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Morphological predictors of lymph node metastasis in early gastric cancer

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Abstract

Background The ability to predict the presence of lymph node metastasis has gained significant importance in recent years due to changes in treatment strategies. Ensuring the absence of lymph node metastasis is crucial in the management of early gastric cancer. This consideration can help avoid radical treatments and facilitate organ-sparing approaches. This study aimed to retrospectively evaluate early gastric adenocarcinoma (T1a-b) cases treated with radical surgery and identify the factors that affect lymph node metastasis.

Methods A retrospective analysis was performed on 360 patients who underwent surgery for gastric adenocarcinoma were reviewed, and 41 patients diagnosed with early gastric cancer were included in the study. The relationship between patient age, gender, tumor stage, tumor size, tumor location, histological subtype, lymphovascular invasion, perineural invasion, ulceration, tumor-infiltrating lymphocytes, and lymph node metastases was analyzed. A cumulative risk score was developed using significant predictors to stratify patients into risk groups.

Results The study cohort consisted of 41 patients, with a mean age of 63 years and 66% male. Notably, none of the 14 patients with T1a exhibited lymph node metastasis, whereas 10 of 27 (37%) patients with T1b presented with lymph node metastasis. Univariate analysis revealed that tumor stage ($p=0.009$), tumor differentiation ($p=0.043$), and lymphovascular invasion ($p=0.006$) were significant predictors of lymph node metastasis. Multivariate analysis identified a significant association between lymphovascular invasion ($p=0.024$) and tumor size ($p=0.05$) with lymph node metastasis. The proposed risk scoring system effectively stratified patients into low, intermediate, and high-risk groups.

Conclusion Examination of radical surgical specimens suggests that organ-preserving methods based on expanded ESD criteria could be a viable option for our population. Tumor stage, histological subtype, tumor size, and lymphovascular invasion were identified as factors influencing the incidence of lymph node metastasis, with tumor stage and lymphovascular invasion emerging as primary determinants. The exploratory scoring model may aid in risk-based clinical decision-making, particularly in selecting candidates for non-surgical treatment.

Keywords Early gastric cancer, Endoscopic submucosal dissection, Gastric adenocarcinoma, Lymph node metastasis, Histological subtype

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Background

Gastric cancer (GC) remains the third leading cause of cancer-related mortality worldwide. However, the rate of early diagnosis has significantly improved over the past few decades [1]. According to recent reports, more than 60% of newly diagnosed gastric cancer cases in Japan are identified as early gastric cancer, underscoring the importance of early detection and treatment [2].

Early gastric cancer is defined as tumors that invade no deeper than the submucosa, regardless of lymph node metastasis (pT1), according to the recent TNM classification [3]. The presence of lymph node metastasis is a significant indicator of patient survival and serves as a critical factor in determining appropriate treatment options. Historically, the standard recommendation was to pursue radical surgery irrespective of lymph node status. However, in the context of early gastric cancer, when it has been confirmed that there is no lymph node metastasis, organ-preserving treatment modalities may now be preferentially considered. There is growing interest in organ-preserving modalities due to their potential to minimize morbidity and mortality while improving the overall quality of life, especially in cases of early gastric cancer. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have become standard procedures for managing early gastric cancer, particularly in Asia [4–7]. The recent expansion criteria of the Japanese gastric cancer guidelines have broadened the criteria for considering ESD, including (1) differentiated non-ulcerating T1a tumors larger than 2 cm, (2) differentiated ulcerating T1a lesions 3 cm or smaller, (3) undifferentiated non-ulcerating T1a tumors 2 cm or smaller, and (4) differentiated non-ulcerating T1b tumors 3 cm or smaller within 500 μ m of the muscularis mucosa [6].

Various studies have identified the factors that predict lymph node metastasis, particularly in Asian populations [8, 9]. The primary objective was to utilize factors such as tumor size, ulceration, tumor histology, depth of invasion, and lymphovascular invasion are critical in determining the likelihood of lymph node metastasis [10–13]. Western guidelines remain more conservative than the increasingly expansive Eastern guidelines, leading to an ongoing debate regarding the optimal approach for evaluating gastric cancer pathology [14, 15].

Distinct variations in lymph node metastasis rates between Eastern and Western studies are evident, with Eastern studies demonstrating superior survival and lower rates of lymph node metastasis. This discrepancy has led to skepticism about the applicability of the “expanded ESD criteria” in Western contexts [8, 10, 11].

