Journal for Re Attach Therapy and Developmental Diversities
eISSN: 2589-7799
2023 June; 6(6s): 367-378

The Psychological and Clinicopathologic Factors Forecasting Lymph Node Metastasis in Early Gastric Cancers: A Single Facility Study in Vietnam

Tran Ngoc Dung[1], Nguyen Tuan Thanh[2], Pham Van Thinh[1], Nguyen Mai Hanh[1], Nguyen Thuy Linh[1], Dang Thai Tra[1], Truong Dinh Tien[1], Dang Son Tung[1], Pham Xuan Huy[3], Lewis A. Hassell[4], Dang Thanh Chung[1]*

[1]Department of Pathology and Forensic Medicine, Military Hospital 103, Vietnam Military Medical University, Ha Noi, Viet Nam.
[2]Bach Mai Hospital, Hanoi, Vietnam.
[3]Department of Pathophysiology, Vietnam Military Medical University, Hanoi, Viet Nam.
[4]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA.
*Corresponding author:
Dang Thanh Chung
Department of Pathology and Forensic Medicine, Military Hospital 103, Vietnam Military Medical University, Ha Noi, Viet
E-mail: dangthnhchung@vmmu.edu.vn.

Received: 09-April-2023
Revised: 15-May-2023
Accepted: 10-June-2023

Abstract

Introduction: Lymph node metastasis (LNM) plays a critical role in predicting the prognosis of early gastric cancer (EGC). However, accurately diagnosing LNM in EGC patients remains a challenge, as reliable methods are currently lacking.

Objectives: This study aims to explore the clinicopathologic characteristics associated with LNM in EGC and identify the risk factors that can predict LNM in patients treated at a central hospital in Vietnam.

Methods: A cross-sectional study was undertaken on EGC patients diagnosed based on histology between July 2018 and December 2019 at a central hospital in Vietnam. Univariate and multivariate analyses were employed to examine clinicopathologic characteristics and identify independent risk factors for LNM.

Results: The univariate analysis did not show any significant associations between age, sex, tumor location, gross appearance, tumor differentiation status, Lauren classification, World Health Organization (WHO) classification, and LNM. However, larger tumor size, deeper tumor invasion, and moderate grade tumor budding were found to be significantly correlated with a higher incidence of LNM. Multivariable logistic regression analysis revealed that low and moderate grade tumor budding independently served as risk factors for LNM.

Conclusions: Tumor size, depth of tumor invasion, and tumor budding are closely linked to LNM in EGC. Specifically, low and moderate grade tumor budding are independent risk factors for LNM and are crucial in the management of EGC. This study provides valuable insights for predicting LNM in EGC patients and enhancing the clinical management of this disease.

Keywords: tumor budding, clinicopathologic characteristics, early gastric cancer, lymph node metastasis.

1. Introduction

The World Health Organization (WHO) defines early gastric cancer (EGC) as a tumor situated in the mucosa or submucosa of the stomach, with or without LNM. EGC refers to a tumor located in the mucosa or submucosa of the stomach, with or without the presence of LNM, according to the definition provided by the WHO [1]. In recent years, the detection of EGC has increased with advances in endoscopy. Patients with EGC have a 5-year survival rate of over 90%, while those with advanced gastric cancer have a rate below 10% [2, 3]. Endoscopic resection is a minimally invasive treatment method recommended for EGC patients with low risk of LNM, which can decrease complications, improve quality of life, and shorten hospitalization [4-6]. Prior to undergoing radical surgery, it is

essential to identify EGC patients with a low risk of lymph node metastasis (LNM) to avoid unnecessary overtreatment. Moreover, it is important to recognize that LNM is the primary factor influencing the prognosis of survival in EGC. [7-10]. Therefore, it is crucial to accurately identify the risk of LNM in order to determine the most suitable treatment approach and prognosis for patients with EGC.

Presently, imaging-based diagnostic techniques like computed tomography, magnetic resonance imaging, and endoscopic ultrasonography lack reliability in accurately determining the precise lymph node metastasis (LNM) status. [11-14]. Hence, certain clinicopathologic characteristics have been identified as potential indicators for predicting the risk of LNM in EGC. These features include age, sex, tumor location, gross appearance, tumor size, tumor differentiation status, Lauren classification, WHO classification, depth of tumor invasion, and tumor budding score. [7, 15-30]. Nevertheless, there exists controversy regarding the significance of these factors in predicting LNM in EGC, necessitating further investigation.

According to GLOBOCAN data in 2020, gastric cancer ranks as the fourth most prevalent cancer in Vietnam, with an annual incidence of 17,906 cases and a 5-year prevalence rate of 24.64 per 100,000.[31]. However, data on EGC in Vietnam are limited, with non-cardia EGC accounting for only 7.6% in central Vietnam [32]. Moreover, no studies have evaluated and identified risk factors for LNM in EGC in Vietnam, despite extensive research conducted in other countries.

In conclusion, EGC holds a favourable prognosis and high survival rate when detected at an early stage. Accurate identification of risk factors for lymph node metastasis (LNM) is crucial for determining the most appropriate treatment approach and predicting patient outcomes. While various clinicopathologic features have been proposed as potential indicators of LNM, their role in this context remains subject to debate. This study aims to elucidate the association between these factors and LNM in EGC patients in Vietnam, where data on EGC is limited, thereby offering valuable insights for the clinical management of EGC in this particular region.

2. Objectives

This study enrolled a total of 60 patients diagnosed with EGC based on histological examination. These patients underwent radical gastrectomy with lymph node dissection. Exclusion criteria included a history of preoperative chemotherapy or radiotherapy, presence of metastatic cancer, or any other type of cancer. The cross-sectional study was conducted at Bach Mai Hospital in Hanoi, Vietnam, spanning from July 2018 to December 2019. The study adhered to the ethical guidelines established by the national research committee and the 1964 Helsinki Declaration. Institutional Review Board of Bach Mai Hospital has been approved. (approval code being 196/QĐ-HVQY and the approval date being January 9, 2018).

