Risk of lymph node metastasis in T1b gastric cancer: an international comprehensive analysis from the Global Gastric Group (G3) Alliance

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ORIGINAL ARTICLE

Risk of Lymph Node Metastasis in T1b Gastric Cancer

An International Comprehensive Analysis from the Global Gastric Group (G3) Alliance

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Objective: We sought to define criteria associated with low lymph node metastasis risk in patients with submucosal (pT1b) gastric cancer from 3 Western and 3 Eastern countries.

Summary Background Data: Accurate prediction of lymph node metastasis risk is essential when determining the need for gastrectomy with lymph node dissection following endoscopic resection. Under present guidelines, endoscopic resection is considered definitive treatment if submucosal invasion is only superficial, but this is not routinely assessed.

Methods: Lymph node metastasis rates were determined for patient groups defined according to tumor pathological characteristics. Clinicopathological predictors of lymph node metastasis were determined by multivariable logistic regression and used to develop a nomogram in a randomly selected subset that was validated in the remainder. Overall survival was compared between Eastern and Western countries.

Results: Lymph node metastasis was found in 701 of 3166 (22.1%) Eastern and 153 of 560 (27.3%) Western patients. Independent predictors of lymph node metastasis were female sex, tumor size, distal stomach location, lymphovascular invasion, and moderate or poor differentiation. Patients fulfilling the National Comprehensive Cancer Network guideline criteria, excluding the requirement that invasion not extend beyond the superficial submucosa, had a lymph node metastasis rate of 8.9% (53/594). Excluding moderately differentiated tumors lowered the rate to 3.4% (10/296). The nomogram's area under the curve was 0.690. Regardless of lymph node status, overall survival was better in Eastern patients.

Conclusions: The lymph node metastasis rate was lowest in patients with well differentiated tumors that were ≤3 cm and lacked lymphovascular invasion. These criteria may be useful in decisions regarding endoscopic resection as definitive treatment for pT1b gastric cancer.

Keywords: definitive treatment, endoscopic resection, gastrectomy, gastric neoplasia, lymph node dissection, overall survival, stomach cancer, submucosal invasion

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E ndoscopic resection has been increasingly adopted as treatment for early-stage gastric cancer over the last decade. Endoscopic mucosal resection is now commonly used worldwide for well-selected gastric stage 1a (T1a) cases, whereas the more technically demanding endoscopic submucosal dissection is more commonly used in Asian than in Western countries stemming from their higher incidence of early-stage gastric cancer.[1] The appropriate use of endoscopic resection as definitive treatment for T1b tumors rather than gastrectomy with lymph node dissection depends largely on the risk of lymph node metastasis (LNM) and remains controversial. As gastric cancer incidence

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and pathobiology vary between Eastern and Western countries, indications for endoscopic resection as definitive treatment in certain countries may or may not apply to other parts of the world. This makes it difficult to ascertain the true risk of LNM for individual patients and impedes treatment decision-making.

The Japanese guidelines from 2020 (2nd edition) consider endoscopic resection of pT1b tumors as definitive treatment if the tumor invades the submucosa < 500 μm, is well or moderately differentiated, $\leq$ 3cm in size, and lacks lymphovascular invasion, and the margins are negative.[2] This recommendation was based on the observation that none of the 145 Japanese patients fulfilling these criteria had LNM.[3] Based on the Japanese guidelines, the American National Comprehensive Cancer Network (NCCN) guideline version 3.2020 adopted similar criteria, substituting the quantitative invasion limit with the more qualitative "does not penetrate beyond the superficial submucosa," and lowering the tumor size limit to ≤2 cm.[4] Given known differences in the epidemiology and subtypes of gastric cancer between Asian and Western patients,[5–14] the paucity of research on LNM risk for T1b tumors in patients from the West leaves a gap in determining the applicability of these criteria. Furthermore, the criteria regarding invasion depth are difficult to apply given that this feature is not routinely assessed in the West, and the NCCN guideline is nonquantitative and thus subject to interpretation.

