Heliyon 9 (2023) e16293

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Predictive factors of lymphatic metastasis and evaluation of the Japanese treatment guidelines for endoscopic resection of early gastric cancer in a high-volume center in Perú

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ARTICLE INFO

Keywords:
Early gastric cancer (EGC)
Lymph node metastasis (LNM)
Predictive factors
Endoscopic mucosal resection (EMR)
Endoscopic submucosal dissection (ESD)

ABSTRACT

Purpose: This study aimed to identify the predictive factors of lymph node metastasis (LNM) in patients with early gastric cancer (EGC) and to evaluate the applicability of the Japanese treatment guidelines for endoscopic resection in the western population.
Methods: Five hundred-one patients with pathological diagnoses of EGC were included. Univariate and multivariate analyses were conducted to identify the predictive factors of LNM. EGC patients were distributed according to the indications for endoscopic resection of the Eastern guidelines. The incidence of LNM was evaluated in each group.
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 $>$ 3 cm, 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 multivariate analysis, a tumor diameter $>$3 cm, submucosal invasion, lymphovascular, and perineural invasion were independent predictors of LMN in EGC. No patient with differentiated, non-ulcerated mucosal tumors presented LNM regardless of tumor size. Three of 17 patients (18%) with differentiated, ulcerated mucosal tumors and $\leq$ 3 cm presented LNM. No LNM was evidenced in patients with undifferentiated mucosal tumors and $\leq$ 2 cm.
Conclusions: The presence of LNM in Western EGC patients was independently related to larger tumors ($>$3 cm), submucosal invasion, lymphovascular and perineural invasion. The Japanese absolute indications for EMR are safe in the Western population. Likewise, Western patients with differentiated, non-ulcerated mucosal tumors, and larger than 2 cm are susceptible to endoscopic resection. Patients with undifferentiated mucosal tumors smaller than 2 cm presented encouraging results and ESD could be recommended only for selected cases.

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https://doi.org/10.1016/j.heliyon.2023.e16293
Received 18 June 2022; Received in revised form 10 May 2023; Accepted 11 May 2023
Available online 15 May 2023

1. Introduction

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 2018 [15], and the Japanese Gastric Cancer Treatment Guidelines 2018 [16]; endoscopic treatment (EMR or ESD) is recommended for patients with differentiated adenocarcinoma, without ulceration (UL0), infiltration of the mucosal layer (T1a) and a tumor diameter $\leq$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. Currently, there is no consensus on whether the indications for endoscopic resection for the treatment of EGC according to the eastern guidelines are applicable in the West. This study aimed to identify the predictive factors associated with LNM in patients diagnosed with EGC treated with radical gastrectomy in Peru and to assess whether the Japanese Treatment guidelines for endoscopic treatment with EMR or ESD are applicable in the western population.

2. Methods

2.1. Study design

In this retrospective cohort 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 of the reporting of observational studies in epidemiology (STROBE) [19].

2.2. Patients' selection

The inclusion criteria were an age $\geq$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 or absence of LNM.

2.3. 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 the differentiation grade. In addition, a complete blood count, renal and hepatic function test, and coagulation profile were routinely completed.

2.4. 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].

2.5. 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 macroscopical pathological evaluation. The presence of possible positive lymph nodes was initially evaluated macroscopically by the surgeon and later by an expert pathologist. A representative part of the tumor lesion was used to prepare the histological slides. 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 (Fig. 1A). Signet ring cell carcinoma and poorly differentiated adenocarcinoma were included as undifferentiated-type EGC (Fig. 1B). Mixed carcinoma was classified according to the quantitative predominance. Ulcerated tumors were diagnosed by endoscopic or histological evidence [16]. The depth on invasion (pT) and the presence of lymph node metastasis (pN) were categorized according to the AJCC TNM classification [24]. Lymphovascular and perineural invasion was evaluated in the pathology slides by hematoxylin-eosin staining (Fig. 2A, Fig. 2B). The expert group of pathologists evaluated both characteristics under direct vision. In patients with inconclusive morphological findings of lymphovascular invasion, an immunohistochemical study with endothelial markers (CD31, CD34, Podoplanin and ERG) was performed. The specimens were examined and reported according to the College of American Pathologists protocol for patients with Carcinoma of the Stomach [25].