This study aims to identify the morphological factors influencing lymph node metastasis in early gastric cancer,

contributing to the varying lymph node metastasis rates reported in different populations within the literature.

Methods

Study design

This retrospective cohort study was conducted using data from patients who underwent surgical resection for early gastric cancer at the Department of General Surgery of the Istanbul Faculty of Medicine.

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (1964) and its subsequent amendments, which emphasize respect for individuals, beneficence, and justice in biomedical research involving human subjects. Ethical approval was obtained from the Istanbul University, Istanbul Faculty of Medicine Ethics Board (approval number: 1779298, May 26, 2023). Due to the retrospective nature of the study, individual informed consent was not required. However, all patients had previously signed institutional consent forms allowing the use of their anonymized clinical data for academic and research purposes.

Patient selection

Patients with confirmed pT1 adenocarcinoma after curative resection for gastric cancer between January 2011 and December 2022 at the Istanbul Faculty of Medicine Department of General Surgery were included. Patients who received neoadjuvant therapy or surgery for recurrent or remnant disease were excluded from the study.

All patients were staged using thoracic and abdominal computed tomography (CT) and Positron Emission Tomography/Computed Tomography (PET/CT) before surgery following endoscopic diagnosis.

A total of 360 patients underwent resection during this period, of whom 41 (11%) were confirmed to have pT1 early gastric cancer. All surgeries were performed by the same team with consistent D2 dissection.

Pathological evaluation was performed by a single gastrointestinal pathologist. Due to the retrospective nature of the study, blinding was not performed.

Variables

The following variables were analyzed: age, sex, tumor location (cardia, corpus, and antrum), tumor size, depth of invasion (intramucosal (T1a) and submucosal (T1b)), ulceration, tumor differentiation (well, moderate, and poor), histologic subtype (adenocarcinoma, signet ring cell carcinoma, mucinous adenocarcinoma), lymphovascular invasion (LVI), tumor-infiltrating lymphocytes, and perineural invasion. The total number of harvested lymph nodes was also analyzed.

The primary endpoint was the association between the variables and LNM. The secondary endpoint was

the eligibility of the patients for ESD according to the expanded criteria.

Statistical analysis

The data were analyzed using Kolmogorov-Smirnov and Shapiro-Wilk tests to assess the normality of quantitative variables. Categorical data are presented as numbers and percentages, while quantitative data are reported as medians with minimum-maximum ranges. The Pearson Chi-Square test was used to compare the effects of categorical variables on lymph node involvement, and the Mann-Whitney-U test was used for non-normally distributed quantitative variables. Logistic regression was used for multivariate analysis of factors affecting lymph node positivity. Statistical significance was set at $p < 0.05$. Statistical analyses were conducted using SPSS Version 28.0 (IBM, USA).

Table 1 Baseline characteristics

Age		63 (33–81)	
Median (min-max)		n	%
Gender (n = 41)	Female	14	34
	Male	27	66
Tumor Location (n = 41)	Cardia	8	20
	Corpus	6	14
	Antrum	27	66
Depth of Invasion (n = 41)	T1a	14	34
	T1b	27	66
Differentiation (n = 38)	Well	2	5
	Moderate	16	42
	Poor	20	53
Tumor Size (cm)		2,5 (0,2–6)	
Median (min-max)		n	%
Tumor size (n = 41)	≤ 2 cm	17	42
	≤ 3 cm	30	73
	> 3 cm	11	27
Ulceration (n = 40)	Positive	24	60
	Negative	16	40
Lymphovascular invasion (n = 34)	Positive	16	47
	Negative	18	53
Perineural invasion (n = 33)	Positive	3	10
	Negative	30	90
Tumor-infiltrating lymphocytes (n = 27)	Positive	10	37
	Negative	17	63
Histologic subtype (n = 38)	Signet ring cell carcinoma	12	32
	Adenocarcinoma	24	63
	Mucinous	2	5
	adenocarcinoma		
Lymph node metastasis (LNM) (n = 41)	Positive	10	24
	Negative	31	76

Risk stratification model

To assess the cumulative effect of significant clinicopathological predictors on lymph node metastasis (LNM), we developed a data-driven risk scoring system using our own patient cohort. Variables were selected based on their statistical association with LNM in univariate analysis and their clinical relevance.

Point values were assigned proportionally to the observed LNM rates within each subgroup. Lymphovascular invasion (LVI) and submucosal invasion (T1b) demonstrated the highest LNM rates (40–45%) and were each assigned 2 points. Poor tumor differentiation and tumor size greater than 3 cm were associated with more modest increases in LNM risk and were each assigned 1 point. This generated a total cumulative score ranging from 0 to 6 per patient.