To examine LNM risk in early-stage gastric cancer, we formed an international collaboration and established the Global Gastric Cancer Group (G3) Alliance, a large cohort of gastric cancer patients from large volume gastric cancer institutions in South Korea, China, Japan, the United States, and Italy, as well as the Netherlands Cancer Registry and the Dutch Gastric Cancer Trial.[15] This dataset enables comparison of LNM risk between global regions, which will broaden knowledge of associated differences in early-stage gastric cancer presentation, treatment, and outcomes.

The aim of this study was to determine the LNM rates for pathological T1b (pT1b) gastric cancer in patients who underwent gastrectomy among groups defined according to pathological tumor characteristics, and compare these rates, as well as other clinical features including survival, between Eastern and Western countries. We also aimed to identify clinical and pathological predictors of LNM and to construct and validate an LNM nomogram.

METHODS

Data Collection

After the study protocol was designed, discussed, and approved by all G3 Alliance members, Institutional Review Board approval was obtained at Memorial Sloan Kettering Cancer Center. Each member institution has a prospectively maintained database of surgical gastric cancer patients that was queried for the purpose of this study. The Dutch cohort was derived from the Dutch Gastric Cancer Trial database and Netherlands Cancer Registry.[16] The Dutch Gastric Cancer Trial randomized patients treated from 1989 to 1993 to either D1 or D2 lymph node dissection.[15] The NCR is a nationwide registry containing data on all patients with a cancer diagnosis since 1989 hosted by the Netherlands Comprehensive Cancer Organization. Nearly 100% of patients with gastroesophageal cancer who underwent surgery since 2010 in the Netherlands are included in the database.[17]

Patient Selection

Databases were queried for patients with pT1b gastric cancer, meaning a tumor invading no deeper than the submucosal layer, and who had undergone a (sub)total gastric resection including lymphadenectomy with negative margins. Inclusion criteria were a histologically confirmed primary T1b gastric adenocarcinoma without neoadjuvant treatment. Exclusion criteria were atypical resections including wedge gastrectomy and completion gastrectomy for recurrent or remnant cancers or following endoscopic resection, gastroesophageal junction cancers, and missing information for one of the following variables: type of surgical resection, pathological tumor location, or pathological lymph node status.

Data Collection

The following variables were collected from each database: age at surgery, sex, race, date of surgery, type of surgery, pathological tumor location, pathological tumor stage (pT) and lymph node status (pN), number of dissected lymph nodes, number of positive lymph nodes, pathological tumor size, differentiation, histology, presence of lymphovascular invasion, date of last follow-up, and date of death, if applicable. pT and pN were determined using the 8th edition of the AJCC staging system.[18]

Statistical Analysis

Patient demographics and clinicopathological characteristics were compared among all 6 countries and Eastern (South Korea, China, and Japan) versus Western (the Netherlands, United States, and Italy) countries by chi-square test for categorical variables and Mann–Whitney U test for continuous variables. Predictors of LNM were identified by univariable and multivariable logistic regression analysis. All factors with a P value of ≤ 0.10 in the univariable analysis were included for multivariable analysis. To build the nomogram, each individual dataset was randomly divided into a training and validation set at a 2:1 ratio, and logistic regression was repeated to identify independent predictors of LNM in the combined training set. Patients with missing values for the variables used in the nomogram were excluded. The discriminative ability of the nomogram in the training and validation dataset was estimated by the area under the curve (AUC). Goodness of fit was evaluated by a calibration plot in the validation set by quantiles of predicted risk. Overall survival (OS) was calculated from the date of surgery until date of death or last follow-up in the survivors. Univariable and multivariable survival analysis were performed by Cox regression analysis. Survival curves were estimated by Kaplan-Meier method and p values by log-rank test. All p values were 2-sided; P values of < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS Statistics for Windows, Version 25.0 (IBM, Armonk, NY), or R version 3.6 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographics, Clinicopathological Characteristics, and LNM Rate

