

# The Risk of Lymph Node Metastasis in Early Gastric Cancer Conforming to Indications of Endoscopic Resection and Pylorus-Preserving Gastrectomy: A Single-Center Retrospective Study

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## Research Article

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# Abstract

**Background:** Lymph node metastasis (LNM) status is an important prognostic factor that strongly influences the treatment decision of early gastric cancer (EGC). This study aimed to evaluate the pattern and clinical significance of LNM in EGC.

**Methods:** Patients with EGC who underwent radical gastrectomy were enrolled. Their clinicopathological features, pathological reports, and prognostic data were collected and analyzed.

**Results:** Three hundred fifty-four patients with EGC were enrolled. The incidence of LNM in patients with EGC was 18.36% (65/354). The rates of D1 and D2 station metastases were 12.1% (43/354) and 6.214% (22/354), respectively. The rates of LNM in absolute indication of endoscopic resection and expanded indication were 3.27% (2/61) and 28.55% (4/14), respectively. Skip LNM was observed in 3.67% (13/354) of patients. For those with middle-third EGC, the metastasis rate of the No. 5 lymph node was 3.05% (5/164). The independent risk factors for LNM were tumors measuring >30 mm, poorly differentiated tumors, and lymphovascular invasion (all  $P < 0.05$ ; area under the curve = 0.783). Five-year disease-free survival rates of patients with EGC with and without LNM were 96.26% and 79.17%, respectively ( $P = 0.011$ ). Tumors measuring >20 mm and LNM were independent predictive factors for poor survival outcome in patients with EGC.

**Conclusions:** Patients with EGC conforming to expanded indications have a relatively high risk of LNM and may not be suitable for endoscopic submucosal dissection. Pylorus-preserving gastrectomy for patients with middle-third EGC remains controversial due to the high metastasis rate of the No. 5 lymph node.

## Background

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related mortality worldwide. In 2018, GC was responsible for over 1,000,000 new cases and an estimated 783,000 deaths globally [1]. About 75% of cases appeared in Asia, particularly in China, Korea, and Japan. China accounted for 50% of the new cases [2]. Over the past several decades, these Eastern Asian countries made great efforts to prolong the survival time and improve the quality of life of patients with GC. One of the great achievements is the improvement of screening strategies for early gastric cancer (EGC) detection. It has been reported that the detection rate of EGC has increased to 61% in Korea [1].

EGC has been defined as a cancer confined to the mucosa or submucosa layer of the stomach, regardless of lymph node metastasis (LNM) [2]. Compared to advanced GC, EGC has a high 5-year survival rate, up to 99%. D2 lymphadenectomy with gastrectomy has been the standard surgical procedure for every stage of GC. The treatment decision for EGC seems complicated, diversified, and controversial compared with that of advanced GC. According to the 2018 Japanese GC treatment guidelines [3], minimally invasive endoscopic resection (ER), such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), have been recommended as alternative curative

treatments for patients with EGC with indications. In addition to ER treatment, some modified surgical procedures such as pylorus-preserving gastrectomy (PPG), segmental gastrectomy, and local resection can be considered for EGC with a low risk of LNM and are not suitable for EMR/ESD to improve quality of life.

LNM status is an important prognostic factor of EGC [4–6]. According to the 2018 Japanese GC treatment guidelines [3], the choice of ER for EGC treatment is mainly dependent on the risk of LNM. LNM in EGC within absolute indications for EMR or ESD has been hypothesized to be negligible (less than 1%). Currently, ESD is widely used as a standard method for EGC in Japan, and its indications are expanded. However, several problems remain. First, although most evidence suggests that the risk of LNM in patients with absolute indications is negligible, the results between these studies have been inconsistent [3]. Second, the expanded indications for ESD are still controversial. Third, the management of cases with noncurative resection after ER has been controversial. Fourth, whether ER treatment is superior or not inferior to traditional D2 lymphadenectomy with gastrectomy in terms of long-term outcomes is still unclear.

Furthermore, skip LNM in GC refers to the presence of extraperi-gastric lymph node involvement without peri-gastric LNM [7]. Some studies have revealed that skip metastasis occurs frequently in cases of GC [7–10]. The existence of skip LNM may seriously influence the treatment decision of EGC. Therefore, a better understanding of the precise pattern of LNM in patients with EGC is important.

There have been relatively few studies on the positive rate of each lymph node station and skip metastasis in EGC [7–11]. In the present study, we aimed to elucidate the precise distribution of LNM in EGC by analyzing the metastasis status of each lymph node station in patients with EGC who underwent D2 lymphadenectomy with gastrectomy and to explore the clinical significance of LNM pattern and skip metastasis in making treatment decisions for EGC.

## Methods

### Patient cohort and data collection

The clinicopathological data of patients (n = 2,245) who underwent radical gastrectomy at the First Affiliated Hospital of Sun Yat-Sen University (January 2010 to December 2018) were retrospectively analyzed. All clinicopathologic data, including age, sex, tumor location, tumor size, histology classification, lymphovascular invasion (LVI), depth of tumor invasion, and LNM were drawn from hospital and pathological records. This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University and conducted in accordance with the principles of the Declaration of Helsinki. The need for informed consent for participation and for approval of all patients was waived.

### Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the depth of invasion was diagnosed as carcinoma in situ (Tis), mucosa (T1a), or submucosa (T1b); and (2) no distant metastasis. Patients were excluded if they had (1) received neoadjuvant therapy or (2) incomplete clinicopathologic information (Fig. 1).

Three hundred fifty-four cases histologically proven to be EGC following the inclusion and exclusion criteria were enrolled (Fig. 1). All patients with EGC were divided into the LNM+ group (n = 65, LNM+: the presence of LNM) or LNM- group (n = 289, LNM-: the absence of LNM). To analyze the LNM rate for the patients with EGC selected by the indications of ESD/EMR, all patients were also divided into four different groups according the absolute and expanded indications of ESD/EMR (Table 1). For submucosal invasive (T1b) EGC, the LNM status was analyzed according to two conditions ( $\leq 2$  cm, differentiated type;  $\leq 2$  cm, undifferentiated type) (Table 1).

## Follow-up

All patients included in this study were regularly followed up using a standardized protocol. Follow-up assessment included abdominal ultrasonography, computed tomography (CT) imaging (of the chest, abdomen and pelvis), and tumor marker tests (including cancer antigen [CA]-19-9, carcinoembryonic antigen [CEA], CA125, squamous cell carcinoma) at each visit. Deaths due to cancer were recorded as events, and deaths secondary to other causes were censored.

## Statistical analysis

All statistical analyses were conducted using the SPSS 24.0 statistical package (IBM Inc., New York) and R (<https://www.r-project.org/>). Continuous variables are described as the mean and standard deviation, and an analysis of variance test was used to compare continuous variables. For categorical variables, Pearson's chi-square test or Fisher's exact test was used to compare the differences between patient groups. Univariate and multivariate logistic regression models, in which all covariates were adjusted simultaneously, was used to determine independent risk factors for LNM in EGC. Kaplan–Meier curves were plotted to evaluate survival outcomes in patients with EGC, and comparisons of prognostic differences between patient groups were performed using the log-rank test. Independent prognostic factors were identified by multivariate analysis using the Cox proportional-hazard model with a stepwise selection procedure. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to quantify the relationship between survival outcome and each clinicopathologic factor. Statistical significance was accepted at a P value < 0.05.

