Ann Surg Oncol (2019) 26:449–455
https://doi.org/10.1245/s10434-018-07119-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Feasibility of Endoscopic Resection in Early Gastric Cancer with Lymphovascular Invasion

Jeung Hui Pyo, MD[1], Hyuk Lee, MD, PhD[2], Yang Won Min, MD, PhD[2], Byung-Hoon Min, MD, PhD[2], Jun Haeng Lee, MD, PhD[2], Kyoung-Mee Kim, MD, PhD[3], Hyeseung Kim, MS[4], Kyunga Kim, PhD[4], and Jae J. Kim, MD, PhD[2]

[1]Center for Health Promotion, Samsung Medical Center, Seoul, Korea; [2]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [4]Statistics and Data Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, Korea

ABSTRACT

Background. Lymphovascular invasion (LVI) is associated with the risk of lymph node metastasis (LNM) and poor survival in gastric cancer patients; however, it is unclear whether LVI is a non-curative criteria component in all patients. We evaluated the risk factors of LNM in LVI-positive early gastric cancer (EGC) patients and identified a subgroup with a negligible LNM risk to assess the feasibility of endoscopic resection in these patients.

Methods. The clinicopathologic and survival data of patients undergoing surgery for gastric cancer were reviewed; LVI-positive EGC patients were selected. Logistic regression analysis was used to test the associations of potential risk factors with LNM, and Kaplan–Meier analysis was used to compare survival curves.

Results. LVI was detected in 1243 (15.5%) patients. In the multivariate logistic analysis, larger tumor size (odds ratio [OR] 1.23, 95% confidence interval [CI] 1.16–1.31; $p < 0.001$), presence of ulcer (OR 1.80, 95% CI 1.15–2.82; $p = 0.010$), undifferentiated histology (OR 1.64, 95% CI 1.25–2.16; $p < 0.001$), submucosal invasion (OR 2.28, 95% CI 1.38–3.76; $p = 0.001$), middle (OR 2.12, 95% CI 1.26–3.55; $p = 0.004$) or lower third location (OR 2.28, 95% CI 1.32–3.60; $p = 0.002$), and younger age (OR 0.98, 95% CI 0.97–0.99; $p = 0.002$) independently predicted LNM in LVI-positive EGC patients. LVI-positive patients fulfilling the absolute endoscopic resection criteria did not have LNM and there was no significant difference in the overall ($p = 0.928$) and disease-specific survival ($p = 0.821$) between these patients and those with LVI-negative EGC.

Conclusions. Additional surgery after endoscopic resection might be unnecessary in LVI-positive patients meeting the absolute criteria for endoscopic resection.

An increase in the incidence of early gastric cancer (EGC) and advances in endoscopic technology have caused endoscopic resection to become a standard treatment for patients with EGC lesions who meet the absolute or expanded criteria.[1–3] Metastatic regional lymph nodes are a significant prognostic factor determining treatment strategies in patients with gastric cancer,[4,5] while lymphovascular invasion (LVI) is a well-known independent predictor of both lymph node metastasis (LNM) and survival in those with gastric cancer, even in the early stage.[6–9] Liu et al.[7] reported that in patients with T1N0M0 cancer, the 5-year survival rate was significantly lower in LVI-positive patients than in LVI-negative patients (71.4% vs. 90.1%). According to the Japanese gastric cancer treatment guidelines,[10] the ability of endoscopic resection to cure the patient is based on a pathologic examination of resected specimens; the presence of LVI is considered non-curative and patients are recommended to undergo an additional surgery. Although patients with LVI are considered to have a high risk of LNM, many patients do not have LNM. It is unclear whether LVI is a non-curative criteria component for patients meeting the absolute indication for endoscopic resection. This raises questions about

First Received: 4 September 2018;
Published Online: 18 December 2018

H. Lee, MD, PhD
e-mail: leehyuk@skku.edu

whether all patients with LVI must undergo an additional surgery after endoscopic resection. Nevertheless, few studies have focused explicitly on the risk of LNM in patients with LVI-positive EGC. Furthermore, while previous studies focused on the prognostic value of LVI, data regarding the risk of LNM in LVI-positive EGC are scarce. Therefore, the aim of this study was to evaluate the risk factors associated with LNM in LVI-positive EGC patients and identify a group with negligible risk of LNM to assess the oncologic safety of endoscopic resection in these patients.