A total of 3726 patients were included: 1858 from South Korea, 700 from China, 608 from Japan, 278 from the Netherlands, 244 from the United States, and 38 from Italy. After grouping the individual databases into global regions, 3166 patients formed the Eastern cohort and 560 the Western (cohorts

TABLE 1. Demographics and Clinicopathological Characteristics. Categorical Variables Are Presented as n (%) and Continuous Variables As Median (Interquartile Range)

	Total (3726)	East (3166)	West (560)	*P*
Age, y	63 (54–71)	62 (54–70)	68 (59–75)	< 0.001
Female	1273 (34.2)	1006 (31.8)	267 (47.7)	< 0.001
Race				< 0.001
White	302 (8.1)	0 (0.0)	302 (53.9)	
Asian	3210 (86.2)	3166 (100)	44 (7.9)	
Black	23 (0.6)	0	23 (4.1)	
Other or unknown	191 (5.1)	0	191 (34.1)	
Year of surgery	2011 (2007–2015)	2011 (2007–2015)	2010 (2001– 2014)	< 0.001
Location				0.023
Proximal third	516 (13.8)	452 (14.3)	64 (11.4)	
Middle third	1245 (33.4)	1062 (33.5)	183 (32.7)	
Distal third	1907 (51.2)	1597 (50.4)	310 (55.4)	
Multiple/diffuse	58 (1.6)	55 (1.7)	3 (0.5)	
Type of surgery				0.011
Distal	2818 (75.6)	2374 (75.0)	444 (79.3)	
Total	825 (22.1)	726 (22.9)	99 (17.7)	
Proximal	83	66 (2.1)	17 (3.0)	
pN positive	854 (22.9)	701 (22.1)	153 (27.3)	0.007
pN status				0.02
0	2872 (77.1)	2465 (77.9)	407 (72.7)	
1	535 (14.4)	440 (13.9)	95 (17.0)	
2	225 (6.0)	186 (5.9)	39 (7.0)	
3a	83[30]	64 (2.0)	19 (3.4)	
3b	11 (0.3)	11 (0.3)	0 (0.0)	
Dissected nodes	34 (25–45)	36 (27–46)	22 (15–32)	< 0.001
Positive nodes	0 (0–0)	0 (0–0)	0 (0–1)	0.008
Tumor size, mm	25 (18–40)	25 (18–40)	25 (15–35)	0.002
Differentiation				0.002
Well	598 (16.0)	539 (17.0)	59 (10.5)	
Moderate	1470 (39.5)	1236 (39.0)	234 (41.8)	
Poor	1454 (39.0)	1220 (38.5)	234 (41.8)	
Unknown	204 (5.5)	171 (5.4)	33 (5.9)	
Signet histology	626 (16.8)	527 (16.6)	99 (17.7)	< 0.001
Unknown	455 (12.2)	237 (7.5)	218 (38.9)	
Lymphovascular invasion	705 (18.9)	600 (19.0)	105 (18.8)	< 0.001
Unknown	299 (8.0)	39 (1.2)	260 (46.4)	

summarized in Table 1; each country's data reported in Supplemental Table 1, http://links.lww.com/SLA/D569). Compared to the Western cohort, the Eastern cohort was more recently treated [median 2011, interquartile range (IQR) 2007–2015 vs median 2010, IQR 2001–2014], younger (median 62 years, IQR 54–70 vs 68, IQR 59–75), included fewer women (32% vs 48%), had fewer tumors located in the distal stomach (50% vs 55%), less often underwent distal gastrectomy (75% vs 79%), had more lymph nodes dissected (median 36 vs 22), and had more well differentiated tumors (17% vs 11%). Frequencies of signet ring cell histology (17% vs 18%) and lymphovascular invasion (19%vs 19%) were comparable, but data regarding these variables were missing in 39% and 46% of the Western patients, respectively (Table 1). Of the total 3726 patients, 854 (22.9%) had pathologically positive lymph nodes; 701 (22.1%) in the Eastern cohort and 153 (27.3%) in the Western (*P* = 0.007) (Table 1). The rate of LNM was lowest in Japan at 19.1% and highest in the Netherlands at 29.5% (Supplemental Table 1, http://links.lww.com/SLA/D569).