2.6. 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.

2.7. 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 were used for the dichotomization of the variable in the univariate analysis. The variables: tumor diameter ($\leq$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 $p \leq 0.05$.

Likewise, patients were distributed according to the indications and recommendations for endoscopic treatment of the Japanese gastric cancer treatment guidelines 2018 (5th edition) [15], patients were divided into three groups: Group 1 (Absolute indication for EMR), group 2 (Novel absolute indications for ESD), and group 3 (Expanded indication).

2.8. 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,

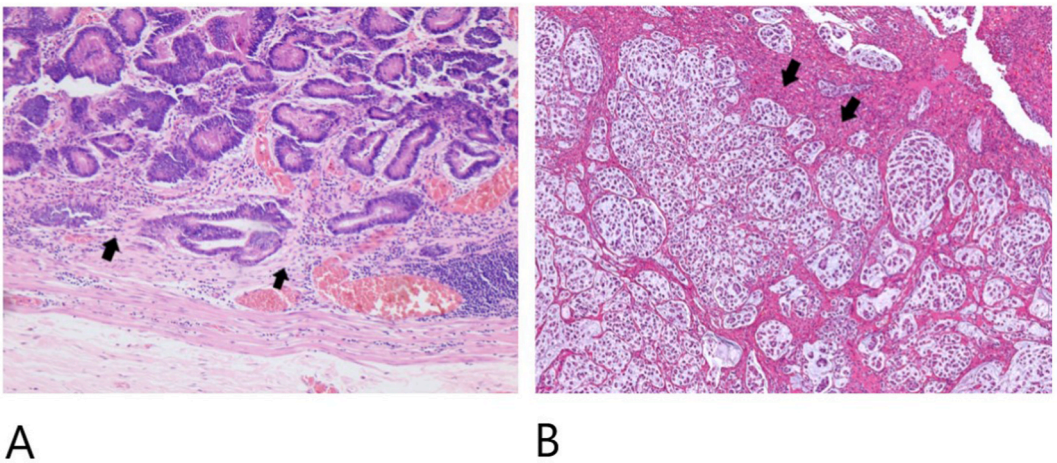

Fig. 1. (A) Tubular Adenocarcinoma (differentiated type) with infiltration of the lamina propria (arrows) and focally involving the muscularis mucosae (pT1a). H&E staining Magnification ×20. **(B)** Signet-ring cell carcinoma (undifferentiated type) infiltrating extensively the submucosa (arrows) (pT1b). H&E staining Magnification ×10.