## Results

### The metastasis status of different lymph node groups in patients with EGC

A total of 2,245 patients with GC who underwent radical gastrectomy with lymphadenectomy at the First Affiliated Hospital of Sun Yat-Sen University between January 1, 2010 and December 31, 2018 were reviewed retrospectively. Three hundred fifty-four cases histologically proven to be EGC following the

inclusion and exclusion criteria were enrolled for the next analysis. Among these 354 cases, there were 27 cases of upper-third EGC, 136 of middle-third EGC, and 142 of low-third EGC.

In this study, the incidence of LNM in EGC was 18.36% (65/354). In order to elucidate the role of LNM in EGC further, we analyzed the positive rate (Table 2) and location distribution (Table 3) of LNM for each lymph node station. As shown in Table 2, the positive rates of No. 3, No. 4, and No. 6 lymph nodes were 4.80%, 3.67%, and 3.95%, respectively, regardless of the tumor location. For tumors located in the upper-third of the stomach with LNM ( $n = 6$ ), the No. 2 and No. 3 lymph nodes had high positive rates of LNM (Table 3). For tumors in the middle-third of the stomach ( $n = 28$ ), No. 3, No. 4, No. 5, and No. 6 LNs had the highest positive rates of LNM. For tumors in the lower third of the stomach, the No. 3 and No. 6 lymph node stations had the highest metastasis rates.

### **Clinicopathological characteristics of patients with EGC according to LNM**

As shown in Table 4, the current study consisted of 224 male patients (63.27%) and 130 female patients (36.72%), with a median age of  $57.50 \pm 11.399$  years (range, 24–85 years). Among these 354 patients, 35 (9.89%) had tumors located in the upper third of the stomach, 165 (46.61%) had tumors located in the middle third of the stomach, and 175 (49.43%) had tumors located in the lower third of the stomach. The mean length and short diameter of the tumor were  $2.254 \pm 1.344$  cm and  $1.808 \pm 1.184$  cm, respectively. Postoperative pathology indicated LVI in 16 cases (4.52%) and poorly differentiated tumors in 185 cases (52.26%). The average number of lymph node dissections was  $37.64 \pm 23.203$ .

There were 61.58% (218/354) patients with intra-mucosal invasion (including Tis and T1a) and 38.41% (136/354) patients with submucosa (T1b) invasion. The percentages of LNM positivity were 12.38% (27/218) in the Tis/T1a group and 27.94% (38/136) in the T1b group ( $P < 0.001$ ) (Table 4). There was no significant difference in the mean age of patients between the two groups, but there was a significant difference between patients aged  $<40$  years and those aged  $\geq 40$  years ( $P=0.006$ ), suggesting that young patients have a higher risk of LNM (risk ratio [RR] = 2.297; 95% CI, 1.333–3.947). Tumor sizes were significantly larger for LNM+ than LNM- ( $P = 0.009$ ). Compared with LNM-, tumor invasion was deeper ( $P < 0.001$ ; RR = 2.256; 95% CI, 1.447–3.518) and showed poor differentiation ( $P < 0.001$ ; RR = 3.328; 95% CI, 1.914–5.787) in LNM+. However, the distribution of other variables including sex, body mass index, tumor marker, and tumor location were similar between the LNM- and LNM+ groups.

### **Univariable and multivariable analysis of LNM in EGC**

The univariable analysis showed that LNM was closely related to age ( $<40$  years), tumor size ( $>3$  cm), depth of invasion (T1b), poor differentiation, and LVI (all  $P < 0.05$ , Table 5). Multivariate analysis showed that tumor size (odds ratio [OR] = 2.948; 95% CI, 1.480–5.872;  $P = 0.002$ ), poor differentiation (OR = 5.879; 95% CI, 2.536–13.628;  $P = 0.001$ ), and LVI (OR = 14.569; 95% CI, 2.493–85.135;  $P = 0.001$ ) were independent predictors for LNM (Table 5). However, age and depth of invasion were not independent predictors of LNM. The receiver operating characteristic (ROC) curve (Fig. 2) was used to validate this

multivariable regression model. This model showed an area under the curve (AUC) of 0.782. Figure 3 presents a nomogram for the prediction of LNM that was constructed based on the selected variables.

### **Correlation factors analysis of the extent of LNM in EGC**

The rates of D1 station metastasis and D2 station metastasis in patients with EGC were 12.1% (43/354) and 6.214% (22/354), respectively (Table 6). An analysis of the clinical pathological characteristics was performed on patients with D1 station or D2 station LNM. There was no significant difference between the occurrence of D2 station LNM and the age, sex, tumor size, differentiation, location, depth of tumor invasion, and LVI. The levels of CA 19-9 and CEA were significantly different between the two groups (10.113 vs. 30.125 U/mL,  $P = 0.001$  and 3.189 vs. 6.861 U/mL, respectively;  $P = 0.003$ ). However, the difference in CA 125 was not significant (Table 6).

### **Analysis of the clinicopathological characteristics of patients with EGC with skip metastasis**

According to the Japanese classification of gastric carcinoma (3rd edition) [12] and the definition of skip metastasis, patients with LNM ( $n = 65$ ) were classified into a no skip metastasis group ( $n = 52$ ) or a skip metastasis group ( $n = 13$ ). The possibility of skip metastasis was 3.67% (13/354) in all patients with EGC. There was no significant difference between the two groups with respect to clinicopathological characteristics (Table 7).

### **Univariate and multivariate analyses of prognostic factors in patients with EGC**

The 5-year survival rates of EGC between the LNM- and LNM+ groups were 96.26% and 79.17%, respectively ( $P = 0.011$ ) (Table 4). The prognostic outcome of patients who were LNM+ was worse than that of LNM- patients ( $P = 0.008$ ) (Fig. 4). The results of the univariate and multivariate analyses for prognostic factors are listed in Table 8. Tumor size (HR, 3.473; 95% CI, 1.372–8.791;  $P = 0.009$ ) and LNM (HR, 4.895; 95% CI, 1.588–15.095;  $P = 0.006$ ) were independent predictive factors for poor survival outcome in patients with EGC.

### **LNM rate in patients with EGC selected by the indications of ESD/EMR**

The 2018 Japanese GC treatment guidelines [3] revealed that the indication for ER depends on the depth of invasion, differentiation type, diameter, and ulcerative findings. The LNM rates of these factors are demonstrated in Table 4. All patients with EGC ( $n = 354$ ) were analyzed according to the absolute and expanded indications of ESD/EMR (Table 1), and only 75 (21.18%) patients conformed to the absolute and expanded indications of ESD/EMR. The rates of LNM in absolute and expanded indications were 2/61 (3.27%) and 4/14 (28.55%), respectively. Subgroup analysis showed that the rates of LNM with respect to the absolute indication of EMR/ESD and absolute indication of ESD 2 group were 0%. The rate of LNM with respect to the absolute indication of the ESD 1 group was 20%. For the submucosal invasive (T1b) EGC, the LNM status was analyzed with two conditions ( $\leq 2$  cm, differentiated type: 7.40%;  $\leq 2$  cm, undifferentiated type: 35.375%), which was consistent with the outcome of the multivariable logistic analysis (Table 5).