LNM Rate According to Pathological Tumor Characteristics

Patients were categorized according to their tumor's differentiation grade, tumor size, and presence of lymphovascular invasion (Table 2A and B). The group fulfilling Japanese guideline criteria for considering endoscopic resection to be definitive therapy (well or moderately differentiated, size ≤3 cm, no lymphovascular invasion), without requirement for limited submucosal invasion depth, had an LNM rate of 12.5% (121/971) (Table 2A). The group fulfilling NCCN guideline criteria (well or moderately differentiated, size ≤2 cm, no lymphovascular invasion), disregarding the invasion depth criterion, had an LNM rate of 53 of 594 (8.9%). LNM rates < 5% were observed in patients with a well differentiated tumor, without lymphovascular invasion, and size ≤3 cm, and even lower rates in tumors ≤2cm or ≤1 cm: 3.4% (10/296), 3.0% (6/200), and 1.6% (1/ 63), respectively (Table 2B). Of the 27 patients with tumors < 1 cm, none had LNM.

Predicting LNM

Factors significantly and independently associated with LNM included female sex [odds ratio (OR) 1.36, 95% confidence interval (CI) 1.13–1.64, *P* = 0.001], increasing tumor size (OR 1.03, 95% CI 1.02–1.03, *P* < 0.001), tumors located in the distal stomach (OR 1.78, 95% CI 1.34–2.38, *P* < 0.001), lymphovascular invasion (OR 2.44, 95% CI 1.99–2.99, *P* < 0.001), and moderate or poor differentiation (OR 2.70, 95% C1 1.99–3.67, *P* < 0.001 and OR 3.07, 95% CI 2.26–4.18, *P* < 0.001, respectively) (Table 3). After multivariable analysis, East versus West was not associated with a different LNM rate.

To develop the nomogram, each country's cohort was then divided into training and validation sets (n = 2492 and

TABLE 2. Proportion of Patients With Lymph Node Metastasis (pN-Positive) According to Differentiation, Tumor Size, and Lymphovascular Invasion[31]

A

Differentiation	Tumor Size, cm	No LVI		LVI	
		Total	pN-Positive	Total	pN-Positive
Well or moderate	≤2	594	53 (8.9%)	134	20 (14.9%)
	≤3	971	121 (12.5%)	241	47 (19.5%)
	> 3	518	134 (25.9%)	156	71 (45.5%)
Poor	≤2	408	58 (14.2%)	102	36 (35.3%)
	≤3	675	119 (17.6%)	177	64 (36.2%)
	> 3	380	120 (31.6%)	80	41 (51.2%)

B

Differentiation	Tumor Size, cm	No LVI		LVI	
		Total	pN-Positive	Total	pN-Positive
Well	≤1	63	1 (1.6%)	11	2 (18.2%)
	≤2	200	*6 (3.0%)*	43	3 (7.0%)
	≤3	296	*10 (3.4%)*	74	9 (12.2%)
	> 3	138	25 (18.1%)	55	19 (34.5%)
Moderate	≤1	106	12 (11.3%)	20	2 (10.0%)
	≤2	394	47 (11.9%)	91	17 (18.7%)
	≤3	675	111 (16.4%)	167	38 (22.8%)
	> 3	380	109 (28.7%)	101	52 (51.5%)

A, Well or moderately vs poorly differentiated tumors. Bolded entries indicate patients meeting criteria for definitive treatment by endoscopic resection according to Japanese (≤3 cm) and NCCN (≤2 cm) criteria. B, Well vs moderately differentiated tumors. Italicized entries indicate patients meeting above criteria but excluding moderate differentiation.