3. Methods

3.1.Patient characteristics and tumor budding score

Patients Clinicopathologic characteristics were collected, including sex, age, lymph node metastasis, tumor location, gross appearance, and tumor size. Based on cytological and structural criteria, the tumor differentiation status classified patients into well, moderately, and poorly differentiated categories [1]. The Lauren classification, which divides gastric cancer into subtypes based on histological features, was also used to categorize the tumors as intestinal, diffuse, or mixed [33]. The WHO classification issued in 2010 classified gastric cancer as tubular adenocarcinoma, poorly cohesive carcinomas, mixed carcinoma, or undifferentiated carcinoma [34]. In EGC, the depth of tumor invasion on the gastric wall was classified as carcinoma limited to the mucosa (pT1a) and submucosa (pT1b), according to the 8th edition of the UICC/AJCC TNM stage classification [35].

The tumor budding scores were analyzed in patients with EGC following the guidelines of the International Tumor Budding Consensus Conference (ITBCC) 2016 [36]. Hematoxylin and eosin (H&E) staining was utilized to assess the tumor budding score in each specimen based on histological criteria. The deepest invasive region and the area with the highest tumor cell density were selected for evaluation. Ten representative hotspots in the specific area of interest were captured using a 20x objective lens, equivalent to a magnification of 200x. The number of tumor buds in each hotspot was counted, and the count was adjusted to tumor buds/0.785mm2 using a conversion factor. Tumor budding was categorized into three grades based on the following scale: Low grade (Bd1): 0-4 tumor

buds/0.785mm2; Moderate grade (Bd2): 5-9 tumor buds/0.785mm2; High grade (Bd3): ≥ 10 tumor buds/0.785mm2.

3.2. Statistical analysis

Categorical variables were presented as frequencies and percentages. The relationship between clinicopathologic characteristics and lymph node metastasis (LNM) was assessed using the Chi-square test and Fisher's exact test. Data analysis was performed using GraphPad Prism 9 software (GraphPad Software, Inc.). Univariate analysis was initially conducted to identify statistically significant factors associated with LNM. Subsequently, multivariate logistic regression analysis was performed among these factors to determine the independent risk factors for LNM. The data analysis was carried out using STATA statistical software (Release 14, College Station, TX: StataCorp LP). Statistical significance was considered at a p-value < 0.05.

The relationship between clinicopathologic characteristics and LNM was assessed using the Chi-square test and Fisher's exact test. GraphPad Prism 9 software (GraphPad Software, Inc.) was utilized for data analysis. Initially, univariate analysis was conducted to identify statistically significant factors associated with LNM. Subsequently, multivariate logistic regression analysis was performed on these factors to determine the independent risk factors for LNM. STATA statistical software was used for the data analysis. A p-value < 0.05 was considered statistically significant.

4. Results

4.1.Clinicopathologic data and associations with lymph node metastasis in patients with early gastric cancer

Table 1 presents the clinicopathologic characteristics of patients with early EGC enrolled in the study. The age of patients ranged from 21 to 83, with individuals aged 60 or above accounting for the majority (61.7%). Males constituted the majority of patients (71.7%) compared to females (28.3%). The incidence of LNM in EGC was 10.0%. Most tumors were located in the antrum (86.7%), with fewer cases in the cardia (5.0%), the body (5.0%), and the pylorus (3.3%). Based on the gross appearance, type 0-III tumors were the most common (58.3%), followed by type 0-II (36.7%) and type 0-I (5.0%). Tumor size was classified into two groups with similar proportions: ≤ 2 cm (48.3%) and > 2 cm (51.7%). The majority of tumors were moderately differentiated (71.6%), followed by poorly differentiated (26.7%) and well-differentiated (1.7%). According to Lauren's classification, intestinal and diffuse subtypes accounted for 54.0% and 46.0% of cases, respectively. Among WHO classifications, tubular adenocarcinoma was the most frequent (80.0%), followed by poorly cohesive carcinomas (13.3%), undifferentiated carcinoma (5.0%), and mixed carcinoma (1.7%). The EGC cases in the study were divided into two groups, with similar rates of pT1a (48.3%) and pT1b (51.7%). The low-grade tumor budding score accounted for the majority of cases (81.7%), followed by moderate-grade (15.0%) and high-grade (3.3%).

Table 1. Clinicopathologic features of early gastric cancer

Characteristics		**n (%)**
Age		
	< 40	6 (10.0)
	40-49	3 (5.0)
	50-59	14 (23.3)
	≥ 60	37 (61.7)
Sex		
	Male	43 (71.7)
	Female	17 (28.3)
Lymph node metastasis		
	Positive	6 (10.0)
	Negative	56 (90.0)
Tumor location		
	Cardia	3 (5.0)
	Body	3 (5.0)
	Antrum	52 (86.7)
	Pylorus	2 (3.3)
Gross appearance		

	Type 0-I	3 (5.0)
	Type 0-II	22 (36.7)
	Type 0-III	35 (58.3)
Tumor size		
	≤2 cm	29 (48.3)
	>2cm	31 (51.7)
Tumor differentiation status		
	Well	1 (1.7)
	Moderately	43 (71.6)
	Poorly	16 (26.7)
Lauren classification		
	Intestinal	27 (54.0)
	Diffuse	23 (46.0)
WHO classification		
	Tubular adenocarcinoma	48 (80.0)
	Poorly cohesive carcinomas	8 (13.3)
	Mixed carcinoma	1 (1.7)
	Undifferentiated carcinoma	3 (5.0)
Depth of tumor invasion		
	pT1a	29 (48.3)
	pT1b	31 (51.7)
Tumor budding score		
	Low (Bd1)	49 (81.7)
	Moderate (Bd2)	9 (15.0)
	High (Bd3)	2 (3.3)

Bd: budding; n: number; WHO: World Health Organization.