## Discussion

EGC was first defined in 1962 by the Japanese Research Society for Gastric Cancer as tumors with invasion limited to the mucosa or submucosa of the stomach, irrespective of lymph node involvement [2]. In the 8th American Joint Committee on Cancer TNM staging system, EGC corresponds to GC with Tis, T1a (mucosa), and T1b (submucosa) stages [13]. Recently, the treatment techniques and strategies for EGC have been updated rapidly. According to the latest Japanese GC treatment guidelines (5th version) [3], EMR or ESD is considered as a standard treatment for patients with EGC with absolute indications and an alternative treatment for EGC with expanded indications. With the development and prevalence of ER (ESD and EMR), the criteria for the indications of ER for EGC have continually expanded. However, there is debate as to whether ER can be used in patients with expanded indications.

Although the 2018 Japanese GC treatment guidelines declared that the possibility of harboring LNM in the tumor with absolute indication is less than 1%. However, most of the data referred to in the guidelines were from Japan [3]. It is still unclear whether the data can be extrapolated to other countries. Here, we revealed that the incidence of LNM in patients with EGC, which confirmed the absolute or expanded indications of ESD/EMR, was obviously higher than that in the Japanese cohort [2, 14–16]. The rates of LNM in the absolute indication of the ESD 1 group (20%) and expanded indication group (28.55%) were obviously higher than 1%. In addition, a meta review [2] in 2018 indicated that the incidence rate of LNM was 2.6% (25/972) in patients who met the expanded criteria. Moreover, a Korean study [17] in 2020 reported that LNMs were found in 6.7% (18/270) of patients with undifferentiated-type EGC who underwent additional surgery after non-curative endoscopic resection. Therefore, caution should be exercised before applying ESD to patients with undifferentiated-type adenocarcinoma and those with tumors bigger than 2 cm despite T1a and differentiated-type adenocarcinoma without ulcerative findings. Further studies are urgently needed to find new methods to distinguish populations with high risk of LNM from EGC conforming to the indications of ER.

It is worth mentioning that the sample size of this study was small. We screened for desirable cases from 2,245 cases of gastric cancer. However, only 15.77% of patients with GC were diagnosed with EGC in our center. The data were consistent with the results of other centers in China. The proportion of cases of EGC in China varies from 10–20%, compared to about 50% in Japan [18, 19]. Moreover, only 21.18% of patients with EGC conformed to the absolute and expanded indications of ESD/EMR in this study. Therefore, more data are needed to draw a firm conclusion.

The Japanese Gastric Cancer Association guidelines suggested a gastrectomy procedure with D1/D1 + lymph node dissection as the standard surgical procedure for cases in which the depth of invasion is clinically diagnosed as T1b without LNM and T1a without LNM, which are not suitable for EMR and ESD. However, our data showed that the rate of D2 LNM in EGC was 6.214%. For these cases, the D1 or D1 + dissection is not sufficient. Furthermore, skip LNM is another factor influencing the determination of the extent of lymph node dissection. Skip metastasis in GC refers to the presence of extra-perigastric LNM without peri-gastric lymph node involvement [10]. There have been few studies on the phenomenon of

jump metastasis and its related mechanism in patients with GC, especially those with EGC [7–11, 20]. The incidence of skip metastasis in patients with LNM in EGC has been reported to range from 2.7–21.6% [9, 20, 21]. In this study, the incidence of skip metastasis in patients with LNM was 3.67% (13/354), which is consistent with prior research results. Liu et al. [8] revealed that tumor size was the only clinicopathologic factor that could predict lymph node skip metastasis in patients with N1 stage cancer (the number of metastatic lymph nodes among the regional lymph nodes is 1–2) undergoing radical surgery. However, no significant related clinical characteristics were found for skip metastasis in our study. Considering the relatively high incidences of D2 LNM and skip LNM in EGC, it is not suitable for these patients to receive D1 or D1 + dissection. Therefore, the identification of these high-risk portions from EGC is urgently needed so that the patients can undergo radical lymphadenectomy.

Regarding the extent of gastric resection, the Japanese GC treatment guidelines have revealed that the standard surgical procedure for cN+ or T2–T4a tumor is total or distal gastrectomy. For cT1N0 tumors, PPG and proximal gastrectomy can be considered depending on the tumor position. PPG is a less-invasive function-preserving procedure that has been applied for the cT1N0M0 middle-third EGC with a distal tumor border at least 4 cm proximal to the pylorus according to the Japanese GC treatment guidelines [3]. The survival and recovery benefits of PPG have already been reported in several retrospective studies [22–24]. However, PPG remains controversial. One of the reasons is that the dissection of the No. 5 lymph node may be incomplete in PPG because the pyloric branches of the vagus nerve are kept to reduce postoperative gastric stasis complications. In previous studies, it was reported that the metastasis rate of No. 5 lymph node in middle-third EGC was only 0.5% [25]. Kong et al. [26] reported that the metastasis rate of the No. 5 lymph node in middle-third EGC with a distal tumor border at least 6 cm proximal to the pylorus was 0% in T1a stage and 0.9% in T1b stage EGC. However, the metastasis rate of the No. 5 lymph node was 3.03% (5/165) for the middle-third EGC in this study (Table 2 and Table 3), which was similar to the result of Seung et al. [27], who reported that the metastasis rate to the No. 5 lymph nodes was 4.2% (52/1245). Seung et al. [27] also pointed out that the presence or absence of metastasis in the No. 5 and No. 6 lymph nodes should be carefully evaluated preoperatively using endoscopic ultrasonography and CT. Therefore, caution should be exercised before performing PPG for EGC given that the risk of No. 5 LNM is high according to our data. Further prospective studies using large case series are necessary to confirm this conclusion. It is worth mentioning that PPG should be performed for GC located in the middle third of the stomach and at least 4.0 cm away from the pylorus according to the guidelines. However, information about the distance from the tumor to the pylorus was unavailable in our database. This limitation weakens our conclusion.

LNM is one of the most important factors influencing the prognosis of EGC. The risk of LNM is a major concern in choosing the optimal treatment for EGC. According to previous studies, the incidence of LNM in patients with EGC regardless of T1a or T1b was 15–24% [28, 29]. Recently, Chen et al. reported that the LNM rate was 16.7% in EGC (8.7% in T1a, 24.6% in T1b) in their retrospective study that enrolled 1,033 patients with EGC [30]. In agreement with results of previously reported studies, our data showed that the incidence rates of LNM were 12.38% in T1a stage, 27.94% in T1b stage, and 18.36% in whole EGC. Classifying the low and high risks of LNM in patients with EGC is important in EGC studies.