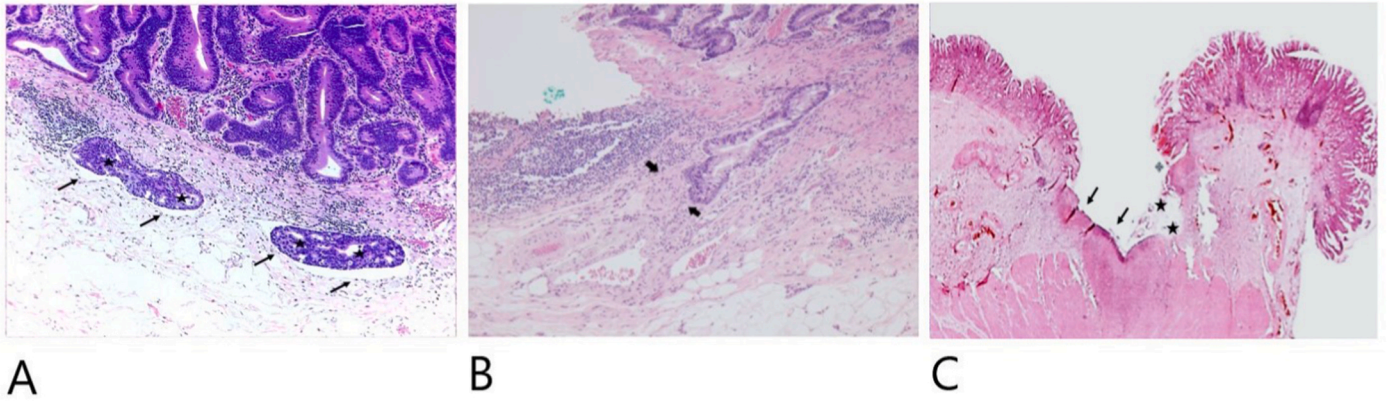

Fig. 2. (A) Lymphovascular invasion: The arrows indicate the lymphatic vessel. The stars indicate the tumor emboli. H&E staining Magnification ×40. **(B)** Perineural invasion by tubular adenocarcinoma (arrows). H&E staining Magnification ×20. **(C)** Ulceration: breach in the gastric muscularis mucosae (arrows). Fibrous tissue and fibrinoid necrosis at the base (stars).

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. The authors declare that this article does not contain personal information that would allow the identification of enrolled patients.

3. Results

3.1. Clinicopathological characteristics

Of 4394 patients treated with radical gastrectomy, 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 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. 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 (Fig. 2C). Two hundred and seventy-nine (56%) patients presented submucosal infiltration (T1b), and 222 (44%) patients presented tumors that infiltrate the mucosal layer (T1a) (Fig. 1). The mean of harvested lymph nodes was 42. Seventy-six (15%) patients presented lymphovascular invasion, and 24 (5%) patients presented perineural invasion (Fig. 2A and B). Clinicopathological characteristics of patients with EGC who underwent radical gastrectomy are summarized in Table 1.

Table 1
Clinicopathological characteristics of patients diagnosed with early gastric cancer and treated with radical gastrectomy.

	All Gastrectomies	LNM (−)	LNM (+)	*p*-Value
	n [a] = 501 (100%)	n = 405 (80.8%)	n = 96 (19.2%)	
Age [b], mean ± SD [c] years	62.4 ± 13.6	62.2 ± 13.7	63.1 ± 13.1	0.554
Gender				0.156
Male *n* (%)	224 (45)	186 (83)	38 (17)	
Female *n* (%)	277 (55)	219 (21)	58 (79)	
Tumor Location *n* (%)				0.66
Upper	24 (5)	20 (83)	4 (17)	
Middle	175 (35)	138 (79)	37 (21)	
Distal	302 (60)	247 (82)	55 (18)	
Tumor Diameter, mean ± SD[d]	3.4 ± 2.5	3.2 ± 2.5	4.2 ± 2.3	**≤0.001**
≤ 3 cm	282 (56)	249 (88)	33 (12)	
> 3 cm	219 (44)	156 (71)	63 (29)	**≤0.001**
Histological Subtype *n* (%)				
Tubular Adenocarcinoma (Tub1/Tub2)	302 (60)	254 (84)	48 (16)	0.072
SRC/Poorly-differentiated adenocarcinoma	156 (32)	122 (78)	34 (22)	
Mixed Carcinoma	43 (8)	29 (67)	14 (33)	
Differentiation *n* (%)				**0.015**
Differentiated-Type	302 (60)	254 (84)	48 (16)	
Undifferentiated-Type	199 (40)	151 (75)	48 (25)	
Ulceration *n* (%)				**≤0.001**
No	396 (79)	333 (84)	63 (16)	
Yes	105 (21)	72 (69)	33 (31)	
Depth of Invasion *n* (%)				**≤0.001**
Mucosal	222 (44)	209 (94)	13 (6)	
Submucosal	279 (56)	196 (70)	83 (30)	
Lymph Nodes Resected, mean ± SD	42 ± 21.4	41.3 ± 20.8	46.2 ± 23.3	**0.044**
Lymph Nodes Metastasis (pN) *n*(%)				**NE**
N0	405 (81)	405 (100)	0	
N1	51 (10)	0	51 (53)	
N2	31 (6)	0	31 (33)	
N3a	10 (2)	0	10 (11)	
N3b	4 (1)	0	4 (3)	
Lymphovascular Invasion *n* (%)				**≤0.001**
Absent	425 (85)	393 (93)	32 (7)	
Present	76 (15)	12 (16)	64 (84)	
Perineural Invasion *n* (%)				**≤0.001**
Absent	477 (95)	402 (84)	75 (16)	
Present	24 (5)	3 (13)	21 (87)	

LNM: Lymph node metastasis, SRC: Signet-ring cell carcinoma, Tub 1: Well-differentiated adenocarcinoma, Tub 2: Moderately-differentiated adenocarcinoma.