The correlation between clinicopathologic characteristics of patients and LNM in EGC is presented in Table 2. Out of the total 60 patients, only six (10.0%) had LNM. The statistical analysis indicated no significant relationship between sex, age, tumor location, gross appearance or histologic classification based on Lauren's or WHO criteria and LNM. However, the findings demonstrated a significant association between larger tumor size, deeper tumor invasion, and tumor budding score with LNM ($p < 0.05$ for tumor size and depth of tumor invasion; $p < 0.0001$ for tumor budding score).

Table 2. Associations of clinicopathologic features

Characteristics		**Lymph node metastasis, n (%)**		**p***
		Positive	Negative	
Age				
	< 40	1 (16.7)	5 (83.3)	
	40-49	11 (33.3)	5 (66.7)	0.3526
	50-59	2 (14.3)	12 (85.7)	
	≥ 60	2 (5.4)	35 (94.6)	
Sex				
	Male	3 (7.0)	40 (93.0)	0.3379#
	Female	3 (17.6)	14 (82.4)	
Tumor location				
	Cardia	0 (0)	3 (100.0)	
	Body	0 (0)	3 (100.0)	0.7950
	Antrum	6 (11.5)	46 (88.5)	
	Pylorus	0 (0)	2 (100.0)	
Gross appearance				
	Type 0-I	0 (0)	3 (100.0)	
	Type 0-II	0 (0)	22 (100.0)	0.0925
	Type 0-III	6 (17.1)	29 (82.9)	
Tumor size				
	≤2 cm	0 (0)	29 (100.0)	**0.0242#**
	>2cm	6 (19.4)	25 (80.6)	

Tumor differentiation status				
	Well	0 (0)	1 (100.0)	
	Moderately	5 (11.6)	38 (88.4)	0.7836
	Poorly	1 (6.3)	15 (93.7)	
Lauren Classification				
	Intestinal	4 (14.8)	23 (85.2)	0.6740#
	Diffuse	2 (8.7)	21 (91.3)	
WHO classification				
	Tubular adenocarcinoma	5 (10.4)	43 (89.6)	
	Poorly cohesive carcinomas	1 (12.5)	7 (87.5)	0.9169
	Mixed carcinoma	0 (0)	1 (100.0)	
	Undifferentiated carcinoma	0 (0)	3 (100.0)	
Depth of tumor invasion				
	pT1a	0 (0)	29 (100.0)	**0.0244#**
	pT1b	6 (19.4)	25 (80.6)	
Tumor budding score				
	Low (Bd1)	1 (2.0)	48 (98.0)	
	Moderate (Bd2)	4 (44.4)	5 (55.6)	**< 0.0001**
	High (Bd3)	1 (50.0)	1 (50.0)	

Bd: budding; n: number; WHO: World Health Organization; p values were determined using the (*) Chi-square test and (#) Fisher's exact test.

4.2. Risk factors for lymph node metastasis in early gastric cancer

To identify the independent risk factors for lymph node metastasis (LNM) among the examined clinical and pathological features, a multivariable logistic regression analysis was conducted on the factors that showed a significant association with LNM in the univariate analysis (Table 3). The results revealed that tumor budding, characterized by low (odds ratio [OR] = 48, p = 0.026) and moderate (OR = 38.4, p = 0.003) scores, independently emerged as risk factors for LNM. The relationship between tumor budding grades and LNM in early gastric cancer (EGC) is illustrated in Figure 1.

Table 3. Multivariate logistic regression analyses of the potential risk factors for lymph node metastasis in early gastric cancer

Variables		**Odds ratio**	**95% Confidence interval**	**p**
Tumor size				
	≤2 cm	1	-	-
	>2cm	1	-	-
Depth of tumor invasion				
	pT1a	1	-	-
	pT1b	1	-	-
Tumor budding score				
	Low (Bd1)	48	1.591 - 1447.691	**0.026**
	Moderate (Bd2)	38.4	3.564 - 413.666	**0.003**
	High (Bd3)	1	-	-

Bd: budding; (-): omitted.