A number of studies have identified the risk factors associated with LNM in EGC [20, 31–35]. They also revealed that LNM in EGC is related to differentiation, tumor size, depth of invasion, and LVI, which is consistent with the results of this study (Table 5). The AUC of the ROC curve (Fig. 2), which validated this multivariable regression model, was 0.783 in this study. In other studies on the prediction of LNM with clinicopathological characteristics, the AUCs of the ROC curves were about 0.69–0.86 [32, 36, 37]. Similarly, the 2018 Japanese GC treatment guidelines [3] predicted the risk of LNM in EGC according to the clinicopathological characteristics including histological types (ulcerative findings), and tumor sizes < 2 cm (non-ulcerative) and < 3 cm (ulcerative). However, the prediction of LNM in EGC by these factors is still not ideal given that the incidence risk of LNM was high in the population of patients with EGC with absolute or expanded indication, as shown in this study. The prediction of LNM in EGC based only on the current routine detection items and pathological examination may not be reliable. Hence, the discovery of more factors that could more accurately predict LNM is still a research interest in the field of EGC. Finally, this study also analyzed the prognosis of patients with EGC and revealed that patients with LNM had a worse prognosis (Fig. 4).

## Conclusions

In summary, the risks of LNM were high in patients with EGC with undifferentiated-type adenocarcinoma and with > 2-cm tumor and expanded indications of ER. In addition, PPG remains controversial due to the high metastasis rate of the No. 5 LN in the patients with middle-third EGC. Hence, physicians should be cautious when choosing a minimally invasive treatment (e.g., EMR, ESD, or PPG) that could carry a risk if the dissection of metastatic lymph nodes is neglected.

## Abbreviations

EGC

early gastric cancer, GC:gastric cancer, LNM:lymph node metastasis, LVI:lymphovascular invasion, EMR:endoscopic mucosal resection, ESD:endoscopic submucosal dissection, PPG:pylorus-preserving gastrectomy, CA:cancer antigen, CEA:carcinoembryonic antigen, HR:hazard ratio, CI:confidence interval, OR:odds ratio, ER:endoscopic resection, RR:risk ratio, ROC:receiver operating characteristic, AUC:area under the curve, CT:computed tomography

## Declarations

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University and was conducted in accordance with the principles of the Declaration of Helsinki. The need for informed consent to participate and for approval of all patients was waived.

### Consent to publish

Not applicable.

## Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

WYZ and WZX extracted the data from and wrote the draft. WYX, WZX, ZZH, and LGH performed the analysis. WYZ and WZ designed the project. WZ and LGH revised the project. All authors have read and approved the final manuscript.

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## References

1. Information Committee of Korean Gastric Cancer Association. Korean gastric cancer association nationwide survey on gastric cancer in 2014. *J Gastric Cancer*. 2016;16:131–40.
2. Abdelfatah MM, Barakat M, Lee H, Kim JJ, Uedo N, Grimm I, et al. The incidence of lymph node metastasis in early gastric cancer according to the expanded criteria in comparison with the absolute criteria of the Japanese Gastric Cancer Association: a systematic review of the literature and meta-analysis. *Gastrointest Endosc*. 2018;87:338–47.
3. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer*. 2020; doi:10.1007/s10120-020-01042-y.
4. Kim JP, Kim YW, Yang HK, Noh DY. Significant prognostic factors by multivariate analysis of 3926 gastric cancer patients. *World J Surg*. 1994;18:872–7; discussion 877-8.
5. Adachi Y, Mori M, Maehara Y, Sugimachi K. Dukes's classification: a valid prognostic indicator for gastric cancer. *Gut*. 1994;35:1368–71.
6. Bozzetti F, Bonfanti G, Morabito A, Bufalino R, Menotti V, Andreola S, et al. A multifactorial approach for the prognosis of patients with carcinoma of the stomach after curative resection. *Surg Gynecol*

- Obstet. 1986;162:229–34.
7. Kim DH, Choi MG, Noh JH, Sohn TS, Bae JM, Kim S. Clinical significance of skip lymph node metastasis in gastric cancer patients. *Eur J Surg Oncol*. 2015;41:339–45.
  8. Liu JY, Deng JY, Zhang NN, Liu HF, Sun WL, He WT, et al. Clinical significance of skip lymph-node metastasis in pN1 gastric-cancer patients after curative surgery. *Gastroenterol Rep*. 2019;7:193–8.
  9. Lee SE, Lee JH, Ryu KW, Cho SJ, Lee JY, Kim CG, et al. Sentinel node mapping and skip metastases in patients with early gastric cancer. *Ann Surg Oncol*. 2009;16:603–8.
  10. Choi YY, An JY, Guner A, Kang DR, Cho I, Kwon IG, et al. Skip lymph node metastasis in gastric cancer: is it skipping or skipped? *Gastric Cancer*. 2016;19:206–15.
  11. Zhao B, Mei D, Zhang J, Luo R, Lu H, Xu H, et al. Impact of skip lymph node metastasis on the prognosis of gastric cancer patients who underwent curative gastrectomy. *J BUON*. 2019;24:693–700.
  12. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer*. 2011;14:101–12.
  13. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin*. 2017;67:93–9.
  14. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer*. 2000;3:219–25.
  15. Hirasawa T, Gotoda T, Miyata S, Kato Y, Shimoda T, Taniguchi H, et al. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. *Gastric Cancer*. 2009;12:148–52.
  16. Abdelfatah MM, Barakat M, Othman MO, Grimm IS, Uedo N. The incidence of lymph node metastasis in submucosal early gastric cancer according to the expanded criteria: a systematic review. *Surg Endosc*. 2019;33:26–32.
  17. Yang HJ, Jang JY, Kim SG, Ahn JY, Nam SY, Kim JH, et al. Risk factors of lymph node metastasis after non-curative endoscopic resection of undifferentiated-type early gastric cancer. *Gastric Cancer*. 2020; doi:10.1007/s10120-020-01103-2.
  18. Zong L, Abe M, Seto Y, Ji J. The challenge of screening for early gastric cancer in China. *Lancet*. 2016;388:2606.
  19. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66:115–32.
  20. Su Z, Shu K, Zheng M, Sun X, Fang Z, Wang G. Sentinel lymph node and skip metastases in gastric cancer: a prospective study. *Hepatogastroenterology*. 2013;60:1513–8.
  21. Sowa M, Kato Y, Nishimura M, Kubo T, Maekawa H, Umeyama K. Surgical approach to early gastric cancer with lymph node metastasis. *World J Surg*. 1989;13:630–5; discussion 635-6.