Based on the distribution of scores and corresponding LNM incidence, patients were stratified into three risk categories: low (0–2 points), intermediate (3–4 points), and high (5–6 points). The relationship between these categories and actual LNM positivity was analyzed descriptively and visualized.

Although the eCura system is widely used to guide post-ESD surveillance, we did not directly apply it for two reasons: first, our cohort consisted entirely of surgically treated patients without actual ESD procedures; second, key eCura variables such as vertical margin status and venous invasion were unavailable in our dataset. Thus, a simplified, exploratory scoring model tailored to our data was developed to enable internal stratification.

Results

Patient characteristics

The study included 41 patients with a median age of 63 years (range: 33–81 years). Among them, 66% (27/41) were male. Tumors were located in the antrum in 66% (27/41) of cases, and 66% (27/41) were submucosal (pT1). Tumor differentiation was classified as poor in 53% (20/38) of cases, and the signet ring cell carcinoma subtype was identified in 32% (12/38). Lymphovascular invasion (LVI) was present in 47% (16/34) of cases, and lymph node metastasis (LNM) was observed in 24% (10 out of 41). The average number of harvested lymph nodes was 27. The baseline characteristics are detailed in Table 1.

Univariate analysis of factors affecting lymph node metastasis

In univariate analysis, lymphovascular invasion ($p < 0.01$), depth of invasion ($p < 0.01$), and tumor differentiation ($p = 0.04$) were significant predictors of LNM. Table 2 presents the results of the univariate analysis.

Variables affecting LNM were analyzed using a logistic regression analysis. Tumor size (OR: 1.75, 95% CI 1–3.06,

Table 2 Univariate analysis of factors affecting LNM

		LNM positive		LNM negative		p
		n	%	n	%	
Age						0,223 ^M
Gender (n = 41)	Female	5	36	9	64	0,267 ^K
	Male	5	18	22	82	
Tumor Location (n = 41)	Proximal	2	25	6	75	0,848 ^K
	Distal	8	24	25	76	
Depth of Invasion (n = 41)	T1a	0		14	100	0,009^K
	T1b	10	37	17	63	
Differentiation (n = 38)	Well and moderate	2	11	16	89	0,043^K
	Poor	8	40	12	60	
Tumor size (n = 41)	≤ 3 cm	7	23	23	77	0,119 ^M
	> 3 cm	3	27	8	73	
Ulceration (n = 40)	Positive	7	29	17	71	0,711 ^K
	Negative	3	19	13	81	
Lymphovascular invasion (n = 34)	Positive	8	50	8	50	0,006^K
	Negative	1	6	17	94	
Perineural invasion (n = 33)	Positive	2	67	1	33	0,174 ^K
	Negative	7	23	23	77	
Tumor-infiltrating lymphocytes (n = 27)	Positive	2	20	8	80	0,678 ^K
	Negative	5	29	12	71	
Histologic subtype (n = 38)	Signet ring cell carcinoma	3	27	8	73	0,629 ^K
	Adenocarcinoma	5	21	19	79	
	Mucinous adenocarcinoma	1	50	1	50	

^M Mann-Whitney U Test^K Pearson Chi-square Test**Table 3** Logistic regression analysis of node positivity

	OR	CI (%95)	p
Age	0,96	0,91 – 1,02	0,211
Gender	1,5	0,08–26,85	0,783
Tumor size	1,75	1–3,06	0,05
Differentiation	5,33	0,95 – 29,81	0,057
Lymphovascular invasion	17	1,81–160,05	0,013
Perineural invasion	6,57	0,52–83,76	0,147
Tumor location(proximal)	1,04	0,17 – 6,22	0,964
Ulceration	1,78	0,39 – 8,27	0,459
Tumor-infiltrating lymphocytes	0,6	0,09 – 3,89	0,592

OR: Odds Ratio, CI: Confidence Interval

$p = 0.05$) and LVI (OR: 17, 95% CI 1.81-160.05, $p = 0.001$) were found to be significant. (Table 3)

Risk stratification analysis

A total risk score ranging from 0 to 6 was calculated for each patient based on the presence of four variables: lymphovascular invasion (2 points), submucosal invasion (2 points), poor tumor differentiation (1 point), and tumor size > 3 cm (1 point). Based on cumulative scores, patients were categorized into low (0–2 points), intermediate (3–4 points), and high (5–6 points) risk groups.