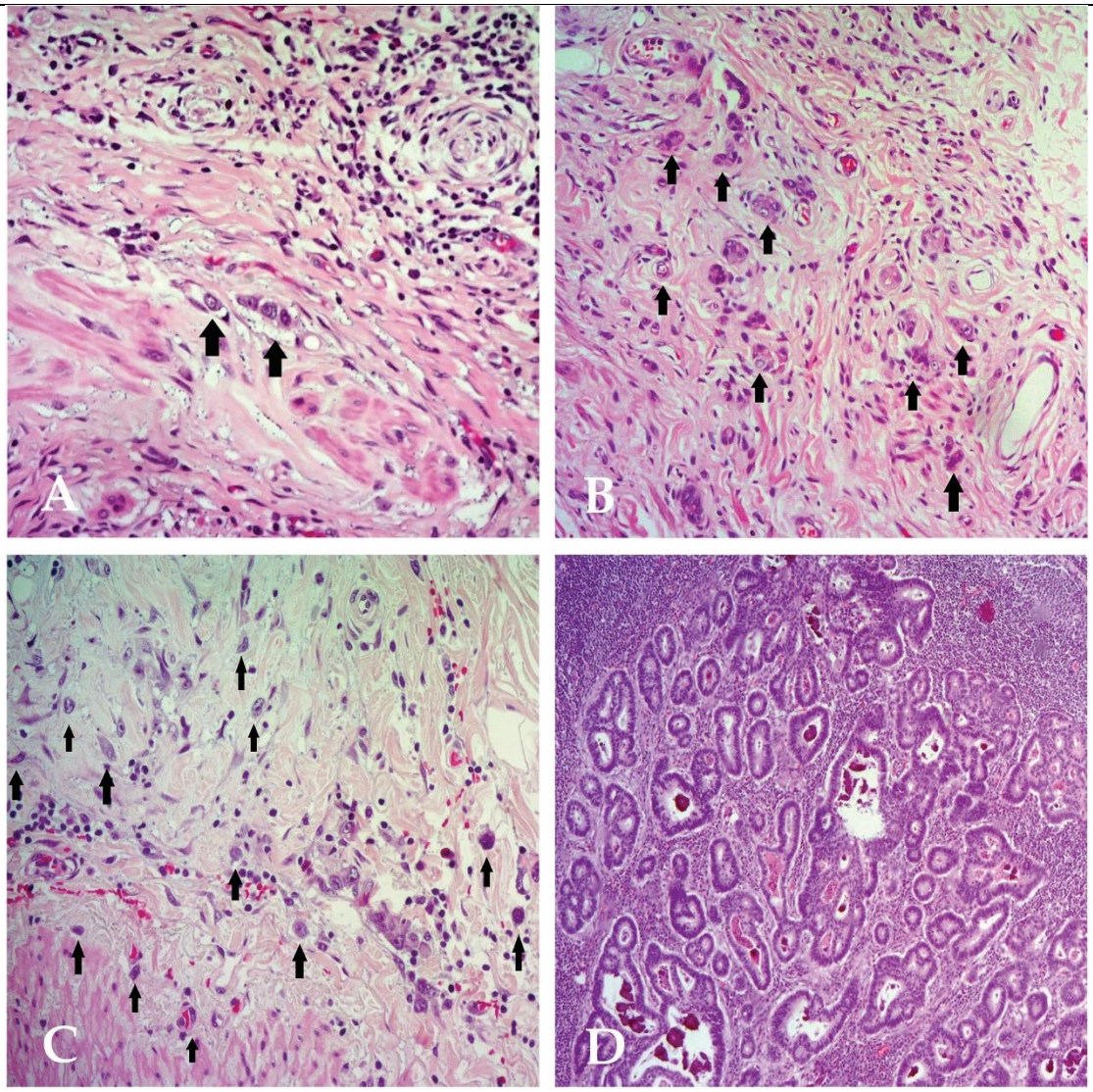

Fig. 1: Histology representative images of tumor budding grades based on the ITBCC 2016 and lymph node metastasis. (A): Low grade of tumor budding (Bd1). (B): Moderate grade of tumor budding (Bd2). (C): High grade of tumor budding (Bd3). (D): Lymph node metastasis in submucosa gastric cancer patient. Arrows indicatetumor bud cell clusters; H&E: 400x.

5. Discussion

Lymph node metastasis (LNM) status is a crucial determinant of treatment selection and prognosis in early gastric cancer (EGC) [37]. In this study, the rate of LNM was found to be 10%. This finding is consistent with earlier reports, such as Lim et al.'s study conducted in Korea which recorded a rate of 9.6% [38], and Sung et al.'s investigation in China which found the rate to be 13.7% [28]. Conversely, other studies have reported higher rates of LNM than our findings. For instance, Wang et al. conducted a study in China, which recorded a rate of 14.1% [39] , while An et al. recorded a rate of 19.4% in Korea [7] , and Gulluoglu et al. found a rate of 27.0% in Turkey [20]. The variations in the LNM rates across studies may be attributed to several factors, including differences in sample size, epidemiological features, geographical location, and sampling methods. Therefore, it is crucial to consider these factors when interpreting the results of different studies.

Our study revealed that a majority of EGC patients (61.7% of cases) were aged 60 years or older. This finding aligns with global data, which indicate that gastric cancer primarily affects older individuals, with a median age of 68 years, and that approximately six out of every ten individuals diagnosed each year are 65 years of age or older. [40]. Furthermore, we observed a higher incidence of EGC in males (71.7%) than females (28.3%), which is consistent with global statistics indicating that males have a higher lifetime risk of developing gastric cancer

than females, with a ratio of 1 in 95 and 1 in 154, respectively [40]. The gender disparity in gastric cancer incidence is thought to be influenced by various factors, including lifestyle habits and physiology, such as postmenopausal status in older women, where decreased levels of estrogen are associated with a reduced risk of developing gastric cancer [41]. Our study found no significant correlation between age, sex, and LNM ($p = 0.3526$ for age and $p = 0.3379$ for sex) in EGC patients, which is consistent with several previous reports [7, 18-20, 42]. However, there is still controversy and inconsistency between studies regarding the relationship between age, gender, and LNM in EGC. For instance, Kim et al. reported that age was associated with LNM ($p = 0.004$) but was not an independent risk factor, while sex was unrelated to LNM [15]. Alternatively, Du et al. found that age was associated with LNM ($p < 0.05$) but was not an independent risk factor in multivariable logistic regression analysis, while sex was associated with LNM ($p < 0.01$) and an independent risk factor (OR = 1.6; $p < 0.05$) [17]. Chen et al. reported that both age and sex were associated ($p < 0.001$) and independent risk factors for LNM (OR = 0.975, $p = 0.004$ for age; and OR = 0.47, $p < 0.001$ for sex) [16]. Hence, additional investigations are necessary to gain a deeper understanding of the intricate relationship between age, gender, and LNM in EGC.

The current study found that the antrum had the highest rate of EGC at 86.7%, which is consistent with previous studies reporting that the most common tumor location is the antrum. Kim et al. reported a prevalence of 57.5% [43], Jeong et al. found it to be 56.0% [44], while Crane et al. noted that 32.2% of EGC cases were exclusively located in the antrum [45]. This pattern may be attributed to the progression of gastric atrophy from the antrum to the body along the lesser curvature of the stomach, which is often influenced by *Helicobacter pylori* infection [46]. These findings emphasize the importance of careful examination of the antrum angle and lesser curvature during endoscopic screening for gastric cancer, particularly in areas with high *Helicobacter pylori* infection rates where these locations are frequently overlooked. Although the current study showed no significant association between tumor location and LNM, which is consistent with several previous studies [7, 15, 16, 19, 20, 42], other studies have reported mixed results. For example, Wang et al. reported a significant association between tumor location and LNM ($p = 0.001$), but it is unclear whether this relationship is an independent risk factor for LNM [18]. Du et al. found that, while univariate analysis showed an association between cardia and corpus/fundus location and LNM ($p < 0.01$), multivariable analysis only identified cardia location as an independent risk factor for LNM (odds ratio = 0.5, $p < 0.05$) [17]. These discrepancies may arise from differences in tumor location classification methods, suggesting that the choice of classification system may impact the evaluation of LNM status in EGC.