1234, respectively). There were no significant differences in demographics or clinicopathological characteristics between training and validation sets (Supplemental Table 2, http://links. lww.com/SLA/D570). In the training set, the same factors were associated with LNM as in the total population (Supplemental Table 3, http://links.lww.com/SLA/ D571); these were incorporated into the nomogram predicting LNM (Fig. 1A). The nomogram's AUC was 0.700 (95% CI 0.675–0.726) in the training set and 0.690 (0.653–0.728) in the validation set (Fig. 1B). The calibration plot shows that the nomogram's predicted risk is less than the observed risk in the low-risk and high-risk groups, and greater than the observed risk in the middle-risk groups (Supplemental Fig. 1, http://links.lww.com/SLA/D568).

Overall Survival

After a median follow–up of 60.7 (IQR 30–100) months, 5year OS was 92.0% among Eastern and 76.5% among Western patients ($P < 0.001$) (Fig. 2A). After adjustment for age, sex, race, number of dissected lymph nodes, lymphovascular invasion, and differentiation, OS remained significantly better in Eastern patients [hazard ratio (HR) 0.54, 95% CI 0.41–0.71, $P < 0.001$] (Supplemental Table 4, http://links.lww.com/SLA/D572). Among pathological lymph node (pN)–negative patients, 5–year OS was 93.2% in the East and 80.4% in the West ($P < 0.001$) (Fig. 2B) and significantly better in Eastern patients after adjustment (HR 0.52, 95% CI 0.37–0.72, $P < 0.001$) (Supplemental Table 4, http://links. lww.com/SLA/D572). In pN-positive patients, 5-year OS was

TABLE 3. Univariable and Multivariable Logistic Regression Analysis for Lymph Node Metastasis