22. Huang C, Yu F, Zhao G, Xia X. Postoperative quality of life after laparoscopy-assisted pylorus-preserving gastrectomy compared with laparoscopy-assisted distal gastrectomy for early gastric cancer. *J Gastroenterol Hepatol*. 2020;35:1712–9.
23. Mao X, Xu X, Zhu H, Ji C, Lu X, Wang B. A comparison between pylorus-preserving and distal gastrectomy in surgical safety and functional benefit with gastric cancer: a systematic review and meta-analysis. *World J Surg Oncol*. 2020;18:160.
24. Eom BW, Park B, Yoon HM, Ryu KW, Kim YW. Laparoscopy-assisted pylorus-preserving gastrectomy for early gastric cancer: A retrospective study of long-term functional outcomes and quality of life. *World J Gastroenterol*. 2019;25:5494–504.
25. Nunobe S, Hiki N, Fukunaga T, Tokunaga M, Ohyama S, Seto Y, et al. Laparoscopy-assisted pylorus-preserving gastrectomy: preservation of vagus nerve and infrapyloric blood flow induces less stasis. *World J Surg*. 2007;31:2335–40.
26. Kong SH, Kim JW, Lee HJ, Kim WH, Lee KU, Yang HK. The safety of the dissection of lymph node stations 5 and 6 in pylorus-preserving gastrectomy. *Ann Surg Oncol*. 2009;16:3252–8.
27. Oh SY, Lee HJ, Yang HK. Pylorus-preserving gastrectomy for gastric cancer. *J Gastric Cancer*. 2016;16:63–71.
28. Barreto SG, Windsor JA. Redefining early gastric cancer. *Surg Endosc*. 2016;30:24–37.
29. Park DJ, Lee HK, Lee HJ, Lee HS, Kim WH, Yang HK, et al. Lymph node metastasis in early gastric cancer with submucosal invasion: feasibility of minimally invasive surgery. *World J Gastroenterol*. 2004;10:3549–352.
30. Chen J, Zhao G, Wang Y. Analysis of lymph node metastasis in early gastric cancer: a single institutional experience from China. *World J Surg Oncol*. 2020;18:57.
31. Zhao B, Huang R, Lu H, Mei D, Bao S, Xu H, et al. Risk of lymph node metastasis and prognostic outcome in early gastric cancer patients with mixed histologic type. *Curr Probl Cancer*. 2020;44:100579.
32. Kim SM, Min BH, Ahn JH, Jung SH, An JY, Choi MG, et al. Nomogram to predict lymph node metastasis in patients with early gastric cancer: a useful clinical tool to reduce gastrectomy after endoscopic resection. *Endoscopy*. 2020;52:435–43.
33. Sugita S, Kinoshita T, Kuwata T, Tokunaga M, Kaito A, Watanabe M, et al. Intramucosal-lymphatic invasion has a slight impact on lymph node metastasis in patients with early gastric cancer. *Surg Today*. 2020;50:484–9.
34. Ishigami S, Natsugoe S, Hokita S, Tokushige M, Saihara T, Watanabe T, et al. Carcinomatous lymphatic invasion in early gastric cancer invading into the submucosa. *Ann Surg Oncol*. 1999;6:286–9.
35. Wang Z, Ma L, Zhang XM, Zhou ZX. Risk of lymph node metastases from early gastric cancer in relation to depth of invasion: experience in a single institution. *Asian Pac J Cancer*. 2014;15:5371–5.
36. Lin JX, Wang ZK, Wang W, Desiderio J, Xie JW, Wang JB, et al. Risk factors of lymph node metastasis or lymphovascular invasion for early gastric cancer: a practical and effective predictive

model based on international multicenter data. BMC Cancer. 2019;19:1048.

37. Zheng Z, Zhang Y, Zhang L, Li Z, Wu X, Liu Y, et al. A nomogram for predicting the likelihood of lymph node metastasis in early gastric patients. BMC Cancer. 2016;16:92.

## Tables

<b>Table-1</b> LNM rate for the EGC patients selected by the indications of ESD/EMR.			
Conditions	LNM-	LNM+	Metastasis rate
Absolute indication of EMR or ESD*	22	0	0%
Absolute indication of ESD 1*	8	2	20%
Absolute indication of ESD 2*	29	0	0%
Expanded indication*	10	4	28.57%
T1b, ≤2 cm, differentiated-type	25	2	7.40%
T1b, ≤2 cm, undifferentiated-type	21	11	34.375%
<p>*Absolute indication of EMR or ESD: A differentiated-type adenocarcinoma without ulcerative findings (UL0), in which the depth of invasion is clinically diagnosed as T1a and the diameter is ≤2 cm.</p> <p>Absolute indication of ESD 1: A differentiated-type adenocarcinoma without ulcerative findings, in which the depth of invasion is clinically diagnosed as T1a and the diameter is &gt;2 cm.</p> <p>Absolute indication of ESD 2: A differentiated-type adenocarcinoma with ulcerative findings, in which the depth of invasion is clinically diagnosed as T1a and the diameter is ≤3 cm.</p> <p>Expanded indication: An undifferentiated-type adenocarcinoma without ulcerative findings in which the depth of invasion is clinically diagnosed as T1a and the diameter is ≤2 cm.</p>			

**Table-2.** The positive rate of each lymph node station in all EGC patient (n = 354).

Station	Case	Positive rate	Station	Case	Positive rate
No.1	9	2.54%	No.7	10	2.82%
No.2	2	0.56%	No.8	6	1.69%
			No.8a	5	1.41%
			No.8p	1	0.28%
No.3	17	4.80%	No.9	2	0.56%
No.4	13	3.67%	No.10	1	0.28%
No.4sa	6	1.69%			
No.4sb	4	1.13%			
No.4sd	4	1.13%			
No.5	11	3.11%	No.11	2	0.56%
No.6	14	3.95%	No.11p	1	0.28%
			No.11d	1	0.28%
			No.12	3	0.85%

<b>Table-3</b> The distribution of LNM in each station in EGC according to tumor location.			
Station	Upper(n=6 cases)	Middle(n=28 cases)	Lower(n=31 cases)
No.1	1	3	4
No.2	2	0	0
No.3	2	8	7
No.4	1	7	5
No.5	0	5	6
No.6	0	7	7
No.7	1	3	6
No.8	0	1	4
No.8a	0	1	4
No.8p	0	0	0
No.9	0	0	1
No.10	0	0	1
No.11	1	1	0
No.11p	1	0	0
No.11d	0	1	0
No.12	1	1	1