The present study utilized the endoscopic superficial appearance classification system to categorize EGC as type 0. Based on the Paris Classification, type 0-I lesions are rare and pose a very low risk of progressing to carcinoma, whereas non-polyposis lesions are classified as flat (0-II) or excavated/ulcerative (0-III) lesions [47]. In our study, type 0-I was the least common, accounting for only 5.0% of cases, while type 0-II and type 0-III accounted for 36.7% and 58.3%, respectively. In other studies, type 0-II lesions represented 70-80% of EGC cases and were recommended for endoscopic resection, whereas most type 0-III lesions were recommended for surgical resection [47-49]. Therefore, the application of this classification system in EGC screening and clinical practice can guide appropriate treatment methods and prognostication [50]. Interestingly, our study revealed no significant association between gross appearance and LNM, which is consistent with several previous studies [7, 17-20]. This finding suggests that gross appearance may not be a reliable predictor of LNM in EGC.

Tumor size is a crucial factor in the choice of treatment for EGC. ESD and EMR are recommended for tumors size $\leq$2 cm with limited mucosa, histologically well differentiated, and no ulceration [51]. Compared to gastrectomy, these methods are less invasive and significantly improve the quality of life for patients with EGC [52]. In our study, 48.3% of patients had tumors size $\leq$2 cm, making it possible to consider using ESD and EMR methods. However, the safety of endoscopic resection is still controversial. For instance, Sui et al. reported that the ratio of LNM was 2.9% in patients with absolute indications for endoscopic resection methods [53]. Additionally, in Yang et al.'s study, when using extended indications for tumors > 2cm, the ratio of LNM was 1.1%, while no cases of LNM occurred in the surgical group [54]. In our study, univariate analysis showed a statistically significant association between tumor size and LNM. This finding is consistent with recent reports, where tumor size > 2 cm is a risk factor for LNM [15, 21-23]. However, the results of our study's multivariable logistic regression analysis did not confirm tumor size as a risk factor for LNM. This discrepancy may be due to our study's small sample size, which is a limitation.

The differentiation status of tumors is a crucial prognostic factor in EGC. Our study found that 1.7% of EGC cases were well differentiated, 71.6% were moderately differentiated, and 26.7% were poorly differentiated. However, the proportion of tumor differentiation varies significantly between studies. For example, Bausys et al. reported that 20.2% of EGC cases were well differentiated, 32.1% were moderately differentiated, and 47.7% were poorly differentiated [42]. Other studies have classified gastric cancer as differentiated and undifferentiated, with varying ratios, including 59.5% and 40.5% reported by Gulluoglu et al. [20], 55.7% and 44.3% reported by Sung et al. [28], and 58.1% and 41.9% reported by An et al. [7]. Thus, the proportion of tumor differentiation grades varies depending on the method of classification used in different studies. In our study, we found no association between tumor differentiation status and LNM, which is consistent with previous reports [28, 38, 55]. However, some studies suggest that tumor differentiation status is associated with LNM [7, 24]. Therefore, the relationship between tumor differentiation status and LNM remains a controversial topic among different studies.

The Lauren classification holds significant importance in the clinical management guidelines for gastric cancer. It classifies gastric cancer into two main types, namely intestinal and diffuse, which exhibit distinct prognoses and treatment approaches. Endoscopic resection is typically employed for the treatment of the intestinal type, whereas gastrectomy with lymph node dissection is recommended for the diffuse type [56, 57]. In our study, we investigated the prognostic value of Lauren classification in EGC by examining its relationship with LNM. We found that the proportion of LNM of intestinal and diffuse types was 14.8% and 8.7%, respectively, and we observed no statistically significant association with LNM ($p = 0.6740$). However, the number of cases studied was small. Other studies have also evaluated the association between Lauren classification and LNM in EGC. For example, Ji et al. reported that Lauren classification was associated with LNM by univariate analysis ($p < 0.0001$), but it was not an independent potential risk factor for LNM in multivariable analysis ($p > 0.05$) [25]. Similarly, Pyo et al. found that the diffuse and mixed types had a higher risk of LNM (OR = 2.09; $p < 0.001$ for diffuse type and OR = 2.02; $p < 0.001$ for mixed type) [26]. Therefore, the association between Lauren classification and LNM in EGC remains inconsistent across studies.

Our study utilized the WHO classification to identify four types of EGC, with tubular adenocarcinoma comprising the highest proportion at 80.0%, followed by poorly cohesive carcinomas (13.3%), undifferentiated carcinoma (5.0%), and mixed carcinoma (1.7%). While proportions vary between studies, tubular adenocarcinoma remains the most commonly reported type. For instance, Kataoka et al. found that tubular adenocarcinoma accounted for 43.2%, followed by poorly cohesive carcinomas at 41.3% [58], while Park et al. recorded the highest proportion of tubular adenocarcinoma at 60.9%, followed by poorly cohesive carcinomas at 37.6% [59]. Aizawa et al. also reported the highest proportion of tubular adenocarcinoma at 46.9%, followed by poorly cohesive carcinomas at 35% [60]. Our study investigated the relationship between the WHO classification and LNM, revealing that the proportion of LNM was highest in poorly cohesive carcinomas (12.5%), followed by tubular adenocarcinoma (10.4%), with no LNM in the remaining types. However, this difference was not statistically significant ($p = 0.9169$). Lai et al. reported that tubular adenocarcinoma increases the risk of LNM in EGC (Hazard ratio = 1.920, $p < 0.001$ for moderately-differentiated adenocarcinomas, and Hazard ratio = 1.920, $p < 0.001$ for poorly-differentiated adenocarcinomas) [27]. Given the paucity of studies examining the relationship between the WHO classification and LNM in EGC, further research is warranted.

