Analysis of risk factors for lymphatic metastasis in patients diagnosed with early gastric cancer

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Abstract

Purpose

This study aimed to identify the clinicopathological factors associated with the presence of lymph node metastasis (LNM) in patients diagnosed with early gastric cancer (EGC) and treated with radical gastrectomy.

Methods

Patients who underwent radical gastrectomy for gastric cancer from January 1990 to December 2019 were identified from a prospectively compiled database.Patients with pathological diagnoses of EGC were included. Univariate and multivariate analyses were conducted to identify risk factors associated with LNM.

Results

From 501 patients with EGC, 96(19.2%) presented LNM.In 279 patients with tumors with submucosal infiltration(T1b), 83(30%) patients had LNM. Among 219 patients who presented tumors > 3cm, 63(29%) patients had LNM. Thirty-one percent of patients with ulcerated tumors presented LMN(33 out of 105). In 76 patients and 24 patients with lymphovascular and perineural invasion, the percentage of LMN was 84% and 87%,respectively. In the univariate analysis, tumor diameter > 3cm, undifferentiated tumors, ulcerated tumors, submucosal invasion, lymphovascular, and perineural invasion showed a significant association with the presence of LNM.In the multivariate analysis, a tumor size > 3cm, submucosal invasion, lymphovascular, and perineural invasion were independent predictors of LMN in EGC. Patients who presented differentiated tumors, without ulceration, infiltration of the mucosa, and a tumor diameter ≤ 2cm, none presented LNM. Four patients(3%) who complied with the new Japanese indications for endoscopic treatment presented LNM.

Conclusions

The presence of lymph node metastasis in patients with EGC was independently related to larger tumors (tumor diameter > 3cm), submucosal invasion, lymphovascular and perineural invasion.

Background

Gastric cancer is the fifth most common cause of cancer-related death worldwide, and in Peru, the age-standardized mortality rate is 17.1 per 100 000 inhabitants [1, 2]. Early diagnosis associated with accurate treatment is the most effective method to reduce overall mortality. EGC was first defined by Murakami in 1971 as an invasive carcinoma restricted to the gastric mucosa and/or submucosa

irrespective of the lymph node status [3, 4]. The overall survival (OS) of patients with EGC treated with radical gastrectomy has been reported to be greater than 90% [5], with an incidence of LNM between 8 and 25% [6–8]. Confirming the absence of lymphatic metastasis is essential since it is the most important prognosis factor and correspondingly delimits the possible subsequent treatments [9, 10]. In addition, the low sensitivity and specificity of imaging studies to detect LMN in patients with EGC increase the need to recognize the risk factors related to its presence [7–9, 11]. In recent decades, two main techniques have been introduced for the treatment of EGC, minimally invasive surgery and endoscopic treatment, the latter being composed of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) [12–14].

According to the Korean Practice Guideline for Gastric Cancer [15], and the Japanese Gastric Cancer Treatment Guidelines [16]; endoscopic treatment (EMR or ESD) is recommended for patients with differentiated adenocarcinoma, without ulceration UL(0), infiltration of the mucosal layer (T1a) and a tumor diameter ≤ 2 cm. This selected group of patients presents a very low risk of LNM, however not all EGC patients can meet these criteria. In recent years, expanded indications for endoscopic treatment have been recommended, but with a moderate or low level of evidence and also leading to a higher possibility of LNM [17]. Therefore, it is important to identify the factors that could predict the presence of LNM in patients with EGC and improve their prognosis. This study aimed to identify the clinicopathological factors associated with the presence of LNM in patients diagnosed with EGC and treated with radical gastrectomy.

Methods

Study design

In this retrospective case-control study conducted at the Abdominal Surgery Department of the National Institute of Neoplastic Diseases (INEN), patients diagnosed with EGC and treated with D1 or D2 radical gastrectomy with curative intent, within the time frame between January 1990 and December 2019 were identified from a prospectively compiled database. EGC was defined as an invasive carcinoma limited to the mucosa and/or submucosa with or without lymphatic metastasis[18]. This study was reported following the Strengthening the reporting of observational studies in epidemiology (STROBE)[19].

Patients’ selection

The inclusion criteria were an age ≥ 18 years, preoperative and postoperative histological diagnoses of early gastric carcinoma, patients treated with distal, total, or proximal radical gastrectomy, D1 or D2 lymphadenectomy, open or laparoscopic surgery, elective surgery; and R0 resection. Exclusion criteria included patients < 18 years old, patients treated with endoscopic resection, histological diagnoses of gastrointestinal stromal tumor (GIST), lymphoma, neuroendocrine tumor (NET), or other gastric malignancies; emergency surgery, palliative surgery, patients diagnosed with locally advanced or advanced gastric carcinoma, and R1 or R2 resections. In the present study, patients were divided into two groups depending on the presence (cases group) or absence (control group) of LNM.