METHODS

Ethics

The need to obtain informed consent was waived by the Institutional Review Board of Samsung Medical Center, Seoul, Korea.

Patients

Data were collected from a prospectively maintained database on EGC (carcinoma limited to the gastric mucosa and/or submucosa, regardless of lymph node status) at Samsung Medical Center, Seoul, Korea. From 2002 to 2013, 8583 patients were enrolled. Patients who were younger than 18 years of age (n = 0), those with a history of gastrectomy for gastric cancer (n = 31) and multiple gastric cancers (n = 389), and those with incomplete data (n = 44) were excluded from the study. Patients diagnosed with papillary gastric adenocarcinoma (n = 110) were also excluded because recent studies have reported that these patients have a poor prognosis, although papillary gastric adenocarcinoma is classified as a 'differentiated type' in the Japanese classification.[11–13] Of the remaining 8008 patients, 1243 (15.5%) had LVI-positive EGC and 6765 (84.5%) had LVI-negative EGC.

Assessment of Outcomes

The primary outcome was the presence of LNM. The studied clinicopathologic data included the patient's age, sex, tumor location (upper, middle, and lower third of the stomach), macroscopic type (elevated [I, IIa, I + IIa, and IIa + IIb], flat [IIb], depressed [IIc and IIc + III], or mixed [others]), presence of an ulcer, size, histology (according to the World Health Organization's 2010 classification),[14] depth of invasion (mucosal or submucosal), LVI, surgery type, and number of dissected lymph nodes. The G1 and G2 grades of the International Classification of Diseases for Oncology (ICD-O) correspond to differentiated type of the WHO classification, while G3 corresponds to undifferentiated type.[15] Patients underwent subtotal or total gastrectomy with D1+ or D2 lymphadenectomy depending on the location of the tumor, according to the Japanese gastric cancer treatment guidelines.[10] Surgical complications were reviewed and classified according to the Clavien–Dindo classification.[16] Patient comorbidity was determined using the Charlson Comorbidity Index (CCI)[17] and the distribution of CCI score was as follows: 0: 1056 (85%); 1: 167 (13.4%); 2: 17 (1.4%); and 3: 3 (0.2%). The proportion of patients with a CCI score $\geq$ 2 was higher, at 1.6%.

All specimens were fixed in 10% formalin and embedded in paraffin, and cut into 5 μm sections. The sections were then stained using hematoxylin and eosin, and a complete histopathologic examination was performed by expert pathologists. In this series, LVI was defined as carcinoma cells that were present within a definite, endothelial-lined space (the lymphatic and/or blood vessels). We did not attempt to distinguish the blood vessels from the lymphatic vessels. Most of the recorded data did not distinguish extensive LVI from non-extensive LVI. Tumors were staged according to the American Joint Committee on Cancer Staging Manual (7th edition).[18]

Postoperative follow-up examinations were scheduled at 3- and 6-month intervals during the first year and annually thereafter. Clinical evaluations including esophagogastroduodenoscopy and abdominal pelvic computed tomography were performed. Follow-up data were prospectively collected and updated until April 2018. Overall survival was defined as the period between the date of surgery and death, and disease-specific survival was defined as the time from surgery to death caused by gastric cancer.

According to the pathologic results of the surgically resected specimens, the tumors were classified into the following indications for endoscopic resection of EGC: absolute (intramucosal tumor, histologically differentiated EGC without ulcerative findings, and size $\leq$ 2 cm) or expanded (criterion I: intramucosal tumor, histologically differentiated EGC without ulcerative findings, and size $>$ 2 cm; criterion II: intramucosal tumor, histologically differentiated EGC with ulcerative findings, and size $\leq$ 3 cm; criterion III: intramucosal tumor, histologically undifferentiated EGC without ulcerative findings and size $\leq$ 2 cm; criterion IV: submucosal invasion $<$ 500 μm [SM1], histologically differentiated EGC, and size $\leq$ 3 cm). To evaluate the feasibility of endoscopic resection in LVI-positive EGC patients, we compared the LNM rate for each criterion of the Japanese endoscopic resection guidelines.[10]