In our study, the distribution of patients with gastric cancer was 48.3% and 51.7% for stage pT1a and pT1b, respectively. The proportion of pT1a and pT1b stages also varied in other studies. For instance, Sung et al. reported proportions of 52.6% and 47.4%, respectively [28], while Wang et al. recorded 83.8% and 16.2% [39], and Gulluoglu et al. reported 30.1% and 69.9% [20]. We observed no LNM cases in the pT1a stage, but pT1b had 19.4% cases by univariate analysis ($p = 0.0244$). Nevertheless, according to the results of multivariate logistic regression analysis, the depth of tumor invasion did not emerge as an independent risk factor for lymph node metastasis (LNM). It is worth noting that previous studies have indicated a higher LNM rate associated with deeper invasion, highlighting its significance as an independent risk factor for LNM in early gastric cancer (EGC).. For instance, Wang et al. demonstrated that pT1a had a 6.0% LNM rate, while pT1b had a 56.2% LNM rate ($p<0.0001$), with the risk of LNM (OR (T1b/T1a) = 20,057, $p<0.0001$) [29]. Similarly, Sung et al. noted that pT1a had a 4.1% LNM rate, while pT1b had a 24.3% LNM rate ($p<0.001$), with the risk of LNM (OR (T1b/T1a)) = 4.91, $p<0.001$) [28].

As a result, increased tumor invasion depth is linked to a greater likelihood of lymph node metastasis (LNM), serving as an independent risk factor in early gastric cancer (EGC). However, due to the limited sample size in our study, further research is needed to establish sufficient statistical power and validate this correlation.

Tumor budding is considered an important prognostic factor for several malignancies, including colorectal cancer, but its role in EGC remains controversial. In our study, we found that 81.7% of EGC cases had low-grade, 15.0% had moderate-grade, and 3.3% had high-grade tumor budding. These results differed from those of previous studies. For example, Yao et al. reported rates of low and high-grade tumor budding as 41.5% and 13.4%, respectively [30], while Yim et al. reported rates of 59.9% and 40.1% for low-grade (Bd1) and high-grade (Bd2, 3) tumor budding, respectively [19]. These differences may have been due to variations in tumor budding grouping, sample size, and study populations. Our study showed that tumor budding scores were associated with LNM, with LNM proportions of 2.0%, 44.4%, and 50% for low, moderate, and high-grade tumor budding, respectively, with $p < 0.0001$ by univariate analysis. Multivariable logistic regression analysis showed that the risk of LNM was OR = 48 ($p = 0.026$) for low-grade tumor budding and OR = 38.4 ($p = 0.003$) for moderate-grade tumor budding. These results were consistent with those of other studies. For example, Yao et al. reported that tumor budding was significantly associated with LNM ($p < 0.01$) and was an independent risk factor for LNM [30]. Similarly, Yim et al. found that the percentage of LNM for low-grade and high-grade tumor budding was 2.9% and 45.7%, respectively ($p < 0.001$), with a hazard ratio of 15,907 ($p<0.001$) for LNM [19]. Gullugolu et al. showed that in patients with pT1b stage and tumor budding, the LNM ratio was 75.9%, higher than in the group without tumor budding (24.1%) ($p<0.0001$), and the risk of LNM for tumor budding was OR = 8,871 ($p<0.0001$) [20]. Du et al. reported that the percentage of LNM was 36.3% in the group with tumor budding, higher than in the group without tumor budding (10.2%) ($p<0.01$), with a risk of LNM for tumor budding of OR = 3.3 ($p<0.01$) [17]. Hence, tumor budding stands as a standalone risk factor for the prediction of lymph node metastasis (LNM) in early gastric cancer (EGC).

However, our study had some limitations, including a small sample size, and being conducted at a single facility, which limits the generalizability of our findings to the entire population of EGC in Vietnam.

Conclusions

Our research revealed that factors such as age, sex, tumor location, gross appearance, tumor differentiation status, Lauren classification, and World Health Organization (WHO) classification were not significantly associated with lymph node metastasis (LNM) in early gastric cancer (EGC). However, tumor size, depth of tumor invasion, and tumor budding showed potential as parameters for assessing and predicting the risk of LNM. Particularly, low and moderate grades of tumor budding emerged as independent risk factors for LNM. These findings underscore the importance of considering tumor budding as a crucial factor in predicting LNM and determining the appropriate treatment approach for EGC patients. To validate our findings and gain a more comprehensive understanding of the risk factors for LNM in EGC, further studies with larger sample sizes and multi-center settings are necessary.

Author contributions

CONCEPTION: Tran Ngoc Dung; Dang Thanh Chung

INTERPRETATION OR ANALYSIS OF DATA: Tran Ngoc Dung; Nguyen Tuan Thanh; Pham Van Thinh; Nguyen Mai Hanh; Nguyen Thuy Linh; Dang Thai Tra; Truong Dinh Tien; Dang Son Tung; Pham Xuan Huy; Lewis A. Hassell; Dang Thanh Chung

PREPARATION OF THE MANUSCRIPT: Tran Ngoc Dung; Nguyen Tuan Thanh; Lewis A. Hassell; Dang Thanh Chung

REVISION FOR IMPORTANT INTELLECTUAL CONTENT: Tran Ngoc Dung; Nguyen Tuan Thanh; Dang Thanh Chung

SUPERVISION: Tran Ngoc Dung; Lewis A. Hassell; Dang Thanh Chung

Refrences

[1] Bosman, F.T., et al., WHO classification of tumours of the digestive system. 2010: World Health Organization.