Preoperative evaluation

The preoperative imaging study consisted of a CT scan of the chest-abdomen and pelvis. Upper gastrointestinal endoscopy was performed in all patients to evaluate the tumoral morphological characteristics and to determine the macroscopic classification [18]. A gastric biopsy was done at the time of the endoscopic evaluation to assess the histological classification and to evaluate the depth of tumor invasion. In addition, a complete blood count, renal and hepatic function test, coagulation profile was routinely completed.

Surgical Procedure

All patients underwent radical gastrectomy with D1 or D2 lymph node dissection. The surgical procedure was selected according to the tumor location [20, 21]. The resection margins and lymph node dissection were determined as established by the Japanese Gastric Cancer Treatment Guidelines[16]. Omentectomy was performed routinely. In patients with tumors located at the posterior gastric wall, bursectomy was indicated. Roux-en-Y reconstruction was carried out after total gastrectomy and Billroth II or Roux-en-Y reconstruction was performed in distal gastrectomy. For patients treated with proximal gastrectomy, the interposed jejunal segment or Merendino procedure was selected as the reconstruction method[22].

Pathological Examination

Surgical specimens were embedded in paraffin and stained in hematoxylin and eosin. The stomach and all adipose connective tissue were routinely consigned for pathological evaluation. The presence of possible positive lymph nodes was initially evaluated macroscopically by the surgeon and later by an expert pathologist. Gastric tumors were classified histologically according to the World Health Organization Classification System [23]. Papillary adenocarcinoma, well and moderately differentiated tubular adenocarcinoma were included as differentiated-type EGC. Signet ring cell carcinoma and poorly differentiated adenocarcinoma were included as undifferentiated-type EGC. Mixed carcinoma was classified according to the quantitative predominance [16]. Ulcerated tumors were diagnosed by endoscopic or histological evidence [24]. Lymphovascular and perineural invasion was scored by the pathologist under direct vision.

Variables Studied

Clinicopathological characteristics (age, gender, tumor location, tumor diameter, histological subtype, tumor differentiation, ulceration, depth of invasion, number of resected lymph nodes, lymphovascular invasion, and perineural invasion), and surgical characteristics (type of gastrectomy, surgical approach, and lymphadenectomy) were evaluated.

Statistical Analysis

The statistical analysis was performed with IBM SPSS version 25.0. A descriptive analysis of variables was done through frequencies, percentages, and summary measures (mean and standard deviation). The association between quantitative variables and the presence of LNM was evaluated with the t-test for

independent samples or its corresponding non-parametric test. The association between qualitative variables and the presence of LNM was evaluated with the Chi-square test, applying the Yates correction if appropriate. Receiver operating characteristic curve (ROC curve) analysis was performed to obtain the optimal cut-off value for the tumor diameter. The optimal cut-off point for tumor diameter was > 3 cm and was used for the dichotomization of the variable in the univariate analysis. The variables: tumor diameter (≤ 3 cm vs > 3 cm), differentiation type (differentiated vs undifferentiated), ulceration (absent vs present), depth of invasion (mucosa vs submucosa), lymphovascular invasion (absent vs present), and perineural invasion (absent vs present) were used in the univariate analysis. Variables with significant associations were chosen for the multivariate analysis (binary logistic regression model). Odds ratio (OR) and 95% confidence intervals (CI) were calculated. Statistical significance was defined as $p \leq 0.05$.

Ethics approval and consent to participate

The present study was evaluated and accepted by the Ethics Committee of the National Institute of Neoplastic Diseases INEN, Lima, Perú. This article complies with current regulations on bioethical research and was carried out following the Ethical Principles for Medical Research Involving Human Subjects, as outlined in The Declarations of Helsinki[25]. The authors declare that this article does not contain personal information that would allow the identification of enrolled patients.