<b>Table-4</b> Clinicopathological characteristics in the LNM- group(n = 289) and LNM+ group (n=65).					
Factor	LNM- (n=289)	LNM+ (n=65)	LNM%	Relative Risk (CI95%)	P-value
<b>Age [year]</b>	56.74 ± 11.084	54.80 ± 12.677			0.301
<b>&lt;40</b>	16	10	38.46%	2.297(1.333-3.947)	0.006
<b>≥40</b>	273	55	16.77%		
<b>Sex</b>					0.373
<b>male</b>	186	38	16.96%		
<b>female</b>	103	27	20.77%		
<b>BMI</b>	21.08± 5.914	21.24± 5.782			0.874
<b>Size (cm)</b>					
<b>Length-diameter</b>	2.091 ± 1.198	2.930 ± 1.689			0.009
<b>Short-diameter</b>	1.713 ± 1.126	2.196 ± 1.342			0.068
<b>&lt;2cm</b>	152	26	14.61%	1.712(0.924-3.174)	0.076
<b>≥2cm</b>	137	39	22.16%		
<b>&lt;3cm</b>	236	39	14.18%	2.496(1.532-4.065)	<0.001
<b>≥3cm</b>	53	26	32.91%		
<b>Tumor marker</b>					
<b>CEA(U/mL)</b>	7.032 ± 81.39	4.394 ± 9.618			0.631
<b>CA125(U/mL)</b>	10.31 ± 9.527	9.995 ± 5.774			0.566
<b>CA199(U/mL)</b>	13.689 ± 59.54	17.703 ± 45.017			0.526
<b>Location</b>					0.765
<b>Upper</b>	27	6	18.18%		
<b>Middle</b>	136	28	17.07%		
<b>Lower</b>	142	31	17.92%		
<b>Depth of invasion</b>					<0.001
<b>Mucosal</b>	191	27	12.38%		

<b>Submucosa</b>	98	38	27.94%	2.256(1.447-3.518)	
<b>Differentiation</b>					
<b>Well/Moderately</b>	155	14	8.28%		<0.001
<b>Poorly</b>	134	51	27.57%	3.328(1.914-5.787)	
<b>Ulcer finding</b>					
<b>Absent</b>	133	36	21.30%		0.172
<b>Present</b>	156	29	15.68%		
<b>Number of lymph node</b>	36.97 ± 24.157	40.63 ± 18.23			0.864
<b>LVI</b>					
<b>Absent</b>	283	55	16.27%		<0.001
<b>Present</b>	6	10	62.5%	3.751(2.422-5.809)	
<b>Recurrence</b>	7	2			
<b>5-year survival rate</b>	96.26%	79.17%			0.011
BMI: body mass index; LNM: Lymph Node Metastasis; LVI: lymphovascular invasion.					
* The 5-year survival rate was the statistical results of survival status of patients with early gastric cancer treated by surgery between January 2010 and March 2015: LNM- 103/107=96.26% LNM+ 19/24=83.33%					

**Table-5: Univariable and multivariable analysis for LNM of EGC patients.**

Factor	Univariable Analysis		Multivariable Analysis	
	OR (CI 95%)	<i>P</i> -value	OR (CI 95%)	<i>P</i> -value
Age(years)				
<40	1			
≥40	0.322(0.139-0.748)	0.008	NA	NA
Tumor size				
<3cm	1			
≥3cm	3.230(1.710-6.101)	<0.001	2.948 (1.480-5.872)	0.002
Depth of invasion				
mucosal	1			
Submucosa	2.743(1.583-4.755)	<0.001	NA	NA
Ulcer				
Absent	1			
Present	0.687(0.400-1.180)	0.173	NA	NA
Differentiation				
Well/Moderately	1			
Poorly	4.214(2.233-7.951)	<0.001	5.879(2.536-13.628)	0.001
LVI				
Absent	1			
Present	8.576(2.993-24.568)	<0.001	14.569(2.493-85.135)	0.001

OR, Odds Ratio, CI, confidence interval, LVI, lymphovascular invasion.

**Table-6:** Clinicopathological characteristics of LNM patients (n=65) in the D1 station metastasis (n = 43) set and D2 station metastasis (n=22) set.

Factor	D1 station*	D2 station*	P-value
Age (years)			
<40	37	18	0.655
≥40	6	4	
Sex			
male	26	12	0.647
female	17	10	
Tumor size			
Length-diameter(cm)	2.938	2.917	0.295
Short-diameter(cm)	2.303	2.000	0.243
<2cm	9	2	0.163
≥2cm	23	16	
<3cm	16	8	0.706
≥3cm	16	10	
Tumor marker			
CEA(U/mL)	3.189	6.861	<b>0.003</b>
CA125(U/mL)	9.702	10.568	0.165
CA199(U/mL)	10.113	30.125	<b>0.001</b>
Tumor location			0.171
Upper	3	3	
Middle	22	6	
Lower	18	13	
Depth of invasion			0.322
Intra-mucosal	16	11	
Submucosa	27	11	
differentiated			

Well-Moderately	8	6	0.421
Poorly	35	16	
LVI			
absent	48	10	0.940
present	9	2	

**\*according to the Japanese gastric cancer treatment guidelines 2018(5th)**

**For Total gastrectomy: D1: No.1-7; D1+: D1 + No.8a, 9, 11p; D2: D1 + No.8a, 9, 11p, 11d, 12a**

**For Distal gastrectomy: D1: No.1, 3, 4sb, 4d, 5, 6, 7; D1+: D1 + No.8a, 9; D2: D1 + 8a, 9, 11p, 12a**

**For pylorus-preserving gastrectomy: D1: No.1, 3, 4sb, 4d, 6, 7; D1+ No. 8a, 9.**

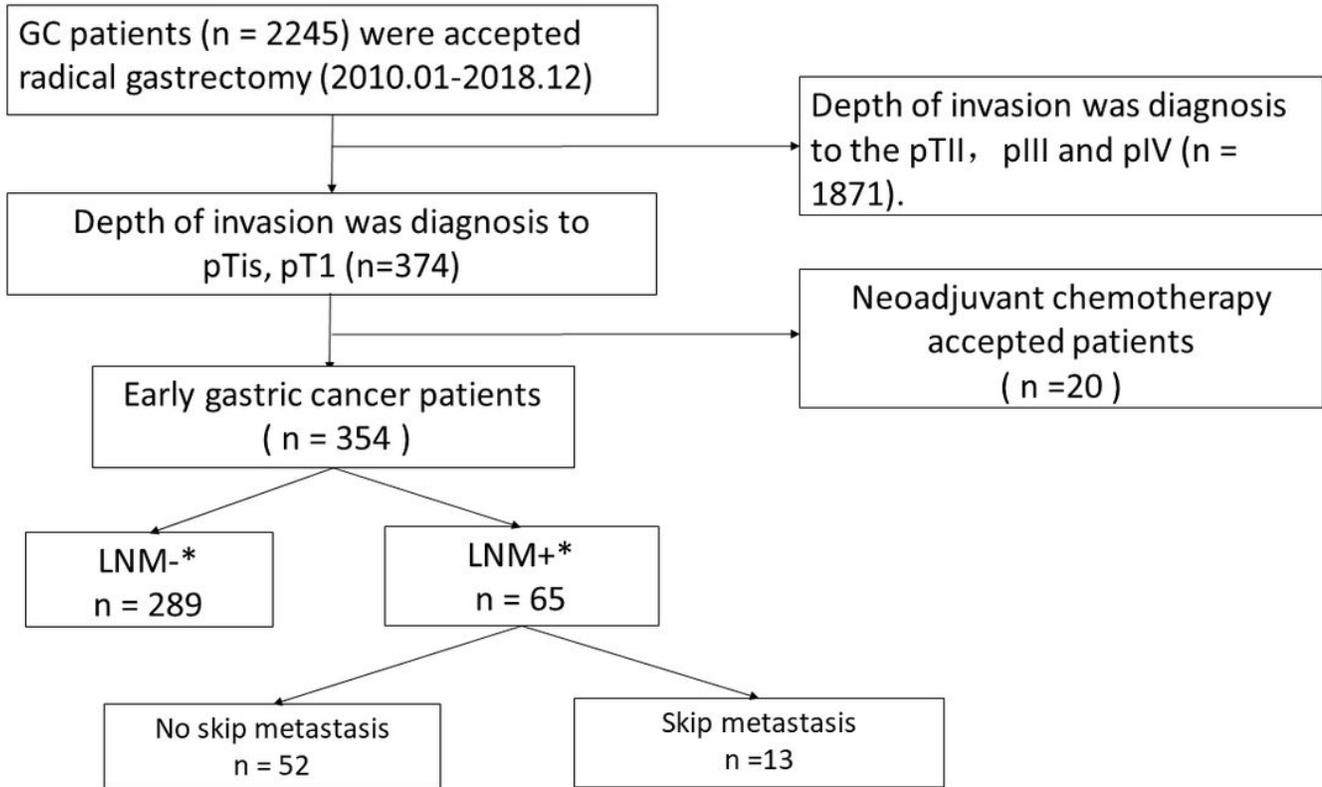
**For Proximal gastrectomy: D1: No.1, 2, 3s, 4sa, 4sb, 7; D1+: D1 + No.8a, 9, 11p.**