Of the 41 patients, 18 (44%) were classified as low risk, 12 (29%) as intermediate, and 10 (24%) as high risk. LNM was observed in 1 patient (5.6%) in the low-risk group,

3 patients (25%) in the intermediate-risk group, and 6 patients (60%) in the high-risk group. A clear trend of increasing LNM prevalence with higher risk score was observed (Fig. 1).

Validation of endoscopic resection criteria

All patients were evaluated according to the criteria for endoscopic resection. Cases meeting the specified criteria did not exhibit lymph node metastasis (LNM). Twelve patients met the expanded ESD criteria in our cohort, and none of the patients had lymph node metastasis. One patient exhibited LNM positivity without LVI. The tumor was classified as T1b, > 3 cm, and poorly differentiated, thus failing to meet specified criteria. (Table 4)

Discussion

In our study, 24% of pT1 gastric adenocarcinomas exhibited lymph node metastasis (LNM), a rate slightly higher than that reported in Eastern studies, but consistent with findings from Western studies. For example, a Japanese study involving 5,265 patients by Gotoda et al. reported 2.2% positive lymph node metastases in 3,016 intramucosal cases (pT1a), and 17.9% in 2,249 submucosal cases (pT1b) [8]. Similarly, Hölscher et al. reported that, reported 10.6% lymph node metastasis in intramucosal tumors and 25.3% lymph node metastasis in submucosal tumors in a study of 121 early gastric cancer cases [16]. A

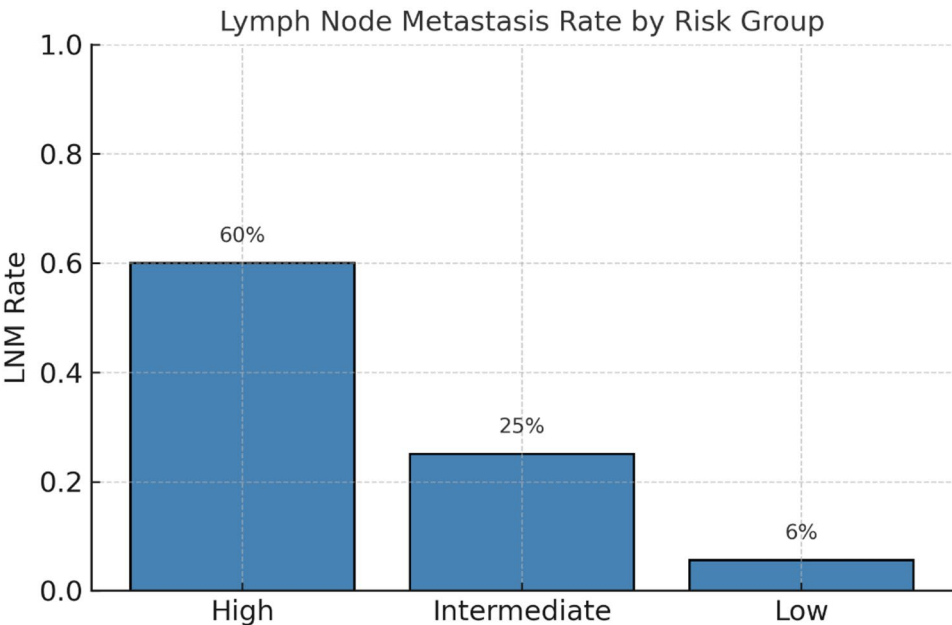


Fig. 1 Lymph node metastasis (LNM) rate by risk group. Patients were stratified into low (0–2 points), intermediate (3–4 points), and high (5–6 points) risk categories based on a cumulative risk score. LNM rates were 5.6%, 25%, and 60%, respectively

Table 4 Validation of ESD criteria

Differentiation	Tumor size	LVI negative			LVI positive		
		Total	LNM positive		Total	LNM positive	
			n	%		n	%
Well and moderate	≤ 2 cm	4	0	0	3	1	33
	≤ 3 cm	6	0	0	5	2	40
	> 3 cm	0			2	2	100
Poor*	≤ 2 cm	2	0	0	3	2	67
	≤ 3 cm	7	0	0	5	4	80
	> 3 cm	4	1	25	3	2	67

LVI: Lymphovascular invasion, LNM: Lymph node metastasis
*Signet ring cell carcinoma and mucinous adenocarcinomas classified as poorly differentiated

recent Canadian study by Watanabe et al. reported lymph node metastasis rates of 3.8% in intramucosal tumors and 41% in submucosal tumors [11]. Disparity between the Eastern and Western pathological standards must be considered when comparing these rates. In Japan, severe dysplastic cytologic atypia, characterized by enlarged vesicular oval nuclei and prominent nucleoli, is sufficient for cancer diagnosis, whereas in the West, evidence of invasion into the lamina propria is required. The difference presents a challenge in defining early cancer, and an ongoing debate persists on this issue [17–19]. In our study, we observed a 37% rate of lymph node metastasis in submucosal tumors.