Statistical Analysis

Continuous variables are presented as the mean ± standard deviation and were compared using Student's *t* test, while categorical variables are presented as numbers with percentages and were compared using the Pearson Chi-square test or Fisher's exact test. Differences between variables were compared using the Mann–Whitney U test for continuous variables and the Chi-square or Fisher's exact tests for categorical variables. The associations of potential risk factors with the outcome (presence of LNM) were tested using a logistic regression analysis. In a multivariate analysis, we adjusted for possible confounding factors, including the patient's age and sex; tumor histology, depth of invasion, size, and macroscopic appearance; presence of an ulcer; and number of examined lymph nodes. P-values and 95% confidence intervals (CIs) were corrected using Bonferroni's method in case of multiple testing. The Kaplan–Meier method and log-rank test were used to compare the survival curves. p values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Comparison of Clinicopathologic Features

Of the 1243 LVI-positive patients, LNM was detected in 452 (36.4%). Table 1 shows the comparison of clinicopathologic features between LNM-positive and LNM-negative patients. Patients with LNM were younger (56.9 ± 11.8 vs. 59.8 ± 11.1; $p < 0.001$) and were more likely to be female (43.7% vs. 35.2%; $p = 0.004$) than patients without LNM. Tumors with LNM were more frequently located in the middle third of the stomach (33.0% vs. 27.3%; $p = 0.006$), more frequently showed the presence of an ulcer (11.1% vs. 5.8%; $p = 0.001$), were larger in size (4.4 ± 2.4 vs. 3.4 ± 1.9; $p < 0.001$), had deeper invasion (94.9% vs. 88.7%; $p < 0.001$), and were more likely to have an undifferentiated histology (58.0% vs. 40.3%; $p < 0.001$) than tumors without LNM. The mean number of examined lymph nodes was significantly higher in the LNM-positive group than in the LNM-negative group (39.5 ± 13.6 vs. 37.6 ± 13.6; $p = 0.016$), whereas the surgery type or follow-up duration was not significantly different between the two groups.

Risk Factors of Lymph Node Metastasis in Lymphovascular Invasion (LVI)-Positive Early Gastric Cancer (EGC) Patients

Among LVI-positive EGC patients, a larger tumor size (odds ratio [OR] 1.23, 95% CI 1.16–1.31; $p < 0.001$), presence of an ulcer (OR 1.80, 95% CI 1.15–2.82; $p = 0.010$), undifferentiated histology (OR 1.64, 95% CI 1.25–2.16; $p < 0.001$), submucosal invasion (OR 2.28, 95% CI 1.38–3.76; $p = 0.001$), middle (OR 2.12, 95% CI 1.26–3.55; $p = 0.004$) or lower third location of the tumor (OR 2.28, 95% CI 1.32–3.60; $p = 0.002$), and younger age (OR 0.98, 95% CI 0.97–0.99; $p = 0.002$) were significantly associated with the risk of LNM (Table 2).

Clinical Outcomes of LVI-Positive ECG Patients, According to the Endoscopic Resection Criteria

Among the 1243 LVI-positive EGC patients, 131 (10.5%) fulfilled the absolute or expanded indications for endoscopic resection, and 1112 (89.5%) were beyond the indications for endoscopic resection. As shown in Table 3, patients fulfilling the absolute endoscopic resection criteria did not have LNM (0/28); however, the rate of LNM increased to 12.5% (3/24), 50.0% (1/2), 25.0% (4/16), and 11.5% (7/61) for those fulfilling the expanded criteria I, II, III, and IV, respectively.

Because we found that LNM did not occur in patients fulfilling the absolute criteria, we additionally compared the long-term outcomes between LVI-positive and LVI-negative patients fulfilling the absolute criteria. Of the 6765 LVI-negative EGC patients, 977 (14.4%) met the absolute indication for endoscopic resection. The 5-year overall survival rates were 94.2% and 100% for LVI-negative and LVI-positive patients, respectively, and the 5-year disease-specific survival rates were 99.8% and 100% for LVI-negative and LVI-positive patients, respectively. The Kaplan–Meier analysis showed that there was no significant difference in the overall ($p = 0.928$) and disease-specific survival ($p = 0.821$) (Fig. 1).