|	Univariable			Multivariable		
	OR	95% CI	P	OR	95% CI	P
East vs West	0.76	0.62–0.93	0.007	0.89	0.64–1.23	0.471
Age, y	1.01	1.00–1.01	0.124			
Female vs male	1.35	1.15–1.58	< 0.001	1.36	1.13–1.64	0.001
Year of surgery	1.01	0.99–1.02	0.428			
Tumor size, mm	1.02	1.02–1.03	< 0.001	1.03	1.02–1.03	< 0.001
Location						
Proximal	1			1		
Middle	1.41	1.08–1.85	0.012	1.28	0.94–1.74	0.112
Distal	1.74	1.35–2.24	< 0.001	1.78	1.34–2.38	< 0.001
Multiple	1.19	0.59–2.38	0.63	1.48	0.70–3.11	0.301
No. of dissected nodes	1.00	1.00–1.01	0.102			
Signet histology	1.07	0.87-1.31	0.529			
Lymphovascular invasion	2.19	1.83–2.62	< 0.001	2.44	1.99–2.99	< 0.001
Differentiation						
Well	1			1		
Moderate	2.45	1.85–3.23	< 0.001	2.70	1.99–3.67	< 0.001
Poor	2.83	2.14–3.73	< 0.001	3.07	2.26–4.18	< 0.001
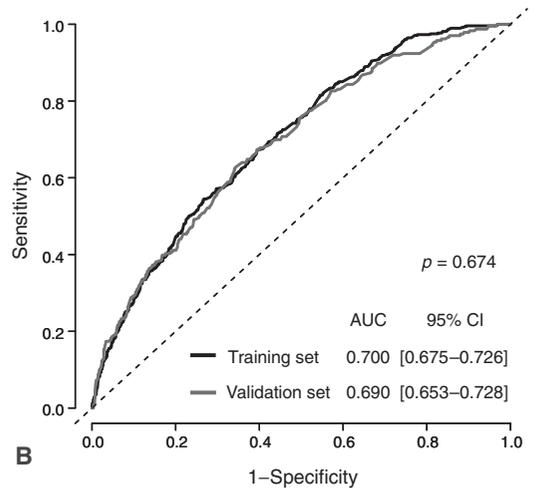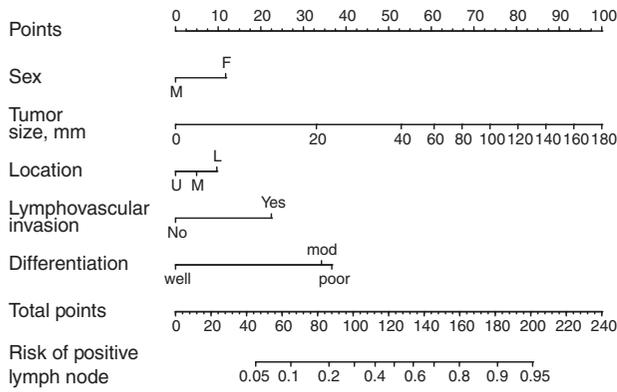
FIGURE 1. Nomogram for lymph node metastasis in pT1b gastric cancer patients. A, Scoring and interpretation. B, ROC curve in the training set (black line) and validation set (grey line).
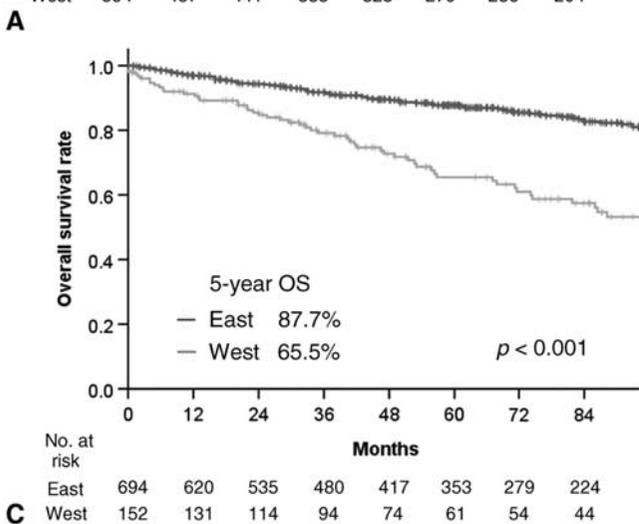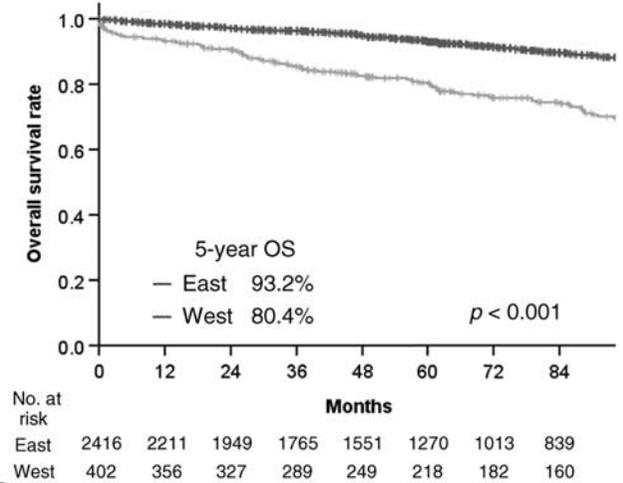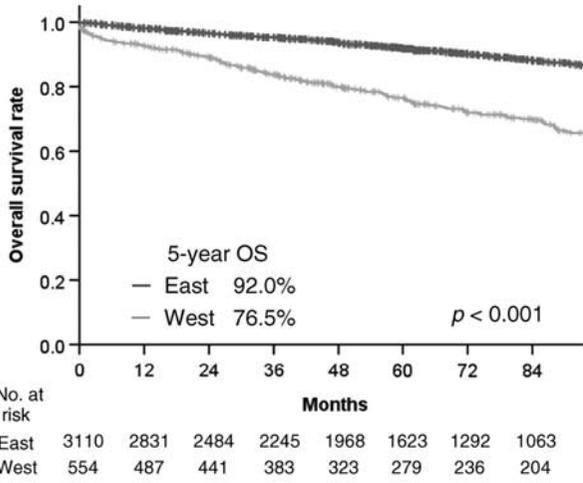

FIGURE 2. Comparison of overall survival. A, Eastern vs Western countries; B, Eastern vs Western countries in pN-negative patients only; C, Eastern vs Western countries in pN-positive patients.