Clinical staging is the initial step in determining treatment options. Endoscopy, CT, PET/CT, and particularly for early-stage cases, endoscopic ultrasound (EUS) are recommended. CT scans can detect the depth of invasion at a rate of 43–82%, whereas PET/CT identifies it

at a lower rate. Additionally, CT can detect lymph node metastasis at a rate of 56%, while PET/CT detects it at a rate of 78%. Although these rates seem improved through combined use, they do not demonstrate high reliability in excluding lymph node metastasis [20–22].

Endoscopic Ultrasound (EUS) is endorsed as a method for assessing the depth of invasion and the presence of lymph node metastasis. However, operator dependency may introduce a level of subjectivity in the evaluation of results. A comprehensive multicenter study revealed that EUS achieves an accuracy of 46.2% in detecting the depth of invasion and an accuracy of 66.7% in identifying lymph node metastasis [23]. When combined with other imaging methods, sensitivity and specificity have been shown to increase. EUS is particularly useful for distinguishing between T1 and T2 stages. In a meta-analysis involving 2,772 patients from 46 studies for differentiating T1 from T2, sensitivity and specificity were found to be 0.85 (95%

CI 0.78 to 0.91) and 0.90 (95% CI 0.85 to 0.93), respectively [24]. Although EUS seems superior to other imaging methods for local staging, particularly in early gastric cancer; however, literature shows varying results due to its operator-dependent nature.

The presence of LNM is a critical factor limiting the use of endoscopic resection for gastric cancer. Curative endoscopic resection with negative margins in LNM-negative gastric cancer is now the standard practice. Therefore, accurate prediction of LNM is essential for successful management of early gastric cancer with endoscopic resection. Factors such as tumor size, histology, and lymphovascular invasion have been identified as important predictors in this regard [7].

In our cohort, lymph node metastasis was detected in 24% of patients with pT1 gastric adenocarcinoma, including 37% of those with submucosal invasion. These findings support the continued necessity of surgical resection in patients who do not clearly meet endoscopic resection criteria. Notably, Petrucciani et al. [25] emphasized that, despite the growing adoption of endoscopic treatment, lymphadenectomy remains crucial for accurate staging in early gastric cancer. Their analysis showed that even among patients meeting endoscopic resection criteria, a small but clinically meaningful proportion exhibited nodal involvement, underscoring the limitations of current predictive models and the ongoing need for surgical lymph node assessment in selected patients.

In the literature, there is debate regarding the total number of lymph nodes required to accurately assess metastasis. A review by Kwee et al. of 40 studies on lymph node metastasis in early gastric cancer highlighted that 16% of these studies included D2 dissection, with emphasis on the number of lymph nodes removed [12]. Current guidelines recommend removing at least 15 lymph nodes to ensure adequate staging [5]. During the study period, D2 dissection was consistently performed at our institution, and we reported a median lymph node harvest of 27, which is in line with current standards.

Tumor location may influence surgical technique and has been suggested as a potential predictor of lymph node metastasis. However, our findings align with those of recent studies that showed no significant relationship between tumor location and lymph node metastasis. A large study by ZeLong et al., which investigated 5440 cases of early gastric cancer, found no significant difference between proximal and distal gastric tumors, consistent with previous Asian studies [13]. Similarly, our study did not find that tumor location was a significant predictor of LNM. (OR:1.04 [95% CI 0.17–6.22], $p=0.14$)

Tumor size was identified as a significant factor in predicting lymph node metastasis, with larger tumors being more likely to exhibit LNM. This factor is now incorporated into the ESD criteria. (OR: 1.6, 95% CI 1–3.05,

$p=0.05$). The role of tumor size in undifferentiated carcinomas remains debatable. Oh et al. in Korea found that tumors smaller than 2 cm without LVI had a low risk LNM rate of 1.5%, and tumors smaller than 0.9 cm showed no LNM [26]. When assessed in conjunction with other variables in the study by Kim et al., encompassing 3246 patients, tumor size was significant [27]. Our findings align with this finding, as smaller tumors without LVI showed a lower risk of LNM.