Surgical Complications

A total of 105 (1.3%) patients had surgical complications, including bleeding (n = 19), perforation (n = 2), surgical site infection (n = 4), wound problem (n = 39), anastomosis leak (n = 6), anastomosis stricture (n = 1), postoperative pneumonia (n = 9), ileus (n = 12), intra-abdominal abscess (n = 7), intestinal obstruction (n = 14), and others (n = 19). Fifty-three (50.5%) patients needed endoscopic or radiologic treatment under regional anesthesia (grade IIIa) or reoperation under general anesthesia (grade IIIb). Two patients had life-threatening

TABLE 1 Comparison of clincopathologic features between lymph node metastasis-positive and -negative patients among early gastric cancer patients with lymphovascular invasion

Variables	LNM negative	LNM positive	*p* value
Total	791 (63.6)	452 (36.4)	
Patient age [mean ± SD]	59.8 ± 11.1	56.9 ± 11.8	< 0.001
Sex			0.004
Male	513 (64.9)	256 (56.4)	
Female	278 (35.2)	196 (43.7)	
Tumor location			0.017
Upper third	77 (9.7)	27 (6.0)	
Middle third	216 (27.3)	149 (33.0)	
Lower third	498 (63.0)	276 (61.1)	
Macroscopic appearance			0.088
Elevated	150 (19.0)	66 (14.6)	
Flat	52 (6.6)	21 (4.7)	
Depressed	460 (58.2)	282 (62.4)	
Mixed	129 (16.3)	83 (18.4)	
Presence of ulcer			0.001
No	745 (94.2)	402 (88.9)	
Yes	46 (5.8)	50 (11.1)	
Tumor size [mean ± SD]	3.4 ± 1.9	4.4 ± 2.4	< 0.001
Depth of invasion			< 0.001
Mucosa	89 (11.3)	23 (5.1)	
Submucosa	702 (88.7)	429 (94.9)	
Histology			< 0.001
Differentiated	472 (59.7)	190 (42.0)	
Undifferentiated	319 (40.3)	262 (58.0)	
Surgery type			0.447
Partial	691 87.4)	388 (85.8)	
Total	100 (12.6)	64 (14.2)	
Number of dissected LNs [mean ± SD]	37.6 ± 13.6	39.5 ± 13.6	0.016
Follow-up duration, years [mean ± SD]	5.6 ± 2.9	5.7 ± 3.2	0.412

Data are expressed as *n* (%) unless otherwise specified

LNM lymph node metastasis, *SD* standard deviation, *LNs* lymph nodes

complications (including complications of the central nervous system) that required management in the high dependency or intensive care unit, but there were no deaths (grade V) due to surgical complications. Cox regression analysis of the predictive factors showed that surgical complications did not affect long-term prognosis ($p = 0.617$ for overall survival and $p = 0.863$ for disease-specific survival).

DISCUSSION

In the current study, the risk factors of LNM were evaluated in LVI-positive EGC patients, and we identified patients with a negligible risk of LNM to assess the feasibility of endoscopic resection in these patients. Our study demonstrated that a larger tumor size, presence of an ulcer, undifferentiated histology, submucosal invasion, middle or lower third location, and younger age predicted LNM in LVI-positive EGC patients. LVI-positive patients who fulfilled the absolute endoscopic resection criteria did not have LNM and there was no significant difference in the overall and disease-specific survival between LVI-positive and LVI-negative EGC patients. To the best of our knowledge, this study is the first to evaluate these risk factors in a large number of LVI-positive EGC patients, controlling for other well-established prognostic variables. This was also the first attempt to identify a subgroup of LVI-positive patients with a negligible risk of LNM by applying the current criteria for endoscopic resection.