Results

Clinicopathological Characteristics

Between January 1990 and December 2019, 4394 patients underwent radical gastrectomy. Of these, 501 (11%) were diagnosed with EGC. The mean age was 62.4 years old. Two hundred and seventy-seven (55%) patients were female and 224 (45%) were male. Most of the patients presented with distal tumors (n=302, 60%), followed by middle tumors (n=175, 35%), and proximal tumors (n=24, 5%). The mean tumor diameter was 3.4 cm. Two hundred and eighty-two (56%) patients presented tumor ≤ 3 cm, and 219 (44%) presented tumors > 3 cm. Tubular adenocarcinoma (n= 309, 62%) was the most frequent histological subtype, followed by signet ring cell carcinoma (n=149, 30%), and mixed carcinoma (n=43, 8%). Three hundred and two (60%) patients exhibited differentiated tumors, and 199 (40%) patients presented undifferentiated tumors. One-hundred and five (21%) patients presented ulcerated tumors. Two hundred and seventy-nine (56%) patients presented submucosal infiltration (T1b), and 222 (44%) patients presented tumors that infiltrate the mucosal layer (T1a). The mean of harvested lymph nodes was 42. Seventy-six (15%) patients presented lymphovascular invasion, and 24 (5%) patients presented perineural invasion. Clinicopathological characteristics of patients with EGC who underwent radical gastrectomy are summarized in Table 1.

Surgical Characteristics

Open surgery was performed in 481 (96%) patients and laparoscopic surgery in 20 (4%) patients. The most frequent surgical procedure was distal gastrectomy 397 (80%), followed by total gastrectomy (n=93, 18%), and proximal gastrectomy (n=11, 2%). D2 lymphadenectomy was carried out in 464 (93%) patients and 37 (7%) patients were treated with D1 lymphadenectomy (Table 2).

Clinicopathological characteristics of patients with lymph node metastasis (LNM)

Ninety-six (19.2%) patients diagnosed with EGC presented LMN. Most of the patients had 1-2 metastatic lymph nodes (pN1) (n=51, 53%), followed by 3-6 metastatic lymph nodes (pN2) (n=31, 33%), 7-15 metastatic lymph nodes (pN3a) (n=10, 11%), and ≥ 16 metastatic lymph nodes (pN3b) (n=4, 3%). The mean tumor diameter was 4.2 cm. Among 219 patients who developed tumors > 3 cm, 63 (29%) patients had LNM. Of 199 patients with undifferentiated tumors, the percentage of LMN was 25 % (48 out of 199). Thirty-one percent of patients with ulcerated tumors presented LMN (33 out of 105). Of 279 patients with tumors that infiltrated the submucosa (T1b), 83 (30%) patients had LNM. In 76 patients and 24 patients with lymphovascular and perineural invasion, the percentage of LMN was 84% and 87%, respectively. The mean of harvested lymph nodes was 46.2. The clinicopathological characteristics of EGC with LMN are summarized in Table 1.

Univariate and multivariate analysis

In the univariate analysis, tumor diameter > 3 cm (p =≤0.001), undifferentiated tumor type (p =0.015), ulcerated tumors (p =≤0.001), submucosal invasion (T1b) (p = ≤0.001), lymphovascular invasion (p = ≤0.001), and perineural invasion (p = ≤0.001) were significantly associated with the presence of LMN in patients diagnosed with EGC (Table 3).

In the multivariate analysis, tumor diameter > 3 cm (OR=1.99, 95% CI, 1.11-3.85), submucosal invasion (T1b) (OR=2.56, 95% CI, 1.21-5.45), lymphovascular invasion (OR= 40.8, 95% CI, 19.1-87.3), and perineural invasion (OR=21.1, 95% CI, 4.77-93.1) were independent risk factors for LMN in patients diagnosed with EGC (Table 4).

Incidence of LMN according to the indications for EMR and ESD of the Japanese gastric cancer treatment guideline 2018 (5th Edition).

Of the patients who underwent radical gastrectomy for EGC, 46 patients met the EMR criteria as an absolute indication. From these, no patient presented LMN. One hundred twenty-eight patients fulfilled the criteria for ESD as an absolute indication, only 4 (3%) patients had LMN. We also assessed the incidence of LMN in patients who met the criteria for endoscopic treatment as an expanded indication, 23 cases were included in this group and none of them presented LMN. The incidence of LMN according to the indications for EMR and ESD of the Japanese gastric cancer guideline is summarized in Table 5.