[a] *n:* Number of patients.
[b] At the date of surgery.
[c] SD: standard deviation.
[d] mean and standard deviation in centimeters.

Table 2
Surgical characteristics of patients diagnosed with early gastric cancer and treated with radical gastrectomy.

	All Gastrectomies	LNM[a] (−)	LNM (+)	*p*-Value
	n [b] = 501 (100%)	n = 405 (80.8%)	n = 96 (19.2%)	
Type of Gastrectomy *n* (%)				0.09
Proximal Gastrectomy	11 (2)	11 (100)	0	
Distal Gastrectomy	397 (80)	324 (82)	73 (18)	
Total Gastrectomy	93 (18)	70 (75)	23 (25)	
Surgical Approach *n* (%)				0.55
Open surgery	481 (96)	389 (81)	92 (19)	
Laparoscopic Surgery	20 (4)	16 (80)	4 (20)	
Lymphadenectomy *n* (%)				0.413
D1	37 (7)	31 (84)	6 (16)	
D2	464 (93)	374 (81)	90 (19)	

[a] LNM: Lymph node metastasis.
[b] *n:* Number of patients.

3.2. 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).

3.3. 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.

3.4. Univariate and multivariate analysis

In the univariate analysis, tumor diameter >3 cm (p = ≤0.001), undifferentiated tumor type (p = 0.015), ulcerated tumors (p =

Table 3
Univariate analysis of risk factors associated with the presence of lymph node metastasis in early gastric cancer patients.

Factor	No. of patients	No. of events	%	Univariate Analysis		
				OR [a]	CI [b] 95%	p- Value
Tumor Diameter						
≤ 3 cm	282	33	12	**Reference**		
> 3 cm	219	63	29	3	1.9–4.8	**≤0.001**
Differentiation						
Differentiated-Type	302	48	16	**Reference**		
Undifferentiated-Type	199	48	25	1.7	1.1–2.6	**0.015**
Ulceration						
Absent	396	63	16	**Reference**		
Present	105	33	31	2.4	1.4–3.9	**≤0.001**
Depth of Invasion						
Mucosa	222	13	6	**Reference**		
Submucosa	279	83	30	6.8	3.6–12.6	**≤0.001**
Lymphovascular Invasion						
Absent	425	32	7	**Reference**		
Present	76	64	84	65.5	32–133	**≤0.001**
Perineural Invasion						
Absent	477	75	16	**Reference**		
Present	24	21	87	37.5	10.9–128.9	**≤0.001**

Event: Patient with lymph node metastasis.
[a] OR: Odds Ratio.
[b] CI: Confidence Interval.

Table 4
Multivariate analysis of risk factors associated with the presence of lymph node metastasis in early gastric cancer patients.

Factor	No. of patients	No. of events	%	Multivariate Analysis		
				OR [a]	CI [b] 95%	p- Value
Tumor Diameter						
≤ 3 cm	282	33	12	**Reference**		
> 3 cm	219	63	29	1.99	1.11–3.85	**0.041**
Differentiation						
Differentiated-Type	302	48	16	**Reference**		
Undifferentiated-Type	199	48	25	1.27	0.65–2.47	0.476
Ulceration						
Absent	396	63	16	**Reference**		
Present	105	33	31	1.53	0.72–3.28	0.265
Depth of Invasion						
Mucosa	222	13	6	**Reference**		
Submucosa	279	83	30	2.56	1.21–5.45	**0.014**
Lymphovascular Invasion						
Absent	425	32	7	**Reference**		
Present	76	64	84	40.8	19.1–87.3	**≤0.001**
Perineural Invasion						
Absent	477	75	16	**Reference**		
Present	24	21	87	21.1	4.77–93.1	**≤0.001**

Event: Patient with lymph node metastasis.
[a] OR: Odds Ratio.
[b] CI: Confidence Interval.