87.7% in the East and 65.5% in the West ($P < 0.001$) (Fig. 2C), and significantly better in Eastern patients after adjustment (HR 0.56, 95% CI 0.35–0.91, $P = 0.020$) (Supplemental Table 4, http://links.lww.com/SLA/D572).

DISCUSSION

We found that the lymph node metastasis rate in pT1b gastric cancer is 23%, and significantly lower in those treated in Eastern countries (South Korea, China, and Japan) than in Western countries (the Netherlands, United States, and Italy). The LNM rates among patients fulfilling current guideline criteria for considering endoscopic resection as definitive treatment for pT1b gastric cancer, without regard for invasion depth, were relatively high, at 8.9% for NCCN and 12.5% for the Japanese guidelines. One of the independent predictors for LNM was moderate differentiation; excluding patients with moderately differentiated tumors lowered the LNM rate to 3.0% for NCCN and 3.4% for Japanese criteria. These findings may be used to inform decision making regarding endoscopic resection as definitive treatment in pT1b gastric cancer.

The overall LNM rate we report is similar to that in a metaanalysis by Kwee et al., which found a median risk of 19%.[19]

However, of the 40 studies included in that analysis, 39 were in Asian populations and most in Japan. Their finding is thus in agreement with our LNM rate of 22% in Eastern countries and 19% in Japan. The only Western study included in the meta-analysis had the highest LNM rate at 33% (8/24).[20] Among the 6 other studies of LNM rates in Western T1b gastric cancer patients,[21–26] 1 reported a substantially lower LNM rate of 9%, but that study included only 15% of patients with ≥15 lymph nodes removed[21]; the other 5 found LNM rates between 25% and 32%,[22–26] concordant with our LNM rate of 27% in Western countries. Although Western patients had fewer lymph nodes resected (median 22 vs 36), the number of nodes resected was not associated with the presence of LNM. We believe the recommendation to examine ≥15 lymph nodes for accurate staging remains adequate.[4,27]

LNM rates in patients fulfilling most criteria for endoscopic resection as definitive treatment in pT1b tumors were relatively high, at 12.5% for the Japanese guidelines and 8.9% for NCCN. Invasion depth was not considered because most pathologists in Western countries do not assess this feature. The former rate is higher than that in a recent meta-analysis of Asian studies, in which the LNM rate in patients fulfilling all of the Japanese criteria, including maximum invasion depth, was 8 of 315 (2.5%).[28] Thus, it appears that excluding this criterion leads to the inclusion of patients who are more likely to harbor LNM. Even considering disadvantages of a surgical resection regarding comorbidity, complications, and quality of life, a predicted LNM risk of 8.9% may be unacceptable; in cases where invasion depth is not assessed, more stringent criteria regarding available information may be necessary. However, the LNM risk threshold is an individual decision for each patient.

Importantly, we found that excluding moderately differentiated tumors from the criteria for definitive treatment substantially decreased LNM risk. Moderate differentiation was seen in a greater proportion of patients compared with well differentiation in most countries: 29% versus 30% of tumors in Japan, 34% versus 11% in Italy, 40% versus 16% in Korea, 42% versus 13% in the US, 43% versus 8% in the Netherlands, and 47% versus 10% in China (Supplemental Table 1, http://links.lww.com/SLA/D569). Although the distinction between well and moderate differentiation is generally considered equivocal and subjective, even in this international cohort, the greater LNM risk in moderately

than well differentiated tumors was consistent across countries (Supplemental Table 5, http://links.lww.com/SLA/D573). This distinct LNM risk has not previously been reported, as other studies have grouped well and moderately differentiated tumors together into "differentiated,"[3,19] as did Japanese and NCCN guidelines.[2,4] The better understanding of factors associated with LNM in pT1b gastric cancer provided here can inform decisions about optimal management of patients after endoscopic resection, in the context of other patient-related variables and preferences.