Discussion

Globally, EGC is more frequently diagnosed in Eastern countries compared to the Western population [26,27]. Countries with national cancer screening programs have been able to increase early diagnosis and reduce gastric cancer mortality[28]. Currently, these countries report a survival rate between 60.3% to 68.9% [29], and patients with EGC represent approximately 50 to 70% of all patients diagnosed with gastric cancer (30,31). The five-year overall survival in EGC patients is greater than 91%, but there is evidence of a survival decrease with the presence of LNM[5]. To the best of our knowledge, the present study reports the largest series in Latin America evaluating the relationship between the clinicopathological risk factors and the evidence of LNM in EGC. Our study shows that a larger tumor diameter (>3 cm), submucosal invasion (T1b), lymphovascular and perineural invasion were independently related to the presence of LNM in EGC. Likewise, EGC patients with differentiated adenocarcinoma, absence of ulceration (UL0), mucosal infiltration (T1a) and a tumor diameter < 2cm did not presented LNM.

The incidence of LNM in patients with EGC is variable worldwide[13,32–34]. Korea and Japan report an incidence between 2 and 9%, and China presents an incidence of LNM as high as 25%[6,10,35]. In western countries, the number of publications on EGC is not as numerous as in Asia, probably due to the lower number of cases and the lack of screening programs [3,7,17,35]. In our series, the incidence of LNM was 19.2% in all EGC patients. Previous publications in Latin America reported similar results, but with a small number of patients[36,37].

Several studies informed that a larger tumor diameter was related to a higher incidence of LNM in EGC patients, nonetheless, the cut-off value remains variable. Bausys et al. [7], reported that EGC patients with tumors > 2 cm presented an increased risk of LNM in the univariate analysis compared to EGC patients with tumors ≤ 2 cm (OR=2.27, 95% CI, 1.12 - 4.59). Nevertheless, no significant difference was observed in the multivariate analysis (p=0.155). In contrast, Chu et al. [11], in the multivariate analysis, reported a cut-off point of 3 cm to assess the risk of developing LNM in EGC patients (OR=1.9, 95% CI, 1.19-3.05). In addition, Gotoda et al. showed that intramucosal tumors > 3 cm exhibit a percentage of LNM of 4.9% compared to 1.1% in T1a tumors ≤ 3 cm. Our results support the cut-off point of 3 cm as an independent risk factor for LNM, and we propose that this variable should be evaluated separately to decide the appropriate treatment in patients with EGC.

In the present study, LNM was evidenced in 30% of patients with submucosal infiltration (T1b) compared to 6% in patients with mucosal infiltration (T1a). In the multivariate analysis, submucosal infiltration was independently related to the presence of LNM in patients with EGC (OR=2.56, 95% CI, 1.21-5.45). Similar results had been reported in multiple publications and the percentage of LNM in T1b tumors ranged from 16% to 42.9% (6,10,37). Likewise, in a retrospective study conducted in Italy, the presence of submucosal infiltration showed a negative effect on 5 and 10 years overall survival (OS)(3). At the time, submucosal tumors are not eligible for endoscopic treatment, and only patients with T1b tumors with no evidence of lymphatic infiltration are eligible for less aggressive surgery (D1/D1+ radical gastrectomy).

Our study indicated that perineural invasion (PNI) was an independent risk factor for LNM in patients with EGC. PNI represents the process of neoplastic invasion of the nerves and, it can be detected without lymphatic or vascular invasion [38,39]. PNI can be diagnosed in a variety of malignant neoplasms and its molecular mechanism is still under investigation. The relationship between the presence of PNI and poor survival has been reported in several malignant tumors and also in gastric cancer[40]. Unlike lymphovascular invasion (LVI), the presence of PNI in EGC has not been included as a risk factor for LNM in international guidelines. Chu et al.[11] in a retrospective study reported that EGC patients who presented PNI had a higher risk of LNM compared to patients with EGC without PNI (p= ≤0.001). Likewise, in a retrospective study conducted in China, multivariate analysis showed that PNI was an independent risk factor for LNM in EGC patients [8]. Further studies are required to assess the prognostic value of PNI in EGC patients. We suggest that PNI should be considered when evaluating the treatment of patients with EGC.

LVI is defined as the evidence of malignant cells within lymphatic or vascular spaces [41]. In gastric cancer publications, LVI has been reported as an independent prognostic factor, especially in N0 patients [42,43]. Our results showed that the presence of LVI was the most important predictor for the presence of LNM in patients with EGC (OR= 40.8, 95% CI, 19.1-87.3). Similarly, in a retrospective study including 12552 patients, the presence of LVI was the furthest significant risk factor for LNM in the multivariate analysis (OR= 15.7, 95% CI, 10.4-23.6)[11]. Likewise, Chen et al [8] conducted a study in which mucosal (T1a) and submucosal (T1b) tumors were analyzed separately, in both groups LVI was the most important factor for LNM. The difficult detection of LVI in endoscopic biopsy is well known and for this reason, additional curative surgery is recommended for patients with positive LVI after endoscopic resection[15]. In addition, in the Japanese gastric cancer treatment guidelines, patients with positive LVI after endoscopic resection are not categorized as endoscopic curability A (eCuraA) or endoscopic curability B (eCuraB)[16]. Based on our results, we suggest that LVI should be carefully evaluated in endoscopic biopsy and endoscopic resection samples. If LVI is confirmed, radical gastrectomy should be selected as the main treatment.