LVI, which refers to the invasion of tumor emboli into the lymphatic spaces, blood vessels, or both, in the peritumoral area, is generally regarded as a critical step in nodal or distal metastasis. Previous studies reported that the LNM rate in LVI-positive EGC patients ranged from 21 to

TABLE 2 Multivariate logistic analysis of factors associated with lymph node metastasis in early gastric cancer patients with lymphovascular invasion

Predictor	OR (95% CI)	*p* value
Histology		< 0.001
Differentiated	1	
Undifferentiated	1.64 (1.25–2.16)	
Depth of invasion		0.001
Mucosa	1	
Submucosa	2.28 (1.38–3.76)	
Tumor location		0.009
Upper	1	
Middle	2.12 (1.26–3.55)	
Lower	2.28 (1.32–3.60)	
Macroscopic appearance		0.245
Elevated	1	
Flat	0.74 (0.4–1.4)	
Depressed	1.13 (0.79–1.61)	
Mixed	1.35 (0.89–2.05)	
Presence of ulcer	1.80 (1.15–2.82)	0.010
Tumor size	1.23 (1.16–1.31)	< 0.001
Patient age	0.98 (0.97–0.99)	0.002
Sex	1.14 (0.88–1.47)	0.328
Number of dissected LNs	1.00 (0.99–1.01)	0.691

OR odds ratio, *CI* confidence interval, *LNs* lymph nodes

under certain conditions, leading us to think that for these patients, additional surgery after endoscopic resection may not be necessary.

Our study results help to further delineate the risk factors of LNM in LVI-positive EGC patients. In agreement with previously reported data, our study demonstrated that pathologic features, including a larger tumor size, submucosal invasion, presence of an ulcer, and undifferentiated histologic type, were independent predictors of LNM. Slightly different from the current guidelines, age, sex, and tumor location were found to be significant risk factors in our study; however, it is difficult to apply these factors in the current indications for endoscopic resection for several reasons, and it is often difficult to localize the tumor in an objective manner. Moreover, there is no clear evidence that age or sex is significantly correlated with LNM in other studies. Therefore, pathologic tumor status seems to be more important than clinical features; however, in cases where it is difficult to determine the patient's therapeutic plan, we may consider age, sex, and tumor location. Future investigations with external validation may be required to verify the significance of these factors.

In patients fulfilling the expanded endoscopic resection criteria (larger tumor size, presence of an ulcer, undifferentiated histology, or submucosal invasion), LVI alone indicates that there is a high risk of LNM; however, in patients meeting the absolute criteria, LVI may not indicate

TABLE 3 Lymph node metastasis rate according to endoscopic resection criteria in early gastric cancer patients with lymphovascular invasion

Depth of invasion	Ulceration	Differentiated (%)		Undifferentiated (%)	
Mucosa	Ulcer (−)	≤ 2 cm	> 2 cm	≤ 2 cm	> 2 cm
		0/28 (0)	3/24 (12.5)	4/16 (25.0)	
	Ulcer (+)	≤ 3 cm	> 3 cm		
		1/2 (50.0)			
SM1		≤ 3 cm	> 3 cm		
		7/61 (11.5)			

SM1 < 500 μm from the muscularis mucosae

54.3%.[13,19,20] The prognostic value of LVI in patients with gastric cancer was described in many independent studies, and is a well-known risk factor of LNM.[4,7,9,13,19–23] Kim et al.[19] reported that LVI was the strongest predictor of LNM in those with endoscopically resected EGC. In a meta-analysis of 13 studies, the pooled OR was 10.88.[21]

LVI is an important component of the non-curative resection criteria[10]; however, can the presence of LVI be considered sufficient to recommend additional surgery in all patients, for the risk of LNM? Although LVI is a clear risk factor of LNM, the rate of LNM seems to be negligible the risk of LNM or long-term survival. This finding is important because, until now, all patients with LVI and endoscopically resected tumors underwent additional surgery; however, because of the negligible risk of LNM and comparable long-term survival, these patients may be treated with endoscopic dissection alone. These findings raise a question that the current basis for EGC meeting the absolute indications for endoscopic resection with LVI should be a non-curative resection criterion. This implies that refinements of the treatment guidelines are needed for EGC patients who are treated with endoscopic resection