[2] Huang, Q., et al., Differences in Clinicopathology of Early Gastric Carcinoma between Proximal and Distal Location in 438 Chinese Patients. Scientific Reports, 2015. **5**(1): p. 13439.
[3] Verdecchia, A., et al., Explaining gastric cancer survival differences among European countries. Int J Cancer, 2004. **109**(5): p. 737-41.
[4] Current status of endoscopic submucosal dissection for early gastric cancer in Korea: role and benefits FAU - Kim, Sang Gyun FAU - Lyu, Da Hyun FAU - Park, Chan Mi FAU - Lee, Na Rae FAU - Kim, Jiyoung FAU - Cha, Youngju FAU - Jung, Hwoon-Yong. Korean J Intern Med, 2019. **34**(4): p. 785-793.
[5] Hahn, K.Y., et al., Comparative study between endoscopic submucosal dissection and surgery in patients with early gastric cancer. Surgical Endoscopy, 2018. **32**(1): p. 73-86.
[6] Choi, I.J., et al., Long-term outcome comparison of endoscopic resection and surgery in early gastric cancer meeting the absolute indication for endoscopic resection. Gastrointest Endosc, 2015. **81**(2): p. 333-41.e1.
[7] An, J.Y., et al., Predictive factors for lymph node metastasis in early gastric cancer with submucosal invasion: analysis of a single institutional experience. Ann Surg, 2007. **246**(5): p. 749-53.
[8] Roviello, F., et al., Number of lymph node metastases and its prognostic significance in early gastric cancer: a multicenter Italian study. J Surg Oncol, 2006. **94**(4): p. 275-80; discussion 274.
[9] Kim, D.Y., et al., Factors related to lymph node metastasis and surgical strategy used to treat early gastric carcinoma. World J Gastroenterol, 2004. **10**(5): p. 737-40.
[10] Baušys, A., et al., P-101 Tumor differentiation is a risk factor for lymph node metastasis in patients with gastric cancer. Annals of Oncology, 2015. **26**: p. iv28.
[11] Maehara, Y., et al., Predictors of lymph node metastasis in early gastric cancer. Br J Surg, 1992. **79**(3): p. 245-7.
[12] Polkowski, M., et al., Endosonography versus helical computed tomography for locoregional staging of gastric cancer. Endoscopy, 2004. **36**(7): p. 617-23.
[13] Hallinan, J.T. and S.K. Venkatesh, Gastric carcinoma: imaging diagnosis, staging and assessment of treatment response. Cancer Imaging, 2013. **13**(2): p. 212-27.
[14] Hasbahceci, M., et al., Diffusion MRI on lymph node staging of gastric adenocarcinoma. Quant Imaging Med Surg, 2015. **5**(3): p. 392-400.
[15] Kim, Y.I., et al., Lymph node metastasis risk according to the depth of invasion in early gastric cancers confined to the mucosal layer. Gastric Cancer, 2016. **19**(3): p. 860-8.
[16] Chen, J., G. Zhao, and Y. Wang, Analysis of lymph node metastasis in early gastric cancer: a single institutional experience from China. World Journal of Surgical Oncology, 2020. **18**(1): p. 57.
[17] Du, M., et al., Tumor Budding and Other Risk Factors of Lymph Node Metastasis in Submucosal Early Gastric Carcinoma: A Multicenter Clinicopathologic Study in 621 Radical Gastrectomies of Chinese Patients. Am J Surg Pathol, 2019. **43**(8): p. 1074-1082.
[18] Wang, Z., et al., Risk of lymph node metastases from early gastric cancer in relation to depth of invasion: experience in a single institution. Asian Pac J Cancer Prev, 2014. **15**(13): p. 5371-5.
[19] Yim, K., W.M. Jang, and S.H. Lee, Modified Tumor Budding as a Better Predictor of Lymph Node Metastasis in Early Gastric Cancer: Possible Real-World Applications. Cancers (Basel), 2021. **13**(14).
[20] Gulluoglu, M., et al., Tumor Budding Is Independently Predictive for Lymph Node Involvement in Early Gastric Cancer. Int J Surg Pathol, 2015. **23**(5): p. 349-58.
[21] Wang, Z., et al., Predictive factors for lymph node metastasis in early gastric cancer with signet ring cell histology and their impact on the surgical strategy: analysis of single institutional experience. Journal of Surgical Research, 2014. **191**(1): p. 130-133.
[22] Saragoni, L., et al., Early gastric cancer: diagnosis, staging, and clinical impact. Evaluation of 530 patients. New elements for an updated definition and classification. Gastric Cancer, 2013. **16**(4): p. 549-554.
[23] Zhang, M., et al., A nomogram to predict risk of lymph node metastasis in early gastric cancer. Scientific Reports, 2021. **11**(1): p. 22873.
[24] Gotoda, 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**(4): p. 219-225.

