGC patients had involvement of 7 or more lymph nodes and suggested that the presence of LNM was a strong risk factor for their tumor recurrence and a strict follow-up should be adhered to for YGCs. However, other studies found no difference in LNM rate between younger and older patients.[12,30,31]

Many scoring systems[29,32,33] have been published in recent years to assess LNM risk in EGC. Fang et al[29] found that female gender, diffuse type, poorly cohesive carcinoma, and LVI were independent risk factors for early distal GC. Kim et al[33] developed a nodal predicting index for submucosal GCs, which involved LVI, submucosal invasion width and depth, as well as infiltrative growth pattern, whereas Pyo et al[32] focused on mucosal-confined signet ring cell carcinoma (SRCC), known to have higher LNM rate. They found that tumor size larger than 1.7 cm, elevated macroscopic type, and LVI were strongly related to LNM. After assigning scores for each item, the cutoff value of 2 yielded an overall diagnostic accuracy of 96%. In our study, we found LVI to be the only independent risk factor for early YGC, which was also mentioned by most studies.[19,33] Apart from taking clinicopathological factors into consideration, a recent study[34] developed a new prediction nomogram, which involved CD44v6 overexpression accompanied by clinicopathological features (larger tumor size, undifferentiated type, and submucosal invasion), with further in vitro studies confirming the role of CD44v6 in cell migration and invasion. So a combination of clinical, pathological, imaging, and molecular modalities should be used in predicting LNM of EGCs before determining the most appropriate treatment plans.[3]

Histologically, most young GC patients have undifferentiated carcinoma, including SRCC, mucinous carcinoma, and poorly differentiated carcinoma. Mixed type was also common in young GC patients.[7,31] As reported previously,[5,20,35] well-differentiated, Lauren intestinal type GC originates from atrophic, IM mucosa, whereas undifferentiated, diffuse type GC originates from foveolar cells of gastric fundic glands, extending laterally along the proliferative zone. Theoretically, young patients should have less atrophy and IM than older GC patients, but in our study, as much as 82% to 84% of early YGC had gastric atrophy

**Table 5**

**Clinicopathological features of 13 cases within endoscopic treatment indications.**

| Case | Age | Gender | Location | Size | Gross type | *Hp* | Differentiation | LVI | Ulceration | LNM |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 32 | F | Antrum | 0.5 | IIc | – | Differentiated | – | – | 0/18 |
| 2 | 38 | M | Antrum | 1.6 | IIb | + | Differentiated | – | – | 0/10 |
| 3 | 36 | F | Incidura | 3.0 | IIb | + | Differentiated | – | – | 0/34 |
| 4 | 40 | F | Antrum | 3.5 | IIb | + | Differentiated | – | – | 3/19 |
| 5 | 23 | M | Incidura | 3.0 | IIb | + | Differentiated | – | – | 0/29 |
| 6 | 30 | F | Body | 3.5 | IIb | + | Differentiated | – | – | 0/24 |
| 7 | 37 | M | Antrum | 2.5 | IIc | + | Differentiated | – | + | 8/21 |
| 8 | 33 | M | Antrum | 0.3 | IIb | – | Undifferentiated | – | – | 0/13 |
| 9 | 36 | F | Antrum | 0.6 | IIb | + | Undifferentiated | – | – | 0/15 |
| 10 | 32 | F | Antrum | 0.6 | IIa | + | Undifferentiated | – | – | 0/19 |
| 11 | 27 | M | Antrum | 1.0 | IIc | + | Undifferentiated | – | – | 0/20 |
| 12 | 31 | F | Body | 1.3 | IIc | + | Undifferentiated | – | – | 0/20 |
| 13 | 25 | F | Pylori | 1.7 | IIc | + | Undifferentiated | – | – | 1/16 |

*Hp* = *H pylori*, LNM = lymph node metastasis, LVI = lymphovascular invasion.