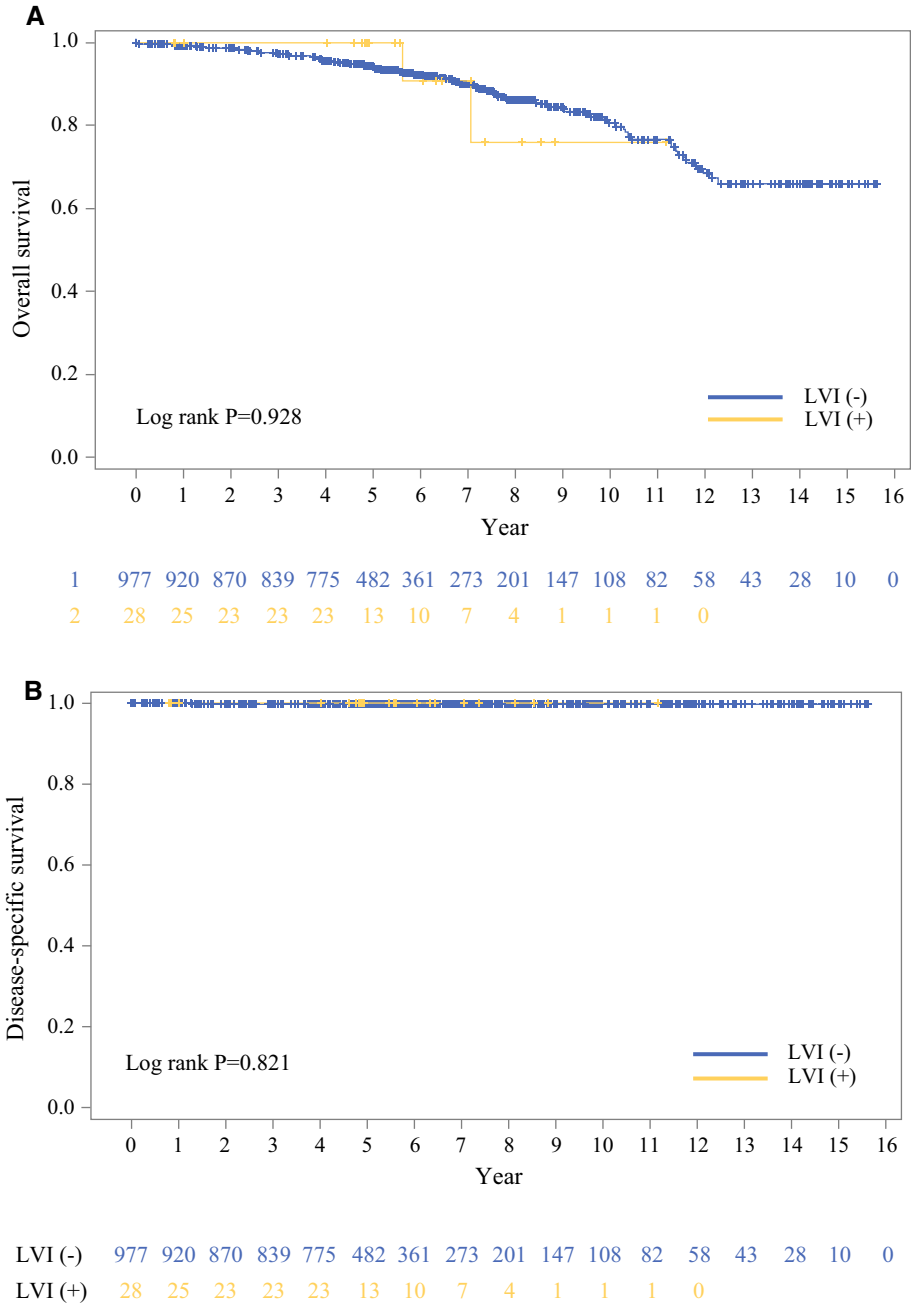

FIG. 1 Kaplan–Meier curve for (**a**) overall survival and (**b**) disease-specific survival in patients meeting the absolute criteria for endoscopic resection, stratified by the presence of LVI. *LVI* lymphovascular invasion

Our study has some limitations. First, it did not distinguish lymphatic invasion from blood vessel invasion. It is possible to identify blood vessels in the lymphatic channel with immunohistochemical staining; however, its clinical significance is not clear. Second, the extent of LVI, which may affect the risk of LNM, was not considered as the extent of LVI was reported in only a few pathologic reports. Third, we only used conventional hematoxylin and eosin staining to detect LVI. Immunohistochemical staining using a primary antibody against ERG, CD31, or D2-40 may have increased our power to detect LVI and decreased interobserver variability in future studies.[24]

CONCLUSION

Endoscopic resection may be sufficient to treat patients with LVI-positive EGC fulfilling the absolute criteria.