Lymphovascular invasion and tumor differentiation were identified as the strongest predictors of LNM in our study, consistent with findings in the literature [7, 8]. In particular, LVI emerged as the most significant factor (OR:17, [95% CI 1.81–160.05], $p<0.01$). This is consistent with previous studies that highlight LVI and depth of invasion as the most important predictors of LNM [9, 28]. Perineural invasion, although significant in other studies, did not show a significant correlation with lymph node metastasis in our study (OR:6.57 [95% CI 0.52–83.76], $p=0.14$).

Our findings allowed us to propose an exploratory risk stratification model for predicting lymph node metastasis (LNM) in early gastric cancer. The model, integrating four key pathological variables, effectively differentiated patients into low-, intermediate-, and high-risk groups with LNM rates of 5.6%, 25%, and 60%, respectively. While preliminary, these results suggest that such a scoring system could assist in refining individualized treatment decisions, particularly when evaluating the suitability of non-surgical approaches such as endoscopic resection.

Although the eCura system is widely used for stratifying LNM risk in patients undergoing endoscopic resection, we did not apply it in our study for two reasons: first, our cohort consisted solely of surgically resected patients who did not undergo ESD; second, essential variables required for eCura scoring—such as vertical margin status and venous invasion—were not consistently available. As a result, we sought to develop a simplified and internally coherent model based on the variables present in our dataset.

Similar predictive models have been reported in the literature. For instance, Sekiguchi et al. developed a risk-scoring model incorporating tumor size, submucosal invasion depth, histological type, ulcerative findings, and lymphovascular involvement to predict LNM in early gastric cancer patients undergoing gastrectomy in Japan [29]. However, to our knowledge, such stratification tools have rarely been validated or developed in Western surgical cohorts. This distinction underscores the potential contribution of our findings to expanding the applicability of risk-adapted treatment algorithms in broader clinical settings. Further validation in larger, multicentric Western cohorts is warranted.

Unlike most existing models for LNM prediction, which have been developed and validated in Eastern populations undergoing endoscopic resection, our scoring system is based on a Western patient cohort that underwent surgical resection with full pathological assessment of resected specimens. This distinction is critical, as it allows for direct histopathological validation of lymph node status and provides insight into a patient group often underrepresented in endoscopic series. Our model therefore contributes to the literature by addressing LNM risk stratification in a surgically treated Western population—a context where external validation of existing risk models remains limited.

This study has several limitations. First, the sample size is relatively small, which may limit the statistical power of both univariate and multivariate analyses. Second, the retrospective and single-center design may introduce selection and reporting biases. Third, certain variables relevant to established scoring systems, such as venous invasion or vertical margin status, were not available in all cases, limiting the direct applicability of external models like eCura. Finally, while our risk scoring model demonstrated promising internal discriminatory capacity, it should be interpreted as hypothesis-generating and requires prospective validation in larger, multi-institutional Western cohorts.

Conclusion

This study demonstrated a higher prevalence of lymph node metastasis in early gastric cancer in Western populations than in Eastern populations, which is consistent with previous literature. Factors such as the depth of invasion, lymphovascular invasion, tumor size, and tumor differentiation are critical in predicting lymph node metastasis. Our findings suggest that the expanded Endoscopic Submucosal Dissection (ESD) criteria may be feasible for use in Western populations. Additionally, the proposed risk scoring system effectively stratified patients into low-, intermediate-, and high-risk groups and may support individualized treatment planning. However, larger-scale studies in both Eastern and Western contexts are needed to validate these findings and further refine the criteria for endoscopic resection in early gastric cancer.

Abbreviations

CT	Computed Tomography
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
EUS	Endoscopic Ultrasound
GC	Gastric cancer
LNM	Lymph node metastasis
PET/CT	Positron Emission Tomography / Computed Tomography

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Author contributions

Research conducted by MKG and HAB, with MB analyzing pathological specimens and reports, while LDE, MI, and AFKG examined data and gathered appropriate cases. HAB and IG analyzed the results and wrote the paper. All authors reviewed and approved the final manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Istanbul University, Istanbul Faculty of Medicine Ethics Board (Approval No. 1779298, dated May 26, 2023). The study was conducted in accordance with the Declaration of Helsinki and its later amendments. Due to the retrospective nature of the study, the requirement for individual informed consent was waived by the ethics committee. However, all patients had previously signed institutional consent forms permitting the use of anonymized clinical data for academic and research purposes.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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