≤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).

3.5. 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. Only one (1.5%) of the sixty-seven patients with differentiated, non-ulcerated mucosal tumors larger than 2 cm presented lymphatic metastasis. Eighteen percent of patients with ulcerated differentiated, mucosal tumors less than or equal to 3 cm presented LNM (3/17). 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 Tables 5 and 6.

4. 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% and 68.9% [29], and patients with EGC represent approximately 50–70% 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 predictive factors and the evidence of LNM in EGC. Likewise, this is the first study in which different eastern guidelines for the treatment of EGC are analyzed to assess whether their application is safe in the Western population. Our study shows that a larger tumor diameter (>3 cm), submucosal invasion (T1b), and lymphovascular and perineural invasion were independently related to the presence of LNM in EGC. Similarly, the absolute indication for EMR of the Japanese gastric cancer guidelines 2018 (5th edition) are applicable and safe for the Latin American population.

The incidence of LNM in patients with EGC is variable worldwide [13,32–34]. Korea and Japan report an incidence of 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 debatable (2 cm vs 3 cm) [7,11]. 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 and we propose that this variable should be evaluated separately to decide the appropriate treatment in patients with EGC. In the present study, submucosal infiltration was independently related to the presence of LNM. Similar results had been reported in multiple publications and the percentage of

Table 5
Incidence of lymphatic metastases according to the indications for EMR and ESD in the Japanese gastric cancer treatment guidelines 2018 (5th edition).

	Patients with lymph node metastasis/total of patients	Incidence %
Absolute Indication of EMR[a]		
Differentiated-type adenocarcinoma, no ulceration, T1a, tumor diameter ≤2 cm	0/46	0
Novel Absolute Indications of ESD[b]		
Differentiated-type adenocarcinoma, no ulceration, T1a, tumor diameter >2 cm	1/67	1.5
Differentiated-type adenocarcinoma, ulcerated, T1a, tumor diameter ≤3 cm	3/17	18
Expanded Indication		
Undifferentiated-type adenocarcinoma, no ulceration, T1a, tumor diameter ≤2 cm	0/23	0

[a] EMR: Endoscopic mucosal resection.
[b] ESD: Endoscopic submucosal dissection.

Table 6
Distribution of patients diagnosed with early gastric cancer according to the novel criteria for Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) of the Japanese gastric cancer treatment guidelines 2018 (5th edition).

Depth of Invasion	Presence of Ulceration		Differentiated Type		Undifferentiated Type	
Mucosal Invasion (T1a)	UL0*	Tumor diameter	≤ 2cm	>2cm	≤ 2cm	>2cm
		Incidence of LNM†	0/46 (0%)	1/67 (1.5%)	0/23 (0%)	4/44 (9%)
	UL1‡	Tumor diameter	≤ 3cm	>3cm	≤ 2cm	>2 cm
		Incidence of LNM	3/17 (18%)	1/9 (11%)	0/3 (0%)	4/13 (31%)
Submucosal Invasion (T1b)		Tumor diameter	≤ 3cm	>3cm	Any diameter	
		Incidence of LNM	13/86 (15%)	30/77 (39%)	40/116 (34%)	

* UL0: Absence of ulceration; † UL1: Presence of ulceration; ‡ LNM: Lymph node metastasis.
Green zone: Absolute indication for EMR or ESD; Blue zones: Novel absolute indications for ESD; Yellow zone: Expanded Indication; Red zones: Relative indications.

LNM in T1b tumors ranged from 16% to 42.9% (6,10,37). At the time, submucosal tumors are not eligible for endoscopic treatment, and only patients with T1b tumors without lymphatic infiltration are eligible for less aggressive surgery.