Our nomogram appears to underestimate LNM risk in patients fulfilling almost all guideline criteria. The reasons for this suboptimal predictive ability (AUC of 0.69 in the validation set) are unclear, as the meta-analysis from Kwee et al found the same variables to be significantly associated with LNM.[19] However, the association between distal stomach tumors and LNM was unexpected. A potential reason is that patients with tumors in the distal stomach have more nodes retrieved and thus a higher chance of finding LNM; however, this was not observed, as the median number of lymph nodes resected in upper, middle, and distal stomach tumors was similar. Another unexpected finding was the lower prevalence of distal stomach tumors in the East versus the West (50% vs 55%), likely resulting from the low prevalence of tumors in this location in Japan (30%) (Supplemental Table 1, http://links.lww.com/SLA/D569). This might be explained by Japan's national gastric cancer screening program, as screened patients more often have cancer in the middle stomach,[29] as confirmed here (49% vs 20%–33% in other countries; Supplemental Table 1, http://links.lww.com/SLA/D569).

Overall survival was independently and significantly better in Eastern patients compared with Western, regardless of lymph node status. The survival rates of patients in each Eastern country were more similar to each other than the survival from Western countries, calling for investigation into the reasons for differences in outcomes of patients with early gastric cancer between global regions. The significant age difference between East and West (median 62 vs 68 years) could cause residual confounding, though our analysis adjusted for this factor. As the clinicopathological characteristics we analyzed were similar between the Eastern and Western cohort, such studies should focus on cancer biology, environmental factors, other patient characteristics, or treatment differences.

Because this study was based on data from the postoperative pathologic report, the findings can only be used to inform decisionmaking after endoscopic resection, not indications for endoscopic resection. Determining initial indications for minimally invasive treatment would require assessment of lymphovascular invasion on biopsy specimens, which is challenging. Such guidelines are further complicated by the fact that clinical assessment of tumor size and invasion depth by endoscopic ultrasound or even newer technology like narrow-band imaging is inexact.

This retrospective multi-institutional cohort study had several limitations. Although data were collected from representative high-volume centers and well-organized databases, practice, type of operation, and pathological evaluations were not standardized, and imaging and surgical video were not centrally reviewed. In addition, the lack of assessment of the degree of submucosal tumor invasion in Western countries limited our ability to precisely compare outcomes with studies from the East. Invasion depth data could have improved our prediction model and the predictive accuracy of our nomogram, and we would likely have found a lower LNM rate in patients with tumors with limited submucosal invasion. To enhance the reliability of predictions regarding outcomes of endoscopic treatment of T1b gastric cancer in the West,

we recommend standardized pathological assessment of submucosal invasion depth.

A well-designed international prospective study could confirm our results. In addition, comparison of survival outcomes between early gastric cancer patients with and without additional surgery following endoscopic resection could validate the usefulness of our nomogram. Furthermore, our nomogram predicting LNM can be applied for gastric cancer patients following endoscopic resection, because this nomogram was created in patients with pathologically confirmed T1b disease and the nomogram includes lymphovascular invasion status, which is unavailable before resection. Although clinical tumor depth data would be difficult to collect in an international multi-institutional study, accurate pre-treatment data would allow creation of a nomogram to predict LNM among early gastric cancer patients to inform the decision of whether to perform an endoscopic dissection. Combining our nomogram (ie, post-endoscopic resection) with such a pre-endoscopic resection nomogram would enable more patient-specific treatment for early gastric cancer patients, which might lead to better oncological outcomes, quality of life, and cost-effectiveness. The strength of our study is the large study population, including multiple countries from the East and West, and the inclusion of representative high-volume centers.

CONCLUSIONS

In patients with pT1b gastric cancer, those treated in Eastern countries (South Korea, China, and Japan) were significantly less likely to harbor LNM than those in Western countries (the Netherlands, United States, and Italy). The LNM rates among patients fulfilling current guideline criteria for considering endoscopic resection as definitive treatment for pT1b gastric cancer, without regard for invasion depth, had relatively high LNM rates, but excluding patients with moderately differentiated tumors lowered the LNM rate from 8.9% to 3.0% for NCCN and from 12.5% to 3.4% for Japanese criteria. These findings may be used to inform decisionmaking regarding endoscopic resection as definitive treatment in pT1b gastric cancer.

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