DISCLOSURE The authors declare that no conflict of interest.

REFERENCES

1. Pyo JH, Lee H, Min BH, et al. Long-Term Outcome of Endoscopic Resection vs. Surgery for Early Gastric Cancer: A Non-inferiority-Matched Cohort Study. *Am J Gastroenterol*. 2016;111:240–9.

2. Pyo JH, Lee H, Min BH, et al. Comparison of Long-Term Outcomes After Non-curative Endoscopic Resection in Older Patients with Early Gastric Cancer. *Ann Surg Oncol*. 2017;24:2624–31.
3. Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol*. 2006;41:929–42.
4. Borie F, Millat B, Fingerhut A, Hay JM, Fagniez PL, De Saxce B. Lymphatic involvement in early gastric cancer: prevalence and prognosis in France. *Arch Surg*. 2000;135:1218–23.
5. Chen R, He Q, Cui J, Bian S, Chen L. Lymph node metastasis in early gastric cancer. *Chin Med J (Engl)*. 2014;127:560–7.
6. Gotoda T, Yanagisawa A, Sasako M, 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;3:219–25.
7. Liu C, Zhang R, Lu Y, et al. Prognostic role of lymphatic vessel invasion in early gastric cancer: a retrospective study of 188 cases. *Surg Oncol*. 2010;19:4–10.
8. Ichikawa D, Kubota T, Kikuchi S, et al. Prognostic impact of lymphatic invasion in patients with node-negative gastric cancer. *J Surg Oncol*. 2009;100:111–4.
9. Liu E, Zhong M, Xu F, et al. Impact of lymphatic vessel invasion on survival in curative resected gastric cancer. *J Gastrointest Surg*. 2011;15:1526–31.
10. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer*. 2017;20:1–19.
11. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer*. 2011;14:101–12.
12. Lee HJ, Kim GH, Park DY, et al. Is endoscopic submucosal dissection safe for papillary adenocarcinoma of the stomach? *World J Gastroenterol*. 2015;21:3944–52.
13. Kang HJ, Kim DH, Jeon TY, et al. Lymph node metastasis from intestinal-type early gastric cancer: experience in a single institution and reassessment of the extended criteria for endoscopic submucosal dissection. *Gastrointest Endosc*. 2010;72:508–15.
14. Bowman FT CF, Hruban RH. Classification of Tumours of the Digestive System. International Agency for Research on Cancer: Lyon; 2010.
15. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) research data record description of cases diagnosed in 1973–2014 (2017). https://seer.cancer.gov/data-software/documentation/seerstat/nov2016/TextData.FileDescription.pdf. Accessed 2 Nov 2009.
16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–13.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–83.
18. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds). AJCC Cancer Staging Manual. 7th ed. New York: Springer-Verlag New York; 2010.
19. Kim H, Kim JH, Park JC, Lee YC, Noh SH, Kim H. Lymphovascular invasion is an important predictor of lymph node metastasis in endoscopically resected early gastric cancers. *Oncol Rep*. 2011;25:1589–95.
20. Gotoda T, Sasako M, Ono H, Katai H, Sano T, Shimoda T. Evaluation of the necessity for gastrectomy with lymph node dissection for patients with submucosal invasive gastric cancer. *Br J Surg*. 2001;88:444–9.
21. Kwee RM, Kwee TC. Predicting lymph node status in early gastric cancer. *Gastric Cancer*. 2008;11:134–48.
22. Kunisaki C, Makino H, Kimura J, et al. Impact of lymphovascular invasion in patients with stage I gastric cancer. *Surgery*. 2010;147:204–11.
23. Bu Z, Zheng Z, Li Z, et al. Lymphatic vascular invasion is an independent correlated factor for lymph node metastasis and the prognosis of resectable T2 gastric cancer patients. *Tumour Biol*. 2013;34:1005–12.
24. Kim S, Park HK, Jung HY, et al. ERG Immunohistochemistry as an endothelial marker for assessing lymphovascular invasion. *Korean J Pathol*. 2013;47:355–64.