Our study indicated that perineural invasion (PNI) was an independent risk factor for LNM, which is in line with similar previous publications [8,11]. PNI represents the process of neoplastic invasion of the nerves and, it can be detected without lymphatic or vascular invasion [38,39]. The molecular mechanism of PNI is still under investigation, however its relationship with decreased survival has been already reported 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 [15,16]. We suggest that the presence of 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, 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 of LNM. Similarly, in a retrospective study including 1262 patients, the presence of LVI was the furthest significant risk factor for LNM in the multivariate analysis [11]. The difficulty in detecting LVI in endoscopic biopsy is well known and for this reason its presence after endoscopic resection does not qualify as curative resection [15,16]. We suggest that LVI should be carefully evaluated in endoscopic biopsy and endoscopic resection samples. If LVI is confirmed, radical gastrectomy should be performed. Likewise, the differentiation grade and the presence of ulceration have been reported as factors related to the presence of LNM [13,35,44–47]; however, the difficulty for its preoperative diagnosis, especially ulceration, is widely known, with a discrepancy between endoscopic and pathological results of up to 46% [48,49].

Indications for endoscopic treatment in EGC had changed over the years and were initially introduced in the literature based on retrospective studies conducted in Japan [6,13]. The group of patients with differentiated mucosal tumors, not ulcerated and less or equal to 2 cm, showed no possibility of lymphatic metastasis and for this reason, were selected for endoscopic treatment. Currently, the absolute indications for treatment with ESD have been extended in the Japanese guidelines 2018 in which larger and ulcerated tumors are included based on a non-randomized clinical trial and with a possibility of LNM less than 1% [6,50], leaving only undifferentiated tumors as an expanded criterion [16]. Nonetheless, these indications differ globally, even among Eastern guidelines [51].

Endoscopic resection has slowly gained acceptance in the West. Currently the rates of en-bloc resection as well as R0 resections are acceptable but not yet comparable with the results of Eastern countries [52]. Even if endoscopic resection is successful, it is important

to evaluate the local recurrence rate in order to confirm curative treatment. In studies published in Western countries, the recurrence rate after endoscopic treatment is higher than in the East [53]. These results can be explained by a discrepancy between the eastern criteria for endoscopic resection and their true applicability in western patients [54].

According to our results, the group of patients accepted for endoscopic treatment by both the Japanese and Korean guidelines did not present lymphatic metastasis. Therefore, we can recommend this treatment to patients with these specific characteristics (Fig. 3), which is consistent with recommendations from previous Latin American guidelines [55]. Sixty-seven patients presented similar characteristics to the previous group but had a larger tumor diameter, and only 1 (1.5%) patient presented LNM. This only case with lymphatic metastasis has a tumor diameter of 4.5 cm and no lymphovascular or perineural invasion was found. Despite this size difference, the overall percentage of LNM in patients with non-ulcerated, differentiated mucosal tumors remained at acceptable values (0.8%). Considering our results and others obtained in the west [7,12,17], we can suggest that endoscopic resection (ESD) is acceptable and safe in this group of patients regardless of tumor diameter (Fig. 3).

Even though the novel Japanese indications recommended endoscopic resection (ESD) for the patients with ulcerated differentiated-mucosal tumors smaller or equal to 3 cm, in our series, 3 of 17 patients (18%) who met these characteristics presented LNM which is in line with similar western studies [12,56]. Given this discrepancy, the recommendation to perform endoscopic resection in Western patients with ulcerated differentiated-mucosal tumors $\leq$ 3 cm is still debatable. (Fig. 3).

In our study, no patients with undifferentiated mucosal tumors $\leq$ 2 cm presented LNM despite the presence or absence of ulceration. However, when the tumor size was greater than 2 cm, the percentage of LNM increased significantly (0 vs 14%). Currently, a clinical trial evaluating endoscopic treatment (ESD) for this patient group reported a 5-year overall survival (OS) of 99.3% but only 71% of curative resection [57]. Despite the encouraging results obtained in our study in patients with undifferentiated mucosal tumors $\leq$ 2 cm, further studies are required to consider routine endoscopic resection in the global population; but it could be recommended in selected Western cases (Fig. 3).