Numerous studies reported that undifferentiated tumors (poorly differentiated tubular adenocarcinoma, signet ring cell carcinoma) had an increased risk of LNM in patients with EGC [6–8,44,45]. In the present study, in the univariate analysis, undifferentiated tumors showed a strong association with the presence of LNM (p= 0.015). Nevertheless, certain retrospective studies reported that patients with undifferentiated tumors, < 15mm, confined to the mucosa or with minimal submucosal invasion (<500 μm) could be considered for endoscopic treatment [46,47].

The presence of ulceration (UL1) has been reported in multiple studies as a risk factor for LNM and is also taken into account as a patient selection criterion for endoscopic treatment [13,35]. Traditionally, the diagnosis of ulceration was made in the pathological evaluation of the surgical specimen[6]. Currently, it is essential to evidence this finding endoscopically since it could change future treatment [48]. Likewise, the discrepancy between pathological and endoscopic ulcers has been reported up to 46% and this could be the reason for our results [49].

Indications for endoscopic treatment in EGC had changed over the years. Initially, it was accepted that only tumors that infiltrate the mucosa (T1a), not ulcerated (UL0), well-differentiated, and with a diameter, less than or equal to 2cm could be treated endoscopically. In addition, three other indications (expanded) were suggested but as a treatment under investigation [18]. Currently, the absolute indications for treatment with ESD have been extended in the Japanese guidelines in which larger and ulcerated tumors are included. Optimal treatment is only discussed for undifferentiated tumors [16]. Nonetheless, these indications differ globally, even among Eastern guidelines [15,50]. In our series, no patient with EGC with differentiated-type adenocarcinoma, UL0, T1a, and tumor diameter ≤ 2cm presented LNM, this result is consistent with previous publications and supports endoscopic treatment for this group of patients. In the present study, four (3%) patients who met the novel Japanese criteria for the absolute indication of ESD as initial treatment presented LNM. Also, evaluating each group of patients separately, we showed that the incidence of LNM was higher in the group of patients with ulcerated tumors and less than or equal to 3cm compared to the group of patients without ulceration and with a tumor diameter greater than 2cm (18% vs 0.9%). Our results indicated that patients who meet these criteria are still required to be further evaluated to improve the selection criteria for ESD.

In addition, in our study, no patient who fulfilled the expanded indication for endoscopic treatment had LNM. Currently, a clinical trial evaluating endoscopic treatment (ESD) for patients with EGC with undifferentiated-type tumors, UL0, T1a, and a tumor diameter ≤ 2m reported a 5-year overall survival (OS) of 99.3% (95% CI, 97.1-99.8), but only 71% of patients achieved a curative resection [51].

Our study should be understood by its limitations. First, the present research is of retrospective origin, although it is based on a prospective database, however, it does not cease to have the limitations of this type of studies. Second, our study presents a limited number of patients compared to Eastern publications. Despite this, our study is the largest series in Latin America.

Conclusions

In conclusion, a larger tumor diameter (> 3cm), submucosal infiltration (T1b), and the presence of lymphovascular and perineural invasion were identified as independent risk factors for the presence of LNM in patients diagnosed with EGC. Likewise, patients diagnosed with differentiated-type adenocarcinoma, without the presence of ulceration (UL0), mucosal infiltration (T1a), and with a tumor diameter less than or equal to 2 centimeters are eligible for endoscopic treatment. Further studies in different population groups are still required to reach a consensus on the absolute indications for endoscopic treatment in patients with EGC.

Declarations

Funding: The authors did not receive support from any organization for the submitted work.

Conflicts of interest: The authors declare that they have no competing interests.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Data availability: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable.

Authors' contributions: EP, FB, and ER designed the work. OP, CB, CL, and IC analyzed and interpreted the data. OP, CB, and EP wrote the main manuscript text. EP, ER, IC, CL, and FB approved the submitted version. All authors reviewed the manuscript.

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Tables

Tables 1 to 5 are available in the Supplementary Files section.

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