and IM, which was still lower than the older cohort (92–94%). We can also see that *Hp* infection rate in these patients was as high as 75.6%. According to the consensus statement regarding *Hp* in China,[36] we recommend *Hp* eradication in patients younger than 45 years without alarming features, with the treatment plan including a regular dose of proton pump inhibitors (PPI), 2 antibiotics and colloidal bismuth subcitrate. But a problem lies in that most of these young patients have not had an endoscopy or previously been tested for *Hp* infection. The true mechanism of the prevalence of undifferentiated type of GC in the younger cohort remains to be solved. Besides, undifferentiated GC infiltrates in a vertical manner, so lymph node involvement would be more likely. However, most studies[37–39] have confirmed ESD as a feasible treatment modality for undifferentiated GC within extended criteria, which yields higher complete and curative resection rates. In undifferentiated GC, many studies have reported that SRCC has more favorable clinicopathological characteristics than other undifferentiated types.[37,40] Choi et al[37] reported that the complete resection rate was higher in SRCC than in poorly differentiated carcinoma, 89.3% versus 75%, but the rate was not statistically significant. Kim et al[40] also reported that the en-bloc and complete resection rates of SRCC were slightly higher than poorly differentiated type. Ha et al[41] found SRCC was more common in young female patients and the LNM rate of SRCC was lower than other undifferentiated GC. In our study, 3 patients fulfilling expanded criteria for endoscopic resection were positive for LNM. We attribute this to the fact that the GCs in younger patients exhibit unique biological features compared to traditional GC, with higher potential for metastasis, suggesting that YGC should be stringently managed.

Perineural invasion (PNI) was reported to be associated with poor outcome and recurrence.[42] Scartozzi et al[43] further analyzed a subgroup of EGC patients with or without LVI/PNI, and confirmed the role of LVI/PNI in patients disease-free survival (DFS) and overall survival (OS). However, in our study, PNI of YGC was significantly lower than that of OGC, a seemingly conflicting result. However, previous reports have shown that YGC had better prognosis than OGC,[30] and other reports have also indicated that poor prognosis of YGC was a result of delayed diagnosis.[44] From here we can see that the lower rate of PNI of YGC maybe one of the reasons for better prognosis, which was consistent with our findings. There may be interobserver differences in the identification of PNI, due to differences in the amount of tissue obtained and amount of time taken to analyze histological sections. So, a larger cohort of younger patients with EGC is warranted.

Recently, studies[28,45,46] have focused on histological mixed-type, which was related to more aggressive biological behavior and poorer outcomes. In our study, 40% of early YGC had mixed-type, much higher than their older counterparts (40% vs 8%). And in the LN positive group of early YGC, 53.3% were mixed-type, slightly higher than in LN negative group, although this difference was not statistically significant ($P = .230$). Compared to the patients with GCs of intestinal and diffuse type, mixed type GC requires consideration of different management and likely closer follow-up. Takizawa et al[45] reported that mixed predominantly undifferentiated type had more LNM than pure undifferentiated intramucosal cancers (19.0% vs 6.0%). Hwang at al[28] also suggested the same trend (20.2% vs 9.3%), and the LNM risk of mixed-type depends on the proportion of the poorly differentiated component, not the SRCC component. Miyamae et al[46] even suggested mixed-type as an independent risk factor of LNM in submucosal cancer. So a careful clinical assessment after endoscopic resection and follow-up plan of mixed-type GC are essential.

A major limitation of our study is the small study sample. Due to lower prevalence of young gastric cancer (YGC) (3–10% of overall GC) and early stage GC (10–20%) in China, a multicenter cohort study is required in order to obtain larger numbers. In addition, our study is retrospective, involving patients from 2005 to 2015, while endoscopic resection procedures, especially ESD, are becoming more widely accepted treatment for EGC in China over the past 2 years, so a detailed endoscopic report (involving magnifying endoscopy and chromoendoscopy findings) were not available for previous cases, potentially leading to some bias. However, we have started a prospective clinical program involving all YGC patients, with focus on mechanisms of tumorigenesis in this group of patients.

## 5. Conclusions

Significant differences were seen between EGC in younger and older patients, indicating a more aggressive pattern of EGCs in younger patients, especially higher LNM. The only independent risk factor of LNM in this group is LVI. Besides, given the high LNM potential of younger patients with EGC, patients fulfilling extended indications for endoscopic resection should be

stringently assessed with multimethod modalities, and close follow-up plan is warranted.

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