**Table-7** Clinicopathological characteristics of LNM patients without skip metastasis (n=52) and with skip metastasis (n=13).

Factor	No skip metastasis	Skip metastasis	<i>P</i> -value
Age (years)			
<40	6	4	0.086
≥40	46	9	
Sex			
male	33	5	0.102
female	19	8	
size			
Length-diameter(cm)	2.950	2.750	0.358
Short-diameter(cm)	2.305	1.786	0.452
<2cm	9	2	0.729
≥2cm	30	9	
<3cm	20	4	0.382
≥3cm	19	7	
Tumor Location			0.054
Upper	5	1	
Middle	26	2	
Lower	21	10	
Depth of invasion			
Mucosal	20	7	0.314
Submucosa	32	6	
differentiated			
Well- Moderately	11	3	0.880
Poorly	41	10	
LVI			
absent	45	13	0.726

<b>Table-8</b> Univariate and multivariate analysis of prognostic factors for early gastric cancer patient				
Factor	Univariable Analysis		Multivariable Analysis	
	HR (CI 95%)	<i>P</i> -value	HR (CI 95%)	<i>P</i> -value
Age(years)				
<40	1			
≥40	1.067(0.141-8.076)	0.950	NA	NA
Tumor size				
<2cm	1			
≥2cm	2.791(0.937-8.317)	0.065	3.473(1.372-8.791)	0.009
<3cm	1			
≥3cm	1.593(0.438-5.792)	0.480	NA	NA
Depth of invasion*				
Mucosal	1			
Submucosa	1.178(0.426-3.259)	0.753	NA	NA
Differentiation				
Well- Moderately	1			
Poorly	1.425(0.531-3.828)	0.482	NA	NA
LVI				
Absent	1			
Present	2.419(0.310-18.885)	0.399	NA	NA
LNM				
Absent	1			
Present	3.512(1.307-9.438)	0.013	4.895 (1.588-15.095)	0.006

## Figures



**Figure 1**

Inclusion criteria for study subjects. LNM-: absence of lymph node metastasis ; LNM+: presence of lymph node metastasis

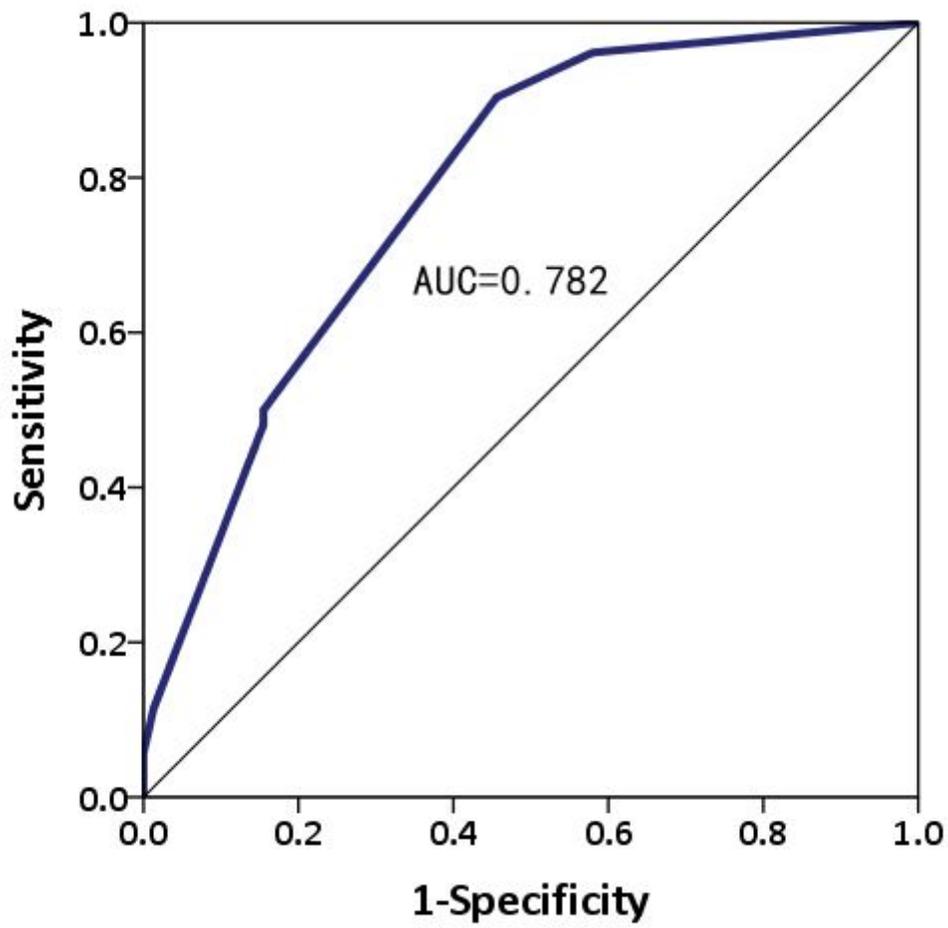
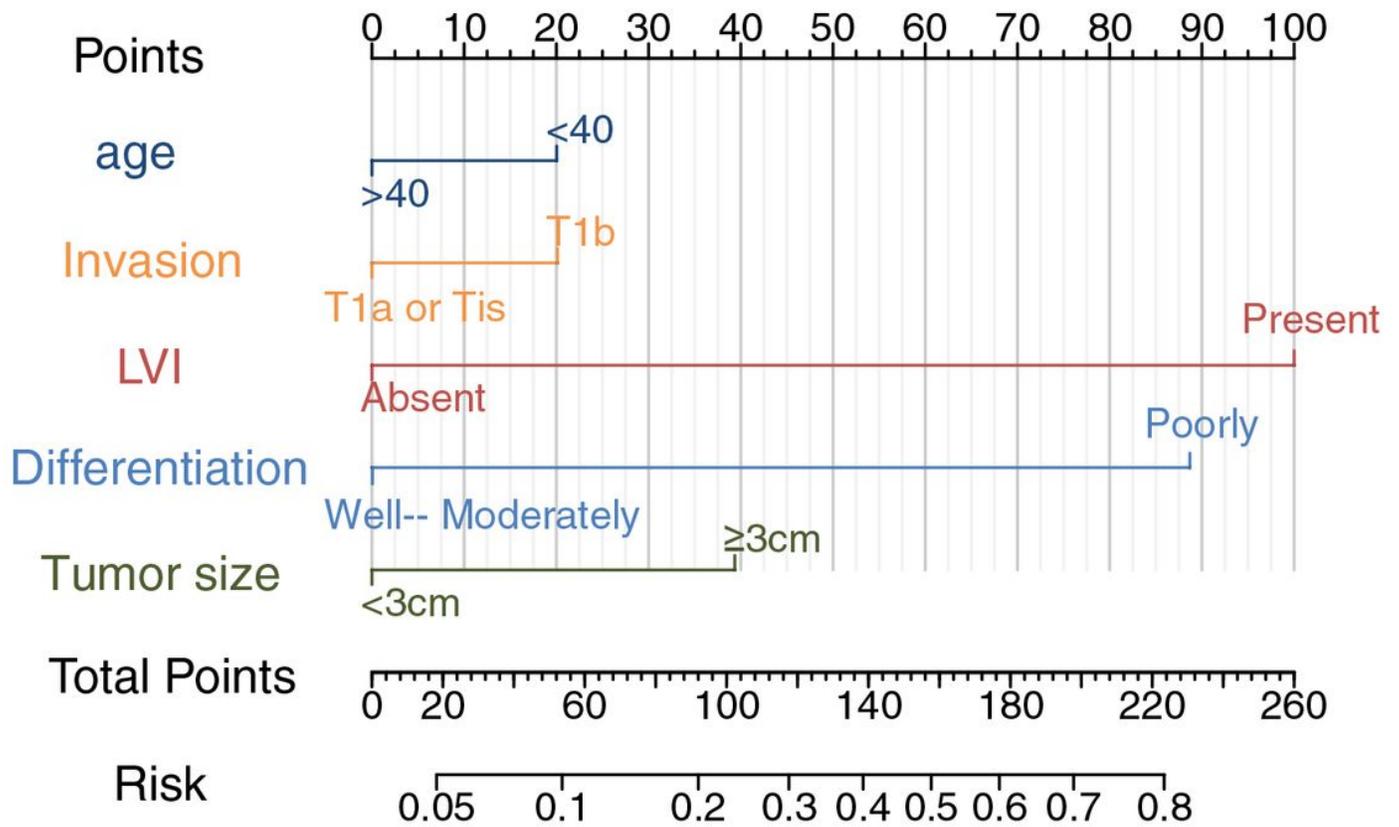