[25] Ji, T., et al., Risk factors for lymph node metastasis of early gastric cancers in patients younger than 40. Medicine, 2017. **96**(37): p. e7874.
[26] Pyo, J.H., et al., Early gastric cancer with a mixed-type Lauren classification is more aggressive and exhibits greater lymph node metastasis. J Gastroenterol, 2017. **52**(5): p. 594-601.
[27] Lai, J.F., et al., Effect of World Health Organization (WHO) Histological Classification on Predicting Lymph Node Metastasis and Recurrence in Early Gastric Cancer. Med Sci Monit, 2016. **22**: p. 3147-53.
[28] Sung, C.M., et al., Predictive factors for lymph node metastasis in early gastric cancer. World J Gastroenterol, 2010. **16**(41): p. 5252-6.
[29] Zheng, Z., et al., A nomogram for predicting the likelihood of lymph node metastasis in early gastric patients. BMC Cancer, 2016. **16**(1): p. 92.
[30] Yao, G., et al., Tumor budding as an indicator for lymph node metastasis and prognosis of early gastric cancer. Journal of Cancer Research and Clinical Oncology, 2022.
[31] Cancer, I.A.f.R.o. Viet Nam Source: Globocan 2020. 2021; Available from: https://gco.iarc.fr/today/home.
[32] Tran, V.H., et al., Non-cardia early gastric cancer in Central Vietnam: noticeable uncommon background mucosa and results of endoscopic submucosa dissection. Endosc Int Open, 2022. **10**(8): p. E1029-e1036.
[33] LAURÉN, P., THE TWO HISTOLOGICAL MAIN TYPES OF GASTRIC CARCINOMA: DIFFUSE AND SO-CALLED INTESTINAL-TYPE CARCINOMA. Acta Pathologica Microbiologica Scandinavica, 1965. **64**(1): p. 31-49.
[34] Fléjou, J.F., [WHO Classification of digestive tumors: the fourth edition]. Ann Pathol, 2011. **31**(5 Suppl): p. S27-31.
[35] Brierley, J.D., M.K. Gospodarowicz, and C. Wittekind, TNM classification of malignant tumours. 2017: John Wiley & Sons.
[36] Lugli, A., et al., Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol, 2017. **30**(9): p. 1299-1311.
[37] Kang, K.J., et al., Endoscopic submucosal dissection of early gastric cancer. Gut and Liver, 2011. **5**(4): p. 418.
[38] Lim, M.S., et al., Predictable factors for lymph node metastasis in early gastric cancer-analysis of single institutional experience. J Gastrointest Surg, 2011. **15**(10): p. 1783-8.
[39] Wang, Y., The predictive factors for lymph node metastasis in early gastric cancer: A clinical study. Pak J Med Sci, 2015. **31**(6): p. 1437-40.
[40] Gunderson, L.L., et al., Cancer of the stomach and gastroesophageal junction, in Abeloff's Clinical Oncology: Fifth Edition. 2013, Elsevier Inc. p. 1240-1270. e7.
[41] Green, J., et al., Reproductive factors and risk of oesophageal and gastric cancer in the Million Women Study cohort. British journal of cancer, 2012. **106**(1): p. 210-216.
[42] Bausys, R., et al., Risk factors for lymph node metastasis in early gastric cancer patients: Report from Eastern Europe country– Lithuania. BMC Surgery, 2017. **17**(1): p. 108.
[43] Kim, K., et al., Clinicopathologic characteristics of early gastric cancer according to specific intragastric location. BMC Gastroenterol, 2019. **19**(1): p. 24.
[44] Jeong, O. and Y.-K. Park, Clinicopathological features and surgical treatment of gastric cancer in South Korea: the results of 2009 nationwide survey on surgically treated gastric cancer patients. Journal of gastric cancer, 2011. **11**(2): p. 69-77.
[45] Crane, S., et al., The changing incidence of oesophageal and gastric adenocarcinoma by anatomic sub-site. Alimentary pharmacology & therapeutics, 2007. **25**(4): p. 447-453.
[46] Kim, S.J. and C.W. Choi, Common Locations of Gastric Cancer: Review of Research from the Endoscopic Submucosal Dissection Era. J Korean Med Sci, 2019. **34**(35): p. e231.
[47] Fujiyoshi, M.R.A., et al., Endoscopic Classifications of Early Gastric Cancer: A Literature Review. Cancers (Basel), 2021. **14**(1).
[48] Kim, G.H., Systematic Endoscopic Approach to Early Gastric Cancer in Clinical Practice. Gut and Liver, 2021. **15**(6): p. 811-817.

[49] Hu, W., et al., Combination of Paris and Vienna classifications may optimize follow-up of gastric epithelial neoplasia patients. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 2015. **21**: p. 992.
[50] Everett, S. and A. Axon, Early gastric cancer in Europe. Gut, 1997. **41**(2): p. 142-150.
[51] jp, J.G.C.A.j.k.k.-m.a., Japanese Gastric Cancer Treatment Guidelines 2021. Gastric cancer, 2022: p. 1-25.
[52] Takizawa, K., H. Ono, and M. Muto, Current indications of endoscopic submucosal dissection for early gastric cancer in Japan. Japanese Journal of Clinical Oncology, 2019. **49**(9): p. 797-802.
[53] Sui, W., et al., Nomograms for Predicting the Lymph Node Metastasis in Early Gastric Cancer by Gender: A Retrospective Multicentric Study. Frontiers in Oncology, 2021. **11**.
[54] Yang, H.-J., et al., Clinical outcomes of endoscopic resection for undifferentiated intramucosal early gastric cancer larger than 2 cm. Gastric Cancer, 2021. **24**(2): p. 435-444.
[55] Feng, F., et al., Prognostic value of differentiation status in gastric cancer. BMC Cancer, 2018. **18**(1): p. 865.
[56] Chen, Y.C., et al., Clinicopathological Variation of Lauren Classification in Gastric Cancer. Pathol Oncol Res, 2016. **22**(1): p. 197-202.
[57] Berlth, F., et al., Pathohistological classification systems in gastric cancer: diagnostic relevance and prognostic value. World J Gastroenterol, 2014. **20**(19): p. 5679-84.
[58] Kataoka, Y., et al., HER2 expression and its clinicopathological features in resectable gastric cancer. Gastric Cancer, 2013. **16**(1): p. 84-93.
[59] Park, K.K., et al., Correlations of Human Epithelial Growth Factor Receptor 2 Overexpression with MUC2, MUC5AC, MUC6, p53, and Clinicopathological Characteristics in Gastric Cancer Patients with Curative Resection. Gastroenterol Res Pract, 2015. **2015**: p. 946359.
[60] Aizawa, M., et al., Evaluation of HER2-based biology in 1,006 cases of gastric cancer in a Japanese population. Gastric Cancer, 2014. **17**(1): p. 34-42.