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 study. Second, our study presents a limited number of patients compared to Eastern publications. Despite this, our study is the largest series in Latin America. Third, the present study involves 30 years of evaluation, which could generate heterogeneity in the population, however, given the small number of EGC patients in the West, a longer period is required.

In conclusion, a larger tumor diameter (>3 cm), submucosal infiltration (T1b), and the presence of lymphovascular and perineural invasion were identified as independent predictive factors of LNM in western patients with EGC. These factors are comparable to Eastern studies. According to our results, the Japanese absolute indications for EMR are safe in the Western population. Likewise, Western patients with differentiated mucosal tumors, non-ulcerated tumors, and larger than 2 cm are susceptible to endoscopic resection. Patients with undifferentiated mucosal tumors smaller than 2 cm presented encouraging results and ESD could be recommended only in selected cases. Randomized clinical trials are still required to identify the subgroups in which overall survival is equivalent between endoscopic resection and standard surgery.

Declarations

Author contribution statement

Oscar Paredes; Carlos Baca: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Renier Cruz: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Kori Paredes; Ivan Chavez: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Carlos Luque-Vasquez: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.

Luis Taxa: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

Eloy Ruiz: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Francisco Berrospi; Eduardo Payet; Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Funding

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

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

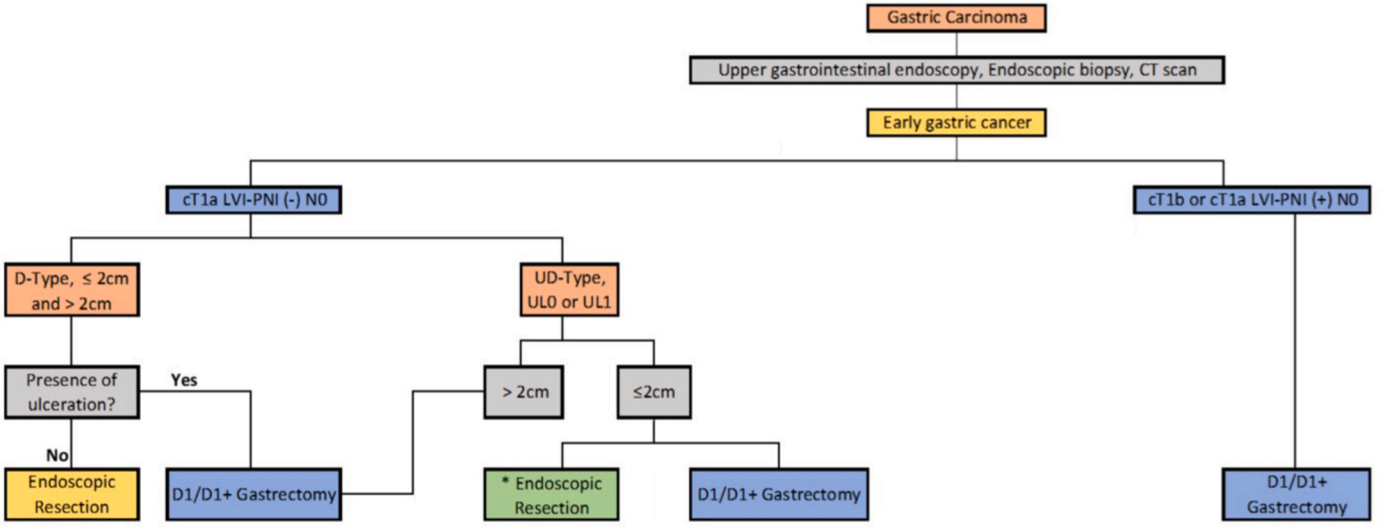

Fig. 3. Algorithm for the management of early gastric cancer according to our results. CT: Computed tomography; LVI: lymphovascular invasion; PNI: perineural invasion; D-Type: differentiated type; UL0: absence of ulceration; UL1: presence of ulceration. * Low grade recommendation, used only for selected cases.

Acknowledgments

The authors would like to thank all the members of the Department of Abdominal Surgery of the National Institute of Neoplastic Diseases INEN, Lima Peru.

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