Figure 2

ROC curve of the multivariable model for predicting LNM in patients with EGC.



**Figure 3**

Nomogram for the prediction of lymph node metastasis in patients with EGC.

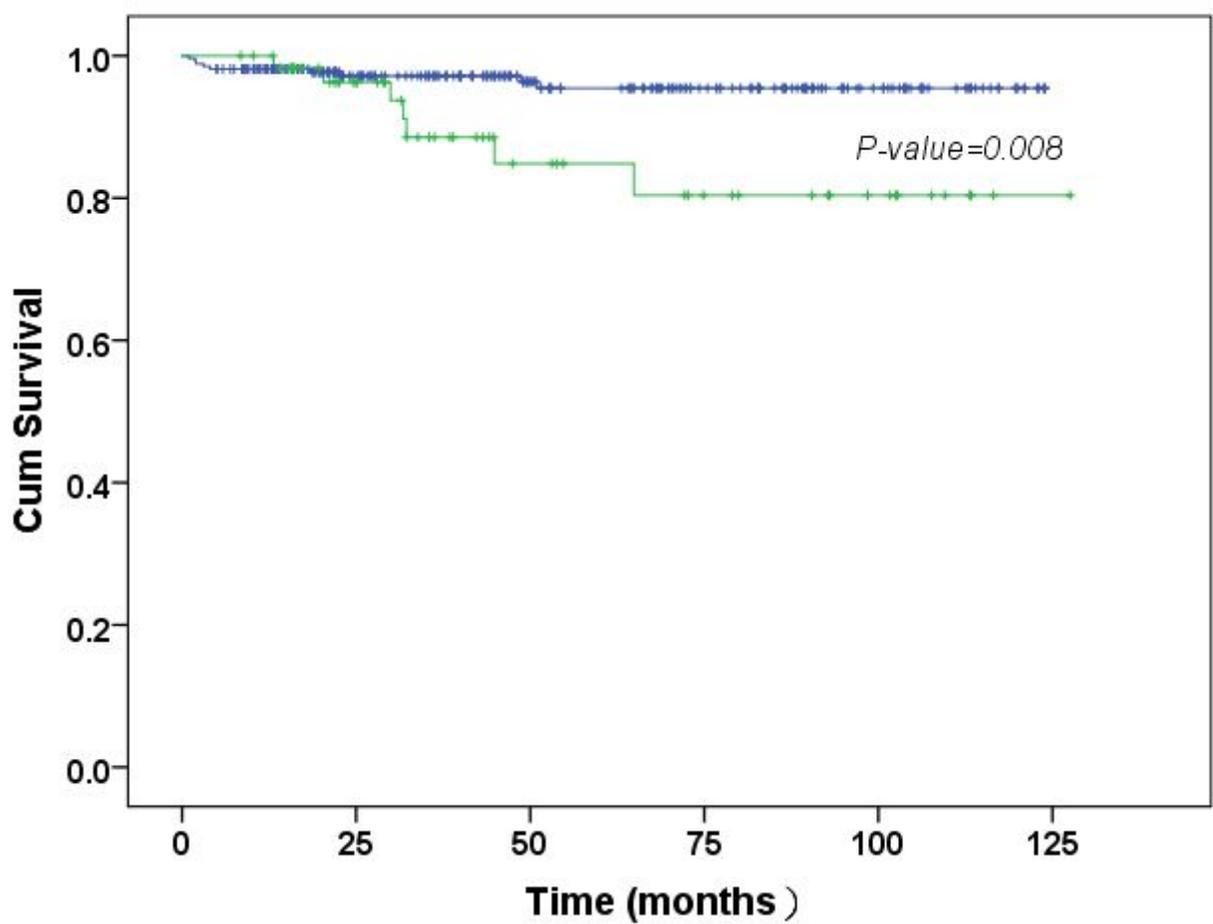


Figure 4

Kaplan–Meier curve of cumulative survival of EGC patients with LNM+ (green) and LNM- (blue). LNM, lymph node metastasis

## Supplementary Files

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